EVIDENCE-BASED MEDICINE TO INFORM PRACTICE: ASSESSING CLINICAL EFFECTIVENESS AND ECONOMIC BURDEN OF MEDICINE

EDITED BY: Kevin Lu and Bin Jiang
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frontiers Research Topics

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EVIDENCE-BASED MEDICINE TO INFORM PRACTICE: ASSESSING CLINICAL EFFECTIVENESS AND ECONOMIC BURDEN OF MEDICINE

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The Effects of Childhood Circumstances on Health in Middle and Later Life: Evidence From China

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Background: This study examined the relationship between childhood circumstances and health in middle and later life. We quantified how childhood circumstances contribute to health in later life, both directly and indirectly, through their effects on potential mediators.

Methods: This study used three waves of data from the national longitudinal survey of the China Health and Retirement Longitudinal Study (CHARLS). The final model in this study included 7,476 eligible respondents aged 45 years and above. We constructed a simple health status measure based on the first principal component of CHARLS survey responses with 25 health-related information. It is a multi-dimensional measurement that comprehensively reflects the individual's healthy aging. We formulated childhood circumstances factors into five domains: childhood health and nutrition, childhood socioeconomic status, access to health care, parental genetics, and adverse childhood experiences. Ordered logit regression was conducted to analyze the relationship between health in middle and later life and childhood circumstances, with other explanatory variables controlled.

Results: Controlling for educational attainment, personal income, and health status in the last wave, adults who experience good childhood health (poor as the base, coefficient 0.448, $p < 0.01$), and better family financial status (worse as the base, coefficient 0.173, $p < 0.01$) have significantly better health during their middle and later life, in comparison, being inconvenient to visit a doctor (coefficient −0.178, $p < 0.01$), and having two or three adverse childhood experiences (0 as the base, coefficient −0.148, $p < 0.01$) are significantly associated with poorer health. Childhood circumstances appear to act both through a lasting effect of initial health and financial status in childhood and through their impact on achievements in adulthood.

Conclusion: Our findings suggest that investments in health during childhood not only contribute to health in later life but also dynamically improve an individual's educational attainment and personal income, as well as other life prospects. All these returns may extend far beyond childhood and continue throughout the lifespan.

Keywords: childhood circumstances, healthy aging, life-course model, panel data, health disparity, economic burden, middle-aged and elderly population

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INTRODUCTION

The phenomenon of population aging has become a global trend (1–3). In 2017, the global population over 60 years old reached 962 million, and this number is expected to increase to 2.1 billion by 2050. China is facing a more difficult aging situation (4). In 2017, one in four of the world's total aging population lived in China, and the proportion of the elderly population in China was 16%. The proportion has changed recently and is expected to further increase to 35% by 2050 (3). A significant contributor to the aging population is that expected longevity has increased dramatically. Currently, life expectancy at birth is at least 77.0 years in China, and it increased by 75% between 1960 and 2015 (5). However, a longer lifespan does not necessarily mean that one's quality of life also improves. The physical, psychological, and cognitive health problems associated with aging are still a concern (6). In 2018, China's quality-adjusted life expectancy per capita was only 68.7 years. The elderly survived an average of more than 8 years with diseases, and the number of functionally limited and partially limited elderly exceeded 40 million. Among the elderly, the proportion of patients suffering from more than one chronic disease was as high as 75%, which accounted for 190 million people (7). For this reason, promoting and achieving healthy aging has become a critical public health issue in China. In particular, most of the health problems mentioned above do not come across suddenly but act as a cumulative process. That also prompts us to pay attention to the link between experiences from earlier life stages and healthy aging.

As an essential part of human capital, health is regarded as a durable product throughout the life cycle since Grossman published his seminal work on the demand for health (8). At present, many research groups continue their work on the long-term impact of childhood circumstances on future health, as well as social life (9, 10). The available evidence indicates that returns on health investment during childhood are higher than in other life stages (11). Recent studies have demonstrated that a wide range of childhood circumstances may lead to health disparity in adulthood (12–14), such as health and nutrition (15), parents' education levels and family socioeconomic status (16, 17), early life development and genetic inheritance (18, 19), adverse childhood experiences (12, 20), and access to medical services in the community (21). Some of these studies have found that adverse shocks during childhood can adversely affect adult health, while other studies have demonstrated the positive effects of childhood interventions on future health (21, 22). However, prior work is generally limited to a subset of childhood circumstances. It is necessary to discuss all these domains of childhood circumstances in the same model, as well as consider that domains may be inter-related.

Previous studies have suggested several pathway models to explain the correlation between childhood circumstances and health. Some life course models emphasize that childhood circumstances have either direct or indirect effects on adult health (17, 23). The direct effects work through the adverse experience itself. The indirect effects limit educational achievements and other life-related better changes, making it challenging to maintain a healthier life in adulthood. Evidence from developed countries has revealed a common phenomenon: children who grow up in a more impoverished environment have worse health outcomes as they age than those who do not, and their educational attainments and labor income tend to be lower (16, 24–26). Furthermore, some studies have explored the indirect effects in greater depth. These studies focused on the role of socioeconomic status in determining adult health and concluded that the association between social achievements and health in later life could not be simply attributed to childhood experiences. Circumstances in early life influence adult circumstances, which, in turn, affect the development of diseases (27–29). The fetal origins hypothesis suggests that malnutrition and health shocks in early life can cause hidden developmental problems in the immune system and vital organs (30, 31). Thus, they directly affect one's health status in all stages of life. This hypothesis also suggests another possible pathway. Children born into poor families are more likely to be exposed to a poor fetal environment, so their future health status is poorer than those in wealthy families. Their future socioeconomic status is also likely to be lower. As a result, the above-mentioned correlation may also appear between socioeconomic status and health in adulthood. From the life-course perspective, it is of great significance to explore how childhood circumstances affect health in middle and later life, especially the dynamic relationship between health and socioeconomic status.

Although some attempts have been made to address the issue of how childhood circumstances influence health status when individuals get old, some of the aspects require further research. First, previous studies of childhood circumstances typically have not included a large number of health outcomes. Most of them examined a single disease or one particular domain of health status, such as acute myocardial infarction (32), or various psychological measures (14). They are useful in estimating prevalence, but these results limit the development of a more comprehensive definition of healthy aging. People are gradually giving new meanings to health, and the multi-dimensional concept of health has been widely recognized by academia (33). Health is not merely the absence of disease or infirmity, but a state of complete physical, mental, and social well-being (34). Specifically, Healthy aging does not only mean an increase in the average life expectancy, but should also focus on all aspects of the quality of life, which is the perfect status in terms of morality, freedom, and happiness. Second, the causal pathway between health and socioeconomic status has not been demonstrated (9, 35), which makes it more complicated to study the pathway from childhood circumstances to health in middle and later life. Slightly fewer attempts at examining these possible pathways in the same research framework have been reported in the literature. Third, most of the existing studies were conducted in developed countries, and the conclusions are not necessarily applicable to populations in developing countries. Compared with these studies, our study has the following two main contributions. First, we have defined a health index that contains various aspects of healthy living information, which measures the degree of an individual's healthy aging. Second, experiences in middle and high-income countries, such as China, may bring more inspiration to developing countries. The generation of

Chinese represented by this research sample has undergone a complicated social change process: the period from the early days of the founding of the People's Republic of China with low-income levels to modern times' rapid development (15, 36). This process can reflect the overall operating law of changes in socioeconomic status and people's health in developing countries. Our study aims at an in-depth understanding of the above issue. We quantified the long-term effects of childhood circumstances on health status in middle and later life, using the ordered logit model based on data from three waves of China's Health and Retirement Longitudinal Study (CHARLS) (37). Due to the difficulty in making causal inferences, we began by presenting reduced-form estimates of the association between childhood circumstances and health in middle and later life. Then, we considered several pathway models to determine whether childhood circumstances directly affect future health and how these circumstances contribute to the dynamic relationship between health and socioeconomic status in middle and later life.

METHODS

Data and the Sample

Data were collected in 2013 and 2015 for CHARLS, as well as in 2014 for a life history survey conducted by the National School of Development at Peking University. CHARLS is a longitudinal study of individuals over age 45. The first wave was conducted in 2011, and follow-up surveys have been conducted every 2 years after that. In 2014, CHARLS included a life-history survey that asked questions about the life experiences of respondents since birth, including their migration and residential history, economic and social conditions in childhood, and so on. For our study, variables associated with childhood circumstances were extracted from the 2014 survey results. Health status and socioeconomic data were obtained from the 2013 and 2015 waves. CHARLS covers all county-level units in mainland China (excluding Tibet, Hainan, and Ningxia). For example, the 2015 sample includes 150 county-level and 450 village-level units, with a total of 11,797 households (20,284 individuals). The survey provides rich data regarding the physical and psychological health, demographics, and socioeconomic status of middle-aged and older adults. More detailed information about CHARLS can be obtained from Peking University's website (38, 39).

Sample Selection Criteria

Our study included individuals who participated in the 2014 survey and responded in either 2013 or 2015 surveys, and we also excluded individuals aged under 45. First, we used the 2014 sample to match the 2015 or 2013 data and obtained two sub-samples for the correlational study. We also deleted observations for individuals under age 45 or with missing values. Then, we merged the data from all three waves and used the 2014 records as the primary sample. Since CHARLS collects unbalanced panel data, there are cases of sample loss and new sample enrollment in each fellow-up wave, so the final three-wave, balanced sample size in our final analysis is 7,636.

Measurement

Health Status Index

We constructed a health index to measure each respondent's health status in the different waves. CHARLS asks respondents a large number of health-related questions. We used 25 of these questions (see **Table 1**), including the following: (i) an indicator of whether the respondent has a poor health status, as measured by self-reported health; (ii) indicators of whether the respondent suffers from major diseases, including 14 medical conditions (hypertension, dyslipidemia, diabetes, cancer, chronic lung diseases, liver disease, heart problems, stroke, kidney disease, digestive disease, psychiatric problems, memory-related disease, arthritis, and asthma); (iii) indicators of whether the respondent has any functional limitations in daily life, measured over five instrumental activities of daily living (i.e., performing household chores, preparing meals, shopping, managing money, and taking medication); (iv) indicators of cognition and depressive symptoms, measured by the respondent's self-reported memory level and the Center for Epidemiologic Studies Depression Scale-10 [CESD-10; individuals with a total score of 10 or higher were considered to have a high risk of depression (23, 40)]; (v) an indicator of physical pain measured by the presence of self-reported pain in various parts of the body; (vi) an indicator of participation in social activities, measured by whether the respondent had participated in 11 daily social activities in the past month.

Childhood Circumstances Factors

The selection of childhood circumstances variables was guided by previous studies, which led us to formulate them into five domains.

Childhood health and nutrition were measured with two variables: (i) self-reported health status before age 15 (categorized as poor, fair, or good); and (ii) ever experienced hunger from birth to age 5 (15, 41).

Childhood socioeconomic status was measured with three variables: (i) family financial status before age 17 (categorized as worse, fair, or better); and (ii) parents' educational attainment (measured by years of education) (27, 42).

Access to health care was measured with two variables: (i) received any vaccinations before age 15; and (ii) experienced inconvenience in visiting a doctor from birth to age 15 (43).

Parental genetics were measured with four variables: (i) parents' longevity (for parents who have passed away, measured as their age at death, and for parents who are alive, measured as their current age); and (ii) whether the respondents' parents are still living (indicators of mother or father still living) (13, 41).

Adverse childhood experiences (ACE) were collected from the answer to 11 questions, including the following: (i) abuse (indicators of often or sometimes being hit by one's father, mother, or other children); (ii) parental depression (indicators of whether the respondent's mother or father displayed ongoing depressive symptoms during most or all of his/her childhood); (iii) parental addiction problems (indicators of whether the respondent's mother or father has had problems with alcoholism, drug addiction, or gambling); (iv) parental marital conflict (an indicator of a fair or poor relationship between the respondent's

TABLE 1 | Health index weights.

Variable	Loading	KMO
Difficulty performing household chores	0.3462	0.7839
Difficulty preparing meals	0.3350	0.7685
Difficulty shopping for groceries	0.3216	0.8474
Self-reported health fair or poor	0.3160	0.8783
Difficulty managing money	0.2933	0.8429
High risk of depression	0.2763	0.8614
Troubled with physical pains	0.2681	0.8363
Difficulty taking medications	0.2256	0.8834
Self-reported memory fair or poor	0.2181	0.8569
Ever experience arthritis	0.1957	0.8399
Ever experience heart problems	0.1711	0.8212
Ever experience chronic lung diseases	0.1492	0.6814
Ever experience stomach disease	0.1491	0.8183
Ever experience hypertension	0.1306	0.7471
Ever experience stroke	0.1259	0.8582
Ever experience kidney disease	0.1219	0.8474
Ever experience memory-related disease	0.1179	0.8747
Ever experience asthma	0.1149	0.6285
Ever experience mental disease	0.1068	0.8834
Ever experience dyslipidemia	0.1024	0.7029
Ever experience diabetes	0.0955	0.7288
Ever participate in any social activity during last month	0.0818	0.8256
Ever experience liver disease	0.0785	0.7897
Ever experience cancer	0.0329	0.7796
Overall	—	0.8114

The variables in the table are ordered by the principal component loadings.

parents, and whether the parents often or sometimes quarreled); (v) indicators of a fair or poor relationship between child and father or between child and mother. The available evidence indicates that experiencing one ACE category is highly correlated with experiencing one or more of the others (12, 44). In line with these studies, an ACE count was also used to classify respondents into four categories: 0 ACEs, 1 ACE, 2-3 ACEs, and 4+ ACEs.

Other Explanatory Variables

The respondents' current socioeconomic status was measured with two variables: (i) educational attainment, measured by years of education, and (ii) personal annual income, measured by the sum of personal labor-related annual income and household asset annual income per capita. Then, the respondent's annual income was categorized as below or above the median (23). Age and gender were included as explanatory variables in all models.

Analytical Strategy

Our health status index measures the weighted average score respondents achieve across all six domains, and higher values indicate a healthier status. After standardizing the data for those 25 health measures mentioned above, we used principal component analysis to reduce dimensionality. We took the first principal component as the health status index, following previous studies (9, 45). The first principal component is the weighted average of these health indicators, where the weights were chosen to maximize the proportion of the variance of health indicators that can be explained by this weighted average. So that index is a standardized variable with a mean of 0 and a variance of 1. We also tested the robustness of the measurement between different subgroups, such as male and female groups, as well as data collected during different waves. However, the results were similar, so we combined all waves and both male and female groups in the same analysis. Finally, we converted the health status index into five quantiles, which can sequentially distinguish populations at different health levels.

Our primary analysis was aimed at estimating the independent effect of childhood circumstances on health status in middle and later life while accounting for the role of the individual's current socioeconomic status and health status in the previous period. To achieve this goal, our analysis was divided into three stages. First, we estimated the reduced form equation, which examined the association between childhood circumstances and health status in middle and later life after controlling for demographic variables. Second, we added contemporary socioeconomic variables to the reduced form equation estimated in the first step, which explored the indirect pathways. In this model, if the coefficients of childhood circumstances changed significantly, then it indicated the existence of an indirect effect; however, if the coefficients did not change much, it demonstrated a direct effect. Third, we added the individuals' previous health status to the model in the second step, which verified the stability of the lasting effect of childhood circumstances and explored the possibility of other potential mediators (46, 47).

RESULTS

Sample Description

The principal component loadings and KMO (Kaiser-Meyer-Olkin) measures of variables are shown in **Table 1**. The health status index assigns higher weights to IADLs, self-reported health, cognition and depressive symptom, and body pains. Much fewer weights are given to specific health problem experiences and social activities participation. The overall KMO value is 0.8114, which means that the commonality among variables is strong, and the analysis can play a better data reduction effect. The variables used in our analysis are summarized in **Table 2**. Each of the samples in **Table 2** corresponds to different panel data combinations: 2013–2014, 2014–2015, and 2013–2015. The first two combinations were used to test the association between childhood circumstances and health status in middle and later life, while the last one was used to explore potential pathway mechanisms. The data in each sample were structured consistently based on the mean and variance of key variables. We can use the third sample to describe the population as follows. In the sample, there are slightly more women (0.4% more) than men, with an average age of 59.92 years. The respondents had an average education level of 6.15 years (equivalent to primary school graduation), their fathers had an average of 2.43 years of education, while their mothers had an average of 0.74 years. In 2015, the annual

income per capita was 10,276.53 yuan. Most individuals reported that their family's financial situation prior to age 17 was worse, while most individuals reported that their health status before age 15 was good. In the sample, 35.2% of the respondents experienced food scarcity at some time between birth and age 5, and 12.9% did not receive any vaccinations prior to age 15. However, 34.68% reportedly had not been exposed to the 11 serious adverse events defined above, and the mothers' average life expectancy and total alive number were higher than those of the fathers'.

Childhood Circumstances and Health Status in Middle and Later Life

Table 3 examines the relationship between childhood circumstances and health in middle and later life. To verify the stability of the main findings, we regressed four models. The first and second models used the respondents' 2015 health status as the dependent variable, while the third and fourth models used 2013 health status data. We also tried different ways to measure the dependent variable. The first and third models used the ordinary least squares model, which regarded health status as a continuous variable. The second and fourth models adopted the order logit model, which regarded health status as an ordered variable. In each model, we controlled for age and gender, and all results were similar. As shown in **Table 3**, the five domains of childhood circumstances all have a significant association with health status in middle and later life. In all cases, good health in middle and later life is significantly associated with five variables: having better self-reported health in childhood, having a higher childhood family financial status, the father having a higher education level, and the mother and father having increased longevity. Poor health in middle and later life is significantly associated with three variables: having experienced hunger in childhood, inconvenience in visiting a doctor, and any ACE. All seven of these variables are statistically significant at the 1% level.

The main differences between these four models are as follows. First, the association between the mother's education and health in middle and later life is also significant but only occurs in model 2 (coefficient 0.017, $p < 0.1$). Second, having received any vaccinations is positively and significantly associated with good health in adulthood. However, it is not significant in model 4 (coefficient 0.070, $p > 0.1$), and there are statistically significant differences in the other three models. Third, there is a statistically significant difference within the ACE domain (1 ACE group). Compared with no ACE, one ACE shows a significant association with health in adulthood. In models 2 (coefficient −0.185, $p < 0.01$) and 4 (coefficient −0.171, $p < 0.01$), this association is significant at the 1% level, but, in models 1 (coefficient −0.114, $p < 0.05$) and 3 (coefficient −0.091, $p < 0.1$), it is significant at the 5 and 10% levels, respectively.

To assess how much of the variance in health is explained by different domains of childhood circumstances, we classified these 11 variables into five domains and calculated the incremental value of the R square (pseudo R square) when each domain was added to the regression with all the other domains. The results obtained are shown at the bottom of **Table 3**. Among these domains of childhood circumstances (take model 1 as an example), those measuring childhood health and nutrition ($\Delta R^2 = 0.0127$, $p < 0.01$) show the most considerable incremental contribution to the sum of R square. The subsequent order is ACE ($\Delta R^2 = 0.0101$, $p < 0.01$) and childhood socioeconomic status ($\Delta R^2 = 0.0086$, $p < 0.01$), and the last is access to healthcare ($\Delta R^2 = 0.0044$, $p < 0.01$) and parental genetics ($\Delta R^2 = 0.0055$, $p < 0.01$). The Wald and LR tests were used to verify statistical significance when adding each domain to the regression. The results strongly suggest that these explanatory variables should be included in the unconstrained model, and they are all significant at the 1% level. Overall, in our models, childhood circumstances are significantly associated with health status in middle and later life, and the effects of demographic variables are also consistent with expectations.

The Mechanism of Childhood Circumstances

Table 4 presents results from ordered logits of health status in middle and later life on childhood circumstances. Column 2 presents the results from the reduced form analysis. Except for the second column, each column added new control variables to the model in the front column. Model 5 included educational attainment and personal annual income in 2015, and model 6 further included the respondents' health status in the previous wave. As mentioned above, it is necessary to consider multiple potential mediators when studying the relationship between childhood circumstances and health in later life. For this reason, in our final regression model, we chose to use health status in the previous wave as the proxy variable of the potential missing variables to solve the problem of endogeneity.

The results in model 5 show that the father's education level (coefficient 0.010, $p > 0.1$) and the respondent's childhood vaccination status (coefficient 0.027, $p > 0.1$) become insignificant when educational attainment (coefficient 0.040, $p < 0.1$) and personal annual income (coefficient 0.402, $p < 0.1$) are added to the reduced model. Beyond these two variables, the other variables remain significant, but the absolute values of coefficients decline slightly. It appears that socioeconomic status can be identified as a potential mediator between some childhood circumstances and middle-aged and elderly health. For example, the effect of vaccination and the father's level of education is absorbed by the individual's socioeconomic status in later life, and this effect works indirectly on health through an individual's current socioeconomic status.

The results of model 6 show that having experienced hunger in childhood (coefficient −0.036, $p > 0.1$), parents' longevity, and 1 ACE (coefficient −0.075, $p > 0.1$) become insignificant when the individuals' health status in the previous wave is added to the regression. In contrast, childhood self-reported health, childhood family financial status, inconvenience in visiting a doctor (coefficient −0.178, $p < 0.05$), and more than one ACE remain jointly significant predictors of health in later life. Furthermore, the absolute values of coefficients for childhood circumstances are in substantial decline, which indicates the

TABLE 2 | Descriptive statistics.

Variable	2014–2015 sample		2013–2014 sample		2013–2015 sample	
	Mean (S.D.)	Observations	Mean (S.D.)	Observations	Mean (S.D.)	Observations
Individual characteristics						
Female	0.503 (0.500)	10,934	0.514 (0.500)	9,489	0.504 (0.500)	7,476
Age in 2015	60.088 (8.806)	10,934			59.920 (8.413)	7,476
Age in 2013			58.891 (8.849)	9,489		
Childhood health and nutrition						
Self-reported health status, before age 15 (1-poor,2-fair,3-good)	2.250 (0.655)	10,934	2.255 (0.652)	9,489	2.266 (0.651)	7,476
Ever experienced hunger, from birth to age 5	0.354 (0.478)	10,934	0.347 (0.476)	9,489	0.352 (0.478)	7,476
Childhood socioeconomic status						
Family financial status, before age 17 (1-worse,2-fair,3-better)	1.727 (0.627)	10,934	1.727 (0.623)	9,489	1.728 (0.619)	7,476
Mother's educational attainment	0.776 (2.164)	10,934	0.693 (2.043)	9,489	0.738 (2.090)	7,476
Father's educational attainment	2.475 (3.410)	10,934	2.340 (3.329)	9,489	2.436 (3.357)	7,476
Access to health care						
Received any vaccinations, before age 15	0.871 (0.335)	10,934	0.859 (0.348)	9,489	0.871 (0.335)	7,476
Experienced inconvenience in visiting a doctor, from birth to age 15	0.089 (0.284)	10,934	0.091 (0.288)	9,489	0.087 (0.282)	7,476
Parental genetics						
Mother's longevity	75.092 (13.328)	10,934	75.348 (13.408)	9,489	75.389 (13.318)	7,476
Father's longevity	73.070 (12.980)	10,934	73.070 (13.140)	9,489	73.212 (12.992)	7,476
Mother still living	0.228 (0.419)	10,934	0.288 (0.453)	9,489	0.257 (0.437)	7,476
Father still living	0.126 (0.332)	10,934	0.165 (0.371)	9,489	0.146 (0.353)	7,476
Adverse childhood experiences (%)						
0 ACEs	34.06	10,934	34.14	9,489	34.68	7,476
1 ACE	20.02	10,934	20.46	9,489	20.22	7,476
2-3 ACEs	29.76	10,934	29.43	9,489	29.68	7,476
4+ ACEs	16.16	10,934	15.97	9,489	15.41	7,476
Health outcomes						
Health status in 2013 (5-quantile)			3.007 (1.392)	9,489	3.079 (1.378)	7,476
Health status in 2015 (5-quantile)	2.907 (1.383)	10,934			2.910 (1.361)	7,476
Adulthood characteristics						
Educational attainment					6.154 (4.016)	7,476
Personal annual income in 2015					10,276.53 (22,518.34)	7,476

The unit of personal income is RMB. The "2013–2015 sample" includes respondents who participated in all three waves of the survey.

existence of other potential mediators. We should be cautious in explaining the significant relationship between the respondents' current health and their health in the last wave. In our model, we assumed that the recursive nature of the health stock is the most important (10, 48). Therefore, this positive relationship can be explained as the result of other unobserved mediators.

DISCUSSION

This study focuses on an essential issue: do childhood circumstances, consisting of five domains, have lasting effects on health status in middle and later life? Using three-wave panel data from CHARLS, we found that an extensive set of childhood circumstances were independently associated with health status among the middle-aged and elderly. For example, childhood health and childhood family financial status have a direct impact on health in later life, and they also indirectly impact adult health by affecting socioeconomic status in the same period. Another example is the father's education, as well as experiencing hunger and vaccinations in childhood, indirectly affect adult health through mediators, such as socioeconomic status in the same period. Moreover, this result indicates that some childhood circumstances also contribute to future resources that could enhance or mitigate this effect. Our study also shows that there is relative importance among different domains of childhood circumstances. We should pay extra attention to these three domains: early childhood nutrition and health, family socioeconomic status, and adverse childhood experiences.

Theories and previous studies suggest that a particular domain of childhood circumstances can lead to differences in physical,

TABLE 3 | Childhood circumstances and health status in middle and later life.

Variable	Model 1 In 2015 (OLS)	Model 2 In 2015 (OLOGIT)	Model 3 In 2013 (OLS)	Model 4 In 2013 (OLOGIT)
Self-reported health status, before age 15 (Poor as the base)				
Fair	0.605***	0.647***	0.450***	0.505***
	(0.057)	(0.057)	(0.055)	(0.061)
Good	0.663***	0.795***	0.559***	0.687***
	(0.059)	(0.059)	(0.057)	(0.063)
Ever experienced hunger, from birth to age 5	−0.120***	−0.149***	−0.100***	−0.151***
	(0.037)	(0.036)	(0.036)	(0.039)
Family financial status, before age 17 (Worse as the base)				
Fair	0.314***	0.299***	0.310***	0.333***
	(0.039)	(0.038)	(0.037)	(0.040)
Better	0.428***	0.441***	0.392***	0.476***
	(0.065)	(0.064)	(0.064)	(0.070)
Mother's educational attainment	0.014	0.017*	0.012	0.015
	(0.009)	(0.009)	(0.009)	(0.010)
Father's educational attainment	0.017***	0.019***	0.016***	0.017***
	(0.006)	(0.006)	(0.006)	(0.006)
Received any vaccinations, before age 15	0.186***	0.151***	0.104**	0.070
	(0.053)	(0.052)	(0.050)	(0.054)
Experienced inconvenience in visiting a doctor, from birth to age 15	−0.398***	−0.389***	−0.400***	−0.419***
	(0.063)	(0.062)	(0.060)	(0.065)
Adverse childhood experiences (0 Aces as the base)				
1 ACE	−0.114**	−0.185***	−0.091*	−0.171***
	(0.050)	(0.048)	(0.048)	(0.051)
2-3 ACEs	−0.270***	−0.336***	−0.258***	−0.374***
	(0.045)	(0.043)	(0.043)	(0.046)
4+ ACEs	−0.585***	−0.671***	−0.445***	−0.637***
	(0.054)	(0.053)	(0.052)	(0.057)
Mother's longevity, in 2015/2013	0.007***	0.006***	0.004***	0.004***
	(0.001)	(0.001)	(0.001)	(0.001)
Father's longevity, in 2015/2013	0.006***	0.005***	0.005***	0.005***
	(0.001)	(0.001)	(0.001)	(0.002)
Mother still living, in 2015/2013	0.110**	0.039	0.080*	0.128***
	(0.049)	(0.047)	(0.046)	(0.050)
Father still living, in 2015/2013	−0.019	−0.001	0.004	−0.014
	(0.060)	(0.058)	(0.054)	(-0.058)
Age, in 2015/2013	−0.042***	−0.045***	−0.031***	−0.033***
	(0.002)	(0.002)	(0.002)	(0.002)
Gender	−0.632***	−0.651***	−0.494***	−0.620***
	(0.035)	(0.035)	(0.034)	(0.037)
Constants	1.094***	Yes	0.961***	Yes
	(0.209)	Yes	(0.202)	Yes
N	10,934	10,934	9,489	9,489
R^2/Pseudo R^2	0.1197	0.0453	0.0975	0.0372
Incremental contribution of variables to R^2/Pseudo R^2				
Childhood health and nutrition	0.0127***	0.0059***	0.0110***	0.0045***
Childhood SES	0.0086***	0.0033***	0.0096***	0.0035***
Access to health care	0.0044***	0.0014***	0.0048***	0.0015***
Parental genetics	0.0055***	0.0013***	0.0031***	0.0014***
Adverse childhood experiences	0.0101***	0.0049***	0.0081***	0.0047***

*Standard errors in parentheses. *p < 0.1, **p < 0.05, ***p < 0.01.*

TABLE 4 | Order logit regression of health status in middle and later life on childhood circumstances and adulthood characteristics.

Variable	Model 4 Base case 2014–2015 sample	Model 5 Included education and personal income in 2015 2014–2015 sample	Model 6 Included health status in 2013 2013–2015 sample
Self-reported health status, before age 15 (poor as the base)			
Fair	0.620***	0.606***	0.371***
	(0.070)	(0.070)	(0.073)
Good	0.787***	0.778***	0.448***
	(0.072)	(0.072)	(0.075)
Ever experienced hunger, from birth to age 5	−0.125***	−0.109**	−0.036
	(0.044)	(0.044)	(0.046)
Family financial status before age 17 (worse as the base)			
Fair	0.342***	0.310***	0.164***
	(0.046)	(0.046)	(0.048)
Better	0.471***	0.360***	0.173**
	(0.079)	(0.080)	(0.082)
Mother's educational attainment	0.011	−0.002	−0.010
	(0.011)	(0.011)	(0.011)
Father's educational attainment	0.022***	0.010	0.005
	(0.007)	(0.007)	(0.007)
Received any vaccinations, before age 15	0.111*	0.027	0.082
	(0.063)	(0.064)	(0.066)
Experienced inconvenience in visiting a doctor, from birth to age 15	−0.354***	−0.324***	−0.178**
	(0.076)	(0.076)	(0.080)
Adverse childhood experiences (0 Aces as the base)			
1 ACE	−0.147**	−0.151***	−0.075
	(0.058)	(0.058)	(0.060)
2-3 ACEs	−0.323***	−0.316***	−0.148***
	(0.052)	(0.052)	(0.054)
4+ ACEs	−0.702***	−0.684***	−0.462***
	(0.065)	(0.065)	(0.068)
Mother's longevity, in 2015	0.005***	0.005***	0.002
	(0.002)	(0.002)	(0.002)
Father's longevity, in 2015	0.006***	0.005***	0.002
	(0.002)	(0.002)	(0.002)
Mother still living, in 2015	0.117**	0.095*	0.078
	(0.055)	(0.055)	(0.057)
Father still living, in 2015	0.069	0.095	0.140**
	(0.067)	(0.067)	(0.069)
Educational attainment		0.040***	0.021***
		(0.006)	(0.006)
Personal annual income, in 2015 (above the median as the base)		0.402***	0.214***
		(0.043)	(0.045)
Health status in 2013 (1st decile of health index as the base)			
2nd decile of the health index			1.373***
			(0.076)
3rd decile of the health index			2.427***
			(0.079)
4th decile of the health index			3.257***
			(0.083)
5th decile of the health index			4.402***
			(0.090)

(Continued)

TABLE 4 | Continued

Variable	Model 4 Base case 2014–2015 sample	Model 5 Included education and personal income in 2015 2014–2015 sample	Model 6 Included health status in 2013 2013–2015 sample
Age in 2015	−0.038***	−0.037***	−0.023***
	(0.003)	(0.003)	(0.003)
Gender	−0.631***	−0.465***	−0.256***
	(0.042)	(0.045)	(0.047)
Constants	Yes	Yes	Yes
N	7,476	7,476	7,476
Pseudo R^2	0.0414	0.0478	0.1839

*Standard errors in parentheses. *p < 0.1, **p < 0.05, ***p < 0.01.*

mental, and cognitive health in adulthood (9, 14, 41, 46). Therefore, the first step of our study focused on whether childhood circumstances are associated with health in middle and later life. First, we applied principal component analysis to 25 health-related questions and constructed a latent index of health status. Considering that most of the input indicators are dichotomous variables, this health index has both continuous and discrete characteristics. Thus, we converted it into a quintile ordinal form. We believe this comprehensive measurement of health status can reflect more information than the commonly used single dimension indicator or "0–1" discrete constructs in the literature (45). In previous research, there is also a measurement that standardizes the averages of multiple health-related indicators to obtain a health score (13). In contrast, our approach can better reflect the differential contribution of indicators to the health index, which means some indicators may have higher weights in explaining health status.

We selected 11 environmental factors in early life as crucial independent variables and formulated them into five domains based on previous experience from the literature. Previous research has emphasized that there may be correlations and cumulative effects between factors in the same domain (20). In our results, we also found this phenomenon. For example, in model 6, only when the events are accumulated to a certain number do adverse childhood experiences have a direct effect on health in later life. Furthermore, this accumulated effect may not appear in the form of a dose-response. Similarly, one domain may be related to others (32), so failure to consider related domains may overestimate the impact of a single domain on health. Therefore, compared to examining each domain in isolation, we tested the interaction between domains and considered them simultaneously in a model. According to the regression coefficients and variance in **Table 3**, all five domains of childhood circumstances are associated with health in middle and later life, which all remain jointly significant after including them in the same model. The influence of childhood health and nutrition is more prominent and is the most considerable incremental value contributing to the variance in health.

Several hypotheses have been formulated to explain the association between early life experiences and adult health (18, 31, 49). Our research provides new evidence for these pathway models based on data collected from the middle-aged and elderly population in China. Consistent with the life-course model, childhood health, childhood family financial status, inconvenience in visiting a doctor, and more than one adverse childhood experience all have a sustained effect on the health of middle-aged and older adults. Consistent with the results of the Whitehall study, the effect of the father's education or vaccination on health in later life is absorbed by the socioeconomic status over the same period (29). This effect appears to work by impacting the individual's educational attainment and personal income in adulthood. Moreover, socio-economic achievements in later life may partially offset the negative impact of childhood circumstances on health in the same period. In addition, the results in models 5 and 6 also illustrate the universality of potential mediators. Our research shows that the effects of experiencing hunger in childhood, parental longevity, and one adverse childhood experience on health in middle and later life are no longer significant after including the previous health status. It appears that in addition to socioeconomic status, there may be potential mediators that form other health pathways. More importantly, the coefficients in model 6 drop considerably, which shows that mediators greatly reduce the direct effect of childhood circumstances and suggests that these results may be misestimated without accounting for indirect effects via mediators. It overestimates the direct effects of childhood circumstances and misses the indirect pathways of childhood circumstances and their impact on health-related resources. Therefore, investments in children's health not only contribute to health in later life but also dynamically improve the individual's educational attainment and personal income, as well as other life prospects. All these returns may extend far beyond childhood and continue throughout the lifespan.

Some specific policy suggestions are now discussed relevant to those study results mentioned above. First, we should avoid further expanding disparity among children in different groups

due to cumulative effects. On the one hand, the state should build a unified child welfare supply system and encourage private resources to supplement public relief projects. On the other hand, the root of the disparity among children lies in their families' poverty (50). Flexible and diverse methods should be adopted to help low-income families improve their socio-economic status. Second, any investment in childhood human capital requires follow-up support measures. For the elderly who have already withdrawn from the labor market, we should pay attention to the social security system's income redistribution effect and increase the level of pensions and pension subsidies for low-income elderly. For the elderly who are not well-educated, we can explore targeted health-related education ways, such as hold community health lectures. Third, we should continue to promote the "integration of medical and elderly care" policy in China, aiming to simultaneously improve healthcare equity and living care quality for the middle-aged and elderly (51).

However, our study has limitations. First, it is necessary to evaluate the accuracy of the data. CHARLS is a retrospective study, and health indicators and critical variables were obtained in the form of self-reports. There may be potential bias when using retrospective questions, either from recall difficulty or deliberate concealment. Therefore, some indicators may be underestimated. For example, when a question involves details from one's distant past, it is often difficult to recall it accurately. Our concern is that underreporting of negative childhood exposures might cause testing errors and impact the significance of variables. Second, for parents' educational attainment, we used a proxy measurement to represent the socioeconomic status of the family. Thus, it may be more appropriate to choose only the father's level of education with time characteristics or change the measurement of the mother's education level to a discrete variable (i.e., distinguish between illiterate and non-illiterate). However, considering the consistency of the data structure, we retain the mother's education level as a continuous variable in our model. Third, in the final model, we matched the data from three waves, so we lost a considerable number of non-equilibrium samples, which only have data recorded in one or two waves. According to the official CHARLS report, during the period between the 2014 life history survey and the 2015 wave, 672 respondents attended no follow-up visits due to death, while 3,265 respondents were lost to follow-up for unknown reasons (38). Therefore, the data may have a sample selection bias. To partially resolve this issue, we separately estimated two sets of samples to check for cohort differences. However, the sample selection problem may have occurred before the 2013 survey. Fourth, questions about the specific period when childhood factors occur and subjective feelings about these experiences are not included in the survey. For example, in addition to the experience of hunger in childhood, the time ranges given by the remaining variables are relatively broad. If we focus the analysis on an earlier stage of childhood, it will help us to understand these phenomena better.

CONCLUSIONS

Our findings emphasize the importance of the life course perspective in studying the impact of childhood circumstances on future health. As this paper has shown, several domains of childhood circumstances have significant effects on health in middle and later life, either directly or indirectly. The results presented in this paper also highlight the role of mediators in the relationship between childhood circumstances and health in later life. The effects of childhood circumstances are passed on to health in later life through their influence on these mediators. An important priority for future research is to identify additional potential mediators. Overall, our findings suggest more attention be paid to investing health capital in early life, and the benefits of these investments will affect the entire lifespan.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found at: China Health and Retirement Longitudinal Survey. (2020). Available online at: http://charls.pku.edu.cn/pages/data/111/zh-cn.html (accessed April 13, 2020).

ETHICS STATEMENT

An ethics waiver request was submitted to the Ethics Review Board of China Pharmaceutical University, and met the requirements for exemption, as the research relied exclusively on secondary use of anonymous information.

AUTHOR CONTRIBUTIONS

TT, YH, and RS: conceptualization, writing—review, and editing. TT: analysis and interpretation of data. TT and YH: writing—original draft preparation. All authors have read, agreed to the published version of the manuscript, and contributed to this manuscript.

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Economic Burden of Myocardial Infarction Combined With Dyslipidemia

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Background: Dyslipidemia is a common comorbidity and an important risk factor for myocardial infarction (MI). This study aimed to examine the economic burden of MI combined with dyslipidemia in China.

Methods: Patients who were hospitalized due to MI combined with dyslipidemia in 2016 were enrolled. Costs were measured based on electronic medical records and questionnaires. The annual costs were analyzed by conducting descriptive statistics, univariable, and multivariable analyses.

Results: Data of 900 patients were analyzed, and 144 patients were dead during the follow-up. The majority of patients were aged 51–70 years (n = 563, 62.55%) and males (n = 706, 78.44%). For all-cause costs, the median annual direct medical costs, direct non-medical costs, indirect costs, and total costs were RMB 13,168 (5,212–29,369), RMB 600 (0–1,750), RMB 676 (0–1,787), RMB 15,361 (6,440–33,943), respectively; while for cardiovascular-related costs, the corresponding costs were RMB 12,233 (3,795–23,746), RMB 515 (0–1,680), RMB 587 (0–1,655), and RMB 14,223 (4,914–28,975), respectively. Lifestyle and complications significantly affected both all-cause costs and cardiovascular-related costs.

Conclusions: Increasing attention should be paid to encourage healthy lifestyle, and evidence-based medicine should focus on optimal precautions and treatments for complications, to reduce the economic burden among MI patients with a comorbid dyslipidemia.

Keywords: economic burden, myocardial infarction, dyslipidemia, older adults, China

INTRODUCTION

There are ∼290 million cardiovascular patients in China, including 11 million patients with coronary atherosclerotic heart disease, in which myocardial infarction (MI) is the most acute and dangerous disease (1). Cardiovascular diseases have long been the leading cause of death among Chinese residents, while the mortality rate of MI in China had been on the rise from 2002 to 2016, particularly since 2005. In 2016, MI's mortality rate in urban and rural areas reached 58.69 per 100,000 and 74.72 per 100,000 individuals in China, respectively (2).

Dyslipidemia is one of the most significant risk factors for MI. Patients with a history of MI are at high risk and should strictly control their low-density lipoprotein-cholesterol levels (LDL-C) (3, 4). According to the 2002 China Health and Nutrition Survey (CHNS) (5), the 2010 China Chronic Kidney Disease Working Group Survey (6), the 2011 CHNS (7), and the 2015 Report on Nutrition and Chronic Diseases of Chinese residents (8), the prevalence of Dyslipidemia in Chinese people aged ≥18 years in 2002, 2010, 2011, and 2012 were 18.60, 33.97, 39.91, and 40.40%, respectively. In the past 10 years, the prevalence of dyslipidemia as well as MI in Chinese adults have risen sharply. It is estimated that elevated serum cholesterol levels will cause 9.2 million patients with cardiovascular disease (CVD) from 2010 to 2030 (9).

MI, in turn, carries a heavy economic burden. In 2014, the annual direct medical costs of cardiovascular and cerebrovascular diseases in China exceeded 130 billion yuan, accounting for over 22% of the total medical costs in the same year (10). At present, there are few studies directly investigating the economic burden of MI in China. The government bulletin showed that the total and average per hospitalization costs of MI in 2016 were RMB 19.085 billion and RMB 26056.9, respectively, with annual average growth rates of 29.15 and 7.12% (1). The costs of MI hospitalizations increased by 56.8% from 2007 to 2012 in Beijing after adjusting inflation (11). Models predict that universal treatments for hypertension and dyslipidemia patients could avert 10–20 million MIs and between 3 and 10 million CVD deaths during 2016–2030, producing a positive social value net of healthcare costs high as USD 932 billion (12).

Studies on the burden of disease in China only focus on patients' hospitalization costs. There has been no relevant study on this extremely high-risk population of MI with dyslipidemia. Therefore, this study combined patients' medical records and questionnaires to investigate the economic burden for patients with MI and dyslipidemia in China's real-world environment. Our research filled the literature gap by providing the most recent data on the economic burden of MI combined with dyslipidemia from the social perspective, and the factors that potentially impact economic burden were analyzed. Therefore, our results may highlight the importance of providing prevention measures and management intervention. The up-to-date data may be used as important cost parameters for economic evaluations, such as cost of illness or cost-effectiveness/utility analysis.

MATERIALS AND METHODS

Study Design

This is a multicenter study combining retrospective cohort and cross-sectional research and was conducted from a social perspective. Six tertiary hospitals from major cities—Beijing, Shanghai, Wuhan, Nanjing, Guangzhou, and Chengdu, China were chosen as research centers for data collection.

Data were collected according to medical record review and questionnaires, including demographic characteristics (gender, age, marital status, type of medical insurance, income, etc.), lifestyle (smoking, drinking, diet, exercise, etc.), disease characteristics (complications and the cause of death, etc.), hospitalization costs and costs of outpatient (medical and pharmaceutical expenses, nursing expenses, loss of time and labor of the patients and their families, etc.). As the simplified questionnaires were used for the deceased, information, such as lifestyle, income, accommodation and transportation expenses, and out-of-hospital visits were not collected and not able to be analyzed accordingly. The medical record review and questionnaires were linked by patients' name as well as the unique ID number or medical card number.

For all patients, their first hospitalization from January 1, 2016 to December 31, 2016 was considered as the index event, and their related 1-year post-index data was collected and analyzed. Key information of the data is shown in **Table 1**, the time frame of all the data was 1-year post-index hospitalization, indicating that the cost of index hospitalization was not included in our study

The study was approved by the Ethics Committees of all the six participating hospitals. Written informed consent was provided by all participants before the data collection and conduction of the research. Before analysis, the patient data were anonymized and de-identified.

Study Population

Inclusion criteria in this study included: patients hospitalized with myocardial infarction (MI) from January 1, 2016 to December 31, 2016. The earliest hospitalization was considered as the index hospitalization; patients for whom in the first blood lipid examination of the index hospitalization, the LDL-C was ≥1.8 mmol/L or were using lipid-regulating drugs. Exclusion criteria included: patients who died during the index hospitalization; patients who participated in clinical trials after the index hospitalization; patients or family members (if the patient had died) who were not willing to participate in survey or could not correctly understand and answer relevant questions due to communication barriers.

Outcomes

This study's primary outcomes were the annual total costs of survivors and deceased, which were reported in all-cause and CV-related costs, as well as the direct medical, direct non-medical, and indirect costs. Here CV-related indicates cardiovascular diseases, including MI, hypertension, post-percutaneous transluminal coronary intervention (PCI), peripheral arterial disease, etc. The secondary outcomes were the

TABLE 1 | Key information about the data.

Variable	Patients	Source
Patient characteristics		
Survival situation	S, D	QS
Cause of death	D	QS
Gender	S, D	EMR
Birthday	S, D	EMR
Height (cm)	S, D	EMR
Weight (kg)	S, D	EMR
Medical insurance	S, D	EMR
Medical history	S, D	EMR
Education status	S	QS
Marital status	S	QS
Employment status	S	QS
Income level (RMB)	S	QS
Smoking	S	QS
Drinking	S	QS
Diet (whole grains)	S	QS
Diet (High-fat and high-cholesterol)	S	QS
Sports	S	QS
Costs (hospitalization and outpatient)		
Direct medical and pharmaceutical expenses	S, D	EMR
Accommodation and transportation expenses	S	QS
Nursing expenses	S	QS
Loss of time and labor of the patients	S	QS
Loss of time and labor of their companions	S	QS
The income of companions	S	QS
Out-of-hospital visit times and costs*	S	QS
Health care products costs	S	QS

S, survivors; D, deceased; QS, questionnaire survey; EMR, electronic medical records.
**Costs incurred in other hospitals and pharmacies.*

influencing factors for the annual total all-cause and CV-related costs of survivors.

Direct medical costs included registration, diagnosis, examination, medicine (including pharmacy purchase), operation, bed fee, material, nursing, and other expenses. The direct medical costs were obtained through electronic medical records. Out-of-hospital direct medical costs of the survivors were obtained through questionnaires, while the deceased's out-of-hospital direct medical costs were not collected.

Direct non-medical costs included expenses related to patient caregivers, accommodation and transportation, and health care products, etc. The survivors' data were collected through questionnaires, while the data of the deceased were not collected.

Indirect costs were calculated by the human capital method (13) to calculate the time and labor loss of the patients and their accompanying family members. The monthly income (sum of the pension and additional monthly income for retirees, sum of the monthly salary and extra monthly income for others) of the survivors was derived from the questionnaires. Such data were also not collected for the deceased.

Statistical Analysis

Described for the baseline characteristics and costs by survival status. Categorical variables were reported as numbers and proportions, and continuous variables were reported as medians and interquartile ranges.

Univariable and multivariable analyses were applied to the study of the economic burden's influencing factors. In the univariable analysis, the chi-square test was performed for categorical variables; the Wilcoxon rank-sum test or the Kruskal-Wallis test was used for continuous variables.

Multivariable analysis was performed in generalized linear model (GLM) with gamma distribution and log link function. Multivariable analysis was not performed for the deceased's total annual costs due to the lack of certain baseline information. Patients' baseline information (age, gender, etc.), lifestyle (smoking, drinking, etc.), and disease history (whether first-episode MI, etc.) were included as independent variables in GLM. The annual all-cause and CV-related total costs of survivors were used as dependent variables.

We combined some variables' classifications in the multivariable analysis since some variables had too many original categories. (a) Medical insurance types: BMISUE, BMISUR, and NRCMS were combined into one category (basic medical insurance). (b) Education status: not graduated from primary school, primary school were combined into primary education; Junior high school, high school, technical secondary school/junior college graduate were combined into medium education; Bachelor, master and doctor were combined into high education. (c) Marital status: unmarried, divorce, and death of a spouse were combined into current single. (d) Employment status: formal employees, individuals, and freelancers were combined into formal wage; Farming, unemployed were combined into non-formal wage.

The significance level was set at $P < 0.05$ with a two-tailed test. Data were analyzed using Stata SE 15 (Stata Software, StataCorp) and SPSS 22.0 (SPSS Software, IBM Corp.).

RESULTS

Patient Characteristics

The baseline information of patients is shown in **Tables 2**, **3**. A total of 900 patients were included in this study, including 756 (84.00%) survivors and 144 (16.00%) deceased. Among the deceased, 109 (75.69%) patients died due to CV-related diseases.

There were more males ($n = 706$, 78.44%) than females ($n = 194$, 21.56%). The average age of all patients was 62.07 years (SD: 11.45), and patients aged 60–70 years were the majority ($n = 307$, 34.11%). In terms of body mass index (BMI), most patients ($n = 450$, 50.00%) were overweight ($23.9 < \text{BMI} \leq 27.9$) or obese (BMI > 27.9) ($n = 134$, 14.89%). Regarding the medical history, 94.67% ($n = 852$) patients were of first-episode MI, 64.67% ($n = 582$) had undergone PCI, and most complications were hypertension ($n = 537$, 59.67%), type 2 diabetes ($n = 276$, 30.67%), and lipid metabolism disorder ($n = 269$, 29.89%). For the type of medical insurance, 88.33% ($n = 795$) had one of the following basic medical insurance which covered majority people in China: basic medical insurance system for urban employees (BMISUE), basic

TABLE 2 | Baseline information of all patients ($N = 900$).

Variable	Number of cases	%
Survival situation		
Survival	756	84.00
Death	144	16.00
Cause of death ($N = 144$)		
Non-cardiovascular causes	35	24.31
Cardiovascular causes	109	75.69
Gender		
Female	194	21.56
Male	706	78.44
Age*	62.07 (SD:11.45)	
Age classification (year)		
18–50	127	14.11
51–60	256	28.44
61–70	307	34.11
70–	210	23.33
Height (cm)*	166.57 (SD:7.04)	
Weight (kg)*	69.39 (SD:11.77)	
BMI (kg/m^2)		
−18.4	22	2.44
18.5–23.9	294	32.67
24.0–27.9	450	50.00
28.0–	134	14.89
Medical insurance		
Basic medical insurance system for urban employees	584	64.89
Basic medical insurance for urban residents	122	13.56
The new rural cooperative medical care system	89	9.89
Full public expense coverage	42	4.67
Uninsured	53	5.89
Other	8	0.89
Medical history		
Myocardial infarction (MI)#	48	5.33
Hypertension	537	59.67
Type 2 diabetes	276	30.67
Disorder of lipid metabolism	269	29.89
Post-PCI	582	64.67
Peripheral artery disease	118	13.11

PCI, percutaneous coronary intervention; BMI, Body mass index.
**Mean and standard deviation were reported.*
#Patients who experienced MI before index hospitalization.

TABLE 3 | Baseline personal and lifestyle information for surviving patients ($N = 756$).

Variable	Number of cases	%
Education status		
Not graduated from primary school	51	6.75
Primary school	53	7.01
Junior high school	220	29.10
High school	176	23.28
Technical secondary school/junior college graduate	164	21.69
Bachelor	80	10.58
Master and doctor	11	1.46
Marital status		
Unmarried	7	0.93
Married	712	94.18
Divorce	12	1.59
Death of a spouse	25	3.31
Employment status		
Formal employees	104	13.76
Individuals and freelancers	40	5.29
Retired	503	66.53
Farming	31	4.10
Unemployed	60	7.94
Other	18	2.38
Income level (RMB)*		
0–2,400	187	24.74
2,401–4,000	186	24.60
4,001–5,500	191	25.26
5,501–	192	25.40
Smoking		
No smoking history/Give up smoking	496	65.61
Sometimes	88	11.64
Often	172	22.75
Drinking		
No drinking history/Give up drinking	515	68.12
Sometimes	186	24.60
Often	55	7.28
Diet (whole grains)		
Often	534	70.63
Sometimes	214	28.31
Never	8	1.06
Diet (high-fat and high-cholesterol)		
Often control	550	72.75
Sometimes control	170	22.49
Never control	36	4.76
Sports		
Often	467	61.77
Sometimes	178	23.54
Never	111	14.68

**Income is grouped according to quartile.*

medical insurance system for urban residents (BMISUR), and the new rural cooperative medical system (NRCMS).

Among the 756 surviving patients, the majority ($n = 560$, 74.07%) were of moderate degree (middle-school or equivalent), most ($n = 712$, 94.18%) were married, up to 66.53% ($n = 503$) were retirees, 49.86% had income more than RMB 2,400 and less than RMB 5,500. In terms of lifestyle, the majority had no history of smoking ($n = 496$, 65.61%) or drinking ($n = 515$, 68.12%), often ate high-fiber foods and grains ($n = 534$, 70.63%) and controlled high-fat and high-cholesterol food intake ($n = 550$, 72.75%); 61.77% ($n = 467$) often exercised.

Total Annual Economic Burden

Table 4 reports the median annual economic burden of the patients. For the all-cause economic burden, the median annual

TABLE 4 | Median annual economic burden.

Variable	Survivors ($n = 756$)	Deceased ($n = 144$)	Total ($n = 900$)
All-cause			
Hospitalization			
Direct medical costs	0 (0–9,885)	0 (0–12,990)	0 (0–10,000)
Direct non-medical costs	0 (0–600)	NA	0 (0–600)
Indirect costs	0 (0–213)	NA	0 (0–213)
Total cost of hospitalization	0 (0–12,756)	0 (0–12,990)	0 (0–12,756)
Outpatient			
Direct medical costs	10,095 (4,143–15,141)	1,142 (0–6,443)	9,006 (2,717–14,565)
Direct non-medical costs	120 (0–600)	NA	120 (0–600)
Indirect costs	423 (0–1,120)	NA	423 (0–1,120)
Total cost of outpatient and emergency	12,146 (5,080–17,997)	1,142 (0–6,443)	10,185 (3,300–17,141)
Total			
Total direct medical costs	13,829 (7,492–29,865)	2,547 (0–21,085)	13,168 (5,212–29,369)
Total direct non-medical costs	600 (0–1,750)	NA	600 (0–1,750)
Total indirect costs	676 (0–1,787)	NA	676 (0–1,787)
Total costs	16,737 (9,224–35,025)	2,547 (0–21,085)	15,361 (6,440–33,943)
Cardiovascular-related			
Hospitalization			
Direct medical costs	0 (0–8,000)	0 (0–0)	0 (0–7,460)
Direct non-medical costs	0 (0–500)	NA	0 (0–500)
Indirect costs	0 (0–0)	NA	0 (0–0)
Total cost of hospitalization	0 (0–10,764)	0 (0–0)	0 (0–10,063)
Outpatient			
Direct medical costs	9,674 (3,383–14,469)	888 (0–5,164)	8,014 (2,257–13,813)
Direct non-medical costs	90 (0–600)	NA	90 (0–600)
Indirect costs	373 (0–1,013)	NA	373 (0–1,013)
Total cost of outpatient and emergency	11,127 (4,083–17,150)	888 (0–5,164)	9,341 (2,744–16,208)
Total			
Total direct medical costs	13,073 (5,977–25,439)	1,960 (0–14,791)	12,233 (3,795–23,746)
Total direct non-medical costs	515 (0–1,680)	NA	515 (0–1,680)
Total indirect costs	587 (0–1,655)	NA	587 (0–1,655)
Total costs	15,314 (7,766–31,682)	1,960 (0–14,791)	14,223 (4,914–28,975)

NA, Not applicable (Data for the deceased was not collected).
All the costs were reported as medians and interquartile ranges.

hospitalization costs, outpatient costs, and annual costs for all patients were RMB 0 (IQR: 0–12,756), RMB 10,185 (IQR: 3,300–17,141), and RMB 15,361 (IQR: 6,440–33,943), respectively. The corresponding average annual costs were RMB 18,641 (SD: 45,429), RMB 14,698 (SD: 23602), and RMB 33,878 (SD: 54,029), respectively.

For the CV-related economic burden, the median annual hospitalization costs, outpatient costs, and annual costs for all patients RMB 0 (IQR: 0–10,063), RMB 9,341 (IQR: 2,744–16,208), RMB 14,223 (IQR: 4,914–28,975). The corresponding average annual costs were RMB 15,480 (SD: 37,233), RMB 12,759 (SD: 19,044), and RMB 28,777 (SD: 43,390), respectively.

The median annual ratio of CV-related costs to all-cause costs was high. The direct medical costs and the hospitalization costs accounted for the largest proportion of total costs.

Univariable Analysis

The univariable analysis results of the annual all-cause and CV-related costs of survivors are shown in **Supplementary Table 1**. The corresponding results of the deceased are shown in **Supplementary Table 2**.

For the survivors, there were significant differences in the annual all-cause costs among patients with different age groups ($P = 0.049$), employment status ($P = 0.023$), income levels ($P = 0.036$), smoking status ($P = 0.016$), drinking status ($P = 0.016$), and dietary control conditions ($P = 0.020$). Complications, such as hypertension ($P = 0.005$), type 2 diabetes ($P = 0.000$), and PCI ($P = 0.033$) significantly affected the annual all-cause total costs. Regarding CV-related costs, patients with different smoking status ($P = 0.009$) and complications including hypertension ($P = 0.003$) and type 2 diabetes ($P = 0.014$) had significantly different costs.

TABLE 5 | Multivariate analysis results of all-cause economic burden on survivors.

Variable		Costs[#]	Coef.	*P*-value
Gender	Male	18,693 (9,425–43,559)	0	
	Female	16,404 (9,102–34,592)	−0.110	0.411
Age classification (year)	18–50	15041 (6,599–23,610)	0	
	51–60	16,710 (8,577–3,149)	0.092	0.552
	61–70	17,344 (9,920–46,418)	0.264	0.136
	70–	18,682 (12,148–34,592)	−0.024	0.901
BMI (kg/m^2)	−18.4	15,007 (4,105–20,191)	0	
	18.5–23.9	16,177 (9,123–43,283)	0.250	0.400
	24.0–27.9	16,912 (8,988–34,770)	0.438	0.135
	28.0–	15,622 (9,425–27,838)	0.163	0.604
Medical insurance	Basic medical insurance	16,712 (9,287–34,837)	0	
	Full public expense coverage	25,998 (13,336–59,013)	0.107	0.643
	Uninsured	15,142 (4,153–21,459)	−0.343	0.128
	Other	13,131 (6,303–29,761)	−0.447	0.315
Education status	Primary education	14,294 (9,887–24,162)	0	
	Medium education	16,851 (9,322–37,300)	0.149	0.328
	High education	17,541 (6,909–37,874)	0.200	0.355
Marital status	Current single	21,626 (10,719–55,221)	0	
	Married	16,603 (9,067–34,542)	−0.361	0.070
Employment status	Formal wage	15,641 (7,243–26,712)	0	
	Non-formal wage	17,619 (10,179–42,556)	0.081	0.617
	Retired	14,884 (9,385–28,025)	0.336	0.126
	Other	10,405 (5,557–16,530)	−0.243	0.433
Income level (RMB)	0–2,400	6,451 (13,941–23,145)	0	
	2,401–4,000	10,588 (18,067–54,158)	0.452	0.003**
	4,001–5,500	10,083 (16,504–31,846)	0.297	0.059
	5,501–	10,771 (20,076–38,021)	0.477	0.005**
Medical history				
Myocardial infarction (MI)	No	16,782 (9,403–35,392)	0	
	Yes	15,628 (5,427–31,846)	−0.194	0.362
Hypertension	No	14,884 (6,528–31,846)	0	
	Yes	17,619 (10,818–36,334)	0.077	0.415
Type 2 diabetes	No	15,221 (8,455–30,050)	0	
	Yes	20,355 (11,110–55,567)	0.259	0.012*
Disorder of lipid metabolism	No	16,124 (8,867–37,586)	0	
	Yes	17,711 (9,524–30,688)	−0.056	0.585
Post-PCI	No	16,910 (9,042–64,246)	0	
	Yes	16,664 (9,258–29,721)	−0.429	0.000**
Peripheral artery disease	No	16,830 (9,219–35,862)	0	
	Yes	15,587 (9,008–31,984)	−0.104	0.447
Smoking	No smoking history/Give up smoking	17,823 (10,131–42,575)	0	
	Sometimes	14,768 (6,002–21,348)	−0.465	0.002**
	Often	14,751 (8,098–27,551)	−0.244	0.047*
Drinking	No drinking history/Give up drinking	17,418 (9,425–43,559)	0	
	Sometimes	16,734 (8,331–28,395)	−0.206	0.065
	Often	13,628 (5,883–21,897)	−0.293	0.116
Diet (whole grains)	Often	17,485 (8,988–34,770)	0	
	Sometimes	15,304 (9,553–36,038)	−0.032	0.771
	Never	19,268 (7,859–49,900)	−0.313	0.489
Diet (High-fat and high-cholesterol)	Often control	17,823 (9,954–37,874)	0	

(Continued)

TABLE 5 | Continued

Variable		Costs[#]	Coef.	*P*-value
	Sometimes control	14,223 (7,286–25,787)	−0.282	0.016*
	Never control	16,568 (7,087–42,316)	−0.134	0.549
Sports	Often	15,978 (7,866–31,846)	0	
	Sometimes	16,877 (9,789–36,038)	0.254	0.030*
	Never	18,595 (10,933–51,003)	0.228	0.091

PCI, percutaneous coronary intervention; BMI, body mass index.
*$p < 0.05$, **$p < 0.01$.*
[#]*All the costs were reported as medians and interquartile ranges.*

For the deceased, there were significant differences in the annual all-cause costs among patients with different causes of death ($P = 0.021$), BMI ($P = 0.049$), and medical insurance type ($P = 0.041$). In addition, substantial differences existed in the annual CV-related costs among patients with different BMIs ($P = 0.019$) and lipid metabolism disorders ($P = 0.049$).

Multivariable Analysis

In the GLM model of annual all-cause total costs, 743 patients whose total costs were not 0 without missing categorical variable data were included. In the GLM model of annual CV-related total costs, 741 patients whose total costs were not 0 without missing categorical variable data were included. In the goodness of fit test of the models, the significance levels calculated by the Deviance test and Pearson Chi-Square test were respectively 1.188 and 1.446 for the all-cause model, 1.277 and 1.415 for the CV-related model, none of which were significant ($P > 0.05$), indicating that the two GLM models fit well.

The multivariable analysis results for annual all-cause and CV-related total costs of the survivors are shown in **Tables 5**, **6**. For annual all-cause costs, patients whose income per month was more than RMB 2,400 and less than RMB 4,000 ($P = 0.003$), and was more than RMB 5,500 ($P = 0.005$), who sometimes did sports ($P = 0.030$) had significantly higher total costs. Having type 2 diabetes ($P = 0.012$) was also influencing factors that significantly increased the all-cause total costs. Patients who sometimes ($P = 0.002$) and often ($P = 0.047$) smoke, sometimes control high-fat and high-cholesterol diet ($P = 0.016$) had significantly lower total costs. Having PCI ($P = 0.000$) was also influencing factors that significantly decreased the all-cause total costs.

While for annual CV-related costs, patients with basic medical insurance, patients whose income per month was more than RMB 2,400 and less than RMB 4,000 ($P = 0.002$), and was more than RMB 5,500 ($P = 0.010$), who sometimes did sports ($P = 0.036$) had significantly higher total costs. Having type 2 diabetes ($P = 0.012$) was also influencing factors that significantly increased the all-cause total costs. Patients who sometimes ($P = 0.003$) and often ($P = 0.005$) smoke had significantly lower total costs. Having MI history ($P = 0.045$) and PCI ($P = 0.012$) was also influencing factors that significantly decreased the all-cause total costs.

DISCUSSION

MI is a public health challenge in China and throughout the world. Dyslipidemia is one of the main risk factors for MI, and it also brings a tremendous economic burden on society. However, unlike some European and American countries, no Asian countries, including China, have measured patients' economic burden with MI combined with dyslipidemia. Our investigation is the first study to investigate the costs of patients with MI combined with dyslipidemia in China from the whole society's perspective using the real-world data in China.

In our study, we reported the median annual all-cause and CV-related costs, related studies were very limited. The hospitalization costs per time of patients with MI in Beijing in 2012 were RMB 29,000 (11), which was slightly higher than that (RMB 23,690 in 2017) in our study. Compared with patients' economic burden with MI in other countries (14–16), our study's annual all-cause and CV-related costs were lower. It may be related to differences in sample sizes, medical resource utilization, and MI treatment in different countries. Besides, in our study, CV-related costs accounted for a large proportion of the total all-cause costs, indicating that CV-related diseases' economic burden was high.

There were significant differences in both annual all-cause and CV-related total costs in terms of gender, BMI, medical insurance, medical history, and other factors. The average age of all patients in our study was 62.1 years, most of them were between 50 and 70 years and male. The characteristics of gender and age are consistent with other studies that reported baseline information (11, 14, 17). Costs were also high in those older and retired patients, especially for males. It was showed that MI's economic burden of patients >60 years was ∼47% of the total costs in 2012 in Korea (18). Older people may have a greater likelihood of suffering from MI (19), may require a more extended hospital stay to achieve the treatment effect (19), and maybe more likely to have other complications (19), resulting in higher costs.

The all-cause and CV-related total costs were significantly higher among patients with type 2 diabetes. The costs of treatment for the disease, the multiple hospital prescriptions required for chronic disease, and the disease progression of MI due to type 2 diabetes (20–22) may result in larger numbers and costs for MI hospitalizations. Patients who had been subjected to PCI had lower total costs, and patients with first-episode MI

TABLE 6 | Multivariate analysis results of cardiovascular-related economic burden on survivors.

Variable		Costs[#]	Coef.	*P*-value
Gender	Male	17,551 (8,000–33,701)	0	
	Female	15,107 (7,661–30,342)	−0.146	0.270
Age classification (year)	18–50	15,041 (6,200–23,140)	0	
	51–60	16,535 (7,830–30,342)	0.109	0.475
	61–70	15,378 (8,362–35,538)	0.204	0.242
	70–	15,085 (8,168–34,492)	−0.083	0.666
BMI (kg/m^2)	−18.4	9,017 (3,867–18,028)	0	
	18.5–23.9	14,693 (7,830–35,685)	0.216	0.464
	24.0–27.9	16,517 (7,174–32,058)	0.361	0.213
	28.0–	14,885 (9,258–27,838)	0.111	0.720
Medical insurance	Basic medical insurance	15,251 (8,029–32,128)	0	
	Full public expense coverage	16,944 (7,801–35,685)	−0.354	0.119
	Uninsured	12,305 (4,153–20,637)	−0.350	0.115
	Other	13,131 (6,250–29,761)	−0.430	0.330
Education status	Primary education	14,227 (8,443–24,162)	0	
	Medium education	15,251 (7,848–32,032)	0.088	0.564
	High education	16,878 (6,200–35,685)	0.197	0.362
Marital status	Current single	18,044 (9,635–44,311)	0	
	Married	15,219 (7,414–30,372)	−0.287	0.146
Employment status	Formal wage	15,467 (5,325–25,396)	0	
	Non-formal wage	15,824 (7,925–34,605)	0.047	0.770
	Retired	15,226 (8,510–32,755)	0.393	0.071
	Other	10,405 (5,557–16,530)	−0.247	0.421
Income level (RMB)	0–2,400	5,145 (13,570–23,145)	0	
	2,401–4,000	10,270 (18,067–49,722)	0.457	0.002**
	4,001–5,500	8,331 (14,283–27,103)	0.277	0.077
	5,501–	7,947 (17,984–34,472)	0.440	0.010*
Medical history				
Myocardial infarction (MI)	No	15,557 (7,925–32,058)	0	
	Yes	12,614 (4,854–22,399)	−0.419	0.045*
Hypertension	No	13,747 (5,285–28,000)	0	
	Yes	16,732 (9,552–33,771)	0.119	0.202
Type 2 diabetes	No	14,652 (6,909–28,395)	0	
	Yes	17,637 (8,577–41,649)	0.261	0.012*
Disorder of lipid metabolism	No	15,358 (7,245–34,229)	0	
	Yes	15,159 (8,343–27,147)	−0.061	0.551
Post-PCI	No	15,598 (7,308–50,294)	0	
	Yes	15,096 (8,000–27,758)	−0.358	0.001**
Peripheral artery disease	No	15,634 (7,848–32,322)	0	
	Yes	14,321 (6,390–24,979)	−0.117	0.391
Smoking	No smoking history/Give up smoking	16,207 (8,673–37,102)	0	
	Sometimes	14,436 (5,177–21,418)	−0.452	0.003**
	Often	14,275 (7,312–23,751)	−0.345	0.005**
Drinking	No drinking history/Give up drinking	15,641 (8,093–36,906)	0	
	Sometimes	15,901 (7,801–26,541)	−0.133	0.230
	Often	12,788 (5,883–21,897)	−0.219	0.234
Diet (whole grains)	Often	15,218 (7,061–30,050)	0	
	Sometimes	15,495 (9,123–34,598)	−0.028	0.793
	Never	19,268 (7,579–49,900)	−0.217	0.628
Diet (High-fat and high-cholesterol)	Often control	15,962 (8,058–33,771)	0	

(Continued)

TABLE 6 | Continued

Variable		Costs[#]	Coef.	*P*-value
	Sometimes control	14,223 (6,611–25,787)	−0.211	0.066
	Never control	16,187 (5,978–36,755)	−0.024	0.916
Sports	Often	14,717 (6,546–29,253)	0	
	Sometimes	16,686 (9,316–34,605)	0.241	0.036*
	Never	16,081 (9,524–39,809)	0.164	0.220

PCI, percutaneous coronary intervention; BMI, body mass index.
*$p < 0.05$, **$p < 0.01$.*
[#]*All the costs were reported as medians and interquartile ranges.*

had higher total CV-related costs. It may be because PCI's efficacy (23, 24) reduces the number of required hospital stay and visits, patients with a first-episode MI need to be more vigilant about their health.

Smoking and diet did not affect all-cause and CV-related total costs of survivors in an expected way. Some studies (25, 26) have shown that never or quitting smoking positively affects the number and risk of hospitalization for MI. The reduction of smoking prevalence decreased the direct medical costs and the mortality of MI that occur before people went to the hospital (27). However, Yegezu et al. (28) observed that survivors with MI were more likely to be smoking patients, and a healthy diet could reduce fat intake, reducing the risk of dyslipidemia. Research showed that the Mediterranean diet reduced cardiovascular death, complications, and hospital admissions of MI (29). In our study, dietary factors had a different impact on the costs than those reported in the above research. The reason may be that patients with high-fat and high-cholesterol intake may also exercise more, resulting in normal blood lipid levels (30, 31). When fat loss from exercise is more than fat intake, the risk of dyslipidemia will be reduced, decreasing costs. More research is needed on the effects of smoking and diet on hospitalization costs and outpatient costs among patients with MI.

The strengths of this study lie in the following. First, from the perspective of target groups, our study is the first to consider the costs of Chinese patients with MI combined with dyslipidemia. Second, from the standpoint of data sources, the study used patients' electronic medical record data as the primary source of real-world data, supplemented by questionnaires. Compared with entirely relying on questionnaires and the patients' subjective recall, the data are more reliable. Third, in terms of costs, compared with similar studies that only consider the direct medical costs or hospitalization costs, the types of costs included in this research are more comprehensive (direct medical costs, direct non-medical costs, and indirect costs). The median annual all-cause and CV-related costs of hospitalization and outpatient of patients are reported, allowing readers to understand the economic burden of this population multi-dimensionally.

Our study also has some limitations. First, data on direct non-medical costs and indirect costs were derived from questionnaires, which can be more subjective than written or electronically recorded data. Second, specific costs regarding medical insurance reimbursement and out-of-pocket were missing; therefore, it was impossible to compare and analyze the out-of-pocket and medical insurance fund expenditures in this study.

CONCLUSIONS

Chinese patients with MI combined with dyslipidemia have high all-cause and CV-related costs, among which hospitalization and direct medical costs account for a large proportion. Our findings suggest that a healthy lifestyle contributes a lot and optimal precautions and treatments for complications should be emphasized, which can help to reduce the economic burden. It is also anticipated that the descriptive annual costs will act as a significant new resource for the cost-of-illness studies as well as economic evaluations regarding this population.

DATA AVAILABILITY STATEMENT

The datasets generated for this article are not readily available because sharing of raw data would be contingent on approval from the research ethics office because of the ethics consideration. Requests to access the datasets should be directed to lihongchao@cpu.edu.cn.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Peking University First Hospital; Wuhan Asia Heart Hospital; Guangdong Provincial People's Hospital; Nanjing Gulou Hospital; Sichuan Provincial People's Hospital; Zhongshan Hospital, Fudan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HL, AM, and PC designed this study. Data were collected and managed by YZ, XS, JC, BX, JT, and ZW. PC and MZ performed the statistics using software and drafted the manuscript. HL and AM supervised the data analysis and proposed suggestions for revising the manuscript. All authors critically reviewed the

manuscript, approved the final version of the manuscript, and agreed to be accountable for the content of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.648172/full#supplementary-material

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Effectiveness and Efficiency of Non-drug Therapy Among Community-Dwelling Adults With Hypertension in China: A Protocol for Network Meta-Analysis and Cost-Effectiveness Analysis

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Introduction: The Chinese government has established a nationwide community-based chronic disease management program since 2009 with hypertension a vital part of it. Though drugs have been proven effective with hypertensive patients, they bring economic burden as well, especially for those who with elevated blood pressure and are potentially eligible for national programs. When the effectiveness of pharmacotherapy-only interventions remains uncertain on these patients, non-pharmacological interventions have demonstrated non-inferior effectiveness and may have economic advantages. To date, there rarely are evidences on the effectiveness and cost-effectiveness of non-pharmacological treatment in comparison with pharmacological interventions for patients with varying severity of blood pressure. This study aims to propose a study for a network meta-analysis and cost-effectiveness analysis to explore what kind of intervention is potentially effective and cost-effective to four specific patient groups, stage I-III hypertensive patients and patients with elevated blood pressure, and to provide recommendations for hypertensive management to Chinese decision makers.

Methods: We will systematically search databases (MEDLINE, PubMed, Cochrane Library, etc.,) for randomized controlled trials and observational studies with qualified study design in recent decade that assess the effectiveness of non-pharmacological, pharmacological, or combined intervention aimed at adult populations who are diagnosed with the above four types of hypertension in China. The effectiveness outcomes will include changes in SBP/DBP, rate of comorbidities, mortality, and health related quality of life. We will use network meta-analysis to compare and rank

effectiveness of different interventions. Subgroup analyses and meta-regression analyses will be performed to analyze and explain heterogeneity. The economic outcome will include cost-effectiveness based on simulation results from Markov models. Under study perspective of Chinese health system, life-time direct cost will be included.

Discussion: This study aims to compare and rank the effectiveness and cost-effectiveness of pharmacological, non-pharmacological and combined interventions for stage I–III hypertensive patients and those who with elevated blood pressure. Compared to existing studies, this comprehensive synthesis of relevant evidences will influence future practice with better efficiency and generalizability for community-based hypertensive management programs in China. The study might also be valuable for other low- and middle-income countries to find their own solutions.

PROSPERO registration number: CRD42020151518

Keywords: non-pharmacological interventions, pharmacological interventions, community-based chronic disease management, hypertension, network meta-analysis, cost-effectiveness, China

INTRODUCTION

Hypertension has a prevalence of 27.9% in residents over the age of 18 years (1) and has affected 270 million people in China alone until 2019 (2). Hypertension is one of the most common chronic diseases of the 21st century. Hypertension is also the most important cardiovascular risk factor and the leading cause of death in China (2). Research from the Chinese Center for Disease Control and Prevention (3) showed that in 2017, the number of people who expired due to hypertension-related diseases in China was 2.54 million, with approximately 69% died from stroke, 54% died from ischemic heart disease, and 41% died owing to other types of cardiovascular disease (CVD). The World Bank estimated that a 1% reduction in annual CVD events caused by hypertension between 2010 and 2040 could save China 10.7 trillion USD (4). According to the latest clinical practice guidelines for hypertension promulgated by the American College of Cardiology (ACC) in 2017, the diagnostic criterion for hypertension has dropped from 140/90 to 130/80 mmHg. This new standard may result in many more patients in China being diagnosed with hypertension (5). With accelerated population aging, together with lifestyle changes in modern society, elevated blood pressure (130–139/80–89 mmHg) and its consequences are too significant to ignore, clinically, economically, and humanistically. According to a study in the United States, 13.7% of American adults had blood pressure levels 130–139/80–89 mmHg, with 1.9% requiring antihypertensive medication (6). Current pharmacological interventions for hypertension are often ineffective and costly in controlling blood pressure, especially when they do not eradicate CVD events due to hypertension. Between 2005 and 2010, even with nearly 82% of American adults with hypertension aware of their status, and ∼75% taking antihypertensive drugs, only 47% of patients with hypertension have uncontrolled blood pressure (7–9). The disease burden is also an unignorable factor. Another study on American population in 2015 showed that although the estimated per person costs associated with treating hypertension alone were 687 USD, the total medical costs with hypertension were much higher (5,458–6,038 USD), of which the cost related to CVD events was 1,067–1,156 USD (10). Furthermore, the widespread use of pharmacological interventions will also cause a medical burden on patients with elevated blood pressure.

Compared with pharmacological interventions, non-pharmacological interventions are community- or, population-based and have potential economic advantages. Currently, effective non-pharmacological interventions may include self-monitoring or self-management (11, 12), physician or pharmacist interventions (13, 14), and lifestyle or behavioral interventions (15, 16). In a study by Tucker et al. (11), self-monitoring was associated with reduced clinical systolic blood pressure (SBP), as compared with usual care at 12 months (−3.2 mmHg, 95% confidence interval [CI]: −4.9 to −1.6]). In a study by Santschi (13), compared with usual care, pharmacist interventions showed a greater reduction in SBP (7.6 mm Hg, 95% CI: 9.0–6.3) and diastolic blood pressure (DBP; 3.9 mm Hg, 95% CI: 5.1–2.8). Williamson et al. (16) found that at 3–6 months, exercise was associated with a reduction in SBP (−4.40 mmHg, 95% CI: −5.78 to −3.01) and in DBP (−4.17 mmHg, 95% CI: −5.42 to −2.93). In addition, according to these studies, the majority of cost of most non-pharmacological interventions was related to labor and overhead spending, attributes that can be easily reduced. A study in Nepal (17) showed that a community-based hypertension management program, including blood pressure monitoring, and lifestyle counseling, vs. usual care achieved an incremental cost-effectiveness ratio (ICER) of 582 USD per disability-adjusted life-year (DALY) averted, demonstrating it to be a highly cost-effective strategy.

Abbreviations: CI, confidence interval; CVD, Cardiovascular disease; DBP, Diastolic blood pressure; ICER, Incremental cost effectiveness ratio; MD, Mean Difference; SBP, Systolic blood pressure.

Starting in 2009, China launched a reform of its primary health care system and established a basic public health service system focusing on chronic disease management (18). Hypertension is one of the main targets of the system. According to the "2017 National Basic Public Health Service Project Relevant Work and Requirements (19)," the per-capita expenditure for patients with hypertension is 1.35 USD per year. Specific projects include inspection, follow-up evaluation (follow-up frequency at least four times a year), and health examination. One study found that from 2009 to 2016, the Chinese government enacted 53 policies and 24 targeted chronic disease management in community health care institutions (20). These policies have achieved great changes in terms of enhancing primary care, community-based facilities were built and talents were trained (21, 22). Despite new policies being implemented in China, pharmacological interventions have not achieved the expected effects. According to one study in a Chinese population, 30.1% of all participants had taken prescription antihypertensive drugs but only 7.2% achieved control (23, 24). Currently in China, individuals with blood pressure ≥140/90 mmHg (25) are defined as being diagnosed with hypertension and are eligible for disease management. However, on the basis of a study in 2018, 46.4% of the Chinese adult population age ≥18 years may be categorized as hypertension using the new criterion of 130/80 mmHg. Regarding this, the application prospects of non-pharmaceutical interventions are enormous, and the need for related evidence to inform public health policies is urgent. However, current systematic reviews and meta-analyses in this area have evaluated one of the following three conditions: (1) conventional drug intervention vs. one kind of non-pharmaceutical intervention (14); (2) one particular drug vs. another (26, 27); (3) one particular kind of non-pharmaceutical intervention vs. usual care (11, 15, 16, 28, 29). There is lack of evidence in comparing all relative non-pharmaceutical interventions.

In this study, we aim to explore the types of intervention that are potentially effective as well as cost-effective for patients with stage 1, 2, or 3 hypertension and patients with elevated blood pressure (which has not been captured in stage 1 in China yet). The specific objectives of this study are as follows: (1) to identify and categorize currently available community-based non-pharmacological hypertension interventions, their applicability in various settings, and their specific measures using a comprehensive search protocol; (2) to evaluate the quality of the available evidence, the combined effectiveness of the interventions, and their ranking, and the reliability of the studies (e.g., heterogeneity, publication bias); (3) to explore potential subgroups (e.g., age, sex, and baseline activities of daily living [ADL]); (4) to develop an economic evaluation model of hypertension, with economic evaluation and ranking of costs and other parameters, by conducting a literature search and survey; (5) to analyze the appropriateness of the interventions and their generalizability in a community-dwelling population with hypertension; to provide a reference for the reform of chronic disease management among Chinese community-dwelling adults with hypertension.

MATERIALS AND METHODS

Study Registration

This study will be conducted and reported under the guidance of the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) checklist (30) and Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement (31). The protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) with registration number is CRD42020151518.

Synthesis of Effectiveness

Inclusion Criteria for Study Selection

Study eligibility criteria are defined according to the PICOS (participants, interventions, comparisons, outcomes, study design) strategy.

Types of Study Designs

For the network meta-analysis, randomized controlled trials (RCTs) and clustered randomized controlled trial (CRCTs) will be included. In addition, quasi-experiments/natural experiments, case-control studies, cohort studies, and other observational studies with pre- and post-test designs will also be included to the extent the data are sufficient for inclusion. Given that this project will focus on community-based or population-based studies, Phase III clinical pharmacology trials will be excluded. Articles will be limited to those published in Chinese and English language within the past 10 years.

Participants

Participants should be Chinese adults >18 years old living in the community. Additionally, they should meet the requirement for one of four specific types of hypertension. The diagnostic criteria are as follows [according to the 2018 Chinese Guidelines for the Management of Hypertension (25)]: (1) patients with elevated blood pressure: 130–139/80–89 mmHg; (2) stage 1 hypertensive patients: 140–159/90–99 mmHg; (3) stage 2 hypertensive patients: 160–179/100–109 mmHg; (4) stage 3 hypertensive patients: ≥180/≥110 mmHg.

Community-dwelling patients with hypertension receiving non-pharmacological treatment, conventional drug intervention, or a combination of the two will be included, regardless of sex or age. According to the new standard of the ACC (5), patients with blood pressure 130–139/80–89 mmHg will also be included among the participants with elevated blood pressure. Community-dwelling patients with hypertension are defined as those who have been living in the community for more than 6 months, are conscious, and are willing to participate in the study (32). Patients with complications (e.g., diabetes mellitus or CVD) will be included, but those with hypertension owing to other causes (secondary hypertension, e.g., pregnancy or medication use) and pulmonary hypertension will be excluded.

We are concerned about the impact of non-pharmacological interventions in people with different levels of hypertension, and therefore we will divide patients into four groups with different stages of hypertension (stage 1, 2, or 3 hypertension and patients with blood pressure 130–139/80–89 mmHg) at the beginning of the study, for subsequent analysis.

Subgroup Analysis

The large heterogeneity of the population will lead to differences in the effectiveness among interventions, and therefore subgroups may also be included in the analysis, including age (young, middle-aged, older), sex, baseline ADL, presence of complications (e.g., diabetes, CVD events including Stroke, Coronary Heart Disease and Acute Myocardial Infarction), urban vs. rural residence, and follow-up time. Other potential subgroups will be included if data are available (employed vs. unemployed, insured vs. uninsured).

Types of Intervention/Comparator or Control Group

The included studies should address at least one type of condition: (1) non-pharmacological intervention vs. conventional drug intervention;(2) non-pharmacological intervention vs. control of usual care; (3) non-pharmacological intervention plus conventional drug intervention vs. conventional drug intervention; (4) other conditions that may be included in the study.

Conventional drug intervention: The scope of conventional drug intervention is set to include commonly used antihypertensive drugs recommended in the "China Hypertension Prevention and Control Guidelines 2018 Revised Edition (25)," including calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, diuretics, and β-blockers.

Non-pharmacological intervention: Considering a broader range of non-pharmacological interventions, we intend to include evidence from studies evaluating the following interventions: patient-level interventions including: lifestyle; psychological interventions; social support; peer education; and self-management; and provider-level interventions including: human resources; service delivery; information technologies; and change management (see **Table 1**). The specific interventions will be acquired using search strategies and will be categorized by the researchers. We will also invite relevant public health experts to advise and verify the types of intervention. Studies that involve the use of multiple interventions will be included in the "combined intervention" and categorized into subgroups.

Control: The placebo (no-intervention) control groups will include routine care and management of hypertension, defined according to the 2018 Chinese Guidelines for the Management of Hypertension (25) and the National Standards for Basic Public Health Service (33) or no patient intervention.

It is important to note that articles included in the meta-analysis will also comprise economic evaluations involving cost accounting. Articles that describe interventions but do not specify expenditures for human and material resources will be excluded.

TABLE 1 | Classification of interventions.

Type of intervention	Intervention measures
1. Service provision	1. Family health worker 2. Health education OR health education 3. Pharmaceutical care OR medication guidance OR pharmacist 4. Family doctor OR community doctor OR general practitioner
2. Service delivery method	1. Community-based OR joint management OR chronic disease management OR health management OR follow-up management OR individualized care 2. Quality of care OR evidence-based medicine OR continuity of care 3. Social support OR peer education 4. Service integration OR preventive medicine integration
3. Lifestyle intervention	1. Lifestyle 2. Patient behavior intervention 3. Sodium intake OR sodium restriction OR sodium reduction OR salt intake OR salt restriction OR salt reduction OR sodium chloride intake OR sodium chloride restriction OR sodium chloride reduction 4. Dietary approach OR diet 5. Weight loss OR weight reduction 6. Smoking cessation 7. Alcohol reduction OR alcohol restriction 8. Sports OR exercise OR physical activity OR physical fitness OR training OR tai chi OR yoga OR Baduanjin qigong OR dance
4. Psychological intervention	Psychological intervention
5. Medical information intervention	1. Telemedicine OR remote monitoring OR remote management 2. Online to offline 3. Internet hospital 4. Smart devices 5. Dynamic monitoring
6. Self-management	1. Self-management OR self-management group 2. Home blood pressure measurement OR self-test blood pressure
7. Chinese medicine	1. Traditional Chinese medicine 2. Acupuncture 3. Gua sha 4. Acupressure 5. Emotional therapy
8. Management transform	Medical union OR medical alliance OR integrated care delivery system
9. Comprehensive intervention	1. Comprehensive intervention measures OR multifaceted intervention OR intervention package 2. Combination of intervention types with at least two measures among the eight types above

Specific search terms will be refined and described after article retrieval is completed.

Outcome Measures

Primary Outcomes

The primary outcomes include changes in SBP/DBP (or blood pressure control rate), CVD event rate, and mortality. The blood pressure control rate is defined as the proportion of community-dwelling patients with hypertension who have SBP <140 mmHg and DBP <90 mmHg (SBP <130 mmHg and DBP <80 mmHg for patients with complications) over a certain period of time (usually 3 months).

Secondary Outcome

The secondary outcome is health-related quality of life (quality-adjusted life-year [QALY] and health utility) assessed using validated scales, such as the EuroQol Five Dimensions questionnaire (EQ-5D) (34). Studies using non-utility scales such

TABLE 2 | Reverse search strategy using PubMed database.

No.	Search Items
#1	Hypertension[Title/Abstract]
#2	(Controlled trial OR Quasi trial OR Case control OR Natural experiment OR Intervention)[Title/Abstract]
#3	Commonly used Western medicines (see **Supplement Materials** for details)
#4	Commonly used traditional Chinese medicines (see **Supplement Materials** for details)
#5	#3 AND #4
#6	(Influencing factors OR Mechanism)[Title]
#7	(Rat OR Pregnancy OR Mouse OR Animal OR Rabbit)[Title/Abstract]
#8	Community[Title/Abstract]
#9	China
#10	#1 AND #2 NOT #5 NOT #6 NOT #7 AND #8 AND #9

TABLE 3 | Forward search strategy using PubMed database.

No.	Search items
#1	Hypertension [Title/Abstract]
#2	(Controlled trial OR Quasi trial OR Case control OR Natural experiment OR Intervention) [Title/Abstract]
#3	Specific type of interventions (classified by the researchers)
#4	Review OR System Review OR Meta-Analysis [Title/Abstract]
#5	(Influencing factors OR Mechanism) [Title]
#6	(Rat OR Pregnancy OR Mouse OR Animal OR Rabbit) [Title/Abstract]
#7	#4 AND #5 AND #6
#8	Community [Title/Abstract]
#9	China
#10	#1 AND #2 AND #3 NOT #7 AND #8 AND #9

as the 36-Item Short-Form Health Survey (SF-36) (35) will only be included if the scores were mapped into health utility values. We will also capture QALY values if reported in an article.

Search Strategies

The search will be conducted using the following databases or search platforms: PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Library, ClinicalTrials.gov, Chinese National Knowledge Infrastructure (CNKI), Chinese Scientific Journal Database (VIP), SinoMed, and Wanfang database.

Two rounds of searches will be conducted, reverse and forward. The reverse search will aim to identify intervention targets. The 2020 International Society of Hypertension global hypertension practice guidelines and the National Insurance Medicine List of China will be screened for drugs used in hypertension treatment; the Boolean operator NOT will be used to exclude studies using drugs in the intervention. The initial screening and a summary of the literature will be performed to identify and summarize non-pharmacological interventions with a high frequency of occurrence. The specific search strategy to be followed is described in **Table 2**.

The forward search is aimed at including studies. We will use a combination of search strategies, developed using the interventions obtained in the previous step, to search and include the relevant literature. The goal of the two-stage search is to ensure the completeness and stability of the included literature. The specific search strategy is shown in **Table 3**.

The studies involving pharmacoeconomic evaluations will be searched to collect relevant cost information, CVD event rates, and risk of death for non-pharmacological interventions, to identify relevant parameters in the economic model.

Screening

All retrieved papers will be imported into NoteExpress (3.2.0.7535, User: China Pharmaceutical University), and two reviewers will read the title and abstract of all identified studies, to select all candidate papers. All duplicates will be eliminated. After title and abstract screening, full text eligible papers will be obtained for further evaluation. If one reviewer is unsure of the eligibility of an article, the full paper will be reviewed again. In the case of differing opinions between the two reviewers, a third reviewer, or other relevant authority will be consulted. All exclusions will be documented, along with the reasons for exclusion. The literature selection process will be illustrated in a flow diagram.

Data Extraction

Two investigators will independently perform the data extraction. We will extract data of basic study characteristics: first author, year of publication, trial information (duration of the trial, registration information), study design (e.g., randomized controlled trial, cluster randomized controlled trial, quasi-experiment, case-control, and nested case-control), population (sample size, age, sex, diagnostic criteria for hypertension, health status, inclusion, and exclusion criteria), interventions (type and frequency of intervention, comparisons), outcomes (primary and secondary outcomes specified and collected, time points reported), setting, and risks of bias (sequence generation of the allocation; allocation concealment; blinding of participants, research personnel, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias). Any disagreement in the data extraction will be resolved through discussion between two investigators, with further disagreement decided by a third investigator or other relevant authority. The distribution of patient baseline data will be determined based on the extracted data, and any literature that deviates from the distribution by a large amount and is clearly irrational will be excluded.

Treatment of Missing Data

If there are any unreported data, we will attempt to contact the authors to obtain the missing information. If the data are still unable to be retrieved, we will include the study in the descriptive analysis, and the impact of missing data will be described in the discussion section.

Risk of Bias Assessment

Two investigators will use relevant tools to evaluate the risk of bias for all included studies. For randomized controlled trials, we will use the Cochrane Risk of Bias Tool to evaluate the following six aspects: random sequence generation, allocation concealment, blinding of outcome assessors, completeness of outcome data, selective outcome reporting, and other potential bias. All six aspects will be evaluated as (1) low risk of bias, (2) unknown risk of bias, and (3) high risk of bias; a high-quality study should include more than four aspects with low risk of bias. However, given that the literature included in this study will mostly involve community-based trials and non-pharmacological interventions, blinding and allocation concealment will be difficult to achieve; therefore, we will make particular note of articles that do not involve blinding and allocation concealment but have valuable data.

Assessment of Study Quality

For cohort studies, we will use the Newcastle-Ottawa (NOS) scale (36) to evaluate studies in terms of cohort selection, comparability between cohorts, outcome measures, and duration and completeness of follow-up. According to the NOS, a higher number of stars obtained after evaluation indicates higher quality of the study, up to a maximum of 10 stars. Generally, articles with at least 5 stars will be included in the meta-analysis.

We will use MINORS (methodological index for non-randomized studies) (37) to evaluate the quality of natural experiments. MINORS contains 12 evaluation items: (1) a stated aim of the study; (2) inclusion of consecutive patients; (3) prospective collection of data; (4) endpoints appropriate to the study aim; (5) unbiased evaluation of endpoints; (6) follow-up period appropriate to the main endpoints; (7) loss to follow up not exceeding 5%; (8) a control group receiving the gold standard intervention; (9) contemporary groups; (10) baseline equivalence of groups; (11) prospective calculation of the sample size; and (12) statistical analyses adapted to the study design. Each item is assigned a score of 0–2, with a maximum score of 24. The scoring is performed as follows: a score of 0 means not reported, 1 means reported but with insufficient information, and 2 means reported and sufficient information was provided.

Quality of Evidence Assessment

We will evaluate the quality of evidence using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) evidence rating approach (38), which classifies the evidence as high, medium, low, and very low quality. According to the GRADE method, we will measure the quality of evidence according to study limitations, imprecision, inconsistency, indirectness, and publication bias.

Network Meta-Analysis

We will perform a network meta-analysis to compare the effectiveness of different non-pharmacological interventions in treating the community-dwelling population with hypertension, and we will rank these and their probabilities. Probability values will be reported using surface under the cumulative ranking curve (SUCRA) and ranked graphically using ranking plots. Both a network meta-analysis based on classical frequency statistics and a network meta-analysis based on the Bayes method will be conducted. Considering that the generalizability and effectiveness of an intervention at community level are not necessarily directly related, and that effectiveness is only one of the factors considered in the economic evaluation in the second phase of this study, a broad ranking will be considered; among the top 20 interventions, several will be selected for subsequent analysis in this study *via* consultation with experts and the researchers.

Effect Size

Risk difference (RD), hazard ratio (HR), and mean difference (MD) will be used for the effect sizes of count data and measurement data, and the risk and mean of each group will also be calculated to provide the basis for later decision tree modeling. Specifically, for SBP and DBP, the MD will be calculated using the confidence interval (CI) of its mean and standard deviation. If the CI is not reported in the literature, we will use the method recommended in the Cochrane Handbook, assuming the standard deviation (SD) correlation coefficient $r = 0.5$, and we will calculate the MD confidence interval based on the baseline and final follow-up SD data.

For the blood pressure control rate, the RR value will be used as an effect measure. For the CVD event rate, we will use the HR value as an index for survival data. Because a QALY is a continuous outcome, we will use the MD as the effect measure.

Assessment of the Transitivity Assumption

Standard methods to test transitivity are lacking, and therefore we will make subjective judgments about transitivity in terms of both clinical and methodological similarity. Clinical similarity includes the population, interventions, and follow-up time of each study, whereas methodological similarity refers to similarity in terms of study quality. Therefore, we will use a narrative approach to discuss the baseline characteristics of patients in the included studies, the definition and measurement of the outcome measures, design of combination therapy, follow-up time, and study practices.

Assessment of the Consistency Assumption

We will compare the consistency of evidence in head-to-head direct comparison and indirect comparison. We will use a node-splitting approach to assess the consistency between the two types of evidence. If there is no or little difference between the results of direct and indirect comparisons, the consistency hypothesis will be considered to be true. If inconsistencies occur, possible reasons for the inconsistencies will be explored in detail and an inconsistency model considered.

Dealing With Heterogeneity and Inconsistency

Heterogeneity among studies will be assessed by comparing the characteristics of patients, interventions, and trial designs, as well as the effect sizes and precision of outcomes, and will be finally assessed using statistical tests. Heterogeneity of the included outcomes will be analyzed using a χ^2-test (test level = 0.05) combined with I^2 quantification. Generally, I^2 values >50% indicates heterogeneity, with values >70% suggesting significant

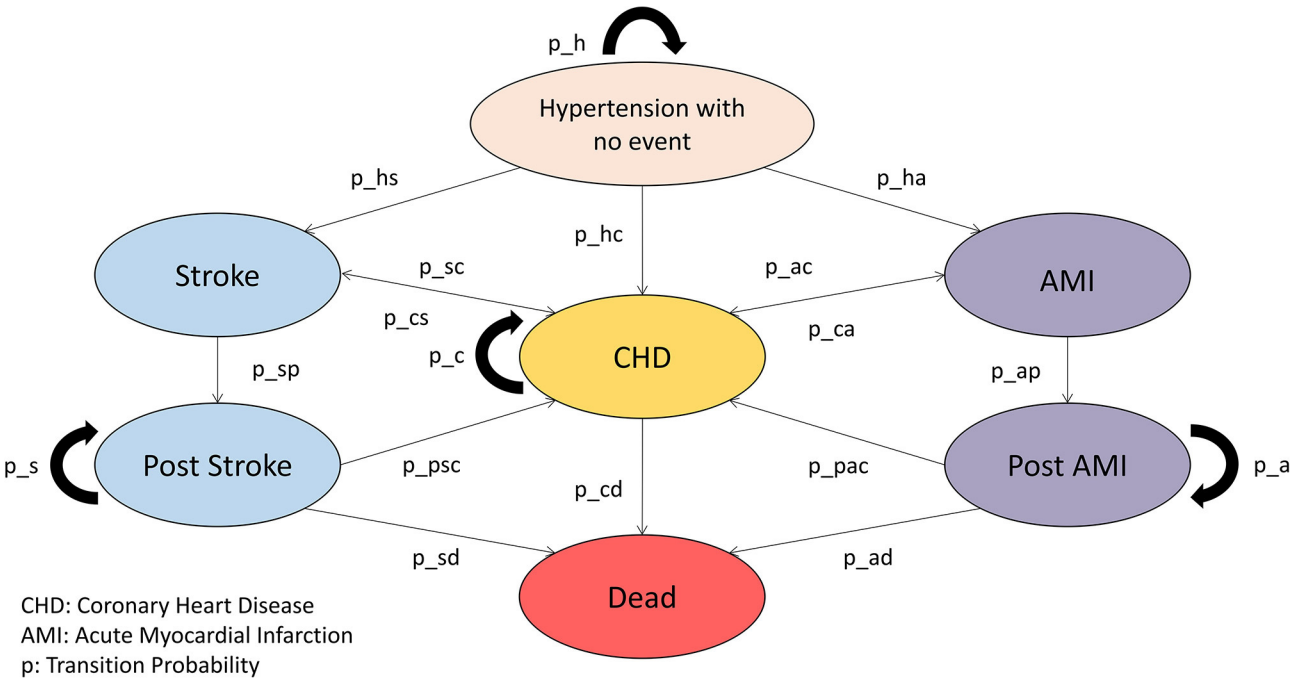


FIGURE 1 | Markov model.

differences across studies. If the statistical heterogeneity among the results is small(with I^2 values smaller than 50%), the fixed-effects model will be used for meta-analysis; if the statistical heterogeneity among the results is large(with I^2 values larger than 50%), the source of heterogeneity will be further analyzed and the random-effects model used for meta-analysis, after excluding the influence of obvious clinical or methodological heterogeneity. If there is obvious clinical or methodological heterogeneity, subgroup analysis and meta-regression will be used to explore the potential causes of heterogeneity and the impact on the combined effect size; alternatively, only qualitative description will be conducted. The test level for meta-analysis is set to $\alpha = 0.05$. Meta-analysis will be performed using Stata SE 15 (StataCorp LLC, College Station, TX, USA).

Publication Bias

If more than 10 studies are included, a funnel plot will be plotted to assess publication bias.

Health Economic Modeling and Cost-Effectiveness Analysis

Research perspective: A society-wide perspective will be applied, incorporating both direct and indirect costs.

A Markov model will be established for the economic evaluation and an independent Markov model constructed for each intervention. The Markov model will be established, as shown in **Figure 1**. Health states of other comorbidities and complications as shown in **Table 4** will also be considered in the Markov model.

Cycle: The cycle duration will be 3 months.

TABLE 4 | Health states in the Markov model.

Category	Health states
Comorbidities	Obesity, diabetes, dyslipidemia
Complications	Stroke, coronary heart disease, acute myocardial infarction, and heart failure

Study duration: The study duration is the patient lifetime.

Economic Parameters

Effectiveness: Effectiveness is represented by life-years, which can be simulated using the Markov model.

Utility values: Utility values for each health state reported in the literature will be entered into the model; if these values were not reported in the literature, the utility data for each health state from an authoritative study of hypertension in China will be referenced, to ensure that the model works under this standard assumption.

Transition probability: The incidence of CVD events reported in the literature for different study time frames is converted to a transition probability according to the model cycle.

$$p = 1 - e^{-rt}$$

where p is the probability of an event occurring within time t of the study mentioned in the article; r is the incidence of that event within time t, and t is the duration of the study (39).

Natural mortality: Data of natural mortality will be obtained by consulting World Health Organization (WHO) data or the Chinese Statistical Yearbook.

Disease mortality: Mortality data for each health state reported in the literature are to be entered into the model. If not reported in the literature, the mortality for each health state will be referenced from an authoritative Chinese study of hypertension to ensure comparability of model time frames under the standard assumptions.

Cost standardization: For costs, all resource consumption items will be standardized (minimum decomposition combined with human capital method to estimate the unit price), based on the description of the intervention in the included studies. The cost of each intervention is calculated by summing the item costs.

Prices: Project prices reported in the literature will be discounted and entered into the model. If not reported in the literature, we will first obtain the validated intervention by combining the standardized operation in the guidelines or by consulting experts, and then weighting the price of drugs and medical services involved in the intervention by obtaining prices from the Chinese public pricing system.

Discounting: We will discount the cost and effect outcomes to 2021 at a 5% discount rate to adjust for costs and outcomes over time. The rate we choose is in accordance with China Pharmacoeconomic Evaluation Guidelines 2019, and is higher than typical discount rates basically because of a faster growing GDP in China (40).

Economic Evaluation

Decision indicator: The ICER is calculated using the following formula:

$$ICER = \frac{\Delta Cost\ of\ Intervention\ B\ than\ Intervention\ A}{\Delta QALYs\ of\ Intervention\ B\ than\ Intervention\ A}$$

Incremental analysis process: (1) eliminate any option with absolute dominance; (2) sort the alternative intervention measures in ascending order of cost; (3) calculate the incremental cost-effectiveness ratio of the intervention with minimal cost vs. zero-treatment and choose the one with cost-effectiveness (defined as ICER $\leq$ threshold of paying for one hypertensive patient effectively managed; (4) calculate the ICER of the second-smallest cost intervention with the remained option and run same decision; (5) make pairwise comparison in sequence until the final option is chosen.

***Threshold*:** China's 2019 GDP per capita (70,892 RMB) (41) will be used as the threshold criterion for cost-effectiveness. Because financial support for non-pharmacological interventions does not come from health insurance but rather from public health funds allocated in local budgets, a higher willingness to pay (e.g., twice the GDP per capita or lower) will be used as the threshold criterion.

Dealing With Economic Uncertainty

Model Assumption

For the model structure, we will follow the economic model of hypertension adopted by the National Institute for Health and Care Excellence (NICE) (42–45), and the model will be validated by Chinese clinical experts.

Parameter Sensitivity Analysis

We will perform single-factor sensitivity analysis as well as probabilistic sensitivity analysis in the economic evaluation model. In the single-factor sensitivity analysis, deterministic sensitivity analysis (DSA), we will use the 95% CI of a single effect size as the fluctuation interval. For parameters lacking variance information, we assume that the relevant parameter fluctuates by 20–30% (considering the large cost uncertainty). Fluctuations in the discount rate range from 0 to 8%. The results of the DSA analysis will be presented in a tornado diagram. For probability sensitivity analysis (PSA), we will use a Monte Carlo simulation (10,000 iterations are expected). Prior distribution of the parameters will be applied, such as a beta distribution for transfer probability, effect value, and mortality, and gamma distribution for costs. The PSA results will be presented using a cost-effectiveness acceptability curve and incremental cost-effectiveness scatter plot.

DISCUSSION

Despite the increasing emphasis on community-based management of hypertension in China (46), compliance (47), affordability, and treatment rates of patients that rely on traditional pharmacological interventions must be improved. At present, a chronic disease management system based on non-pharmacological interventions has been established in Chinese communities; therefore, identifying community-appropriate interventions is of great importance for community health, representing an important direction for primary care and integrated health services moving forward and a challenge for policy makers. A variety of non-pharmacological interventions exist for hypertension, but comprehensive studies comparing their effectiveness and affordability are lacking. This study proposes a protocol for a network meta-analysis to synthesize all existing evidence and an economic evaluation on the cost-effectiveness of existing non-pharmacological hypertension interventions using an innovative and reliable method to classify different interventions. Study findings will provide implications for policymakers to identify the cost-effective alternative strategies, for local health systems to choose the best intervention package according to their actual resource levels, and provide community physicians and administrators with a basis for interventions. The methodology of this study will have implications for the management of other chronic diseases in the Chinese public health care system.

When classifying different groups of patients, we mainly rely on the 2018 Chinese Guidelines for the Management of Hypertension (25), which may miss some risk stratifications of in guidelines of other countries. When implementing this study, we will also discuss the influence of different guidelines [for example, ISH 2020 guidelines for HTA management and 2018 ESC/ESH guideline (48, 49)].

We hope that the results of our study would support evolutionary programs of chronic disease management

nationwide, especially for population with risk factors but disease-free under current program inclusion criteria. We also hope that appropriate intervention strategies could be provided to precisely targeted patient groups based on comprehensive evidence of effectiveness, efficiency, and generalizability.

This study has several limitations. First, we expect there to be heterogeneity of interventions (including the "conventional" medication regimen in controls) across the papers that we identify. Second, because the trials will be community-based, the quality of the literature involved in this study will vary. Third, in constructing the economic model, the study may be biased because there is insufficient data arising from studies conducted in China. Therefore, some inputs may be obtained from jurisdictions outside of China. Fourth, we will address standardization of the cost approach. Finally, the literature included in this study will be in Chinese and English language only, which may exclude some relevant studies published in other languages conducted in the Chinese population; thus, language bias may be present.

AUTHOR CONTRIBUTIONS

WT conceptualized the research idea, developed the research design, and performed critical revision of this manuscript. TS drafted the manuscript. XL drafted and registered the protocol. JZ, XZ, CZ, DM, and LZ contributed to the study design. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.651559/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Inhibition of Fibroblast Activation in Uterine Leiomyoma by Components of *Rhizoma Curcumae* and *Rhizoma Sparganii*

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Background: The herbs *Rhizoma Curcumae* and *Rhizoma Sparganii* (RCRS) are often used in traditional Chinese medicine for the treatment of uterine leiomyoma (UL). The effectiveness of RCRS for the treatment of UL has been confirmed in our previous studies.

Purpose: This study aimed to investigate the molecular mechanism by which RCRS inhibits the activation of fibroblast activation protein (FAP) and prevents UL in rats.

Study Design and Methods: A Sprague Dawley (SD) rat model of UL was established via estrogen and progesterone load combined with external stimulation. Histological analyses, enzyme-linked immunosorbent assays, and western blotting were performed to evaluate the effect of RCRS on UL and elucidate its mechanism of action.

Results: Our data showed that the treatment of SD rats with RCRS significantly reduced the expression of extracellular matrix component collagen, FAP, and transforming growth factor beta (a FAP-activating factor) and the phosphorylation of the cell proliferation pathway-related signaling factors AKT/MEK/ERK.

Conclusion: Our results suggest that RCRS is effective in the prevention and treatment of UL in rats, and RCRS may exert its functions by inhibiting the activation of tumor-associated fibroblasts and cell proliferation and by improving the tumor extracellular matrix.

Keywords: fibroblast activation protein, *Rhizoma Curcumae*, *Rhizoma Sparganii*, tumor-associated fibroblasts, traditional Chinese medicine, uterine leiomyoma

INTRODUCTION

Uterine leiomyoma (UL) is the most common type of benign reproductive tract tumor in women of childbearing age, with an incidence rate of ∼70%, of which 25–50% of patients exhibit clinical symptoms (1). Because fibroblasts are the main stromal cells of UL, UL is also referred to as uterine fibroids (2). The principal drugs used in the clinical treatment of UL include mifepristone, letrozole, and vitamin D. Surgical treatment is currently the primary means of clinical treatment of UL, and

hysterectomy is the only definitive cure for UL. However, these treatments have serious side effects; thus, it is important to identify effective and safe methods to treat UL.

Rhizoma Curcumae (RC) and *Rhizoma Sparganii* (RS) (RCRS) are frequently used in patients with gynecological diseases such as uterine fibroids, dysmenorrhea, and ovarian cysts to improve blood circulation and remove stasis. A combination of RC (*Curcuma phaeocaulis Valeton*) and RS (*Sparganium stoloniferum* Buch. -Ham.) is a representative medication for UL treatment in traditional Chinese medicine (TCM) (3). Chemical analyses have shown that RS mainly contains volatile oil, flavonoids, saponins, organic acids, and other functional ingredients (4). Total flavonoids are one of the major active ingredients of RS and possess pharmacological effects such as anticoagulation, antithrombotic, and anticancer effects. Zedoary turmeric oil is a volatile oil extracted from RC. As an effective antitumor drug, the main active ingredients of zedoary turmeric oil are curcumin, curcumin diketone, and β-elemene (5, 6).

RCRS, a combination of total flavonoids and zedoary turmeric oil, has a significant therapeutic effect on experimental UL (7). Our previous studies have confirmed that the therapeutic effects of RCRS on UL include improvement of pathological status, reduction of volume, and inhibition of myoma cell proliferation (7). Another study showed that the therapeutic effect of RCRS on UL might be related to the regulation of endocrine levels (8). The results of a metabolomics study confirmed that RCRS can reverse abnormal metabolism in rats. However, its mechanism of action remains poorly studied (9). Because of the multi-channel and multi-target characteristics of TCM, the key targets of RCRS are unclear and require investigation. ULs are composed of leiomyoma cells, fibroblasts, and a large number of extracellular matrices (ECMs) (10). Studies have shown that RCRS inhibits the proliferation of leiomyoma cells, but the mechanism remains to be elucidated. Most studies on UL have focused on leiomyoma cells, but the mechanisms underlying the activation of tumor-associated fibroblasts (TAFs) and UL development are unclear.

In this study, we used a rat model of qi stagnation and blood stasis UL, in which UL was induced via estrogen and progesterone load combined with external stimulation. The way of modeling has been verified to be reliable and repeatable (11). This model is more suitable for TCM experiments according to the basic theory of TCM combined with western medical theory and experimental zoology. Because fibroblast activation leads to the development of UL, we assumed that RCRS inhibits UL by inhibiting TAF activation. The results of this study should provide an experimental basis for using TCM for the treatment of UL.

Abbreviations: UL, uterine leiomyoma; TCM, traditional Chinese medicine; RCRS, *Rhizoma Curcumae* and *Rhizoma Sparganii*; ECM, extracellular matrix; TAF, tumor-associated fibroblasts; ER, estrogen receptor; PR, progesterone receptor; E2, estradiol; P, progesterone; FAP, fibroblast activation protein; TGF-β, transforming growth factor beta.

MATERIALS AND METHODS

Preparation of Herbal Extract

The volatile oil of RC was prepared and validated as described in our previous study (11). A voucher specimen (NO.EZ 0704) was deposited at the Chengdu University of Traditional Chinese Medicine, Chengdu, China. RS was identified by Professor Teng Peng of the Department of Pharmacy, Chengdu University of Traditional Chinese Medicine. For preparation of total flavonoids of RS, we weighed RS powder, added eight volumes of 70% ethanol, heated and extracted twice (1.5 h each time), recovered the extract after filtration. Concentrate the extract with a rotary evaporator and put it in a water bath for drying. After dissolving and diluting the extract with 70% ethanol, it was poured into a macroporous resin for filtration, and the filtrate was collected and dried the extract in a 45°C drying oven to a constant weight. A voucher specimen (NO.SL 0704) was deposited at the Chengdu University of Traditional Chinese Medicine.

Three concentrations of the compound were used: 66.7% extract (6.67 g/kg), 33.3% extract (3.33 g/kg), and 16.7% extract (1.67 g/kg). All extracts were stored at 4°C until use.

Preparation of Herbal Decoction

The herbs (RS:RC = 1:1) were crushed and soaked in water for 2 h. Herb fragments were decocted twice: for 1 h for the first extraction and 0.5 h for the second extraction. Following mixing and filtering, the decoction was concentrated to 0.67 g of crude drug/mg and stored at 4°C.

Rats

Rat care and experimental procedures were performed under a protocol approved by the Animal Ethical Committee at the Chengdu University of Traditional Chinese Medicine (Animal Ethics Approval Number NO. 2017-08). Female specific pathogen-free Sprague Dawley (SD) rats [Animal License No. SYXK (Chuang) 2014-049] were purchased from Chengdu Dashuo Experimental Animal Tech (China). All rats were adaptively fed with *ad libitum* access to standard rodent diet and water for 4 days. All animals were anesthetized with 2% pentobarbital sodium (0.25 ml/100 g) and sacrificed by cervical dislocation after 5 weeks.

Study Design

Seventy-two SD rats were randomly divided into nine groups: control group, model group, RCRS-treated groups (66.7, 33.3, and 16.7%), RC-treated group, RS-treated group, decoction-treated group, and a positive control group. Gongliuxiao capsule is used as a positive medicine. The UL model was established following adaptive feeding. The UL model is established by the method that has been verified before (11). The control group rats received no treatment. The remaining eight groups were administered diethylstilbestrol (1.35 mg/kg) intragastrically every day and 1 mg progesterone intramuscularly three times a week for 5 weeks.

At the beginning of the fourth week, the eight experimental groups of rats were injected subcutaneously with epinephrine hydrochloride (0.5 mg/kg/d), and one external stimulus was applied 4 h after the injection: (1) reversal of day and night, (2)

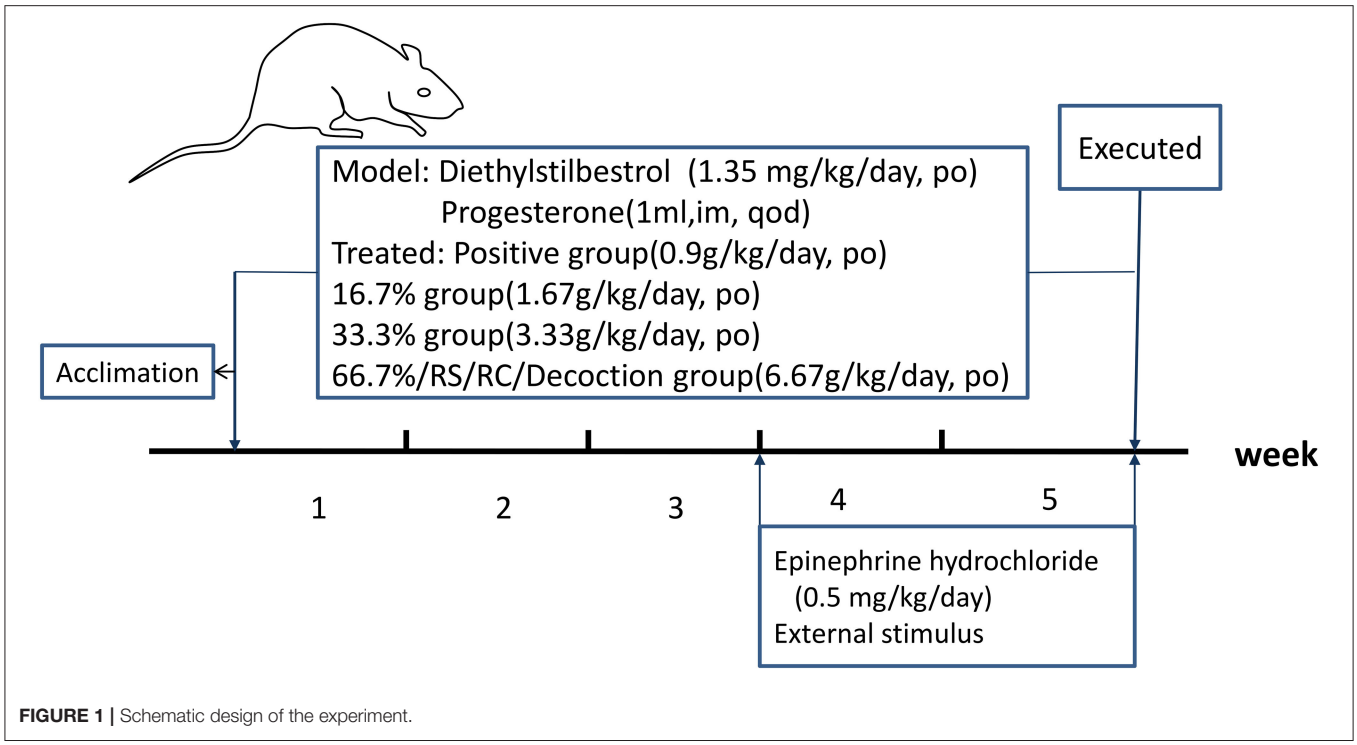


FIGURE 1 | Schematic design of the experiment.

continuous stimulation with 60 db noise for 3 h, (3) continuous hanging upside-down for 10 min, and (4) water bath at 5–10°C for 4 min. This lasted for 2 weeks; each stimulus was applied ≥twice in 2 weeks.

At the beginning of modeling, the drug was administered to the intervention groups at the same time, and the corresponding groups were administered separately (**Figure 1**). After 5 weeks, rat serum was collected for enzyme-linked immunosorbent assay (ELISA) after anesthesia; the rat uterus was divided into two parts: one for paraffin embedding and one for western blot analysis.

Histological Analyses

For hematoxylin and eosin staining, the uterus was fixed overnight in 4% paraformaldehyde. Then, it was embedded in paraffin, sectioned, and stained.

For immunohistochemistry analysis, the paraffin blocks were sectioned and blocked with a blocking buffer. Immunostaining was performed using the primary antibodies estrogen receptor (ER; anti-rabbit, ab3206, Abcam), progesterone receptor (PR; anti-rabbit, ab16661, Abcam), and fibroblast activation protein (FAP; anti-rabbit, ab28244, Abcam) and visualized using goat anti-rabbit antibody (SP-9001, Beijing Zhong Shan Golden Bridge Biotechnology, China) and 3,3′-diaminobenzidine stain.

Enzyme-Linked Immunosorbent Assays

Rat serum samples were collected, diluted, and divided into two aliquots. One aliquot was used to measure estradiol (E2) levels, and the other aliquot was used to measure progesterone (P) levels. The assays were performed using ELISA kits purchased from Nanjing Jiancheng Bioengineering Institute (#R20181226 and #R20181227 for E2 and P, respectively). The absorbance at 450 nm was measured using a Multiskan MK3 microplate reader (Thermo Fisher Scientific Inc., Waltham, MA USA).

Western Blotting

Uterus tissues were cut, homogenized, and centrifuged, and the supernatant was aspirated for use. Protein determination was performed using a BCA protein quantification kit (PICPI23223, Thermo Fisher Scientific). Glyceraldehyde 3-phosphate dehydrogenase was used as a loading control for error correction.

Statistical Analysis

Data were analyzed using one-way analysis of variance. The results are expressed as the mean + standard deviation. A p-value of <0.05 was considered statistically significant. A nonparametric test was used if the data did not conform to a normal distribution.

RESULTS

Identification of Total Flavonoids

The yield of total flavonoids is 0.267%. A total of 10 flavonoid compounds were isolated from RS, and their structures were identified. These compounds included 1,3-O-diferulyl glycerol, ferulic acid, vanillic acid, 5-hydroxymethyl furfural, β-sitosterol palmitate, β-sitosterol, rutin, kaempferol, succinic acid, and α-palmitic acid monoglyceride (**Figure 2**).

Establishment of the Rat Model

The rats in the model group displayed hair loss, decreased food intake, and slow increase in body weight.

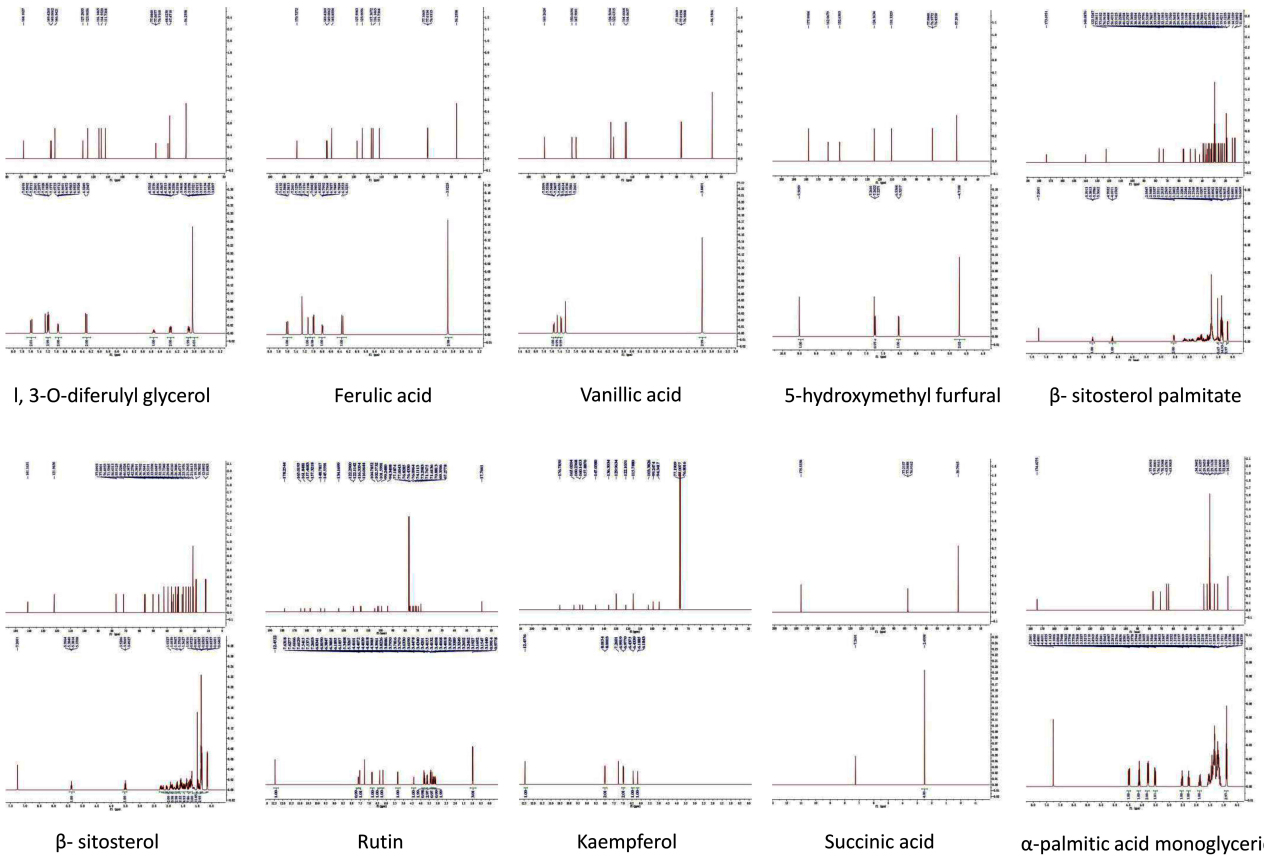


FIGURE 2 | Compounds in the total flavonoids of Rhizoma Sparganii. Seventy percentage ethanol was used to extract the total flavonoids of Rhizoma Sparganii, and 10 compounds were identified, including 1,3-O-diferulyl glycerol, ferulic acid, vanillic acid, 5-hydroxymethyl furfural, β-sitosterol palmitate, β-sitosterol, rutin, Kaempferol, succinic acid and α-palmitic acid monoglyceride.

The uterus of rats in the model group was dull, its texture was hard, and there were abnormalities, nodules, and macroscopic edema (**Figure 3A**). The transverse diameter and vertical diameter of the uterus in the model group increased, and the volume of the uterus also increased significantly.

Pathological examination showed that compared with those in the control group, the uterine myometrial cells of the model group were disorganized, the thickness of the muscle layer was different, the outline of the muscle fibers was unclear, and the muscle fiber cells showed varying degrees of deformation and even necrosis (**Figure 3B**). This result is similar to the histopathological changes in uterine fibroids in human clinical patients. Meanwhile, the levels of estrogen and progesterone in the serum and uterus of the model group were significantly higher (**Figures 4A–D**).

These results demonstrated that the rat model of UL was successfully established.

Effects of RCRS on the Appearance of the Uterus in Rats

Compared with the model group, the uterus of a rat that received medication was mostly symmetrical, the texture became soft, the thickness was uniform, and the uterine surface was smoother than the model group with no obvious swelling or ecchymoses. Several nodules can be seen on some uteri (**Figure 3A**).

Effects of RCRS on Histological Changes of the Uterus

There were six (6/8) cases in the positive group, six (6/8) cases in the model group, six (6/8) cases in the RC-treated group, five (5/8) cases in the RS-treated group, three (3/8) cases in the (16.7%) RCRS-treated group, five (5/8) cases in the (33.3%) RCRS-treated group, and five (5/8) cases in the (66.7%) RCRS-treated group showing different degrees of degeneration (**Figure 3B**). The myometrium was disorderly arranged and varied in thickness. The muscle fibers were unclear and exhibited light-staining. The muscle fibers displayed varying degrees of degeneration and necrosis. The nucleus volume increased, and hyalinization could be seen in the muscle fibers. These results show that RCRS treatment can significantly improve the UL histological conditions.

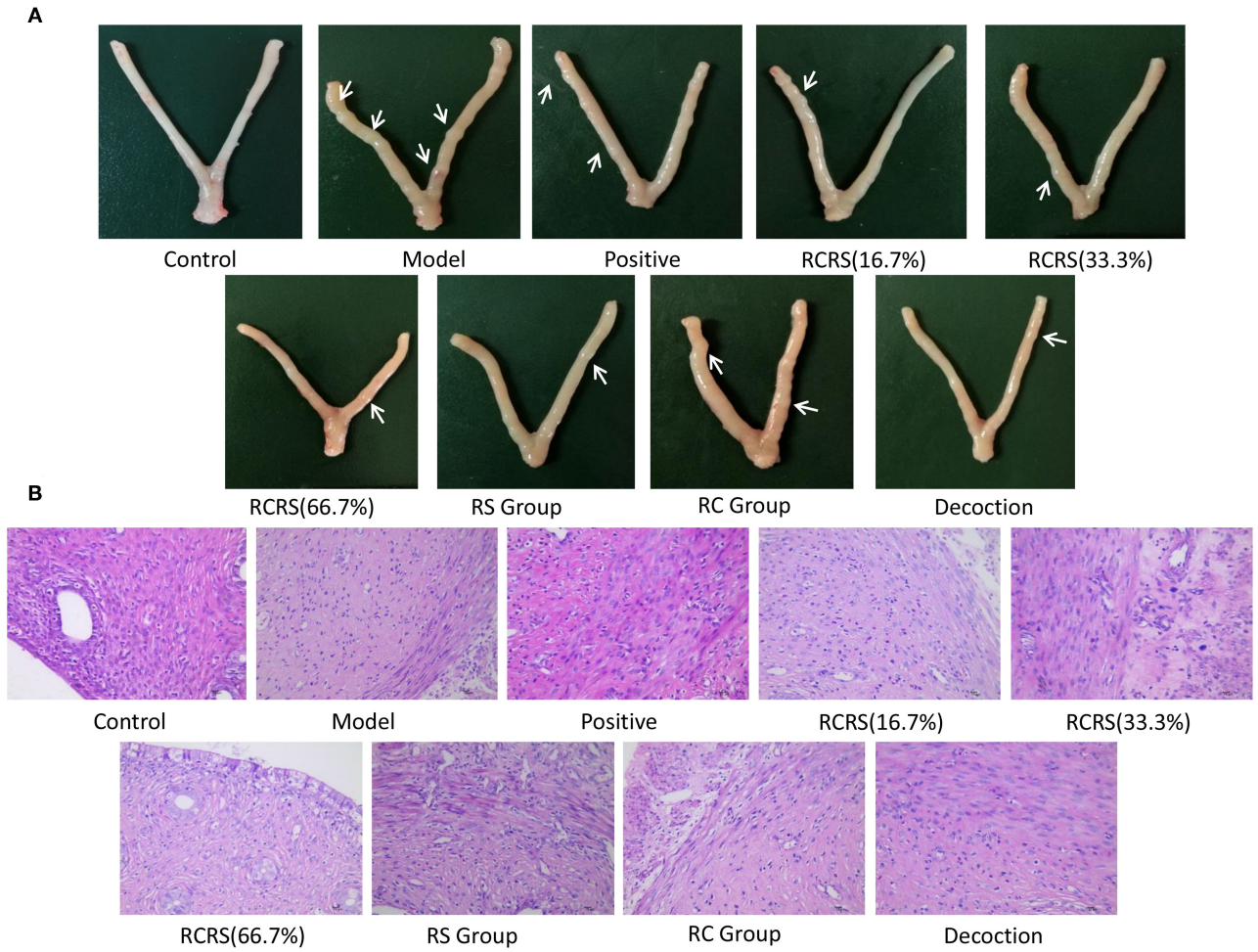


FIGURE 3 | Preparation of uterine fibroid model by estrogen and progesterone load combining with external stimulation. **(A)** Representative uterus appearance of rats in each group. **(B)** Representative histological changes of uterus in each group ($n = 8$; magnification 400 ×).

Effects of RCRS on the Expression of FAP in the Uterus

Immunohistochemistry analyses showed that the expression of FAP in the model group ($p < 0.05$) significantly increased compared with the control group. The expression of FAP in the RCRS-treated group (16.7%) was also increased. The effect of RCRS seemed to be dose-dependent as the low dose of the drug had a weaker inhibitory effect on FAP expression.

Compared with the model group, FAP expression was significantly decreased following RCRS (66.7%) or RC treatment ($p < 0.05$). The positive control group showed a similar inhibitory effect on FAP expression ($p < 0.01$) (**Figure 5A**).

Western blot analysis results are similar to Immunohistochemistry results. FAP expression was significantly decreased following RCRS (33.3%) (66.7%) or RC treatment ($p < 0.05$), compared with the model group (**Figure 5B**).

Effects of RCRS on the expression of transforming growth factor beta (TGF-β) in the uterus.

Western blot analysis showed that the expression of TGF-β was significantly increased in the model group compared with the control group ($p < 0.01$).

Compared with the model group, the expression of TGF-β in the uterus in all drug intervention groups was significantly decreased ($p < 0.05$). However, no statistical differences were detected in the control group. In the positive group, the expression of TGF-β was similar to that of each drug intervention group ($p < 0.01$) (**Figures 6A,B**).

Effects of RCRS on the Proliferation Signaling Pathway in the Uterus

To investigate the effects of RCRS on the expression of proteins regulating cell proliferation and apoptosis, we analyzed the expression of AKT, ERK1/2, and MEK via western blot. The results showed that RCRS treatment had no significant effect on the expression levels of these proteins. However, compared with those in the control group, the phosphorylation levels of

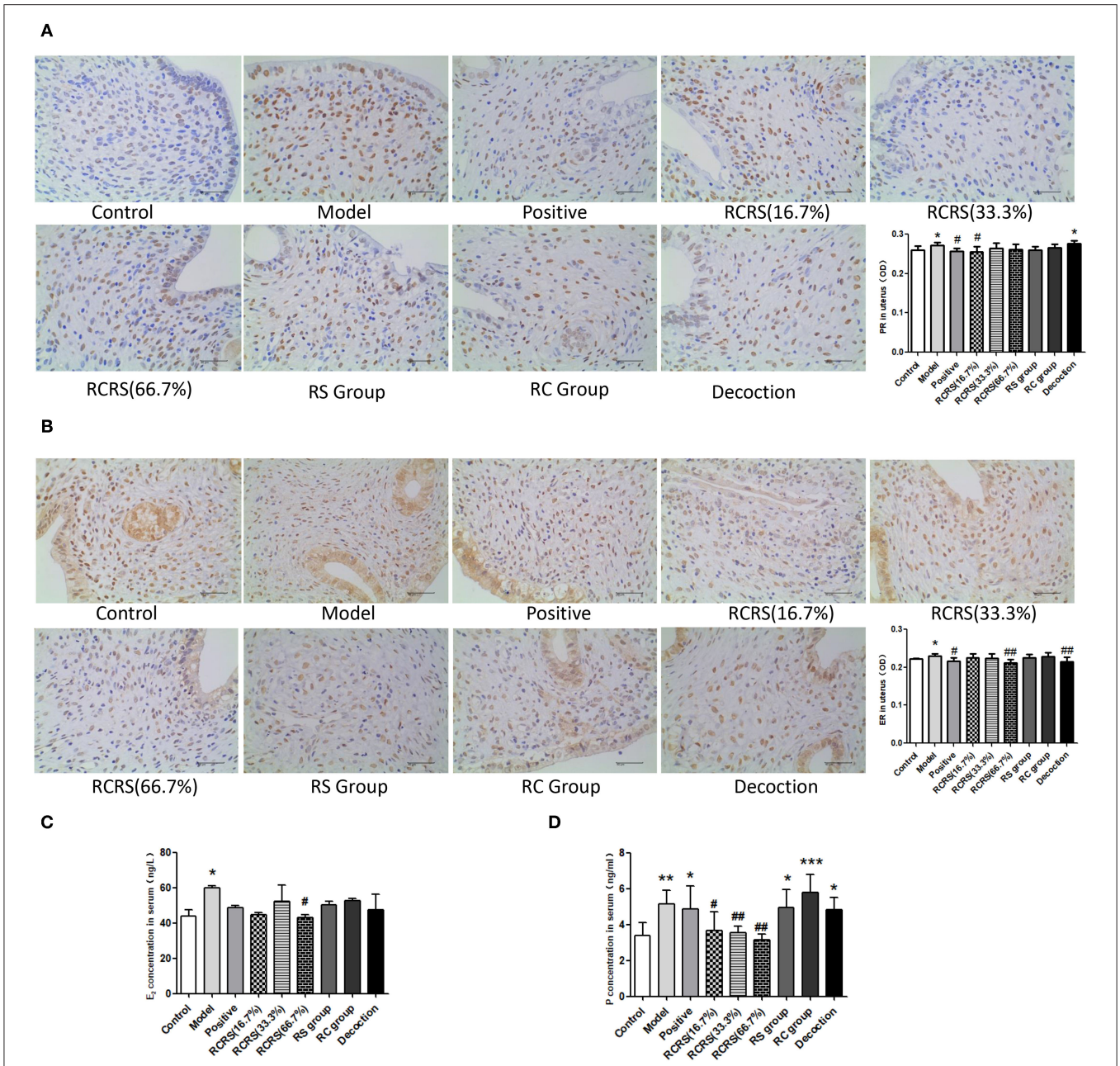


FIGURE 4 | The result of estrogen and progesterone. Immunohistochemistry shows levels of **(A)** PR and **(B)** ER in uterus. The levels of **(C)** E_2 and **(D)** *P* in serum were measured by ELISA ($n = 8$; mean + SD, ###$p < 0.001$, ##$p < 0.01$, #$p < 0.5$ compared with control group; ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$ compared with control group; magnification 400 ×).

AKT, ERK1/2, and MEK in the model group were significantly increased ($p < 0.001$; $p < 0.001$). The phosphorylation levels of AKT, ERK1/2, and MEK were significantly reduced in the drug intervention group compared with those in the model group. The positive group had similar effects on AKT and ERK1/2 phosphorylation ($p < 0.01$; $p < 0.001$; $p < 0.05$) (**Figures 7A–D**).

Effects of RCRS on the ECM in the Uterus

To study the effect of RCRS on the ECM of rat uterus, the expression of collagen I, an important component of the ECM, were analyzed by western blot. Compared with the control group, the expression of collagen I protein in the model group was significantly increased ($p < 0.001$; $p < 0.05$).

Compared with the model group, except for the RS-treated group, the drug intervention groups reversed the expression of collagen I to varying degrees ($p < 0.05$). This difference was particularly significant in the RCRS-treated (16.7%)/(66.7%) groups ($p < 0.01$). Compared with the model group, the level of collagen I in the positive group was also decreased ($p < 0.001$) (**Figures 6A,C**).

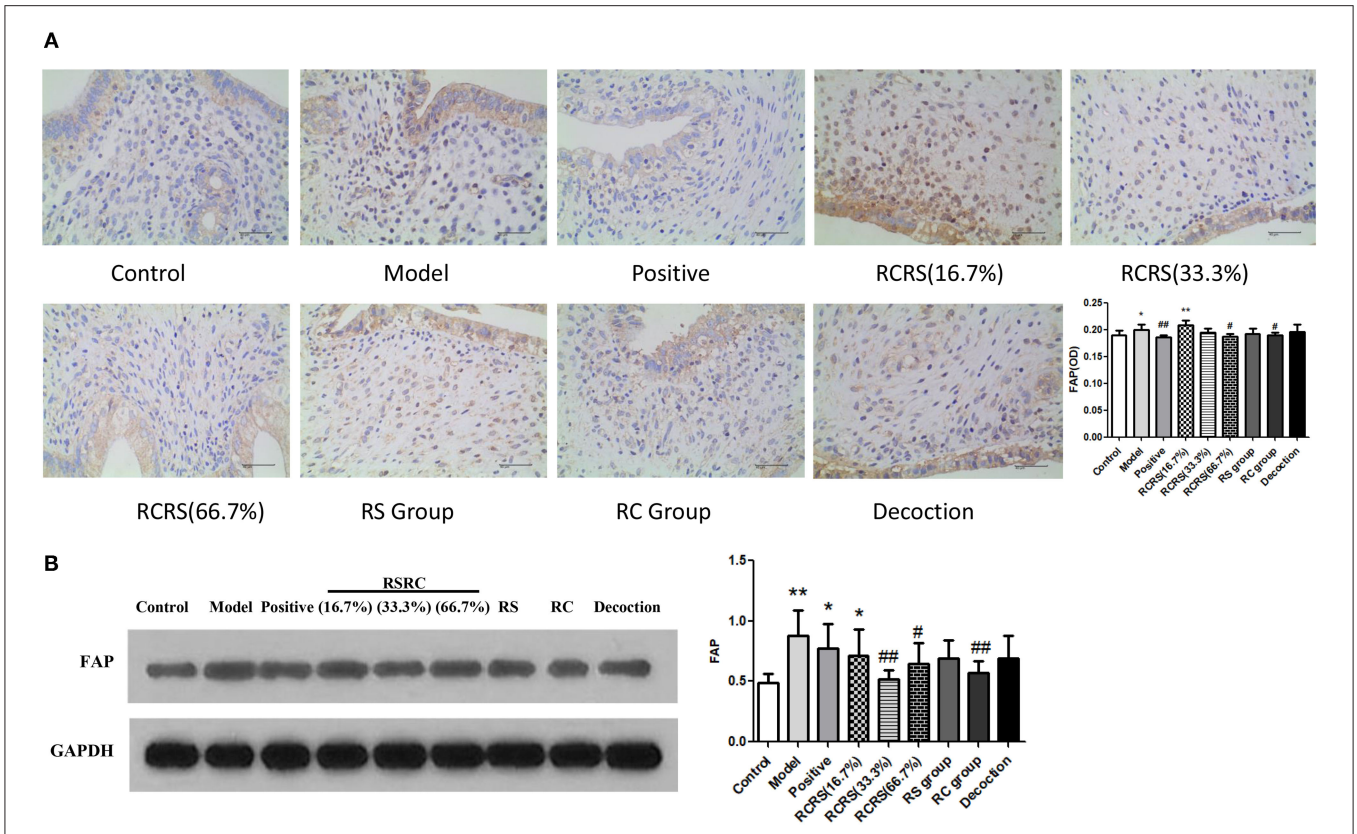


FIGURE 5 | Effects of RCRS on the expression of FAP in uterus. **(A)** representative immunohistochemistry graphics of FAP in uterus. **(B)** representative western blotting band of FAP ($n = 8$; mean + SD, ##$p < 0.01$, #$p < 0.5$ compared with model group; **$p < 0.01$, *$p < 0.05$ compared with control group; magnification 400 ×).

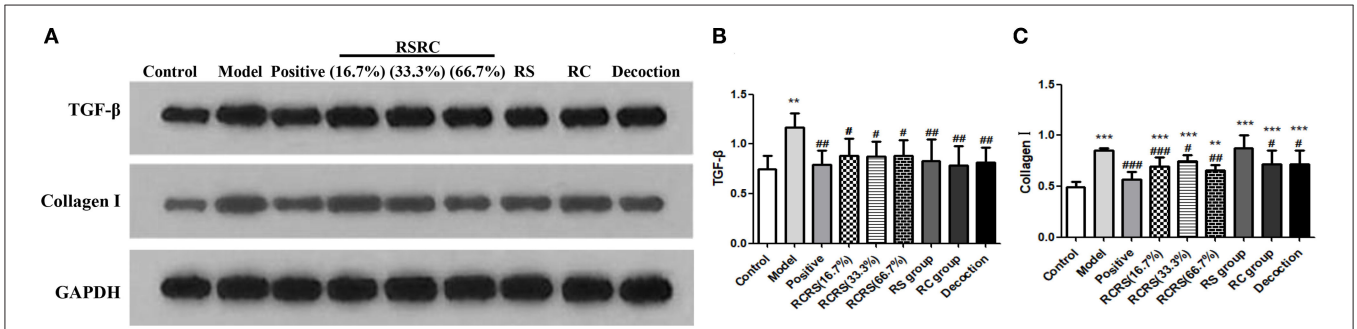


FIGURE 6 | Effects of RCRS on the expression of TGF-β and extracellular matrix in uterus. **(A–C)** Representative western blotting band of TGF-β, collagen I ($n = 6$; mean + SD, ###$p < 0.001$, ##$p < 0.01$, #$p < 0.5$ compared with model group; ***$p < 0.001$, **$p < 0.01$ compared with control group).

DISCUSSION

ULs, also known as fibroids, affect up to 70% of women before menopause and cause various clinical problems, such as excessive uterine bleeding, dysmenorrhea, infertility, and miscarriage (12). Uterine fibroids are considered estrogen-dependent tumors, and their development is closely related to the coordination of estrogen and progesterone. However, to the best of our knowledge, no report has evaluated the effects of RCRS on the TAFs of UL. Therefore, in this study, we aimed to address this issue using a well-established rat model of UL. Morphological and pathologic data showed that RCRS treatment significantly improved the symptoms of UL. Accordingly, we further examined whether RCRS improves UL by inhibiting TAF activation. As shown previously, approximately 80% of fibroblasts are activated in tumor tissues, and FAP plays a crucial role in fibroblast activation (13, 14). Santos et al. showed that the deletion of the *FAP* gene in

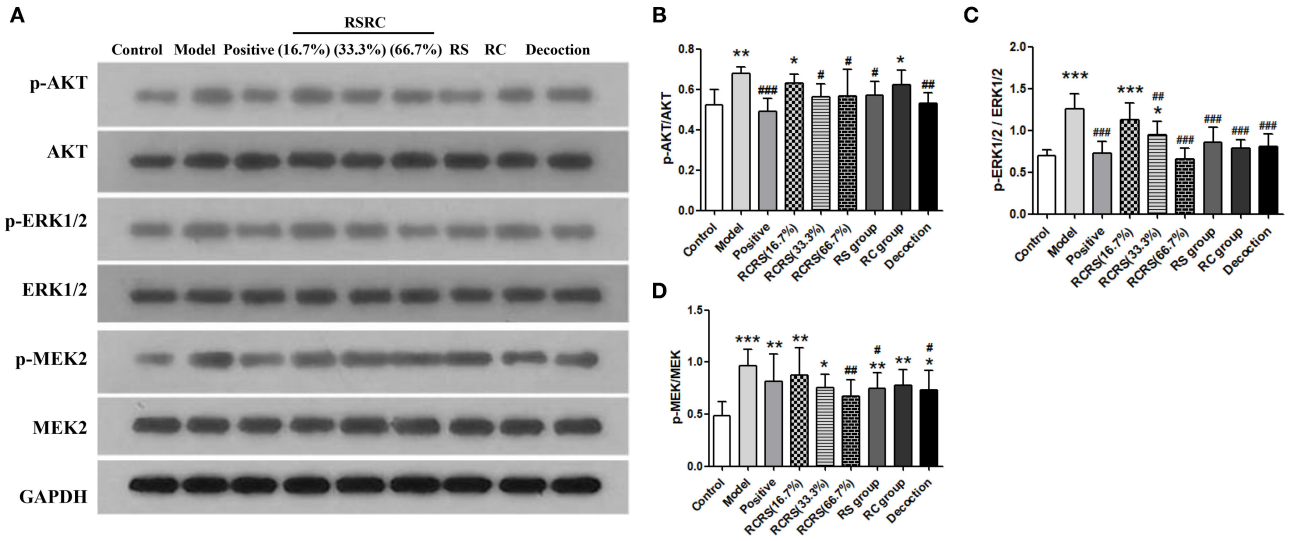


FIGURE 7 | Effects of RCRS on the proliferation signaling pathway in uterus. **(A–D)** Representative western blotting band of p-AKT, AKT, p-ERK1/2, ERK1/2, p-MEK2 and MEK2 ($n = 6$; mean + SD, ###$p < 0.001$, ##$p < 0.01$, #$p < 0.5$ compared with model group; ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$ compared with control group).

TAF significantly decreased tumor cell proliferation activity, suggesting that FAP plays a key role in promoting tumor cell proliferation through TAF activation (15). Indeed, the western blotting results showed that the expression of FAP in the uterus was significantly decreased in the RCRS component compatibility, indicating that FAP can be inhibited by RCRS component compatibility, which inhibits the activation of UL fibroblasts.

TGF-β has pleiotropic effects and plays a key role in cell growth, differentiation, and immune response, and TGF-β1 has a significant influence on pathological changes of fibroids (16). TGF-β can promote TAF activation and induce normal fibroblast transformation (17). Our data showed that the expression level of TGF-β1 increased in the uterus in the model group, suggesting that increased FAP expression occurs due to the increase in TGF-β expression. RCRS treatment reversed these effects, suggesting that RSRC inhibits TGF-β expression and thus UL development.

Abnormal cell proliferation is one of the characteristics of uterine fibroid formation (18). The PI3K/AKT and MAPK/ERK signaling pathways are classical pathways related to cell proliferation and apoptosis (19, 20). It has been reported that AKT inhibitors can activate the AKT pathway in uterine fibroids, which increases the phosphorylation level of AKT compared with that in normal uterine tissue, suggesting that AKT is a potential biomarker for UL (21). Our results showed that the phosphorylation levels of AKT, ERK, and MEK were elevated in the model group, whereas those of AKT, ERK, and MEK were reduced after treatment with RCRS component compatibility. It has been shown that silencing of the TAF phenotype protein FAP can decrease the phosphorylation levels of AKT, ERK, and MEK (22), indicating that AKT, ERK, and MEK phosphorylation levels are associated with *FAP* expression and TAF activation; this result is consistent with our findings. These results indicate that the therapeutic effects of the total flavonoids of RS, volatile oil of RC, and their compatibility on UL may be related to the inhibition of FAP of TAF.

ULs are mainly composed of fibroid cells, fibroblasts, and ECM. ECM mainly includes collagen I, fibronectin, and laminin. A large amount of ECM deposition in uterine fibroid tissue is an important factor in the promotion of tumor development and metastasis (2). Tumor stroma is an important factor in promoting tumor development and metastasis. It is mainly composed of ECM, fibroblasts, inflammatory cells, and vascular smooth muscle cells.

Additionally, fibroblasts are in a static state in normal tissues and are stimulated by factors such as trauma to secrete a large amount of ECM protein (23–25). Therefore, the effects of RCRS component compatibility on collagen I in the uterine tissue of UL model rats were investigated. The results showed that the expression level of collagen I was reduced by the total flavonoids of RS and volatile oil of RC after treatment. However, the ability of the RCRS component compatibility to regulate the expression of collagen I in uterine tissue suggests that its mechanism of action for UL treatment may be related to RCRS component compatibility inhibiting TAF activation by inhibiting FAP expression.

RCRS are a commonly used drug pair in TCM. They are often used in 1:1 combination to treat various gynecological diseases. The compatibility of TCM can improve the performance of RCRS and enhance the therapeutic effect. Some scholars have separated and identified components in RCRS and have found that the mixed liquid contains more active ingredients than the simple

RC/RS liquid and that the active ingredients extracted from the mixed liquid have better antioxidation and antitumor effects. In the experiment, a group of RCRS component compatibility was set up, and a single component group of total flavonoids of RS and a single component group of volatile RC oil were also set up. The results showed that the P level in the serum of UL rats in the RCRS component compatibility was significantly decreased and the PR, FAP, collagen I, and TGF-β levels in UL rat uterus tissues were significantly inhibited. Comprehensive analysis showed that the RCRS component compatibility was superior to the one component of the total flavonoids of RS and volatile oil in RC for the treatment of UL. Modern medicine uses a combination of drugs in the process of treating diseases, and the treatment effect is often better than that of a single drug. In TCM, the concept of drug combination has been practiced for thousands of years and has been validated in the clinical treatment of several diseases. Our experimental results also illustrate the scientific and effective theory of the compatibility of TCM.

CONCLUSION

A rat UL model was established to evaluate the effect of RCRS on UL. The results show that RCRS can significantly improve the macroscopic and pathological state of the uterus in rats with UL, reduce the expression levels of TGF-β and FAP in the uterus, decrease the expression levels of signal factors (AKT, ERK, and MEK) in the cell proliferation-related pathway, and regulate the secretion of collagen I in the ECM. The findings that RCRS achieves the effect of treating UL by inhibiting the activation of TAF, the expression of factors in the cell proliferation pathway (AKT, ERK, and MEK), and collagen I in the ECM. The data may provide a new idea and therapeutic approach for UL and lay the foundation for further investigation for the treatment of UL.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by the Animal Ethical Committee at the Chengdu University of Traditional Chinese Medicine (Animal Ethics Approval Number NO. 2017-08).

AUTHOR CONTRIBUTIONS

YF: validation, investigation, and writing-original draft. YZ: validation, data curation, and writing-original draft. YL: ideas and methodology. TP: resources. YK: resources. XS: writing-reviewing and editing. GW: writing- reviewing and editing. FP: conceptualization, writing-reviewing and editing. CY: conceptualization, writing- reviewing and editing, and project administration. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.650022/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Assessment of Physician's Knowledge of Potential Drug-Drug Interactions: An Online Survey in China

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Background: Drug interactions are the most common preventable cause of adverse drug reaction, which may result in drug toxicity or undesired therapeutic effect with harmful outcomes to patients. Given the rising use of combination therapies, the main objectives of this study were to estimate the degree to which physicians can identify potential drug-drug interactions (PDDIs) correctly and to describe the common source of information used by physicians when they need to check PDDIs.

Methods: A cross-sectional survey utilizing a self-administered online questionnaire was conducted among physicians in China. Participants were asked to classify 20 drug pairs as "no interaction," "may be used together with monitoring," "contraindication," and "not sure." We also collected data on the physician's source of information and altitude toward the PDDIs. An ordinary least square regression model was performed to investigate the potential predictors of PDDI knowledge.

Results: Eligible questionnaires were obtained from 618 physicians. The respondents classified correctly 6.7 out of 20 drug pairs, or 33.4% of the drug interactions investigated. The number of drug pairs recognized by respondents was ranged from 0 to 16. The percentage of physicians who recognized specific drug pairs ranged from 8.3% for no interactions between conjugated estrogens and raloxifene, to 64.0% for the interaction between dopamine and phenytoin. When the respondents want to check PDDI information, the most commonly used source of information was package inserts (n = 572, 92.6%), followed by the Internet or mobile Apps (n = 424, 68.6%), consultation with clinical pharmacists (n = 384, 62.1%), medical textbooks (n = 374, 60.5%), knowledge base in Chinese (n = 283, 45.8%), and other physicians (n = 366, 59.2%). In the multiple regression analysis, the significant predictors of a higher number of recognized drug pairs were years of practice and altitudes toward PDDIs.

Conclusion: In this online survey accessing physician's ability to detect PDDIs, less than half of the drug pairs were recognized, indicating unsatisfactory level of knowledge about the clinically significant drug interactions. Continuing education and accessible electronic database can help physicians detecting PDDIs and improve drug safety.

Keywords: drug-drug interaction, PDDI, adverse drug event, survey, knowledge, medication

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INTRODUCTION

A drug-drug interaction occurs when the pharmacokinetic or pharmacodynamic properties of a drug are altered when two or more drugs are taken simultaneously (1, 2). The interactions between two or more drugs may exist antagonistic or synergistic effect, both of which lead to drug toxicity or undesired therapeutic effect with harmful outcomes to patients (3–5). The potential drug-drug interactions (PDDIs) were identified in around 30% of the prescriptions in the outpatient (6) and oncology departments in China (6, 7). Even though the prevalence data is largely lacking in China, the PDDIs may be more prevalent in intensive care settings (8) and hematology (9, 10), based on the data from other countries. Patients experienced a PDDI are generally associated with a longer hospital stay (11) and higher medical costs (12, 13), leading to substantial financial burden on healthcare systems as well as on patients and society (14).

Physicians play a key role in preventing and reducing the risk of PDDIs and associated adverse outcomes. Unlike other countries such as the United States (U.S.), the clinical decision support system, which assists clinicians to detect PDDIs, is not commonly available in China. Physicians rely on their own knowledge to recognize PDDIs when writing a prescription. Even with the help of clinical decision support system, the performance of such system in terms of accurately identifying PDDIs was still unknown in China. Unsatisfactory performance of these systems has been reported in U.S (15, 16). For example, large variations in the electronic databases were reported (17–20), resulting in confusions among clinicians. In a recent study comparing three commercial knowledge databases – First DataBank (FDB), Micromedex, and Multum, it was found that the overlap of drug pairs in all these three knowledge bases was as low as 5%, and the number of alerts generated for serious PDDIs were ranged from 25 to 145 alerts per 1,000 prescriptions (18). Despite the suboptimal performance of computerized systems, clinicians tend to override the automated alerts and may ignore PDDIs (21).

To our best knowledge, however, no studies have attempted to test physician's knowledge of PDDIs in China. Internationally, few studies assessed the ability of clinicians to detect PDDIs and their sources of drug information (22–25). In a postal survey of U.S. prescribers, response from a 16-item questionnaire suggested that prescribers were able to detect 42.7% of drug combinations (22). In another survey using simulated prescription profiles, 67% of 2-drug combinations were categorized correctly by pharmacists (23). In addition to the PDDI knowledge, the source of information contributes to the irrational use of medicines. For example, if physicians rely on the drug information from pharmaceutical companies rather than evidence-based guidelines, incorrect medication use may occur (26). But limited data is available for where the physicians obtained their PDDI information in China.

China has become the second largest pharmaceutical market in the world. With the rising use of medications, it is becoming increasingly urgent to navigate potential ways reducing the risk of PDDIs. In 2019, the National Health Commission (NHC) released opinions on strengthening rational use of medicines to address the emerging issue in patient safety. As such, understanding the physician's knowledge level of PDDIs is warranted to develop evidence-based strategies and policies to improve patient care. Therefore, the objective of this study was 3-fold: [1] to estimate the degree to which physicians can identify PDDIs correctly; [2] to describe the source of information that physicians used; [3] to understand their altitude with respect to improving knowledge level of PDDIs.

MATERIALS AND METHODS

Study Design

This study employed a cross-sectional study design. We carried out an anonymous, online survey that was open to practicing physicians in Shanghai, China, from November 1 to December 15, 2020. This study was approved by the Institutional Review Boards of Minhang Hospital of Fudan University. The study protocol and gave an exemption from full review. Written informed consent was waived for this study because of the anonymous survey approach. This study followed the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) (27).

Survey Questionnaire

The questionnaire, which accessed the knowledge level of PDDIs, was created based on previous studies and clinical practices in China (22, 24, 28). This questionnaire has been reviewed by an expert panel that consisted of physician, pharmacists, outcomes researcher. The questionnaire included three sections; the first section was to ask physician's characteristics, including age, gender, education, years of practice, and specialty. The second section was to access physician's knowledge for PDDIs. Participants were asked to classify the 20-drug pairs into four categories: "no interaction" ($n = 5$), "have interaction, may be used together but with monitoring" ($n = 8$), "contraindication" ($n = 7$), and "not sure." Each correct answer was given one point, with a maximum score of 20. These DDI pairs are commonly used in the literature testing the knowledge level of PDDIs (22, 24, 28). We selected these drug pairs because they are frequently used in China with significant clinical impacts. The last section was to understand the source of information. As various sources of drug information may be used to check for PDDIs, the participants were expected to choose multiple answers from the options given. We also evaluated physician's altitude on the prevention of PDDIs. The 5-point Likert scale was used to allow the participants to express the extent they agree or disagree with the four statements regarding their altitude toward of avoiding PDDIs in practice. The questionnaire was shown in the **Appendix**.

Participants Recruitment

To reach a representative sample of physicians, following the previous research (29), we first selected 20 clinical pharmacists as the original delivers who invited the physicians in their units to participate. Physicians working in both community clinics and hospitals were invited to participate. Then we sent out private messages via WeChat that included a link to web-based questionnaire through an internet survey portal (https://www.

wjx.cn/). WeChat is the largest social media platform in China and has been widely used to distribute online surveys (30, 31). Each WeChat account was allowed to answer the questionnaire once to avoid multiple response from the same participants. A total of 900 participants were invited in this survey and 709 physicians participated the survey. The response rate was 78.8%.

The returned questionnaire was considered as eligible if [1] all the questions related to the PDDIs were answered; [2] the time spent on answering the questionnaire was within the range of 2–20 min, which was considered as typical timestamps. In the questionnaire development stage, we collected the feedbacks from a small group of physicians on whether the survey questions were clear. The typical timestamps were determined by the time they spent on completing the questionnaire. This approach has been applied in previous studies (30, 32). If the respondents submitted the same answers for all the PDDIs questions, then the questionnaire was excluded from the analysis.

Data Analysis

For descriptive analysis, frequency distributions (e.g., percentage) was used to describe categorical variables and means were used to describe continuous variables, respectively. Fisher's exact test was for categorical variables and Student's *t*-test was used for continuous variables. The mean was calculated to describe the score of PDDI questions. We also constructed an ordinary least square regression model to examine the potential predictors of PDDI knowledge, including physician's demographics, specialty, type of hospitals, practices, and their altitude toward PDDIs. The selection of these factors was based on the practices in China. The number of drug pairs categorized correctly was used as dependent variable, and the physician's self-reported characteristics and altitude on the PDDIs were included as independent variables. On the basis of parsimony, the interaction terms were not included in the regression model because the interacting effect of independent variables is difficult to interpret (22). Statistical significance was determined at a-level of 0.05. All statistical analyses were performed using SAS 9.4.

RESULTS

Characteristics of Respondents

After discarding 88 questionnaires that deemed ineligible based on predefined criteria, 618 (or 88%) of 706 questionnaires were included in the analysis. As shown in **Table 1**, the majority (42.6%) of respondents were aged between 30 and 39 years old; 353 (57.1%) were female, and 256 (41.4%) held a graduate degree. Most of physicians worked in community hospitals (38.8%) and tertiary hospitals (38.8%), and 25.9. 18.8, 35.1, and 14.6% of the respondents having practiced for <5 years, 5–9 years, 10–19 years, and more than 20 years, respectively. 40.0% of the respondents were internal medicine or family medicine physicians.

TABLE 1 | Self-reported characteristics of physicians who participated in the survey ($n = 618$).

Characteristics	Number of participants (*n*)	Percentage (%)
AGE		
20–29	127	20.6
30–39	263	42.6
40–19	171	27.7
50+	57	9.2
GENDER		
Male	265	42.9
Female	353	57.1
EDUCATION		
High school	1	0.2
College/Bachelor degree	361	58.4
Graduate/Master degree	256	41.4
TYPE OF HOSPITAL		
Community hospital	240	38.8
Secondary hospital	66	10.7
Tertiary hospital	240	38.8
Private hospital/others	72	11.7
YEARS OF PRACTICE		
<5	160	25.9
5–9	116	18.8
10–19	217	35.1
20–30	90	14.6
>30	35	5.7
SPECIALTY		
Internal/general medicine	247	40.0
Surgery	92	14.9
Emergency medicine	44	7.1
Others	235	38.0

Knowledge of PDDIs

Table 2 presents the frequencies (percentages) of respondents choosing each answer of the 20-drug pairs. On average, the respondents classified correctly 6.7 out of 20 pairs, or 33.4% of the drug interactions investigated. The number of drug pairs recognized by respondents was ranged from zero to 16. The percentage of physicians who recognized specific drug pairs ranged from 8.3% for no interactions between conjugated estrogens and raloxifene, to 64.0% for the interaction between dopamine and phenytoin.

For the five drug combinations without interactions, 9.8% of the respondents answered correctly. For the 15 drug combinations that were considered as having interactions, which include both "contraindication" and "have interaction but may be used together with monitoring," 41.2% of them were categorized correctly by the respondents. Of particular, 15.1% of respondents categorized correctly for the six drug pairs having contradicted interactions, while 60.2% of the respondents categorized them as "needs to have close monitoring." For the seven drug pairs that were deemed with clinical significance by the expert panel (33), the majority of respondents detected the interactions, but 10% of the respondents still categorized as "no interaction" and 15% of them answered "not sure."

Source of PDDI Information

The respondents' source of PDDI information was shown in **Figure 1**. When the respondents wanted to check PDDI information, the most commonly used source of information

TABLE 2 | Frequencies (percentages) of physician's response to PDDIs[a].

Drug pairs	No interaction	May be used together but with monitoring	Contraindication	Not sure
Acetaminophen/codeine and amoxicillin	**124 (20.1%)**	337 (54.5%)	28 (4.5%)	129 (20.9%)
Warfarin and sulfamethoxazole/trimethoprim	44 (7.1%)	**376 (60.8%)**	104 (16.8%)	94 (15.2%)
Warfarin and digoxin	**79 (12.8%)**	377 (61.0%)	77 (12.5%)	85 (13.8%)
Digoxin and amiodarone	26 (4.2%)	**334 (54.0%)**	185 (29.9%)	73 (11.8%)
Cyclosporine and rifampicin*	48 (7.8%)	381 (61.6%)	**108 (17.5%)**	82 (13.2%)
Digoxin and itraconazole	56 (9.1%)	**390 (63.1%)**	94 (15.2%)	78 (12.6%)
Digoxin and sildenafil	**53 (8.6%)**	371 (60.0%)	114 (18.5%)	81 (13.0%)
Simvastatin and itraconazole	62 (10.0%)	361 (58.3%)	**113 (18.3%)**	83 (13.3%)
Sildenafil and isosorbide mononitrate*	47 (7.6%)	373 (60.3%)	**102 (16.5%)**	97 (15.6%)
Conjugated estrogens and raloxifene	**51 (8.3%)**	387 (62.6%)	79 (12.8%)	101 (16.3%)
Theophylline and ciprofloxacin*	83 (13.4%)	**357 (57.8%)**	75 (12.1%)	103 (16.7%)
Pimozide and ketoconazole*	70 (11.3%)	366 (59.1%)	**73 (11.8%)**	110 (17.7%)
Warfarin and fluconazole	59 (9.6%)	**384 (62.1%)**	82 (13.3%)	93 (15.0%)
Alprazolam and itraconazole*	87 (14.1%)	373 (60.4%)	**65 (10.5%)**	93 (15.0%)
Digoxin and clarithromycin*	73 (11.8%)	**382 (61.7%)**	52 (8.4%)	112 (18.0%)
Warfarin and sulfinpyrazone*	50 (8.1%)	**383 (61.9%)**	101 (16.3%)	85 (13.7%)
Dopamine and phenytoin	40 (6.5%)	**396 (64.0%)**	95 (15.4%)	88 (14.2%)
Fexofenadine and metoprolol	**58 (9.4%)**	396 (64.0%)	62 (10.0%)	103 (16.6%)
Itraconazole and quinidine	40 (6.5%)	382 (61.7%)	**100 (16.2%)**	97 (15.6%)

[a]*Bold text indicates the correct answers based on the Lexi-Interact.*
**Indicates that these drug pairs were considered as clinically significant.*

was package inserts ($n = 572$, 92.6%). The less commonly used information sources were Internet or mobile Apps ($n = 424$, 68.6%), consultation with clinical pharmacists ($n = 384$, 62.1%), medical textbooks ($n = 374$, 60.5%), knowledge base in Chinese ($n = 283$, 45.8%), and consultation with other physicians ($n = 366$, 59.2%).

Altitude Toward PDDIs

As shown in **Figure 2**, 88.0% of respondents reported that they always checked PDDIs while prescribing for patients, among them, 28.6% agreed with the statements and 59.4% strongly agreed, respectively. 69.1% of respondents agreed that they would consider PDDIs while prescribing. Less than half of the respondents agreed that the PDDI information were useful for their practice, but 78.0% of them had the willingness to improve their knowledge for PDDIs.

Predictors of PDDI Knowledge

In the multiple regression analysis, it revealed that significant predictors of a higher number of recognized drug pairs were years of practice ($p = 0.015$) and altitudes toward PDDIs (**Table 3**). Respondents who reported to check references for PDDIs detected more drug interactions than those who did not look for PDDIs ($p = 0.029$). Respondents who reported to consider PDDIs while prescribing for patients had lower score for PDDIs than those who did not ($p = 0.011$).

DISCUSSION

In this online survey accessing physician's ability to recognize PDDIs, less than half of the interacting drug combinations were recognized by the physicians who responded to the survey, which is consistent with previous studies conducted in the U.S. (22) and Central Saudi Arabia (28). Based on the participants' response, it seems that some potentially harmful drug interactions may not be detected by many physicians. For the seven drug combinations that are considered as contradicted, nearly 80% of the respondents categorized incorrectly. This insufficient detection of contradicted drug combinations could be partly explained by that the use of these drugs requires close monitoring, and hence a large proportion (around 60%) of respondents chose "use with monitoring" rather than "contradicted." However, up to 25% of the physicians still remained unsure or unaware of these serious PDDIs. In addition, the participants were asked to restrict the use of references, which may contribute the relatively poor performance of recognizing PDDIs (22, 34).

Our findings also revealed that package inserts were the most commonly used information source for physicians when they need to check PDDIs, which is a major risk factor for incorrect medication use (26). As the electric databases or computerized systems are not widely available in China, it would be difficult for physicians to stay current with the best available evidence. With the busy working schedule, it appears to be impossible for physicians to check package inserts for every potential drug interaction they found, leading to substantial threats to the patient safety. Therefore, easily accessed scientific resources should be available for physicians to improve drug safety. Even with the assistance of the computerized systems to detect PDDIs, preventing DDIs is still difficult especially when more drugs are a part of a patient's daily schedule (35). Pharmacists and physicians tend to be desensitized to the alerts that are given by the software

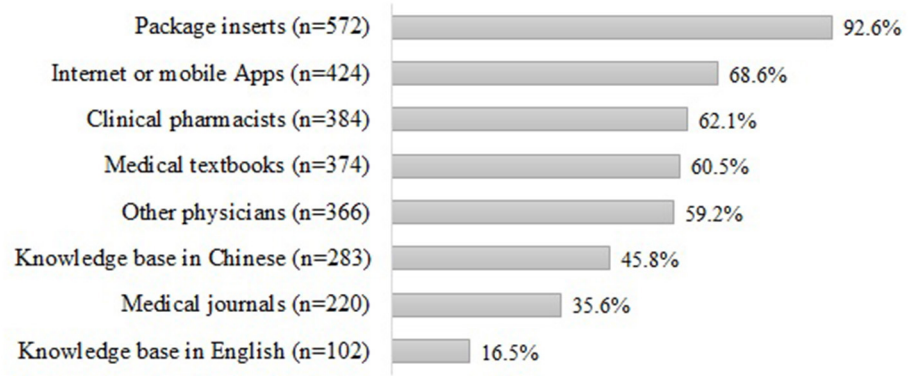


FIGURE 1 | Source of information for PDDIs[a]. [a]Sum may not be 100% because respondents were allowed to choose multiple answers.

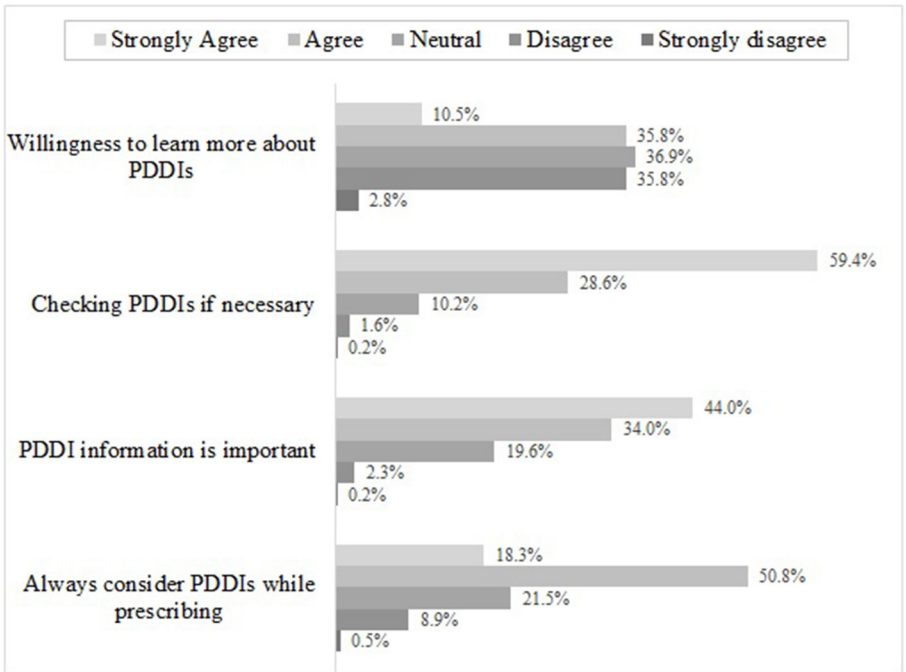


FIGURE 2 | Physician's altitude toward PDDIs*. *Sum may not be 100% because respondents were allowed to choose multiple answers.

systems (36), mainly because they are given the option to override those alerts with mild or insignificant clinical outcomes (35, 36). Overriding alerts may become a habit for many pharmacists; in some clinical settings, the override rates could be as high as 71.9%, which may rise the tendency of a pharmacist or physician to override a harmful PDDI (37). Hence, the burning issue of drug interaction won't be easily fixed by the implementation of the computerized system, a multi-facetted approach is necessary to improve drug safety.

This study also attempted to investigate the predictors of physician's PDDI knowledge. Due to small sample size, few predictors, including years of practice, type of hospital, and altitude toward PDDIs, were statistically significant. Higher scores for PDDIs were reported among physicians working in the secondary hospitals, potentially because they tend to provide care to a wide spectrum of non-surgical conditions and might be more familiar with the PDDIs included in the questionnaire. Noticeably, our analyses indicated the strong association between self-reported willingness to check references and knowledge of PDDIs as demonstrated by correct responses to drug pairs. Our finding highlighted the importance of raising awareness of PDDIs among physicians, possibly through continuing education with a specific focus on the most harmful PDDIs. Furthermore, two-thirds of physicians would consult with pharmacists if they have question regarding PDDIs. Recently, the pharmacist's role in improving patient care has been recognized in China. For

TABLE 3 | Predictors of the knowledge level for PDDIs[a].

Characteristics	Estimate	Standard Error	*p*
AGE			
20–29 years	Ref	–	–
30–39 years	−0.04	0.25	0.875
40–19 years	−0.53	0.33	0.111
50+ years	1.44	0.51	0.005*
GENDER			
Male	Ref	–	–
Female	0.14	0.16	0.368
EDUCATION			
High school	−2.96	1.84	0.108
College/Bachelor degree	0.22	0.18	0.242
Graduate/Master degree	Ref	–	–
YEARS OF PRACTICE			
<5 years	Ref	–	–
5–9 years	−0.29	0.25	0.261
10–19 years	0.12	0.27	0.670
20–30 years	0.56	0.38	0.138
>30 years	1.40	0.57	0.015*
TYPE OF HOSPITAL			
Community hospital	Ref	–	–
Secondary hospital	0.55	0.26	0.035*
Tertiary hospital	0.18	0.21	0.389
Private hospital/others	−0.28	0.27	0.298
SPECIALTY			
Internal/general medicine	Ref	–	–
Surgery	−0.33	0.24	0.162
Emergency medicine	−0.36	0.31	0.245
Others	−0.15	0.17	0.397
ALTITUDE			
Always consider PDDIs while prescribing	−0.24	0.10	0.011*
Willingness to learn PDDIs	0.12	0.08	0.147
Considering PDDI as useful	−0.14	0.11	0.200
Looking for PDDI information	0.26	0.12	0.029*

[a]*Predictors were estimated from the an ordinary least square regression.*
*$p < 0.05$.

example, the review of prescription by clinical pharmacists was mandated in tertiary hospitals in Shanghai. The physician-pharmacist collaboration model, in which pharmacists are included in the multidisciplinary heath care team, has been piloted in some tertiary hospitals. Most of PDDIs are preventable through quick response and effective team collaborations, therefore, more efforts should be pioneered in building up the physician-pharmacist collaboration to improve pharmaceutical care (7).

There are several limitations in this analysis. First, our findings have limited generalizability and may not reflect the general doctor population in terms of their level of knowledge about PDDIs. Despite of the efforts in the distribution of questionnaire, only a small proportion of physicians in China responded. Hence, the findings cannot be generalizable to all Chinese physicians. Second, selection bias may exist because physicians who were familiar with PDDIs were more likely to participate the survey. As such, it will be impossible to understand the knowledge level of those physicians who did not participate the survey. Third, the questionnaire used to test the knowledge level of PDDIs is not validated, even though it was developed based on the existing studies (22, 24, 28). The 20-drug pairs might not be adequate to reflect the extent of knowledge applicable to the huge number of PDDIs. Hence, the physician's knowledge about PDDIs may not be well-accessed in this study. However, these DDI pairs have significant clinical impacts and every practicing physicians should be familiar with them. Last, we only included a couple of predictors for PDDI knowledge level, the lacking of confounders may cause inaccurate results of the multivariate regression model.

In conclusion, this study indicates unsatisfactory knowledge level about clinically significant drug interactions among physicians. This study also provides insights into where the physicians obtain their drug information. Continuing education and accessible electronic database can help physicians detecting PDDIs and improve drug safety.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Institutional Review Boards of Minhang Hospital of Fudan University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JY and CS: concept and design. CS, BH, CW, and GS: acquisition, analysis, or interpretation of data. CS and JY: drafting of the manuscript. JY, GS, BH, CW, and CS: critical revision of the manuscript for important intellectual content. JY: statistical analysis. JY and BH: administrative, technical, or material support and supervision. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.650369/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Economic Evaluation of Rituximab + Recombinant Human Thrombopoietin vs. Rituximab for the Treatment of Second-Line Idiopathic Thrombocytopenic Purpura in China

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Objective: This study aimed to compare the economic evaluation of recombinant human thrombopoietin+rituximab (rhTPO + RTX) vs. RTX as second-line treatment for adult patients with immunologic thrombocytopenic purpura in China.

Methods: The Markov model was used in our research. The response rate and relapse rate data were derived from two clinical trials and one retrospective study. Cost and utility values were derived from published literature, a third-party database, and healthcare documents. In addition, one-way sensitivity analysis and probabilistic sensitivity analysis were performed to observe the stability of the model and data source.

Results: In the Markov model, compared with RTX, rhTPO+RTX yielded an additional 0.04 QALYs, with an incremental cost of 2,802 USD. The ICER was 69,097 USD/QALY. According to the results from the one-way sensitivity analysis, complete response of rhTPO+RTX, utility of complete response and response of RTX were the main drivers in the model. The results from the probabilistic sensitivity analysis demonstrated that there was a 100% probability that rhTPO+RTX was not cost-effective vs. RTX alone at a threshold of $10,805/QALY and an 84% probability at a threshold of $32,415/QALY.

Conclusion: RTX+rhTPO was not more cost-effective than RTX alone as second-line treatment for adult patients with immunologic thrombocytopenic purpura in China.

Keywords: cost-effectiveness (CE), immunologic thrombocytopenic purpura, rituximab, RhTPO, Markov model

INTRODUCTION

Idiopathic thrombocytopenic purpura (ITP), also referred to as primary immune thrombocytopenia, is a disorder mediated by autoimmunity that mainly leads to the increased destruction and decreased production of platelets (1). The disease is characterized by lower peripheral platelet counts than normal. In adults, ITP is a chronic disease with a very low rate of spontaneous remission, requiring drug intervention (2). Epidemiological research on ITP in China shows that the incidence of ITP is ∼9.5 in 100,000 per year, and its incidence in adult females is greater than that in adult males (2:1 ratio), which might be related to the fact that adult

women are more likely to develop autoimmune system diseases (3). Chronic ITP causes a certain socioeconomic burden and decreases patients' quality of life due to the occurrence of bleeding and the increase in mortality (4). Approximately 8.7% of patients have another autoimmune system disease, bleeding or thrombosis. The death risk of ITP patients is 1.5 times higher than that of the general population (5). Various studies have shown that adult ITP patients incur significant medical costs (the costs are mainly driven by the costs of hospitalization, bleeding, medication, and surgery) and have lower productivity at work. From the global perspective, the economic burden of chronic ITP at present has been illustrated. In Europe, the annual hospitalization cost was ∼€ 26,581 per patient in 2007, and the cost of emergency medicine for bleeding caused by ITP was also high in France (6). In the US, the annual cost of drug treatment alone for ITP has been estimated to be ∼$28,000 on average for each patient per year (2000−2003) (7). Positive treatment was recommended for adult ITP patients with platelet counts lower than 30×10^9 or between 30 and 50×10^9 and with bleeding or bleeding risk based on the current evidence (8).

In China, glucocorticoids and intravenous immunoglobulin G are usually used as first-line treatment for adult ITP patients (9). However, the side effects of the long-term use of glucocorticoids need attention. Second-line treatment includes rituximab (RTX), recombinant human thrombopoietin (rhTPO), rhTPO+RTX, and splenectomy. The study of Zhou et al. (10) found that RTX combined with rhTPO as second-line treatment had high benefits in terms of the remission rate and the control of the recurrence rate, so this combination has been recommended by the Chinese guideline on the diagnosis and management of adult primary immune thrombocytopenia (version 2020) (9). However, compared with RTX monotherapy, the cost of combination therapy is relatively high, and there is no related economic evaluation in China. The purpose of the study was to evaluate the cost-effectiveness of rhTPO+RTX as second-line treatment in patients with chronic ITP in China.

METHODS

Patient Population and Model Structure

A treatment-sequence Markov model was developed to assess the cost-effectiveness of rhTPO+RTX vs. RTX as second-line treatment for adult chronic ITP patients who had failed to respond to corticosteroids or who had experienced relapse. The patient cohort was defined as having similar characteristics as patients from the rhTPO+RTX phase 3 trial (10). All of the patients were assumed to be non-splenectomized, and the median age was assumed to be 42 years. The following two treatment strategies were compared (**Figure 1**):

Since decitabine is recommended as third-line treatment for adult chronic ITP patients (9), it was assumed that decitabine was received after splenectomy in this pathway. After failing RTX/rhTPO+RTX, patients moved on to splenectomy followed by decitabine.

A Markov model with an embedded decision tree was used with a month cycle, and a 30-year time horizon was taken in the base-case analysis, developed from the perspective of the Chinese health care system. A 30-year time horizon was thought to be appropriate, since adult ITP tends to be a chronic disease and the median age of the patients was 42; a 1-month cycle was used to match the evaluation schedule used in the clinical trial of rhTPO+RTX/RTX, splenectomy, and decitabine. Costs and outcomes were discounted at a 5% annual rate, as recommended by the China Guidelines for Pharmacoeconomic Evaluations (11). The treatment sequence used in the model was based on the Chinese guidelines on the diagnosis and management of adult primary immune thrombocytopenia (version 2020) (9).

The model was driven by platelet response (platelet count $\geq 30 \times 10^9$/L), which determined effectiveness and progression along the treatment pathway (**Figures 2**, **3**). The patients started on the first treatment in the pathway and progressed to the next treatment or were managed with the watch-and-wait strategy if they did not have a complete response (CR) or response (R) or overall response (OR = CR+R) if they experienced relapse (platelet count $< 30 \times 10^9$/L) after responding. Each relapse on active treatment was followed by one cycle period of the watch-and-wait state before initiating the next active treatment.

Clinical Inputs

Clinical efficacy data were derived from three clinical trials. The efficacy of each treatment within the model was characterized by the following parameters:

- Probability of CR and R with rhTPO+RTX/RTX treatment;
- Probability of OR with splenectomy treatment and decitabine treatment;
- Time to relapse with platelet count $<30 \times 10^9$/L of patients with an initial response (including CR, R, and OR) to rhTPO+RTX/RTX treatment, splenectomy treatment, and decitabine treatment.

Efficacy data for rhTPO+RTX/RTX were taken from an open-label prospective randomized controlled clinical trial in 12 centers in China reported by Zhou et al. (10). This study compared the efficacy and safety of RTX plus rhTPO with RTX alone in patients with ITP who had failed to respond to corticosteroids or who had experienced relapse. The patients were randomized at a ratio of 2:1 into 2 groups: the combination group (rhTPO+RTX, $n = 77$) and the monotherapy group (RTX, $n = 38$). The probability of CR and R in the rhTPO+RTX/RTX treatment group was also considered in the Markov model because the study found that the combination of RTX and rhTPO could significantly increase the CR rate, which might bring more benefit to patients.

Efficacy data for splenectomy treatment were taken from one retrospective review of the experience at Institute of Hematology & Blood Diseases Hospital between 1990 and 2003 with adults with chronic ITP (12). Data from 149 chronic ITP patients were retrospectively analyzed, and relapse-free survival was estimated by Kaplan–Meier analysis. In addition, data for decitabine treatment was taken from a prospective, multicenter study that evaluated the efficacy and safety of low-dose decitabine in adult patients with refractory immune thrombocytopenia by Zhou et al. (13).

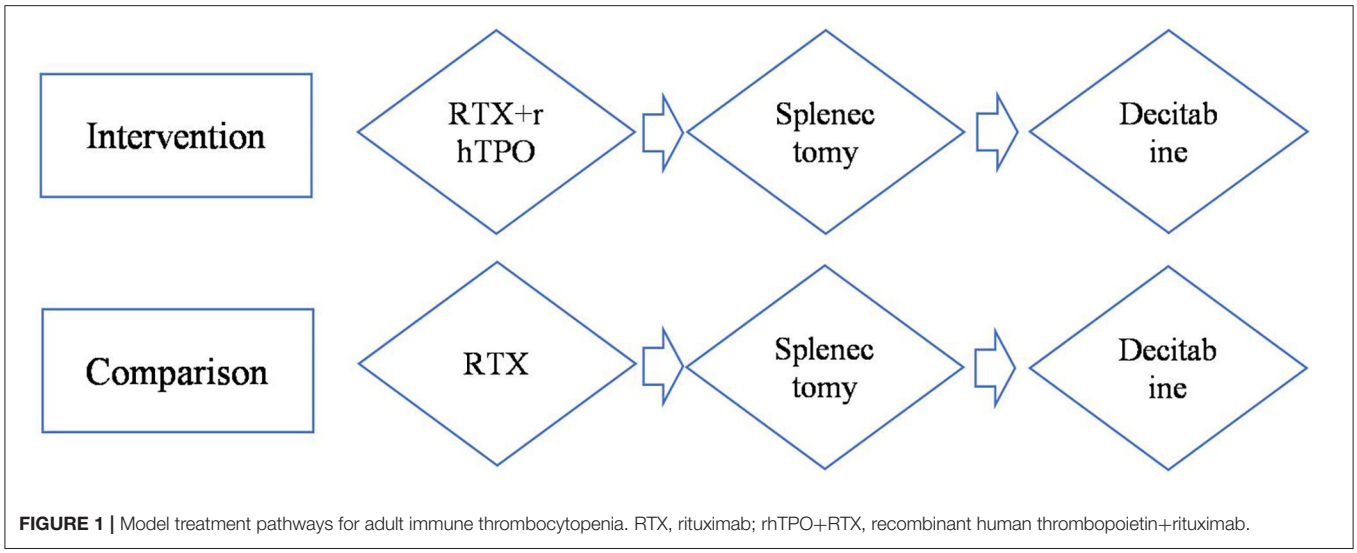


FIGURE 1 | Model treatment pathways for adult immune thrombocytopenia. RTX, rituximab; rhTPO+RTX, recombinant human thrombopoietin+rituximab.

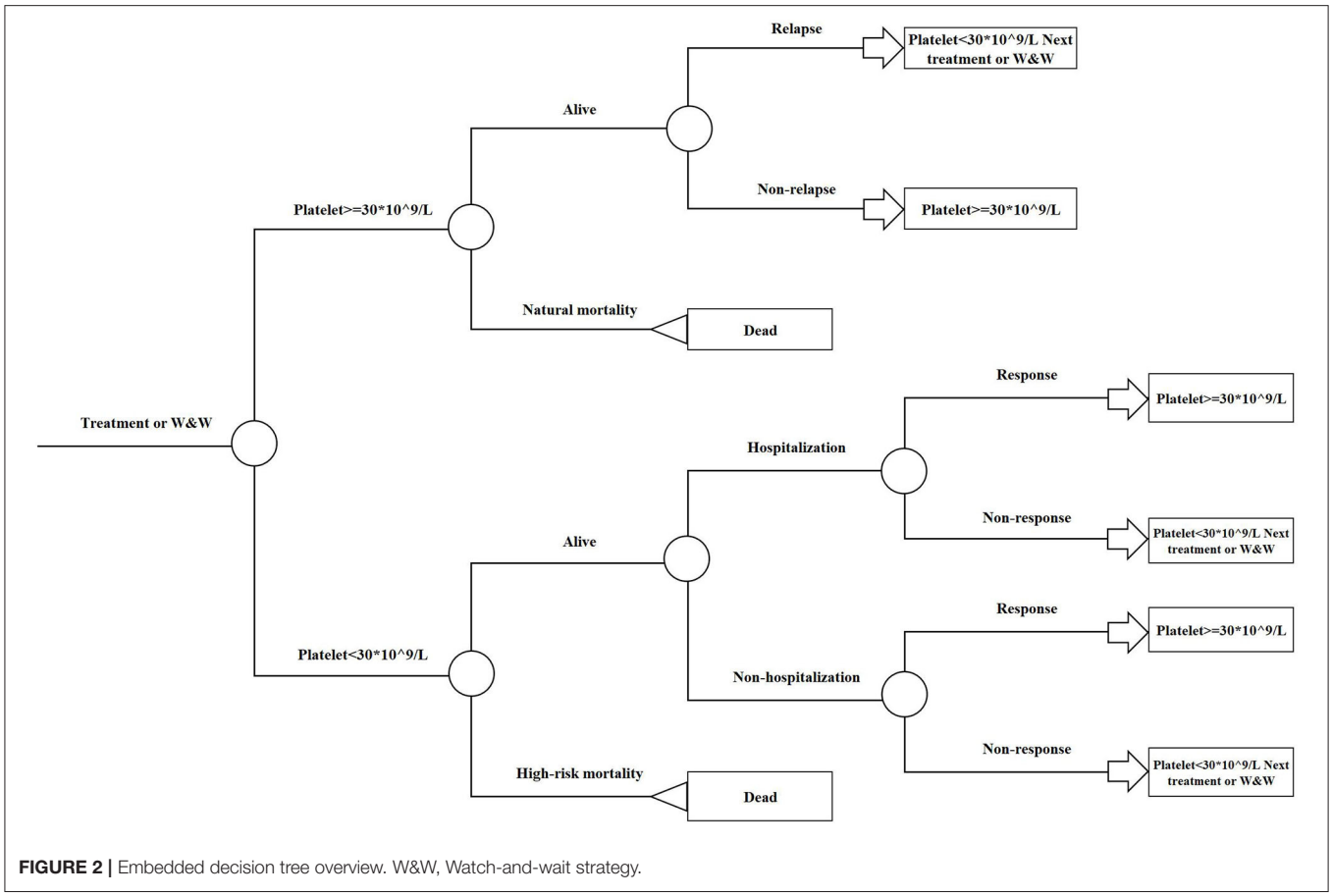


FIGURE 2 | Embedded decision tree overview. W&W, Watch-and-wait strategy.

The time to relapse in rhTPO+RTX/RTX treatment was estimated by fitting parametric survival distributions to pseudo-individual participant data (IPD) derived from digitized Kaplan-Meier curves from the study by Zhou et al. (13), and pseudo-IPD data were extracted with Engauge Digitizer software. We considered five standard parametric models to fit two curves: exponential distribution, Weibull distribution, Gompertz distribution, loglogistic distribution, and lognormal distribution. The lognormal distribution was the best-fitting curve according to the Akaike information criterion (AIC) (**Supplementary Material**). The exponential distribution was used to fit the time to relapse in splenectomy treatment and

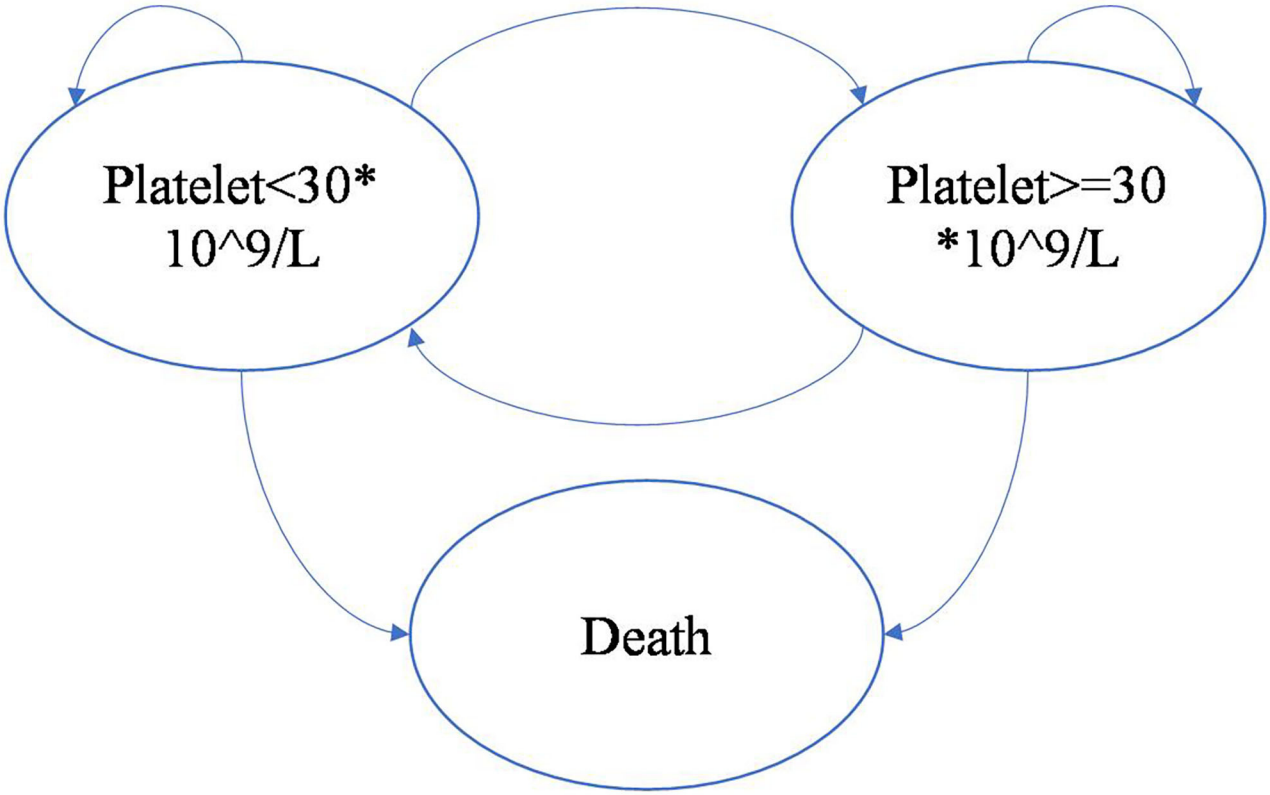


FIGURE 3 | Markov model overview driven by platelet response.

decitabine treatment because its constant risk was suitable for the memoryless characteristics of the Markov model. Although it is important to consider adverse events in the treatment of ITP, the incidence of events was not clearly explained in the literature, and the available evidence of its impact on cost and quality of life was limited. Therefore, the cost and disutilities of adverse events were not included in the model.

Hospitalization Events

In the study by Portielje et al. (5), the incidence of hospital admissions was assessed. The study showed that for those who did not respond to the treatment, the incidence of ITP-related admissions per 1,000 person-years was 183. The per-cycle probability of the incidence was calculated as 0.0167.

Mortality

The model included both natural mortality and high-risk mortality. When platelet count $\geq 30 \times 10^9$/L, natural mortality derived from the Chinese life tables was used, and when platelet count $<30 \times 10^9$/L, high-risk mortality, which was assumed to be 1.5 * natural mortality according to the study by Portielje et al., was used (5).

Utility

Due to the lack of utility data for Chinese adult ITP patients, utilities from a time trade-off (TTO) survey conducted in the UK were included in our base-case analysis (14). TTO analysis was used in that survey to directly measure the utility values for 359 adult patients with ITP of the general public, and some assumptions were made as follows:

- The utility when platelet count $\geq 30 \times 10^9$/L was assumed to be the same as sufficient platelets ($\geq 50 * 10^9$/L) with no outpatient bleed state in TTO analysis;
- The utility when platelet count $<30 \times 10^9$/L was assumed to be the same as low platelets ($<50 * 10^9$/L) with no outpatient bleed state in TTO analysis.

Costs and Resource Use

Costs were assessed in dollars, with 2020 values, from the perspective of the Chinese health care system. The drug acquisition and costs associated with splenectomy treatment and hospitalization events were considered in the model. The resource use and costs were derived from a third-party database (www.yaozhi.com) and published literature (15, 16) in China.

All patients were assumed to weigh 65 kg (17) when estimating the dosages of decitabine treatment, and there was no dose sharing between patients according to the situation in China. The

TABLE 1 | I Key inputs for the Markov model.

	Deterministic	Distribution	Low	High	References
QoL utility (per year)					
CR utility	0.86	Beta	0.78	0.95	(14)
R utility	0.84	Beta	0.76	0.86	(14)
NR utility	0.54	Beta	0.49	0.59	(14)
Clinical inputs					
CR of rhTPO+RTX	0.45	Beta	0.36	0.54	(10)
R of rhTPO+RTX	0.34	Beta	0.27	0.41	(10)
CR of RTX alone	0.24	Beta	0.19	0.28	(10)
R of RTX alone	0.47	Beta	0.38	0.57	(10)
OR of splenectomy treatment	0.83	Beta	0.66	0.99	(12)
OR of decitabine treatment	0.51	Beta	0.41	0.61	(13)
Hospitalization	0.18	Constant			(5)
Direct costs per cycle ($)					
Cost of rhTPO	2,883	Gamma	2,860	3,016	YAOZHI
Cost of RTX	1,021	Gamma	628	1,474	YAOZHI
Cost of splenectomy treatment	1,545	Gamma	1,171	1,545	(15)
Cost of decitabine treatment	313	Gamma	226	618	YAOZHI
Cost of hospitalization	3,294	Gamma	1,647	4,940	(16)
Cost of administration	1.4	Gamma	1	2	Health document
Discount	0.05	Constant	0	0.08	(11)

RTX, rituximab; rhTPO+RTX, recombinant human thrombopoietin+rituximab; CR, complete response; R, response; NR, non-response; OR, overall response.

TABLE 2 | Base-case cost-effectiveness of rhTPO+RTX compared with RTX.

	rhTPO+RTX	RTX
Total costs	8,789	5,987
QALYs gained	10.89	10.85
	rhTPO+RTX vs. RTX	
Incremental total costs	2,802	
Incremental QALYs gained	0.04	
ICER	69,097	

RTX, rituximab; r hTPO+RTX, recombinant human thrombopoietin+ rituximab.

clinical inputs, utilities and costs used in the model are shown in **Table 1**.

Model Outputs

The total costs and quality-adjusted life years (QALYs) per patient and the incremental cost-effectiveness ratio (ICER) were calculated.

SENSITIVITY ANALYSIS

One-Way Sensitivity Analysis

One-way sensitivity analysis was performed to identify the parameters to which the model was most sensitive. The upper and lower limits of the inputs were defined by 95% confidence intervals where possible and derived from the original literature or with plausible variation around the base-case values by 20%.

Probabilistic Sensitivity Analysis

Probabilistic sensitivity analysis (PSA) was conducted using 1,000 iterations to examine parameter uncertainty over the entire model, and cost-effectiveness acceptability curves (CEACs) were then calculated.

Ethics

The data was based on previously published trial, not from the database or the medical records. We used the Engauge Digitizer software to get the time to relapse information from the figures in the paper and reconstructed data by ourselves, which was explained in the Section "Clinical Inputs." Besides, the utilities and costs were derived from the published literatures, so ethics approval or specific consent procedures were not required for this study.

RESULTS

Base Case

The base-case model results (**Table 2**) indicated that rhTPO+RTX treatment resulted in an average of $2,802 higher costs for 0.041 QALYs over a 30-year timespan than RTX. In the base-case analysis with a 30-year time horizon, the economic, and health outcomes calculated using the Markov model are presented in **Table 2**. We found that the ICER in the Markov model was $69,097/QALY, which was higher than the willingness-to-pay thresholds of $10,805/QALY (1 GDP per capita) and $32,415/QALY (3 GDP per capita) in China.

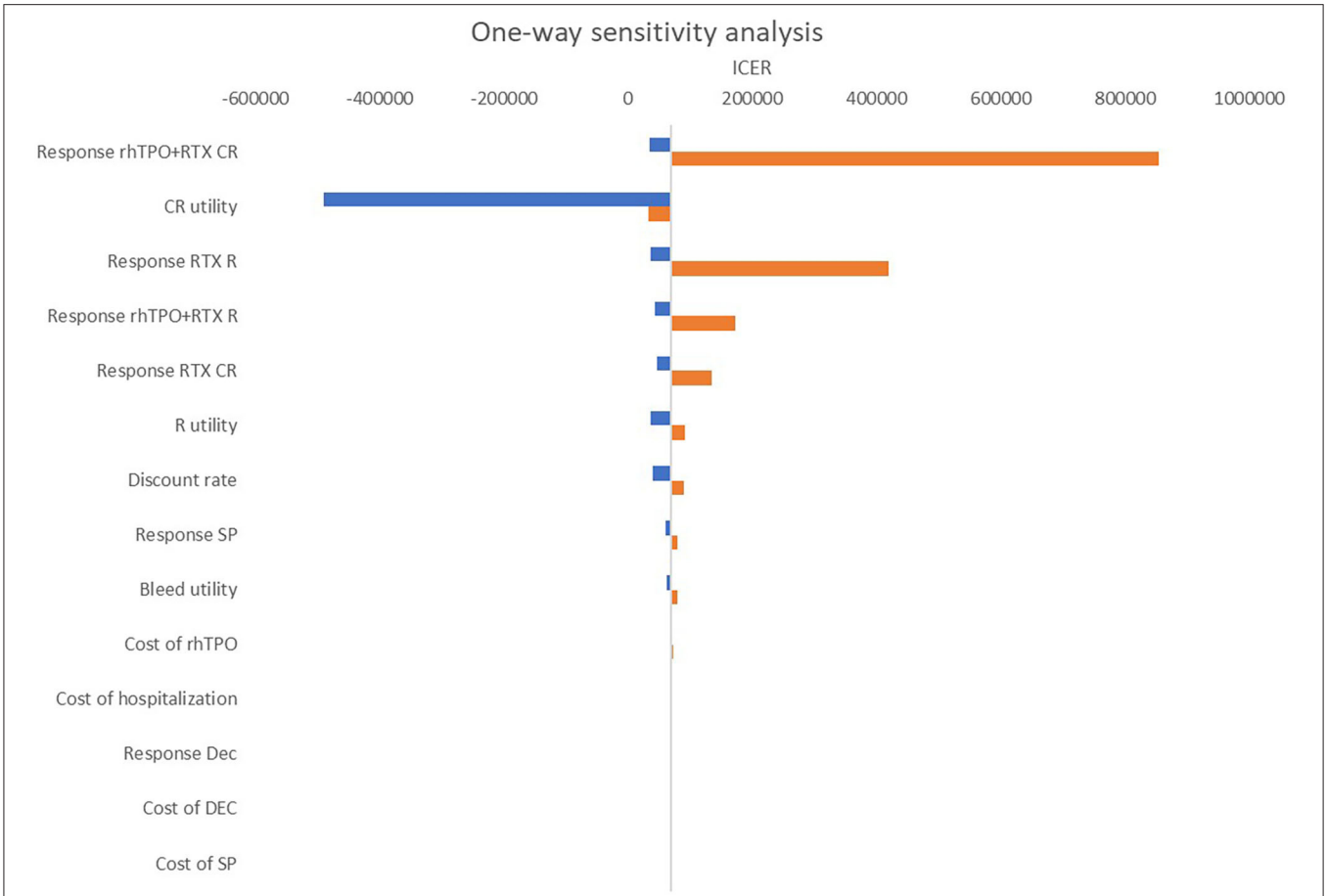


FIGURE 4 | One-way sensitivity analysis: rhTPO+RTX vs. RTX. RTX, rituximab; rhTPO+RTX, recombinant human thrombopoietin+rituximab; CR, complete response; R, response; NR, non-response; Dec, decitabine; SP, splenectomy.

One-Way Sensitivity Analysis

Figure 4 shows the results of the one-way sensitivity analysis. The main driver variables were CR of rhTPO+RTX, utility of CR and R of RTX. It should be noted that changes in these variables might cause the result to be reversed at a threshold of \$10,805/QALY ∼ \$32,415/QALY.

Probabilistic Sensitivity

The CEACs at different willingness-to-pay thresholds in the model are shown in **Figure 5**. The results from PSA showed that treatment with RTX alone was more cost-effective than treatment with rhTPO+RTX in the majority of cases (**Figure 5**). There was a 100% probability that rhTPO+RTX was not cost-effective vs. RTX alone at a threshold of \$10,805/QALY and an 84% probability at a threshold of \$32,415/QALY (**Figure 5**).

DISCUSSION

According to the base-case results, the total utilities of the rhTPO+RTX group were higher because the probability of CR and overall response in the rhTPO+RTX group was higher. The results of this economic evaluation indicated that rhTPO+RTX treatment was more costly and more effective than RTX alone for the second-line treatment of adult ITP. The estimated ICER was \$69,097/QALY in the model, which indicated that rhTPO+RTX treatment was not cost-effective for the second-line treatment of adult ITP in China. According to the results from the one-way sensitivity analysis, CR of rhTPO+RTX, utility of CR and R of RTX were the main drivers in the model. The CEAC showed that there was a 100% probability that rhTPO+RTX was not cost-effective vs. RTX alone at a threshold of \$10,805/QALY and an 84% probability at a threshold of \$32,415/QALY, which confirmed the conclusion based on the base-case results.

There are many clinical symptoms of primary immune thrombocytopenia, including asymptomatic thrombocytopenia, skin and mucosal hemorrhage, severe visceral hemorrhage, fatal intracranial hemorrhage, etc. The disease will bring a certain loss of quality of life to patients. In China, RTX is approved for (1) relapsed or refractory, low-grade or follicular, CD20-positive B-cell non-Hodgkin's lymphoma as a single agent; (2) previously untreated follicular, CD20-positive B-cell non-Hodgkin's lymphoma; and (3) previously untreated and previously treated CD20-positive chronic lymphocytic leukemia (http://zy.yaozh.com/instruct/20180711sms/142.pdf). Although

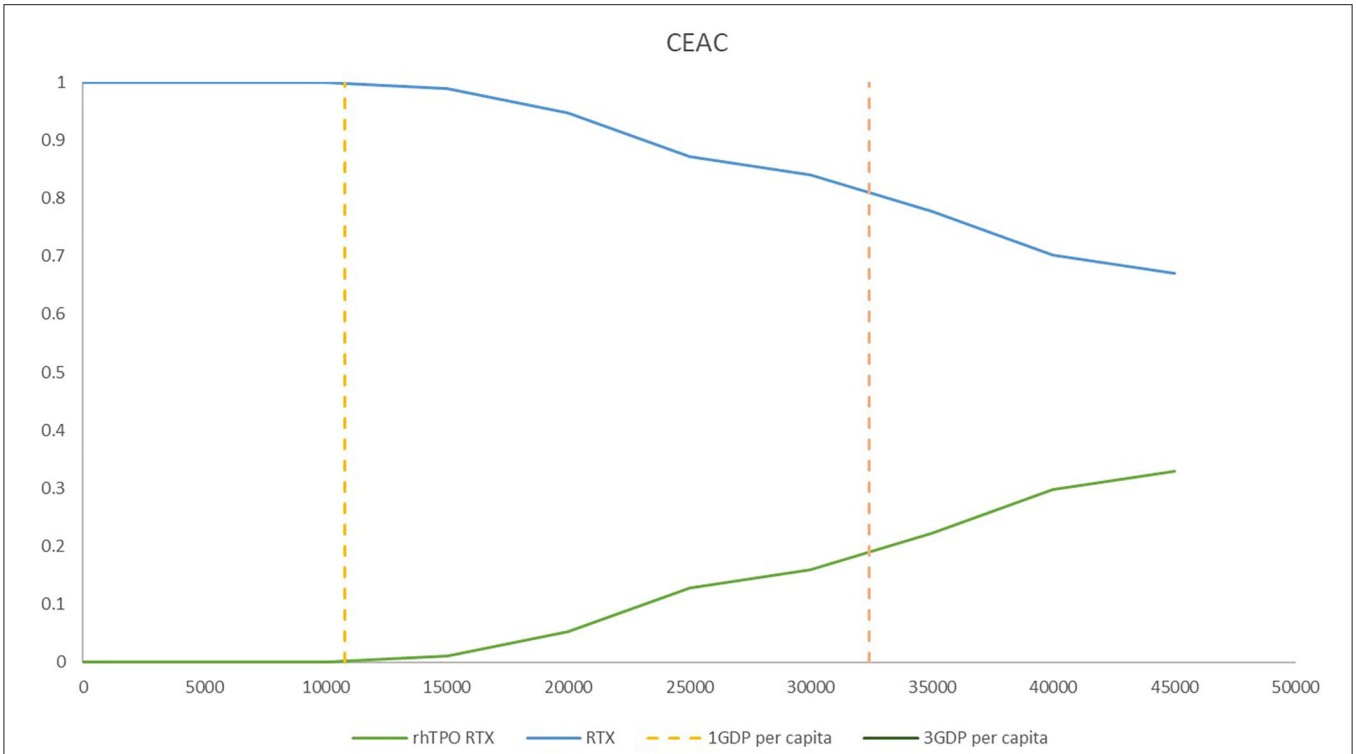


FIGURE 5 | Cost-effectiveness acceptability frontier for rhTPO+RTX and RTX. RTX, rituximab; rhTPO+RTX, recombinant human thrombopoietin+rituximab.

it has not been approved for the treatment of adult primary immune thrombocytopenia, RTX alone and rhTPO+RTX have been listed in the Chinese guidelines on the diagnosis and management of adult primary immune thrombocytopenia (version 2020) as a clear recommendation (9). Although there is consensus among clinical experts confirming the effectiveness and safety of the two therapies, the question of whether they are cost-effective in clinical application has been unanswered in China. To the best of our knowledge, this study is the first in China to compare the economic evaluation of rhTPO+RTX and rituximab alone for the treatment of adult chronic ITP.

Several limitations also need to be recognized in our study. First, due to the lack of preference-based research on Chinese adult immune thrombocytopenia patients, utility value data for Chinese adult patients with ITP were not available. At the same time, there was not enough evidence to support the utilities obtained by the mapping method, so utilities from the UK TTO study were used for analysis. Second, this article did not consider adverse events in the study. The reasons were as follows: (1) according to clinical inputs, the probabilities of adverse events with these two treatment strategies were relatively low and close, without a significant difference; (2) there was not enough evidence to support the cost of related adverse events and the disutilities of adverse events, which would have a certain impact on the final ICER. Besides, in this article, we assumed that all patients had never received splenectomy treatment, which might be slightly inconsistent with the real-world situation; however, considering that the number of patients who had received splenectomy treatment recorded in clinical inputs was <10%, this would not lead to a great bias. In addition, we could find the overall response of RTX alone in the clinical trial is 71.1%, which is higher than most previously reported OR results (18, 19), which might affect the final results to some extent. The data used in the manuscript was from clinical trials because there was no related information about the efficacy of the rhTPO+RTX in the real-word evidence and data from the same source could reduce the heterogeneity of research. For hospitalization events, difference of the hospitalization rates might exist for two types of treatments (rhTPO+RTX vs. RTX) due to the difference of efficacy and response rates for two treatments. For the higher CR and OR of rhTPO+RTX, the hospitalization rates would be lower in this group, which would lead to the lower ICER. Finally, for the complex real-world situations, generalizability is also a limitation. According to the Chinese guidelines on the diagnosis and management of adult primary immune thrombocytopenia (version 2020), there are other second-line treatment options like eltrombopag, romiplostim, azathioprine, cyclosporine A, danazol, vinca alkaloid etc, which may affect the model treatment pathways and further impact the cost evaluations.

CONCLUSION

In summary, the treatment of rhTPO+RTX, compared with rituximab monotherapy, is likely to be not cost effective in China as second-line treatment for adult patients with immunologic thrombocytopenic purpura.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

The data was based on previously published trial, not from the database or the medical records. We used the Engauge Digitizer software to get the time to relapse information from the figures in the paper and reconstructed data by ourselves, which was explained in the Section Clinical Inputs. Besides, the utilities and costs were derived from the published literatures, so ethics approval or specific consent procedures were not required for this study.

AUTHOR CONTRIBUTIONS

MR, YW, and HL developed the economic model and performed the analyses. MR, ZF, and YS interpreted the results and wrote the draft manuscript. MR, YW, ZF, HL, and AM reviewed, analyzed, and interpreted the data. MR and HL contributed to the design of the primary model and the interpretation of the results. All authors reviewed and approved the final version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.657539/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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A Study of Patient Preferences for the Treatment of Non–small Cell Lung Cancer in Western China: A Discrete-Choice Experiment

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Background: Non–small cell lung cancer (NSCLC) is the most common histologic type of lung cancer, accounting for 70–85% of all lung cancers. It has brought a heavy burden of disease and financial cost to families, society, and the nation of China. Patients have differing preferences for treatment because of their varying physical conditions and socioeconomic backgrounds, which ultimately affects the choice of treatment as well as treatment outcomes. For better and sustained health outcomes, it is vital to understand patients' preferences. We can then provide medical services to match these preferences and needs rather than basing treatment on our clinical viewpoints alone.

Objectives: The aim of this study was to elicit patient preferences for treatment using a discrete-choice experiment and to explore the value/importance that patients place on the different attributes of treatment in order to provide a basis for clinical decision making and patient health management.

Methods: The study was conducted with NSCLC patients from three typical hospitals in southwestern China. After identifying patient-relevant treatment attributes via literature review and qualitative semi structured interviews, a discrete-choice experiment (DCE) including seven patient-relevant attributes was conducted using a fractional factorial SAS design. The empiric data analyses of patients were performed using mixed logit models.

Results: NSCLC patients ($N = 202$) completed a survey via a face-to-face interview. Among the seven attributes, the following were considered important: progression-free survival, disease control rate, cost, weakness/fatigue, and nausea/vomiting; mode of administration and rash were considered less important. A clear preference for an increase in progression-free survival and disease control rate was demonstrated. Compared with 5 months of progression-free survival, respondents were willing to pay more (19,860 RMB) for 11 months of progression-free survival (coef.: 0.687). Compared with a 60% rate of disease control, respondents were willing to pay more (19,940 RMB) for a 90% rate of disease control (coef.: 0.690).

Conclusions: This study demonstrates the value of DCEs in determining patient preferences for the treatment of NSCLC. The results indicate that not only efficacy factors (such as progression-free survival and disease control rate) were considered but

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also other factors (such as side effects and treatment costs) and trade-offs between attributes were held to be important. These results are in accord with expectations and can provide evidence for more effective and efficient treatment results. Furthermore, the current results can increase benefits if the presented therapies can be designed, assessed, and chosen based on patient-oriented findings.

Keywords: discrete-choice experiment, non-small cell lung cancer, patient preference, evidenced-based, mixed logit model

BACKGROUND

In 2018, some 9.6 million people died of cancer worldwide; of these, 2.09 million died of lung cancer (1). Non–small cell lung cancer (NSCLC) is the most common histologic type of lung cancer, accounting for 70–85% of all lung cancer (2). Advanced patients face the challenge of high mortality and low survival rates; only 15% of these patients live as long as 5 years after diagnosis (3, 4). NSCLC brings a heavy disease and economic burden to families, societies, and the nation of China. In 2016, Migliorino et al. estimated that the overall health care cost in Italy over 16.4 months of observation was 25,859 euros per patient (5). In China, lung cancer takes first place in terms of incidence and mortality, and NSCLC has also brought a heavy economic burden to Chinese families (6, 7). Ding's calculations show that the average cost of hospitalization for a patient with NSCLC in a tertiary hospital in China is 26,958 RMB (8). With the development of targeted therapy over the past decade, the emergence of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) has brought important breakthroughs to the treatment of advanced NSCLC. According to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline in Oncology: Non–Small Cell Lung Cancer, version I 2015 (9, 10), the diagnosis and treatment of advanced NSCLC emphasize tumor molecular detection and targeted therapy guided by molecular detection. EGFR-TKIs have become the standard first-line treatments for advanced NSCLC with an *EGFR* mutation or *ALK* gene fusion. However, the high cost of targeted drugs deters many patients. Bie et al. calculated that the monthly cost of targeted therapy was about 12,317–19,062 RMB (11). Patients' preferences may vary owing to their different physical conditions and socioeconomic backgrounds; these ultimately affect the choice of treatment and its effects (12). Given that the assessment and choice of medical resources performed by patients and medical service providers are not identical, simply evaluating the therapeutic effect from the perspective of the medical service provider may not meet the actual needs of patients. This is why it is important to consider patient choice when determining a course of treatment. It is not only the key to improve compliance of patients, but also an important way to improve the health service utility and optimize resource allocation under the current patient-centered medical model.

As an attribute-based measure of benefit, discrete choice experiments (DCEs) have been increasingly utilized in health economics to examine the importance of an attribute in health care delivery, with consideration given to both to the patient experience and health outcomes, as well as to trade-offs between these and willingness to pay (WTP) for different attributes (13). DCEs are a stated-preference method that involves the generation and analysis of choice data and the creation of hypothetical markets that can be constructed to suit relevant research questions (14). These types of studies feature a high degree of realism and are easy for patients to handle (15). Typically, DCEs are implemented as surveys in which respondents are presented with several choice sets, each containing several alternatives between which respondents are asked to choose (16). The dependent variable in a patient preference study is choice, while the independent variables are the attributes and levels characterizing the alternatives. Econometric analysis yields estimated preference parameters, which represent the influence of specific attributes or attribute levels on choices (17). As an effective method to quantify patient preferences for different treatments, discrete choice experiments are practical within the context of many different cultures.

Researchers outside of China have adopted discrete choice experiments to demonstrate the treatment preference of patients with malignant tumors. Studies conducted within China, however, have primarily focused on exploring information demand in patients with malignant tumors. Very few studies have been conducted on how to choose anti-cancer treatment for patients before accepting therapy, and no academic research has been conducted on the treatment preferences of patients with non-small cell lung cancer (NSCLC). This study, which utilized a discrete choice experiment to explore the main factors, as well as the degree of influence of each factor, on treatment preference from the perspective of NSCLC patients, was conducted to provide policy and decision-making advice for relevant decision-making departments within the government.

METHODS

Discrete-Choice Experimental Methodology

A discrete-choice experiment (DCE) survey was developed following good research practices for stated-preference studies as outlined by a report of the ISPOR Conjoint Analysis Good Research Practices Task Force (18). This method is based on the assumption that decisions can be described by a number of key attributes and that an individual's choice is influenced by

the levels of these attributes (19). Each respondent has to make trade-offs between attributes and the levels of said attributes (15).

Identifying the Attributes of Treatment

To select attributes for this study, "non-small cell lung cancer," "main therapeutic drugs," "main efficacy indicators," "main safety indicators," "pharmacoeconomics indicators," "preference research," and "influencing factors" were used to search the official website of WHO, CNKI, CBM and other Chinese journal literature databases as well as Elsevier, EMBASE, PubMed and MEDLINE (time range from literature reports to June 2017). According to the results of literature research, a semi-structured interview, which was then utilized in conducting qualitative interviews with NSCLC patients, was drawn up among the relevant physicians and experts to clarify the exact meaning of each attribute and level.

Assigning Levels to the Attributes

Based on the results of the aforementioned literature review and semi-structured interviews, seven attributes of treatment preference for patients with NSCLC were determined. Among these, treatment cost was a continuous variable, and disease progression-free survival, control rate, rash, nausea/vomiting, weakness/fatigue, and mode of administration were categorical variables. Six attributes were assigned three levels, while the mode of administration attribute was assigned two levels. A list of these attributes and levels is presented in **Table 1**.

Study Participants

According to geographical location, level of economic development, and the particular attributes of respondents, sampling was conducted using judgment sampling. NSCLC patients from three tertiary hospitals in Chengdu, which is the most concentrated city of patients with lung cancer in Western China, were chosen as the survey subjects: West China Hospital, Sichuan University, Sichuan Provincial People's Hospital, and Sichuan Cancer Hospital.

Patients were eligible for this study if they (1) were 18 years of age or over, (2) had a confirmed diagnosis of NSCLC, (3) had received chemotherapy in the past (including both outpatient and inpatient treatment), and (4) had provided informed consent. Patients were excluded for this study if they (1) had been diagnosed with mental illness or were unable to cooperate with the survey, (2) had received only drug donation treatment (patients who received partial drug donation were not excluded), or (3) did not complete the questionnaire.

According to Orme's calculation, the minimal sample size recommended for this study was at least 84 (20). Considering the need for subgroup analysis of disease severity, patient gender, age, economic status, health insurance status, and so on, a sample size of 300 NSCLC patients was required to guarantee statistically robust estimates (16). The survey was administered on September 29, 2017. Judgment sampling was conducted according to geographic location, level of economic development, and the particular attributes of the respondents. The questionnaire's sample size and sampling distribution are shown in **Table 2**.

Ethical approval for the patient preference study was granted by the Human Research Ethics Committee, Fudan University, Shanghai, China, approval number IRB#2017-09-0638.

Choice of Hypothetical Treatment Models

The combination of attributes and attribute levels (six attributes with three levels and one attribute with two levels) resulted in $3^6 \times 2^1 = 1{,}458$ potential hypothetical treatment models and 1,062,153 choice pairs. In order to develop the minimal number of necessary choice pairs that would allow for the estimation of all main effects, a fractional factorial design was utilized (17, 21). Finally, a D-efficient, main-effects experimental design alternative set with 18 choice pairs was developed using SAS version 9.3 software. In this alternative set, each respondent would make choices in 18 different choice tasks. An example of a choice task is presented in **Table 3**.

Development of Questionnaire and Data Collection

The DCE questionnaire commenced with a detailed written description of each attribute and its levels, followed by a set of DCE questionnaires. Questions regarding sociodemographic characteristics, demographic information (e.g., age, gender, marital status, living situation, and smoking habit), and the patient's experience with NSCLC (e.g., time since diagnosis, cancer type, cancer stage, and past experiences with therapy) were asked.

The DCE scenarios generated the patient preferences by presenting respondents with a series of hypothetical treatment scenarios while systematically varying attribute levels based on an experimental design. In our study, patients were presented with hypothetical treatment models described in terms of the treatment attributes and asked to choose from two hypothetical models, treatment A and treatment B.

A pilot test that involved investigating 30 NSCLC patients from West China Hospital was conducted to modify the questionnaire (The data from these 30 patients were not included in the data analysis of the formal investigation). Oncologists from the West China Hospital were consulted to evaluate the quality of the questionnaire.

Data Analysis

Statistical Model

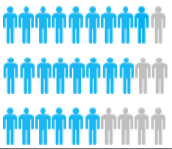
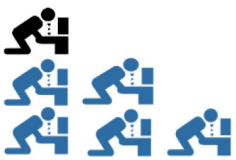
DCEs are mainly based on the random utility theoretic (RUT) framework. Under this framework, an individual respondent is assumed to choose the alternative for which he or she holds the highest utility (20). Models were estimated using Stata software version 14.0; we made use of a mixed logit model (MXL) (16, 21).

The utility $U_{n,j,t}$ patients n derive from a particular choice of treatment, $j \in \{1, 2, \cdots, J\}$ in the choice task set t consists of two parts:

$$U_{n,j,t} = A_{n,j,t} + \varepsilon_{n,j,t} \quad (1)$$

where $A_{n,j,t}$ is the observable partial utility, and $\varepsilon_{n,j,t}$ is the unobservable partial utility. Besides, $A_{n,j,t}$ can be expressed as

TABLE 1 | Attributes and levels for the choice tasks.

Attributes	Description to patients	Levels and Level description		Abridged general view
Progression-free survival	It refers to the time from the start of treatment until the tumor appears to be further deteriorated; this study fixes the overall survival and gives a choice of progression-free survival over time.	High Medium Low	11 months 8 months 5 months	
Disease control rate	The number of cases with remission and stable lesions after treatment accounted for the number of cases that could be evaluated.	High Medium Low	90% 75% 60%	
Rash	Treatments can cause a varying degrees rash for as long as you take the treatment.	None Mild Moderate	No rash <1/10 of the body more than 1/3 of the body	
Nausea and vomiting	Treatments can cause nausea and vomiting as long as you take the treatment.	Mild Moderate Severe	1 time in 24 h 2–5 times in 24 h more than 6 times in 24 h	
Weakness and fatigue	When you take the treatment you may feel even weaker or more tired.	Mild Moderate Severe	It is difficult to do physical exercises such as climbing stairs or running. Can't work and take care of yourself. You need to remain in bed	
Cost	How much will you pay for the treatment.	High Medium Low	5 ten thousand per months 2.5 ten thousand per months 1 ten thousand per months	
Mode of administration	In general, treatments can be administered by infusion or taken as pills.	Infusion Oral		

the linear combination of the m observable treatments $\mathbf{T} = [T_1, T_2, \cdots, T_m]^T$ with weight vector β, i.e.,

$$A_{n,j,t} = f\left(\mathbf{T}_{n,j,t}\right) = \beta_0 + \beta^T \mathbf{T}_{n,j,t} = \beta_0 + \beta_1 T_{1,n,j,t} + \beta_2 T_{2,n,j,t} + \cdots + \beta_m A_{m,n,j,t}$$

Each attribute—such as progression-free survival and disease control rate has its corresponding weight $\beta_0, \beta_1, \cdots, \beta_m$. $\varepsilon_{n,j,t} \sim \mathcal{N}\left(0, \sigma^2\right)$ is a random effect of observable factors on utility, which can be assumed as a function of treatment alternatives and individual preference differences.

The probability $P_{n,j,t}$ of patient n choosing treatment i in the choice task set t to obtain the maximum utility $U_{n,j,t}$ can be shown as Equation (2):

$$\begin{aligned} P_{n,j,t} &= \mathbb{P}\left[U_{n,i,t} > U_{n,j,t}\right] \\ &= \mathbb{P}\left[A_{n,i,t} + \varepsilon_{n,i,t} > A_{n,j,t} + \varepsilon_{n,j,t}\right] \\ &= \mathbb{P}\left[A_{n,i,t} - A_{n,j,t} > \varepsilon_{n,i,t} - \varepsilon_{n,j,t}\right], \quad \forall j \neq i \end{aligned} \tag{2}$$

If the random term $\varepsilon_{n,i,t}$ obeys the "independence between unrelated options," a multinomial logit model can be applied.

TABLE 2 | Patients' preferences study on treatment of non-small cell lung cancer–collection of the questionnaires.

Institution	Patient questionnaire	Effective questionnaire	Effective rate
West China Hospital,Sichuan University	100	77	77.0%
Sichuan Provincial People's Hospital	150	104	69.3%
Sichuan Cancer Hospital	50	21	42.0%
Total	300	202	67.3%

TABLE 3 | Example choice set of the discrete-choice experiment.

1	A treatment		B treatment	
Progression-free survival	8 months		5 months	
Disease control rate	60%		75%	
Rash	<1/10 of the body		No rash	
Nausea and vomiting	1 time in 24 h		2–5 times in 24 h	
Weakness and fatigue	Can't work and take care of yourself.		It is difficult to do physical exercises such as climbing stairs or running.	
Cost	5 ten thousand per months		2.5 ten thousand per months	
Mode of administration	Infusion		Oral	
Which choice do you prefer?				

Otherwise, a nested logit model or a mixed logit model can be used to estimate the parameters in the above equation.

Statistical Analysis

A mixed logit model was used to analyze DCE data. Except that the cost (copayment) is specified as a continuous variable in all models, other attribute variables are encoded as virtual variables. All the coefficients of the model are assumed to be of normal distribution.

The model regression coefficient ($\beta_0 - \beta_m$) reflects the nature of the treatment plan and the direction and size of the choice of treatment options. Positive regression coefficients indicate that this attribute has a positive effect on the preference (e.g., the longer the progression-free survival, the more likely the patient to choose the treatment). On the contrary, there is a negative effect (for example, the greater the side effects, the more likely the patient not to choose the treatment). The absolute value of the regression coefficient reflects the influence of the attribute on the choice intention of treatment. When the monetary attributes of the treatment cost (copayment) were included in the study, the monetary value of the nonmonetary attributes of the treatment could be estimated as a negative ratio of the regression coefficient of the nonmonetary attributes to the regression coefficient of the monetary attributes of the treatment cost (copayment). Thus, DCEs can be used to analyze the patient's willingness to pay to change the level of an attribute—that is, the monetary value of the level of an attribute. A positive sign indicates that the patient is willing to pay more for the attribute, whereas a negative sign indicates compensation for the patient's ability to accept the attribute. Assuming that T_1 represents the cost of treatment, the monetary value of the treatment attribute T_m can be expressed as Equation 3:

$$\mathrm{WTP}\,(T_m) = \frac{\frac{\partial U}{\partial T_m}}{\frac{\partial U}{\partial T_1}} = \frac{\beta_m}{\beta_1} \tag{3}$$

Cost was the only variable that could logically be coded as a continuous variable. Levels of efficacy, side effects, and mode of administration are descriptive and thus categorical. One level of each attribute was chosen as a reference level (omitted level). We utilized dummy-variable coding to allow for a parameter to be estimated for remaining levels. In the dummy-variable coding, each nonomitted attribute level is assigned a value of "1" when the level is present in the corresponding profile and "0" when another nonomitted level is present in the corresponding profile (22). However, unlike effects coding, all nonomitted levels are coded as "0" when the omitted level is present. To account for clustering and preference heterogeneity, a mixed logit model was estimated using Stata 14.0.

The parameters of the choice model for each attribute level can be expressed as regression coefficients. Positive parameter estimates indicate a positive utility and are associated with a regression coefficient greater than zero, as a positive utility would be associated with a preferred choice. Otherwise, there is a reverse

TABLE 4 | Demographics and baseline characteristics of the sample.

Sample characteristic	Subjects *N* = 202	Percentage (%)
Gender - no.		
Male	123	60.9%
Female	79	39.1%
Age – years		
55 years and younger	83	41.1%
55–65 years	60	29.7%
65 years and older	59	29.2%
Mean	58.6	
Economic level - RMB		
50,000 RMB and less	100	49.5%
More than 50,000 RMB	76	37.6%
Unknown	26	12.9%
Marital Status - no.		
Married	193	95.5%
Not married	1	0.5%
Divorced	3	1.5%
Windowed	5	2.5%
Education level - no.		
Primary school and below.	40	19.8%
Junior school certificate	66	32.7%
High school certificate	31	15.3%
Vocational school	13	6.4%
Junior college	24	11.9%
Bachelor degree	27	13.4%
Master degree or higher	1	0.5%
Employment status – no.		
Employed full-time	16	7.9%
Self-employed	18	8.9%
Unemployed	46	22.8%
Retired	84	41.6%
Unable to work due to cancer	38	18.8%
Smoking habit - no.		
No	86	42.6%
Yes	116	57.4%
Living situation – no.		
Live alone	5	2.5%
Live with children	24	11.9%
Live with spouse	130	64.4%
Live with children and spouse	41	20.3%
Others	2	1.0%
Time since diagnosis – no.		
<6 months	92	45.5%
6 months−1 year	74	36.6%
1–2 years	22	10.9%
2–5 years	10	5.0%
More than 5 years	4	2.0%
Cancer type – no.		
Adenocarcinoma	136	67.3%
Squamous	61	30.2%
Adenocarcinoma and squamous	2	1.0%
Large cell carcinoma	0	0.0%
Others	3	1.5%
Cancer stage – no.		
Stage Ia, Ib (non-advanced)	14	6.9%
Stage IIa, IIb (non-advanced)	38	18.8%
Stage IIIa (non-advanced)	39	19.3%
Stage IIIb (advanced)	31	15.3%
Stage IV (advanced)	80	39.6%

effect. The magnitude of the absolute value of the regression coefficient reflects the extent to which the attribute influences treatment choice intention.

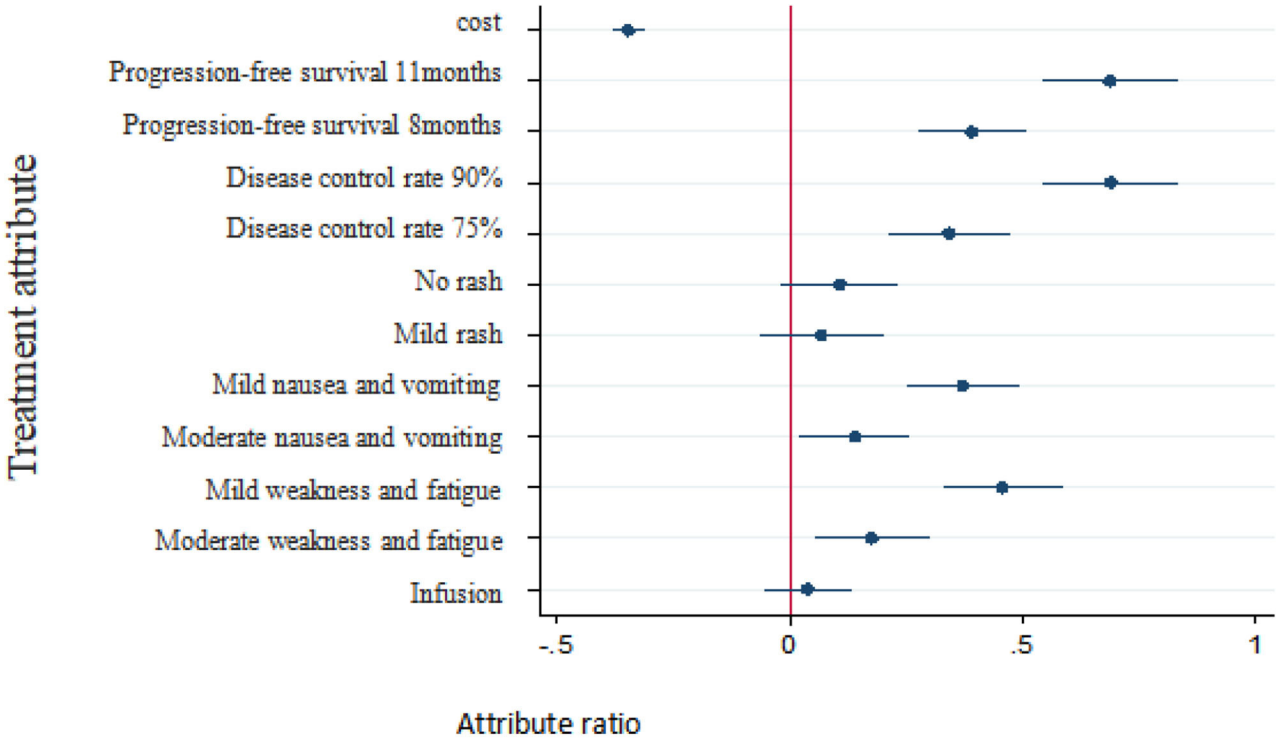
An alternative approach to evaluating importance is to measure the willingness of respondents to make trade-offs. This methodology is consistent with welfare economics (14, 23, 24). As we included cost as an attribute, we were able to estimate willingness to pay. Within the context of treatment profiles, inclusion of a price proxy (such as cost) allows the researcher to estimate the monetary value of attributes of a treatment. In other words, the researcher is able to determine how much a respondent would be willing to give up in order to obtain an improvement in other aspects of the treatment. This can be estimated as the ratio of the value of the coefficient of interest to the negative of the cost attribute (25).

RESULTS

Of the 300 questionnaires sent out to the patients, 202 usable questionnaires were returned, giving a response rate of 67.3%. **Table 4** reports the social demographic characteristics of the respondents. Of the 202 respondents, 79 were female and 123 were male. The average age of the respondents was 58.6 years with a range of 35–79 years. The majority of respondents was male (60.9%), married (95.5%), unemployed (83.2%), smokers (57.4%), and lived with a spouse (64.4%). The largest number of respondents self-reported having been diagnosed with NSCLC <6 months earlier (45.5%), whereas 36.6% were diagnosed between 6 and 12 months and 17.9% more than a year earlier. The majority of respondents reported an adenocarcinoma NSCLC histology (67.3%) and had late-stage disease, with 34.6% reporting stage III and 39.6% reporting stage IV.

As shown in **Table 5**, when patients were choosing an NSCLC treatment, the following factors affected their decisions: progression-free survival, disease control rate, nausea/vomiting, weakness/fatigue, and cost. The more important factors were progression-free survival and disease control rate, followed by weakness/fatigue, nausea/vomiting, and cost. Patients were more inclined to prefer a longer lasting progression-free survival, higher disease control rate, fewer instances of nausea/vomiting or weakness/fatigue, and less cost for treatment, whereas they showed no preference for mode of administration or rashes.

TABLE 5 | Preference of treatment attributes and levels for patients with non-small cell lung cancer.



The monetary value of each nonmonetary attribute of treatment can be estimated as the negative of the ratio of the nonmonetary attributes regression coefficient to the monetary attributes cost regression coefficient. Therefore, willingness to pay for changes in the attribute level of a certain treatment can be analyzed by discrete-choice experiments. The plus sign indicates a patient's willingness to pay for obtaining the attribute level and the minus sign indicates his or her willingness to compensate for accepting the attribute level. The regression results of patients' preferences for treatment as well as their estimated willingness to pay and 95% confidence intervals are shown in **Table 6**.

The results showed that, compared with the reference level, respondents were willing to pay 19,860 RMB per month for 11 months of progression-free survival and were willing to pay 19,990 RMB per month for a 90% disease control rate. Additionally, in exchange for milder weakness and fatigue, respondents were willing to pay 13,200 RMB per month, and in exchange for milder nausea/vomiting, 10,755 RMB per month.

The changes in simulation results of patient demand probability after improving treatment are shown in **Table 7**. It can be seen from the results that the improvement of the treatment plan had an important influence on the choice preference of stakeholders.

Probability changes with patient needs compared with the reference level (i.e., baseline): (1) With treatment cost increased to 50,000 RMB per month, the probability of choosing the treatment was reduced by 59.91%. With treatment cost increased to 25,000 RMB per month, the probability of choosing the treatment was reduced by 25.37%. (2) With progression-free survival increased to 11 months, the probability of choosing this treatment program increased by 33.06%. With the progression-free survival increased to 8 months, the probability of choosing the treatment increased by 19.29%. (3) With disease control rates increased to 90%, the probability of choosing the treatment increased by 33.17%. With disease control rates increased to 75%, the probability of choosing the treatment increased by 16.88%. (4) With mild nausea/vomiting, the probability of choosing the treatment increased by 18.38%. With moderate nausea/vomiting, the probability of choosing the treatment increased by 6.95%. (5) With mild weakness and fatigue, the probability of choosing the treatment increased by 22.44%. With moderate weakness and fatigue, the probability of choosing the treatment increased by 8.75%. No statistically significant change in the probability of rash or mode of administration was observed.

DISCUSSION

At present, discrete-choice experiments have been adopted to demonstrate the treatment preferences of patients with malignant tumors as well as other conditions such as diabetes and low back pain. They have also been used in Community Pharmacy Asthma Services (24). However, few studies have been conducted on how patients in China would choose an anticancer treatment prior to beginning therapy. Our study was based on a sample of patients residing in western China. Analysis of treatment preferences of patients with NSCLC showed that patients prefer treatment with longer progression-free survival, higher disease control rates, fewer side effects (e.g.,

TABLE 6 | Regression results and WTP.

Attributes of treatment	β	Coefficient (Standard error)	WTP (ten thousand) (95% CI)
Cost	β1	−0.346*** (0.0173)	–
Progression-free survival 11 months (Reference level: 5 months)	β2	0.687*** (0.0748)	1.986 (1.560; 2.412)
Progression-free survival 8 months (Reference level: 5 months)	β3	0.391*** (0.0590)	1.129 (0.789; 1.470)
Disease control rate 90% (Reference level: 60%)	β4	0.690*** (0.0744)	1.994 (1.583; 2.404)
Disease control rate 75% (Reference level: 60%)	β5	0.341*** (0.0668)	0.985 (0.609; 1.362)
No rash (Reference level: Moderate rash)	β6	0.107 (0.0644)	0.310 (−0.059; 0.680)
Mild rash (Reference level: Moderate rash)	β7	0.068 (0.0679)	0.198 (−0.192; 0.588)
Mild nausea and vomiting (Reference level: Severe nausea and vomiting)	β8	0.372*** (0.0625)	1.075 (0.693; 1.457)
Moderate nausea and vomiting (Reference level: Severe nausea and vomiting)	β9	0.139* (0.0604)	0.402 (0.051; 0.754)
Mild Weakness and fatigue (Reference level: Severe Weakness and fatigue)	β10	0.457*** (0.0656)	1.320 (0.918; 1.722)
Moderate Weakness and fatigue (Reference level: Severe Weakness and fatigue)	β11	0.175** (0.0627)	0.507 (0.143; 0.872)
Infusion (Reference level: Oral)	β12	0.0381 (0.0476)	0.110 (−0.159; 0.380)
Constant term	β13	0.0903 (0.0503)	–
Sample size		202	
Observation value		7,272	
log likelihood function		−2,050.0408	

WTP presented in ten thousand RMB per month; 95% confidence intervals in parentheses.
**Significant at 5% level, **significant at 10% level, ***significant at 1% level.*
Chi-square Test: $\chi^2 = 52.78$, $P = 0.0000$.

TABLE 7 | Simulated preferences for treatment under various potential treatment scenarios.

Attributes and reference level	The change in the probability	95% Confidence intervals
Cost: 5 ten thousand (ref: 1 ten thousand)	−59.91%***	(−64.26%; −55.57%)
Cost: 2.5 ten thousand (ref: 1 ten thousand)	−25.37%***	(−27.75%; −23.00%)
Progression-free survival: 11 months (ref: 5 months)	33.06%***	(26.53%; 39.60%)
Progression-free survival: 8 months (ref: 5 months)	19.29%***	(13.72%; 24.86%)
Disease control rate: 90% (ref: 60%)	33.17%***	(26.69%; 39.66%)
Disease control rate: 75% (ref: 60%)	16.88%***	(10.52%; 23.24%)
Rash: none (ref: moderate)	5.36%	(−0.93%; 11.65%)
Rash: mild (ref: moderate)	3.42%	(−3.22%; 10.06%)
Nausea and vomiting: mild (ref: severe)	18.38%***	(12.47%; 24.30%)
Nausea and vomiting: moderate (ref: severe)	6.95%*	(1.06%; 12.84%)
Weakness and fatigue: mild (ref: severe)	22.44%***	(16.34%; 28.55%)
Weakness and fatigue: moderate (ref: severe)	8.75%**	(2.66%; 14.85%)
Mode of administration: Infusion (ref: Oral)	1.91%	(−2.75%; 6.57%)

**Significant at 5% level, **significant at 10% level, ***significant at 1% level.*

nausea/vomiting and weakness/fatigue), and lower treatment costs, while rash and mode of administration were basically irrelevant to them. These results are in line with the expectations of treatment based on commonality and total experience (26).

In 2012, Bridges explored the trade-off between the attributes of treatment options for patients with advanced NSCLC in the United Kingdom (27). Mühlbacher et al. studied the treatment preferences of German NSCLC patients and found that progression-free survival and cancer-related symptoms had important effects on treatment decisions (15). Our study observed similar results that progression-free survival was most important for patients and mode of administration was less important, which is not consistent with expectations. The results show that patients had a tendency to choose infusion, which may have been an artifact related to the population of patients being investigated. Specifically, Chinese patients are accustomed to receiving infusion therapy. Thus, the cultural differences and medication habits over the past 20 years may bring about the difference of preference. The results of willingness to pay shows that respondents were willing to pay more for higher disease control rates and longer progression-free survival. Compare to the reference level 5 months, patients were willing to pay 19,860 RMB a month for 11 months of progression-free survival. In the evaluation of pharmacoeconomics, referring to China's per capita GDP of three times in 2018, the acceptable cost of a QALY is about 193,800 yuan, which is 16,150 yuan converted

to 1 month of healthy life. The reason of the WTP results of patients' perspective evaluation were higher may be the DCE was based on the assumption scenarios and the payment level was determined subjectively by patients, and Chengdu is a big city with relatively higher income compared to the national average, may also leading to higher acceptable cost of a QALY. Besides, the framework of the DCE questionnaire, especially costs, which depends on the policy of reimbursement of each countries, and options, will affect the results of WTP (25, 28, 29).

Besides these attributes, there are other factors such as gender, age, economic level, education level, working status, smoking history and tumor stage may have an impact on the treatment options of patients with NSCLC, especially for WTP. For example, our study showed that compared with the reference level, in order to obtain 90% disease control rate, the patients with higher economic level are willing to pay about 26,200 RMB more per month than the patients with lower economic level. The same goes for the factor of education level.

CONCLUSION

Our study found that important factors affecting the treatment choice for patients with NSCLC included primarily progression-free survival and disease control rate. Secondary factors were cost, nausea/vomiting, and weakness/fatigue, whereas rash and mode of administration were relatively unimportant. A focus on progression-free survival and disease control rate will greatly increase the choice probability of patients with NSCLC, and improvements in cost will significantly reduce the choice probability of patients with NSCLC.

Based on a theoretical analysis of DCEs, this study quantitatively analyzed the treatment preferences of patients with NSCLC via a discrete-choice model. This model avoids the dilemma of the choice of treatment in actual clinical practice and solves an issue with traditional patient preference analysis methods, which are unable to quantitatively analyze the treatment of NSCLC patients with the attributes of each treatment. Our paper reveals how Chinese lung cancer patients evaluate different aspects of drug therapy and their outcomes. Therefore, these data can be used to combine patient evidence with clinical evidence, thus filling a gap in existing knowledge. Furthermore, incorporating patient perspectives into treatment and reimbursement decisions can optimize the allocation of scarce resources.

LIMITATIONS

There are some limitations to our study. First, the seven most important attributes may not reflect the effects of other attributes on preferences. Second, although treatment cost was included in the treatment attributes to quantify the monetary value of nonmonetary attributes, there is still controversy about the appropriateness of willingness to pay estimates in using mixed logit models based on discrete selection experimental data. It will be necessary to discuss and verify the inclusion of monetary attributes in the future. Third, there is no standard sample size for conducting DCEs at present; therefore, extending the research results to the general population of patients with NSCLC may not be appropriate.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Key lab of Health Technology Assessment, Ministry of Health (Fudan University). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MH and YC conceived and designed the research. FL, HH, JW, and SH collected data and conducted the research. FL and HH wrote the initial paper and had primary responsibility for final content. MH revised the paper. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The Impact of COVID-19 on Primary Care General Practice Consultations in a Teaching Hospital in Shanghai, China

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Background: The COVID-19 (2019 novel coronavirus disease) pandemic is deeply concerning because of its massive mortality and morbidity, creating adverse perceptions among patients likely to impact on their overall medical care. Thus, we evaluated the impact of the COVID-19 pandemic on the pattern of primary care consultations within a Shanghai health district.

Methods: A retrospective observational cohort study was performed, with data analyzed concerning the pattern of patient visits to general practitioners within the Tongren Hospital network (the sole provider of general practice to the population of 700,000). Data from all general practice consultations for adults were collected for the first 6 months of 2020, which included a 60-day lockdown period (January 24–March 24, 2020) and compared to corresponding data from the first 6 months of 2019. We evaluated changes to the numbers and patterns of primary care consultations, including subgroup analysis based on age, sex, and primary diagnosis.

Results: A substantial reduction in patient visits, associated with increased median age, was observed during the first wave of the pandemic in the first 6 months of 2020, compared to the same interval during 2019. Additionally, reduced reappointments and waiting times, but increased costs per visit were observed. When analyzed by primary disease diagnosis, patient visits were reduced for all the major systems. The most striking visit reductions were in cardiovascular, respiratory, endocrine, and gastrointestinal diseases. However, psychological disorders were increased following lockdown, but there was also a dramatic fall in consultations for depression. Reduced monthly patient numbers correlated with both rate of reappointment and average waiting time during the first 6 months of both 2019 and 2020, but an inverse correlation was observed between

cost per visit and monthly patient numbers. Specifically during the lockdown period, there was ∼50% reduced patient visits.

Conclusions: The lockdown has had a serious impact on patients' physical and psychological health. Our analysis provides objective health-related data that may inform the current controversy concerning the balance between the detrimental effects of the use of lockdown vs. the use of a more targeted approach to eliminate viral transmission. These data may improve decision-making in medical practice, policy, and education.

Keywords: COVID-19, GP, primary care, lockdown, demographic pattern, psychological disorders

BACKGROUND

The 2019 novel coronavirus disease (COVID-19), caused by infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, was originally discovered in late December 2019 (1). Because of a lack of sufficient knowledge of the SARS-CoV-2 virus transmission dynamics during the initial stages, the outbreak of COVID-19 was transmitted at extraordinary speed, i.e., reaching every province/autonomous region in China within months (2). Currently (as at January 21, 2021), data on the extent of the pandemic are as follows: the pandemic has involved 215 countries and territories, with a reported total of 95,321,880 confirmed cases; including a total of 2,058,227 deaths (3).

Shanghai, located in the eastern coastal region of China, is one of the largest modern cities in China with a population of ∼25 million (including regular and transient residents) (4). Shanghai contributes to ∼4% of the GDP of China (5). The first officially confirmed COVID-19 case was reported in Shanghai on January 20, 2020 (6). In an attempt to stop viral transmission, the highest level of public health emergency response was initiated by the Shanghai Government, implementing a strict lockdown that commenced on January 24, 2020, including the mandatory wearing of face masks in public, no public gatherings, maintaining social distancing, and school and factory closures (7, 8). Only absolutely necessary grocery shops were allowed to open (9). Because of the effectiveness of the initial strict lockdown measures, there have subsequently been almost no new indigenous COVID-19 cases reported in Shanghai, with only a few cases of COVID-19 imported from other cities/regions (10). The total number of COVID-19 cases confirmed in Shanghai was 394 or 712 on March 21 or June 30, 2020, respectively (11, 12). Thus, the control measures that have been implemented have been extremely successful, particularly considering the size of the whole population of Shanghai, of ∼25 million. As a result of this success, the public health emergency response was downgraded to class 2 and then class 3 on March 24 and May 9, 2020 (10, 13, 14), respectively, and almost all schools in Shanghai have been allowed to reopen, following the initial use of online teaching only during March and April 2020 (15).

Transmission of the highly infectious SARS-CoV-2 virus is mainly due to its S spiking protein, which enables binding to ACE2 on host cells (16). This mechanism of transmission is consistent with the most common clinical presentations of COVID-19 being in the respiratory, cardiovascular, and/or renal systems (17), where ACE2 is highly expressed, especially among those patients who have preexisting chronic conditions within these systems.

Worldwide the key control strategy for the pandemic has been the implementation of extensive national or regional lockdowns and home confinements, in an attempt to control further disease transmission, which has been implemented in almost every country/region where an outbreak of COVID-19 has occurred (18). Thus, the pandemic of COVID-19 has become the most challenging and frightening event of this millennium to almost all people throughout the world, resulting in unprecedented global anxiety and distress within communities worldwide, which represents a natural psychological response to what the population believes are randomly changing conditions over which individuals have almost no control (19). There are two major contributing factors to the abnormal psychosomatic outcomes within the general population, which are expected to continue to increase significantly, these being the continuing evolution of the COVID-19 pandemic itself, as well as the extremely stressful information concerning COVID-19, which continues to bombard the population through the media (20). Thus, there is a special term for this psychological disorder, i.e., coronaphobia (21).

However, scientific and public health experts have questioned the harsh lockdown approach to the control of the pandemic, most recently in the Great Barrington Declaration, authored by Kulldorff, Gupta, and Bhattacharya, and released on October 4, 2020. The declaration is critical of the damaging physical and mental health impacts of the prevailing COVID-19 policies that incorporate a strict lockdown, but rather recommends the use of focused protection for at-risk groups only (22). Qualified support has been provided by the World Health Organization (WHO), who have called for world leaders to stop locking down their countries and economies. Dr. Nabarro, the Senior UN WHO System Coordinator for Avian and Pandemic Influenza, has indicated that the lockdown has not achieved the intended levels of lifesaving, but has dramatically and potentially catastrophically increased extreme poverty (23). An additional source of considerable concern and consequent anxiety has been scientific uncertainty concerning the path to effective definitive pandemic control; for example, a limited number of reports of reinfection with SARS-CoV-2 has been placing into doubt the ability of vaccination and consequent herd immunity to quickly

and effectively control the pandemic and provide a further challenge to the current rationale for continued lockdowns (24).

Within Shanghai, the traditional and most effective way for both primary care and specialist medical consultation and treatment to occur has been via visits in person to hospital outpatient departments. However, during the pandemic, alternative approaches have been introduced and encouraged for the conduct of safer medical practice, for example, telephone and/or online consultations (25). A combination of psychological and physical issues associated with the pandemic may modify the choice of how patients may choose to consult with doctors and other health professionals. Thus, it remains to be clarified if COVID-19 has affected the demographics of patient visits to primary care general practice outpatient departments. Furthermore, the possibility that changes in the pattern of visits will modify the progression of diseases individually and across communities needs to be studied.

Despite the major achievement in controlling transmission of infection in Shanghai during the outbreak of COVID-19, with only 712 infections among a population of 25 million during the first wave, there were still substantial impacts of the pandemic on the general population, including patients' visits to hospitals. Shanghai Tongren Hospital, a general teaching hospital, is located in the Changning District, in the western region of Shanghai. The Department of General Practice within the hospital is the center for primary health care for the district and includes a network of 10 community health service centers (general practice outpatient departments), which manage the primary health care for all of the >700,000 people within the general population of this district. There are no private doctors or clinics within China, except for a few clinics run especially for overseas tourists visiting China. Thus, we are able to capture all of the general population primary care activity within the system. There are no obstacles to accessing the primary health system, as no appointment is needed prior to visiting general practitioners (GPs) in these hospital centers, although an online booking system is available. Access is at reasonable and affordable cost, subsidized by the government. Thus, the universality of the primary care system in China contrasts with that in many Western countries, where both cost and eligibility for services, often from multiple service providers, are a frequent characteristic of primary care. If the presenting medical issue was unable to be solved within the primary care environment, these patients were referred to specialists.

It is still unclear what the exact impact of the COVID-19 lockdown has been on the number of patient's visits, the pattern of visits, the pattern of different disease presentations, and the cost of patient visits, compared to the same period in the previous year. This study aimed to determine whether there were any changes in these parameters for outpatient visits to the primary health care centers during the pandemic, in comparison to data acquired during the same period in the previous year, prior to the COVID-19 outbreak in Shanghai. Because of the relatively large size of the population covered by the outpatient GP clinics network within Tongren Hospital, which is the only primary care service that covers almost 5% of the Shanghai population, the data are expected to provide some solid and convincing evidence to demonstrate the impact of COVID-19 within the general population, as well as provide supporting data for defining and updating recommendations for patient care for specific disease commodity packages, as defined by WHO. The Series of disease specific datasheets (DCPs) are a series of disease specific datasheets that list the critical commodities and the technical specifications recommended for each form of disease (26, 27).

Our data may provide some useful information for GPs to deal more effectively with COVID-19 and maintain a high level of health within the population, by adopting and adapting to different approaches compared to those used before.

METHODS

Study Design

A retrospective simple cross-sectional observational cohort study was conducted within the Department of General Practice in Tongren Hospital in Shanghai and was approved by the Medical Ethics Committee of the hospital (no. 2020-079-01), strictly following the World Medical Association's Declaration of Helsinki. The information about the patients was obtained from the Center of Electronic Health Records in Tongren Hospital. All data obtained from patients were deidentified prior to analysis and strictly followed the guidelines of Helsinki. Written consent was obtained from all of the patients when they were registered with the clinics that the deidentified data can be used for public health purposes.

Data that were collected were from the Center database and included all the patient data for patients who visited GP outpatient clinics in person from January to June 2020, as well as the same period in 2019. As the pediatric outpatient department is a separate entity, the ages of the patients included in the current Outpatients study were all ≥12 years.

The inclusion criteria were that any of the patients who visited in the outpatient Department of General Practice for any medical problem were included within the period specified in the current study. There were no exclusions, except that all patients younger than 12 years were transferred to the pediatric department and allowed to utilize the adult Department of General Practice. Notably, we included all the outpatients who were transferred to being inpatients of the Department of General Practice in the current study, although the proportion of these patients was very small (<0.1%).

The cost per patient visit was obtained from the electronic health record system, including consultation fee, any laboratory tests, medication fee, and any related cost(s). The Chinese medical system is different from the Western system in that the prescribed medications are obtained in the pharmacy of the hospital. In addition, the patients with a medical insurance card from the government pay a relatively small amount of fees incurred above.

Statistical Analysis

Quantitative variables were expressed as means with SEM, and qualitative variables were expressed as percentages. Differences were evaluated using the χ^2-test for categorical variables and

t-test for normally distributed variables. Correlations between two variables were detected using the Pearson test. For all the statistical analyses, $p < 0.05$ was considered significant. All analyses were performed using GraphPad Prism 8.0.1.

RESULTS

Overall Outpatients Visits

Table 1 summarizes the overall patient characteristics for this study. There was nearly a 30% drop in the total number of GP visits to the outpatients at Shanghai Tongren Hospital in the period from January to June in 2020, compared to the same period in 2019 (55,293 vs. 77,706) (**Figure 1A**). The average age of the patients was significantly higher over these 6 months in 2020 than that in 2019 (61.43 ± 0.1 vs. 59.89 ± 0.1 years; $p < 0.001$) (**Figure 1B**). In the first 6 months of 2020, the overall outpatient numbers were decreased by 21, 32, 50, 29, 29, or 8%, respectively, compared with the same period in 2019 (**Figure 1C**; $p < 0.01$), the biggest difference between these 2 years was observed in March. Additionally, a dip in visits was observed in February in both years, which corresponds with the Chinese New Year holiday period (January 24, 2020). The 2019 data show two peaks, one in January and one in March, which correspond to the peak of winter-associated illnesses and a rebound in demand following Chinese New Year, respectively. A rebound was not observed in March 2020.

Demographic Characteristics

To further determine if the age factor contributed to the change in outpatient visits during the COVID-19 period, these patients were divided into three groups: <40, 40–64, and ≥65 years. The number of outpatient visits decreased by 43, 29, or 23%, within the age groups of <40, 40–65, and ≥65 years, respectively, in 2020, compared to that in 2019 (**Table 1**, **Figure 2A**). However, only a significant difference between the 2020 and 2019 was observed for the age groups <40 or ≥65 years ($p < 0.001$), but not in the 40- to 65-year age group (**Table 1**, **Figure 2A**). When the outpatient visits were analyzed on a monthly basis, in the patients' group <40 years, there was no obvious difference between these 2 years within January (**Table 2**, **Figure 2B**). However, within the subsequent months, the visits by patients dropped by 58, 71, 54, 47, or 29% in February, March, April, May, and June in 2020, respectively, compared to the corresponding months in 2019 (**Table 2**, **Figure 2B**; $p < 0.05$). However, within the 40-65-year group, the outpatient visit numbers dropped by 24, 33, 49, 28, 29, or 10% from January to June in 2020, compared to the outpatient visits during the same period of 2019 (**Table 2**, **Figure 2C**; $p < 0.01$). Finally, in ≥65-year group, the outpatient visits in the first 5 months dropped by 25, 21, 43, 18, or 22%, compared with the same period of 2019, but the outpatient visits returned to a similar level by June 2020 compared to June 2019 (**Table 2**, **Figure 2D**; $p < 0.05$). Interestingly, there was a significant difference between 2020 and 2019 among all these three groups when the monthly trend of outpatient visits was analyzed (**Table 2**, **Figures 2B–D**; $p < 0.05$). Notably, for all age groups, the largest fall in monthly visits during 2020, compared to 2019, occurred in March 2020.

Next, we investigated if there was a difference between groups stratified by sex. Among all patients, 30,525 (55.2%) or 43,610 (56.1%) were female in 2020 or 2019 ($p < 0.001$), respectively (**Table 1**, **Figure 2E**). Among male patients, visits dropped 19, 27, 47, 29, 30, and 9% in January, February, March, April, May, or June in 2020, respectively, compared to the corresponding months in 2019 (**Table 2**, **Figure 2F**; $p < 0.01$). Similarly, for female patients, the visits dropped 23, 36, 52, 29, 29, 8% in the first 6 months of 2020 compared to the same period of 2019 (**Table 2**, **Figure 2G**; $p < 0.01$).

Cost per Visit for the Hospital

The median cost of per patient visits to outpatients was 1.3-fold higher in the first half of 2020 compared to the same period in 2019 (¥347.9 ± 1.5 vs. 264.7 ± 1.0) (**Table 1**, **Figure 3A**; $p < 0.001$). The patients pay only a fraction of this cost, based on their income. When analyzed on a monthly basis, the cost per visit in January 2020 was similar to that of the same period in 2019 (**Figure 3B**). However, the cost per visit increased in February and peaked in March 2020, at a cost that was 1.55-fold higher than that in January 2020. The cost per visit decreased slightly, by ∼10%, in April, May, and June 2020, compared to March 2020. Compared to the cost per visit each month in 2019, the cost per visit during February to June 2020 was increased by a similar amount over these 5 months, specifically, 1.32-, 1.40-, 1.40-, 1.40-, or 1.32-fold higher in 2020, compared to the corresponding months in 2019 (**Figure 3B**; $p < 0.01$).

By contrast, analysis of the rate of reappointment by month showed that the gap between the 2 years was largest in January and then progressively decreased between February and May, with almost no significant difference by June between these 2 years (**Figure 3C**; $p < 0.01$). Specifically, the rate of reappointment in the first 6 months of 2020 was decreased by 29, 21, 21, 9, 13, and 1% ($p < 0.01$), respectively, compared to the corresponding months in 2019.

Similarly, the average waiting time from January to June 2020 was significantly lower by 35, 69, 54, 44, 37, and 25% in each month, compared to the same periods during 2019 (**Figure 3D**; $p < 0.01$).

Categories of Diseases

The patients' attendances were grouped into nine medical systems based on their most important medical diagnosis at each visit. These data are presented in **Tables 1**, **2**.

The largest category of disease diagnosis was cardiovascular disease (CVD) (**Table 1**, **Figure 4**). The number of patients diagnosed with CVD was decreased by 29% in the first half of 2020 compared to the same period of 2019 (**Table 1**, **Figure 4**). Similar reductions in 2020, compared to 2019, were seen in other diagnostic categories of illness, specifically decreased numbers of patients with respiratory (55%), endocrine (22%), gastrointestinal (24%), neurological (7%), urological (8%), musculoskeletal (6%), or hematological (15%) diseases were observed (**Figure 4**). Interestingly, the number of patients with other diseases (except for the 8 systems described above) was increased by 9% in the first half of 2020 compared to that in 2019. Although the absolute number of the patients diagnosed with CVD decreased

TABLE 1 | Demography of patient visits in the first 6 months of 2020 during the first wave of the COVID-19 outbreak, compared to corresponding data from 2019.

Characteristics	Jan–Jun 2019	Jan–Jun 2020	*P*-value
Total number	77,706	55,293	–
Age, mean (SEM), yrs	59.89 (0.1)	61.43 (0.1)	<0.001
Age groups, *n* (%)			
<40 yrs	12,451 (16.0)	7,102 (12.8)	<0.001
40–64 yrs	32,683 (42.1)	23,117 (41.8)	0.36
≥65 yrs	32,572 (41.9)	25,074 (45.3)	<0.001
Sex, *n* (%)			
Male	34,096 (43.9)	24,768 (44.8)	<0.001
Female	43,610 (56.1)	30,525 (55.2)	<0.001
Cost, mean (SEM) (¥)	264.7 (1.0)	347.9 (1.5)	<0.001
Diseases, *n* (%)			
Cardiovascular	29,636 (38.1)	21,048 (38.1)	0.79
Respiratory	17,406 (22.4)	7,904 (14.3)	<0.001
Endocrine	9,072 (11.7)	7,034 (12.7)	<0.001
Gastrointestinal	9,261 (11.9)	7,000 (12.7)	<0.001
Neurology	3,884 (5.0)	3,629 (6.6)	<0.001
Urology	1,119 (1.4)	1,028 (1.9)	<0.001
Musculoskeletal	1,531 (2.0)	1,436 (2.6)	<0.001
Hematology	372 (0.5)	316 (0.6)	0.02
Others	5,425 (7.0)	5,898 (10.7)	<0.001
Psychology, *n* (%)			
Depression	163 (0.2)	74 (0.1)	<0.01
Anxiety	288 (0.4)	319 (0.6)	<0.001
Insomnia	1,099 (1.4)	1,403 (2.5)	<0.001
Total	1,550 (2.0)	1,796 (3.2)	<0.001

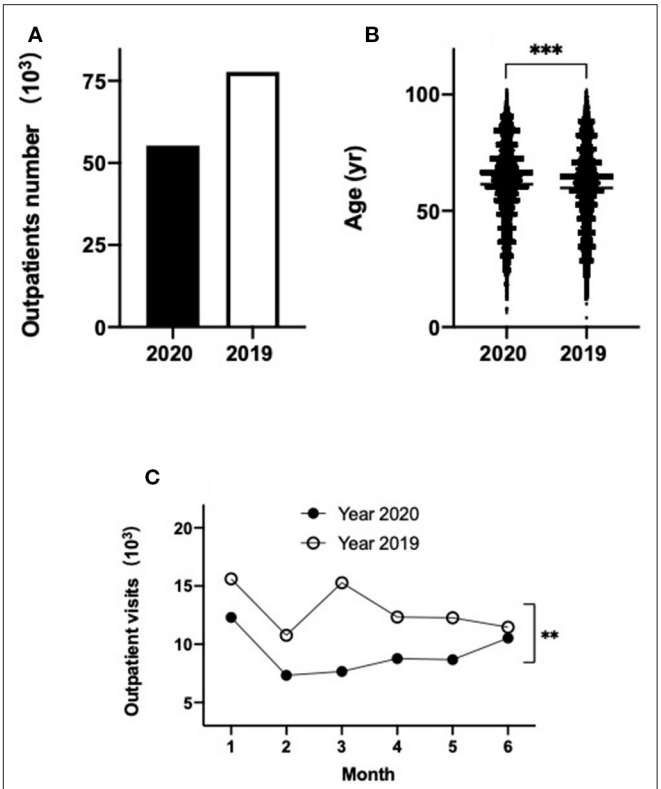


FIGURE 1 | Outpatients visits at Tongren Hospital primary care clinics during the first 6 months of 2020 (black) compared to 2019 (empty) **(A)**; age distribution of patients in 2020 versus 2019 **(B)**; outpatients visits each month over the first six months of 2020 (black) and 2019 (empty) **(C)**. $^{**}p < 0.01$, $^{***}p < 0.001$.

significantly, the proportion of these patients' number (not the absolute patients' number) was not significantly different between 2020 and 2019. However, a significant difference was observed for the proportion of all the other eight categories of illness between 2020 and 2019 (**Table 1**, **Figure 4**; $p < 0.05$).

When examined by monthly trend, the number of patient consultations with CVD was decreased by 25, 18, 47, 28, 34, or 16% each month between January to June in 2020, compared to consultations over the same monthly periods during 2019 (**Table 2**, **Figure 5A**; $p < 0.01$). However, a more drastic drop for patient consultations with respiratory diseases was observed, showing a 10, 59, 76, 73, 74, or 50% drop from January to June in 2020, compared to the corresponding months in 2019 (**Table 2**, **Figure 5B**; $p < 0.05$). The patients with endocrine disease were decreased by 28, 19, 43, 23, or 20% between January and May, but then increased 5% in June 2020, compared with the corresponding months of 2019 (**Table 2**, **Figure 5C**; $p < 0.05$). The number of gastrointestinal disease patients was reduced by 22, 46, 44, 10, 18, or 6% each month from January to June during 2020, compared to the same period in 2019 (**Figure 5D**; **Table 2**; $p < 0.05$). Notably, the largest drop in consultations occurred in March 2020 for CVD (47%), respiratory disease (76%), endocrine disease (43%), neurological disease (31%), urological disease (40%), and other diseases (unspecified) (30%), whereas the largest drop in consultations occurred in February for gastrointestinal (46%) and hematological diseases (47%), and finally, the largest drop in consultation occurred in January for musculoskeletal disease (30%) (**Table 2**, **Figures 5A–I**).

Furthermore, with the exception of CVD, respiratory disease, and gastrointestinal diseases, a rebound of patient consultations was seen during the second half of the 6-month period under study, generally by April, May, or June 2020, where the number of consultations occurring in one or more of these months in 2020 exceeded the monthly consultations observed in the corresponding months in 2019. The diagnostic categories in which a rebound of cases was observed were endocrine (June), neurology (May), urology (May), musculoskeletal (April), hematology (May), or other diseases (April) (**Table 2**, **Figures 5E–I**).

A significant difference in the monthly trend data was observed among cardiovascular, respiratory, endocrinologic, and gastrointestinal diagnostic categories between 2020 and 2019 (**Figures 5A–D**; $p < 0.05$), but there was no significant difference of monthly trend among neurology, urology, musculoskeletal, hematology, and other diseases between 2019 and 2020 (**Table 2**, **Figures 5E–I**).

Psychological Factors

Patients whose primary diagnosis was of psychological disease were a subset of the other diseases (unspecified) diagnostic

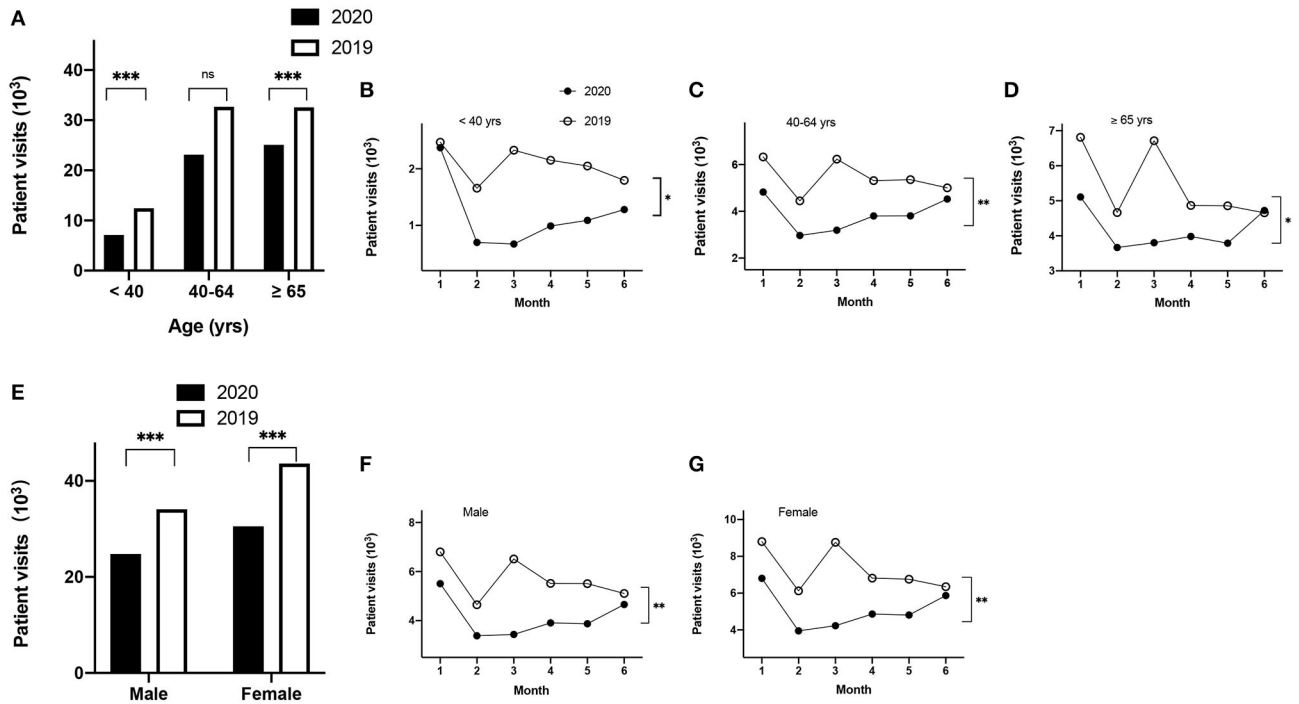


FIGURE 2 | Demographics of patient visits stratified by age and sex. Patients visits for the three aged groups over the first 6 months (<40, 40–64, ≥65 years) **(A)**; monthly distribution of patients visits for the subgroups <40 years **(B)**; 40–64 years **(C)**, and ≥65 years **(D)**; patient visits for male or female patients in 2020 compared to 2019 **(E)**; monthly distribution of patients visits for males **(F)** and females **(G)**. $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

category. It has been reported that psychological factors contribute to the choice of activities undertaken by people generally, including decisions concerning visiting doctors (28). The total numbers of patients presenting with psychological problems in 2019 and 2020 were 1,550 and 1,796, respectively, which correspond to an increase of 1.2-fold in the first half of 2020 compared to 2019 (**Table 1**, **Figure 6A**; $p < 0.001$). To further understand these data, we undertook subgroup analysis by classifying all of the patients with psychological problems into three categories: depression, anxiety, or insomnia. The number of depression patients was substantially decreased by 55% in the first half year of 2020 compared to 2019 (**Table 1**, **Figure 6A**; $p < 0.01$), whereas the number of anxiety or insomnia patients was increased by 11 or 28%, respectively, in the first half of 2020 compared with that in the same period of 2019 (**Table 1**, **Figure 6A**; $p < 0.001$).

The monthly trend data for the total number of patient visits with psychological problems were lower during January to March 2020, compared with 2019 (**Table 2**, **Figure 6B**). However, during April to June 2020, the number of visits for psychological problems substantially exceeded the consultation numbers seen during the corresponding months of 2019 (**Table 2**, **Figure 6B**). When the monthly trend data for psychological illnesses were analyzed for each of the three psychological illness categories, substantial differences were observed. In the case of the patients with depression, the number of consultations was dramatically lower in the first 3 months of 2020 (a decrease of 76, 79, or 71% for January, February, and March 2020, respectively), compared to the corresponding months of 2019, while during the second 3 months of the study period, case consultations for depression trended back toward the corresponding 2019 levels (decreases of 27, 33, and 0.1% for April, May, and June 2020, respectively) (**Table 2**, **Figure 6C**; $p < 0.01$). By comparison, consultation numbers for anxiety or insomnia patients were similar or slightly below consultation levels seen in 2019 during January to March, whereas the number of consultations for anxiety and insomnia were substantially larger during April, May, and June 2020, compared to the corresponding months during 2019 (**Table 2**, **Figures 6D,E**). However, a significant difference between the 2020 and 2019 data was observed only for the depression group ($p < 0.01$), but not in the anxiety or insomnia groups or the total psychological group (**Table 2**, **Figures 6B,D,E**; $p > 0.05$).

Correlation Between the Monthly Patients' Number vs. Reappointment, Average Waiting Time, Cost per Visit, or COVID-19 Confirmed Cases

The number of patients who attended the outpatient clinics each month was determined for each monthly interval during the first 6 months of 2019 and 2020 (corresponding to a total of 12 data

TABLE 2 | The monthly patients number from January to June in 2020 and 2019, with age, sex, disease in major systems and psychological disorders.

Characteristics	2019						2020						*P* value
	Jan	Feb	Mar	Apr	May	Jun	Jan	Feb	Mar	Apr	May	Jun	
Age groups													
<40 yrs	2,469	1,658	2,328	2,151	2,050	1,795	2,372	700	672	989	1.089	1,280	0.01
40–64 yrs	6,328	4,450	6,232	5,314	5,357	5,003	4,828	2,965	3,194	3,800	3,805	4,525	<0.01
≥65 yrs	6,812	4,663	6,716	4,866	4,857	4,657	5,109	3,668	3,803	3,981	3,789	4,724	0.03
Sex													
Male	6,804	4,646	6,513	5,517	5,509	5,107	5,508	3,384	3,438	3,906	3,874	4,658	<0.01
Female	8,805	6,125	8,763	6,814	6,755	6,348	6,801	3,949	4,231	4,864	4,809	5,871	<0.01
Diseases													
Cardiovascular	5,905	3,957	5,930	4,781	4,646	4,417	4,425	3,236	3,138	3,464	3,058	3,727	<0.01
Respiratory	3,961	2,914	3,251	2,743	2,580	1,957	3,548	1,183	774	732	680	987	0.01
Endocrine	1,855	1,262	1,774	1,372	1,387	1,422	1,344	1,025	1,004	1,058	1,116	1,497	0.02
Gastrointestinal	1,627	1,173	1,871	1,468	1,558	1,564	1,259	633	1,048	1,324	1,270	1,466	0.03
Neurology	717	473	745	646	666	637	621	411	514	626	723	734	0.52
Urology	216	124	203	179	205	192	169	95	122	159	213	270	0.61
Musculoskeletal	314	197	313	236	215	256	220	140	236	274	256	310	0.62
Hematology	65	59	63	67	65	53	54	31	40	49	71	71	0.21
Others	949	612	1.126	839	942	957	679	579	793	1.084	1.296	1.467	0.64
Psychology													
Depression	38	29	31	22	24	19	9	6	9	16	16	18	<0.01
Anxiety	59	50	62	35	47	35	46	43	56	55	68	51	0.40
Insomnia	203	148	231	156	173	188	189	158	208	260	294	294	0.09
Total	300	227	324	213	244	242	244	207	273	331	378	363	0.25

intervals). The rate of reappointment and average waiting time for each monthly interval were then determined, and these data were found to positively correlate with the number of patient visits for that month, for the combined data derived from the first half of both 2019 and 2020 ($R^2 = 0.79$, $p = 0.0001$; $R^2 = 0.63$, $p = 0.002$) (**Figures 7A,B**). By cost, the cost per visit was inversely correlated with the number of patients per monthly interval ($R^2 = 0.5991$, $p = 0.003$) (**Figure 7C**). No significant correlation was observed between the outpatient visit number per monthly interval for the first 6 months of 2020 and the confirmed COVID-19 cases number for all of Shanghai during the same period in the first half of 2020 (**Figure 7D**).

Lockdown

During the period of lockdown in Shanghai (January 24 to March 24, 2020), the overall total number of outpatient visits was decreased to 40% compared with the same period of 2019 (**Figure 8**; $p < 0.001$). **Figure 8** shows the daily number of patient visits for the period 7 days before lockdown (January 17, 2020), until 60 days after lockdown commenced during 2020. These 2020 data have been compared to the corresponding daily data from 2019, with the two data sets being aligned at the first day of Chinese New Year (February 5, 2019, and January 25, 2020). The rationale for this alignment is 2-fold: first, the Chinese New Year holiday substantially affects the pattern of consultations before, during, and after the holiday, and second, the commencement of lockdown occurred on New Year's Eve (January 24, 2020). Several features emerge from **Figure 8**. First, from day 10 until day 60 after lockdown, a 7-day periodicity can be observed during both 2019 and 2020, corresponding to the normal working week. Second, zero patient attendances are observed for the 3 days of clinic closure corresponding to the Chinese New Year closure during 2019 (February 5–7, 2019) and 2020 (January 25–27, 2020), respectively. Third, a substantial reduction in patient visits occurred on all days contained within this graph, both during the week before lockdown/Chinese New Year and during the 10 weeks after lockdown.

Finally, when analyzed on a daily basis, there was no significant correlation between the outpatients' visits each day and the number of confirmed COVID-19 cases on that day ($R^2 = 0.0122$, $p = 0.3964$) (**Figure 9**) during the lockdown period in Shanghai.

DISCUSSION

Our current study was a simple cross-sectional analysis without adjustment for any confounders or secular changes during the 18-month period of the study. In the current study, we have demonstrated that outpatient visits in primary care dropped 30% in the first half of 2020, compared with the same period of 2019. We believe this observation is most likely due to the pandemic of COVID-19 over this 6-month interval for the following reasons. First, the health authorities actively discouraged patients from engaging in face-to-face visits to hospital/outpatient departments unless it was absolutely essential but instead encouraged telephone and/or online consultations

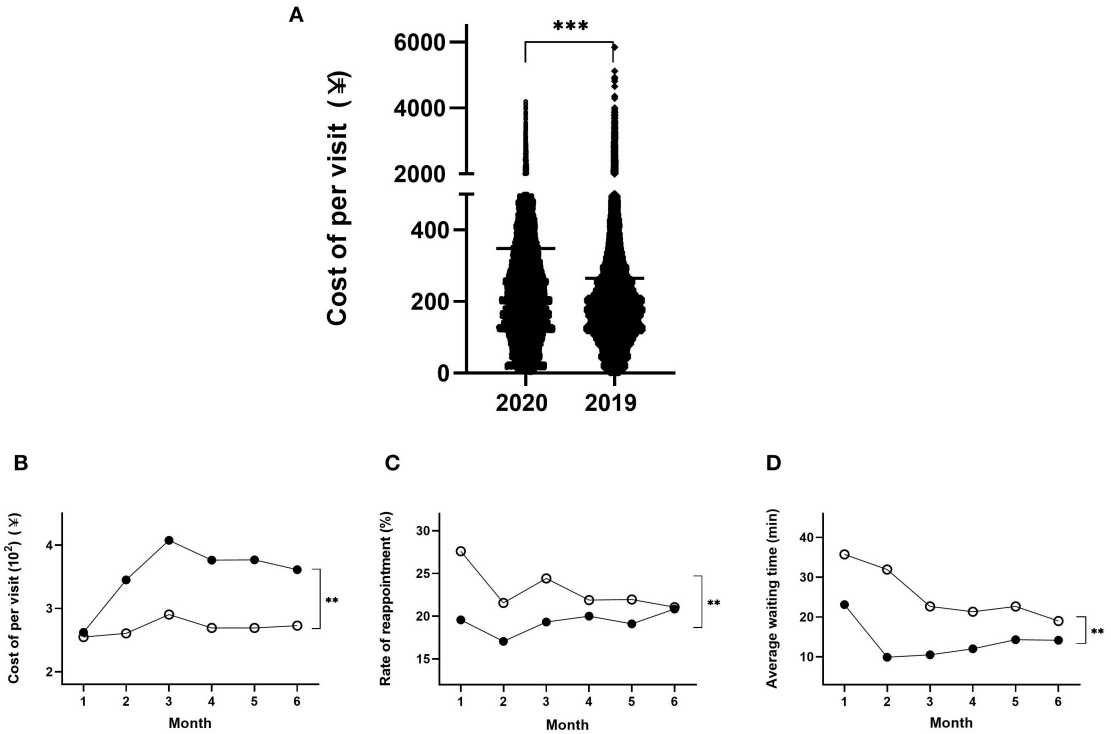


FIGURE 3 | Demographics of the cost per visit among patients over the 6 months in 2020 and 2019 **(A)**; the monthly distribution of patients cost per visit **(B)**; reappointment rates **(C)** and average waiting time **(D)** in 2020 and 2019. $^{**}p < 0.01$, $^{***}p < 0.001$.

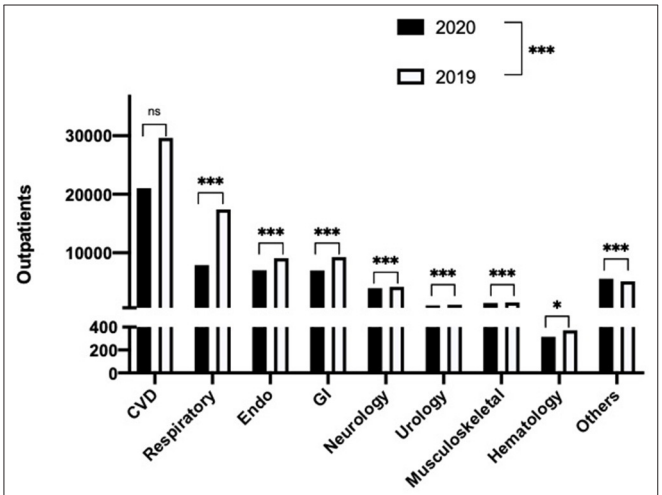


FIGURE 4 | Subgroup analysis by primary diagnosis of patient visits for the eight major diagnostic systems, plus others (unclassified) in 2020 and 2019. $^{*}p < 0.05$, $^{***}p < 0.001$.

(29, 30). Second, we hypothesize that the patients were fearful of possible transmission of COVID-19 while moving through the community and especially attending a health care facility, such as the outpatient clinic, because media reports correctly emphasized a greater chance of being contaminated in these high-disease areas (2), influencing their decision to limit attendance at outpatient clinics.

Additionally, a restriction order from the authorities was made to limited social activities (31), especially during the lockdown period in Shanghai (32), which emphasized that hospital visits should be curtailed unless medical review became absolutely necessary. A drastic drop in Outpatient visits was observed in the week before lockdown (January 17–24, 2020) and in February 2020, which was mainly due to the strong message/instruction from the health authority that advised people to minimizing exposure within their environment, especially within hospitals (33). In addition, a reduction in the outpatient visits was observed during the traditional Chinese New Year (January 24–February 2), during which there is a closure of outpatient clinics for 3 days. Notably, Chinese culture also supports an avoidance of seeing doctors within the New Year period (34). These factors are all consistent with the reduced outpatient visits observed during late January and February 2020.

When attendance at outpatients was stratified by age, the largest fall in attendances was observed among relatively younger patients (<40 years), who may have less critical medical conditions, and/or may be able to cope better for a longer period of time while staying at home without consulting a doctor, whereas the elderly patients are more likely to have more severe preexisting medical conditions and therefore may have to seek medical attention more quickly (35). Additionally,

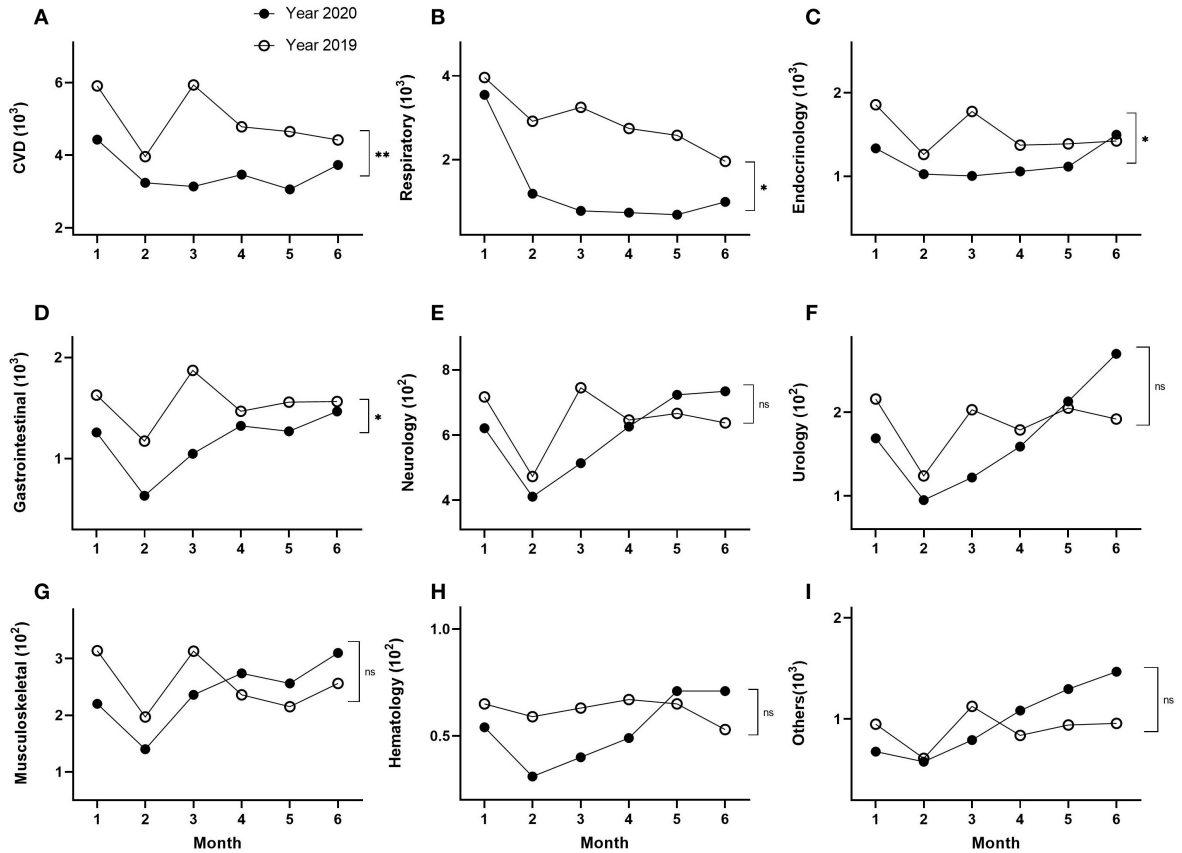


FIGURE 5 | Subgroup analysis of monthly distributions of visits stratified by primary diagnosis, cardiovascular disease **(A)**, respiratory **(B)**, endocrine **(C)**, gastrointestinal **(D)**, neurology **(E)**, urology **(F)**, muscular-skeletal **(G)**, hematology **(H)**, and others (unclassified) **(I)**, respectively. $^*p < 0.05$, $^{**}p < 0.01$.

while all patients were encouraged to use telephone or online consultations where possible by the health authorities, to minimize potential exposure to the COVID-19 outbreak (36), younger patients may be more likely to engage with technology-driven consultations, such as video consultations, compared to older patients (37).

On the other hand, among the senior age group (≥65 years), the observed reduction in outpatient visits might also be due to a combination of both the restriction orders from the authorities, as stated above, and persistent media reporting, where there was a strong message correctly stating that elderly patients are more vulnerable to SARS-CoV-2 viral attack (38), which is likely to have also contributed to limiting the inclination of elderly patients to attend hospitals/outpatient clinics, in addition to their generally reduced mobility (39).

Finally, within the middle-aged group (40–64 years), it was not surprising that there was no significant difference in the outpatient visits in this group, because these patients are more mobile, and they likely perceived that their risk of contracting/dying from this potential viral attack was minimal. This perception was supported by extensive media reporting that risk of death was primarily increased by the presence of preexisting chronic conditions, which are relatively few within this middle-aged group.

Despite restrictions beginning to ease by April 2020 (restrictions were eased on March 24, 2020), it is surprising that the outpatient visits were persistently low in the following months, that is, April and May 2020. By contrast, the outpatient visits in March, April, and May 2019 returned to similar levels observed during January 2019, with a dip in consultations only occurring in relation to Chinese New Year in February 2019. Finally, outpatient visits returned to similar levels in June 2020, comparing 2020 and 2019, which probably is due to the population gaining confidence that effective control of COVID-19 had been achieved, following the restrictions implemented against SARS-CoV-2 during the first 5 months of 2020 (40).

When outpatient visits data were stratified by sex, a reduction in both male and female patients was observed during the first half of 2020, compared to that in 2019. Of interest, the proportion of male patient visits was slightly but significantly higher in 2020 compared to that in 2019. Although there is a minor difference between male and female patients, the significance is negligible and will not be discussed further.

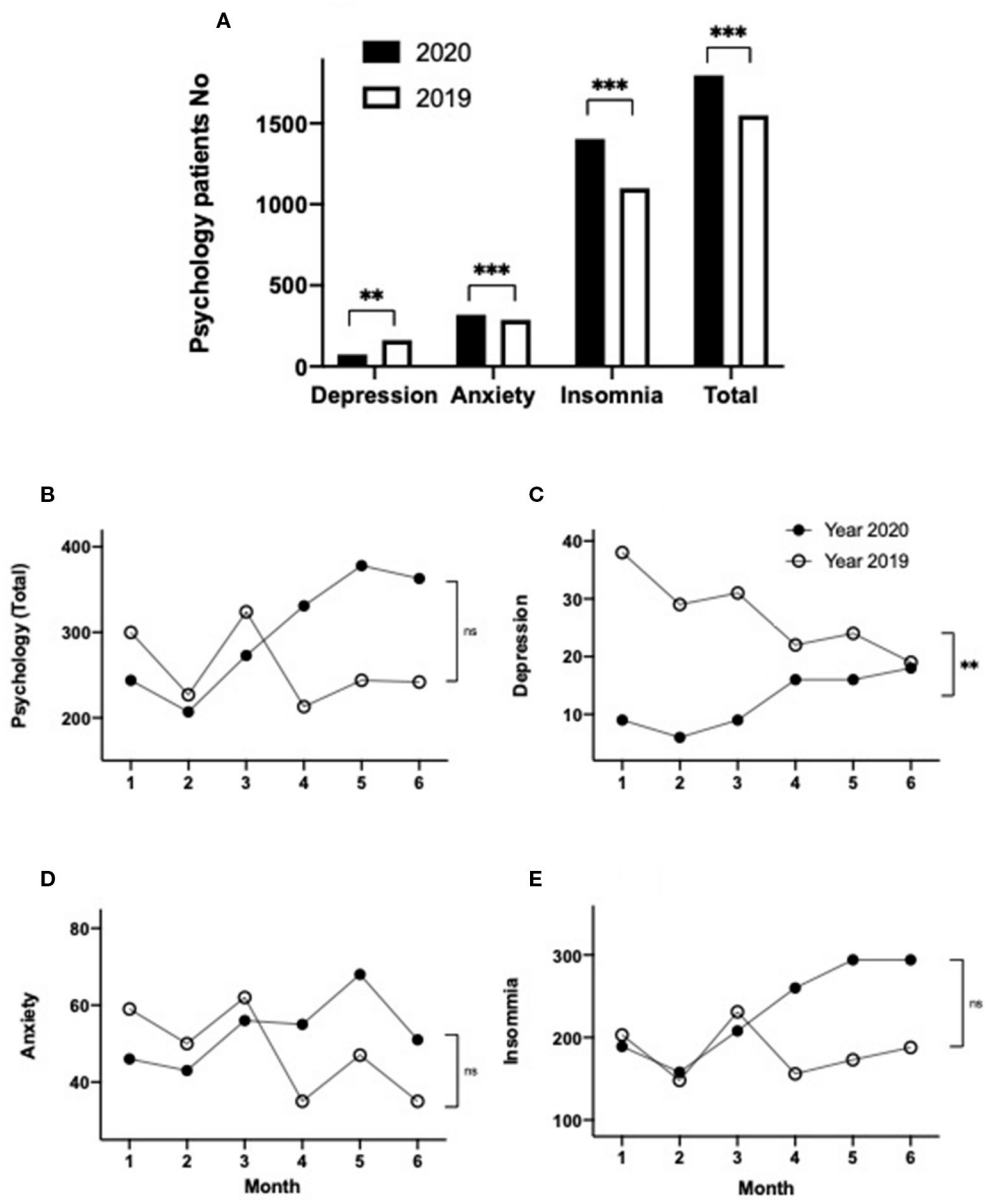


FIGURE 6 | Demographics of patient visits with a primary diagnosis of psychological disorders, including depression, anxiety, insomnia, and the total number of psychological visits in 2020 and 2019 **(A)**; subgroup analysis of monthly distributions of all psychology patients **(B)**, depression **(C)**, anxiety **(D)**, insomnia **(E)** over the first 6 months in 2020 and 2019. $^{**}p < 0.01$, $^{***}p < 0.001$.

The outpatient visits monthly trend data demonstrated that outpatient visits were decreased by ∼20% during January 2020, compared to visits in 2019, which was probably largely due to the timing of the Chinese New Year (January 25, 2020), while the Chinese New Year occurred a week later in 2019 (February 5, 2019). Nevertheless, attendances specifically during the week prior to Chinese New Year/lockdown in 2020 had fallen substantially, when compared to the week before Chinese New Year in 2019, indicating that a heightened awareness of the risk of COVID-19 may have already occurred among the community in Shanghai. Subsequently, the extent of the fall in outpatient visits continued to become and remained lower during February to May for each month in 2020, compared to that in 2019, which was probably due to the direct impact of COVID-19 (41), for the reasons stated above. However, patient visits returned almost back to the same levels in June 2020 compared to 2019, which we believe is due to the outcomes of effectively controlling COVID-19, which reduced anxiety concerning the pandemic (42). There was no difference in the pattern(s) of monthly distributions of attendances in male or female patients within the first half year 2020, compared to that of 2019. The similar

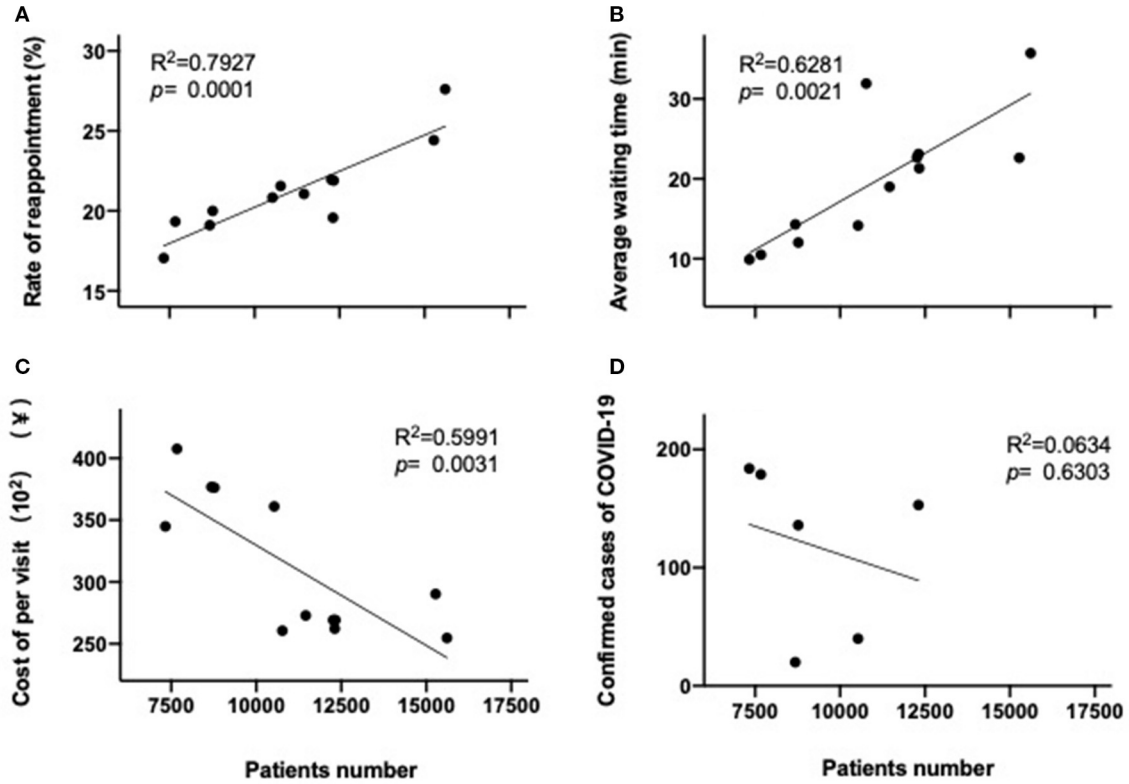


FIGURE 7 | Correlation between patient visits per month and reappointment rate **(A)**, average waiting time **(B)**, or cost per visit **(C)** in the first 6 months of both 2020 and 2019, or number of confirmed COVID-19 patients in Shanghai **(D)** in the first 6 months of 2020.

distributions observed were not too surprising, for the reasons explained above.

We also observed that the average cost per visit in the first half year in 2020 was significantly higher than that in 2019, especially during February and March 2020. We believe that the higher cost was due to several potential factors. First, patients preferred and were encouraged to minimize the number of visits that they needed to make to the clinics and so chose to accumulate and discuss the health problems they may have in one consultation, rather than several consultations. Similarly, patients and their doctors chose to prescribe larger quantities of medications and other health interventions per visit, to compensate for the longer gap between visits, an approach that was encouraged by the Shanghai Health Authority for minimizing cross contamination, especially for COVID-19 (43). Monthly distribution of costs reached a higher plateau during April, May, and June 2020, compared to the same period during 2019, possibly due to the changed habits that had developed during the COVID-19 outbreak.

Both patient's concerns and the health policies promulgated by the health authorities may also explain the substantially reduced rate of reappointment in the first half year of 2020, compared to that in 2019. The reduced waiting time may be a consequence of both a reduction in the overall number of outpatients and as a consequence of health authorities attempting to minimize the time spent within health facilities, to minimize the risk of transmission. These data are also consistent with the data concerning decreased outpatient visits and increased costs described above.

Patient attendance data were also evaluated by the disease diagnosis category. The number of CVD patient attendances was decreased by almost 30% in the first half year of 2020, which is consistent with the overall reduction in attendances during COVID-19, for the general reasons discussed above (44). However, notably this reduction persisted throughout the period to June 2020, suggesting that patients may also have perceived, correctly, that chronic CVD placed them at additional risk of more severe COVID-19 disease. Consequently, these data support the possibility that patients with CVD were deliberately avoiding attending outpatients, because of their well-founded anxiety about their specific risk due to cardiovascular morbidity. These patient perceptions were likely further enhanced by the extensive media coverage that emphasized the increased risk of COVID-19 for patients suffering from chronic CVD. This media coverage is likely to have received additional traction with the public because of the slightly simplistic focus within the media that emphasized that the heart and major organs express a high level of ACE2, which is the binding site for COVID-19 (45). Notably, the role of ACE2 in severe morbidity and mortality during COVID-19 infection is substantially more complex (45).

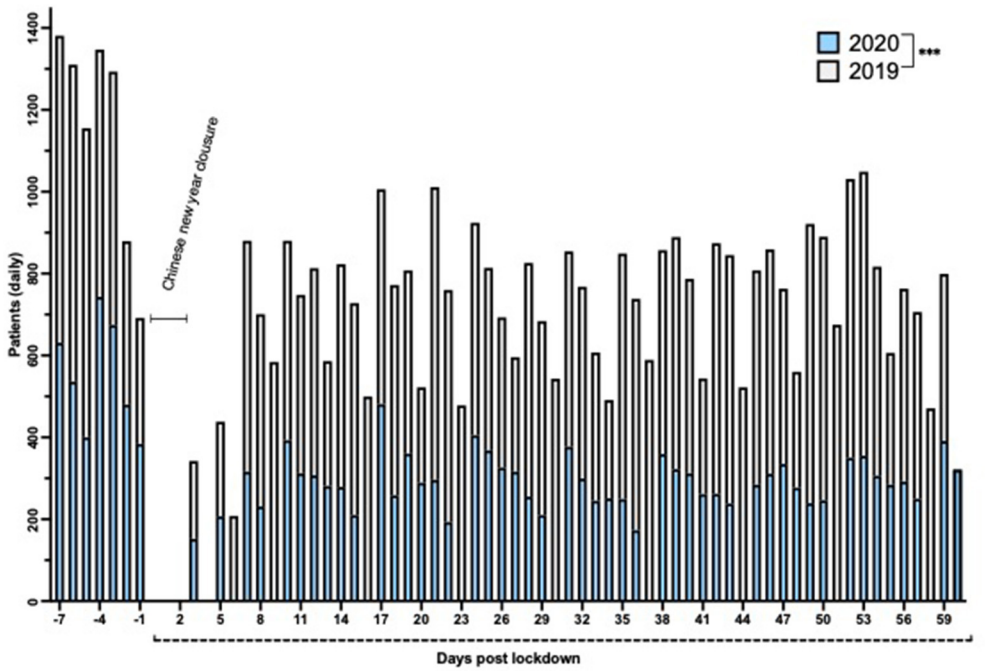


FIGURE 8 | Number of daily patient visits over a 67-day period in 2020 (empty) compared to 2019 (gray). The days were aligned by Chinese New Year (February 5, 2019, and January 25, 2020). Day 1 corresponds to the first day of lockdown (January 24, 2020). ***$p < 0.001$.

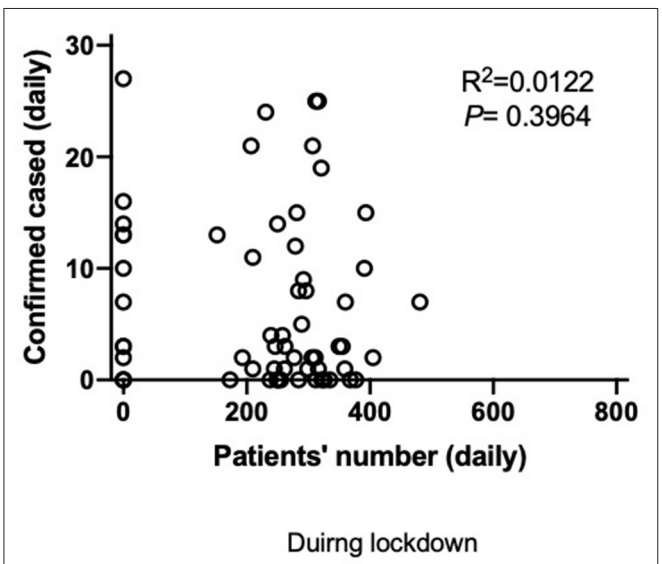


FIGURE 9 | Correlation between the number of daily visit to outpatients in Tongren Hospital and the number of confirmed COVID-19 patients within Shanghai.

Similarly, there was a >50% reduction in respiratory disease patient attendances. The possible explanations for these data encompass both media reporting, which emphasized that the first organ to be attacked by SARS-CoV2 and the most likely organ to fatally fail is the lungs (2), combined with more general patient anxiety. An additional factor that may have contributed to reduced respiratory consultations is that restrictions, including wearing masks and social distancing, may have reduced the rate of other respiratory infections, such as the common cold and influenza, which would normally be increased during the winter months in China (46). Unfortunately, our data do not contain sufficient detail to evaluate this possibility in the context of the Tongren Hospital outpatient clinics. In addition, there were only 712 COVID-19 patients (12) among 25 million population (4) in Shanghai, supporting the substantially reduced respiratory consultations.

Endocrine, gastrointestinal, and hematology attendances dropped by ∼20% during the first half of 2020, while there was a minimal fall in neurology, urology, and musculoskeletal attendances. It is reasonable to speculate that endocrine, gastrointestinal, and hematological disease symptoms may be able to be tolerated and deferred for a moderate period of time and were consequently seen by the population as being symptoms that were not critical for simply surviving. On the other hand, the diagnoses encompassed within neurological disease (e.g., stroke), urology (e.g., urinary retention), and musculoskeletal disease (e.g., painful and mobility-limiting arthritis; fractures) are all diagnoses that are more difficult or impossible to defer. Another interesting observation was that other (unclassified) diseases were increased, which might reflect anxiety and uncertainty among patients and a strong desire for reassurance and clarification as soon as possible.

A particularly important set of observations that emerges from our data relates to psychological illnesses. Our results found

a higher number of outpatient visits for overall psychological-related issues in the first 6 months of 2020 compared to 2019, including, specifically, a rise in anxiety and insomnia. This rise was most pronounced during April to June, which was after community transmission of COVID-19 infection had largely been overcome and the lockdown had been eased, which may be due to the chronicity of the psychological impact of COVID-19 on the general population, resulting in a quite long-term and heavy residual psychological impact (47). The rise in anxiety and insomnia is understandable, as these conditions are often related to acute psychological stress (48).

However, disturbingly, we observed that consultations for depression fell during the first half of 2020, compared to that in 2019 and only returned to normal levels in June 2020. Depression is a relatively more severe condition than anxiety and insomnia (49) and is characterized by a lack of overall motivation, which may include an increased reluctance to consult with health care professionals. A combination of media advice and lockdown rules may have compounded the lack of motivation among depressed patients, leading to a potential serious deficit in their care. Depression is known to be worse in winter, sometimes referred to as seasonal affective disorder (50), so the level of consultation for depression during January 2019 was higher than during June 2019. However, the monthly data for outpatients attendances during 2020 show a profound reduction (>80%) in January 2020, with a subsequent flattening of consultations for depression during the first half of 2020. The immediacy of the reduction in consultations for depression in January 2020 may reflect the highly sensitive nature of depression, where a relatively small trigger to decrease motivation may have a profound impact on seeking help. Overall, as COVID-19 was controlled and people were releasing from lockdown from late in March 2020, people's confidence was built up, and activities, including hospital visits, started to return toward normal (51).

There was a significant correlation between the monthly patients number and reappointment or waiting period for each month during the first half year of 2020, which is consistent with the gradual increase in patient numbers occurring as the COVID-19 crisis settled, and there was a build-up in confidence (52). There was an inverse correlation between cost per visit and patient numbers in the current study. This may be due to more frequent visits during the latter part of the first 6 months of 2020, requiring less/smaller prescriptions (43). However, no correlation was observed between the number of COVID-19 cases diagnosed and patient numbers attending outpatients, which may be due to the very small numbers of COVID-19 cases in the city (712 only in Shanghai among a population of 25 million). A larger study that incorporates data from the whole country may be able to demonstrate such a correlation. Overall, these data that demonstrate a reduction in COVID-19 infections to near zero by the end of lockdown further support the successful nature of the restriction orders utilized in controlling transmission of COVID-19 in Shanghai (53).

We acknowledge that there are limitations in the current study. First, this was a single-center study, although the hospital covers >700,000 members of the general population. In the future, we will conduct a multiple-center study with a larger pool size and different ethnic backgrounds. Second, there were no data from the telephone and/or online consultations included in the current study, which might partly explain the reduced numbers of face-to-face clinic consultations. Third, there were no COVID-19 patients included, as these patients were managed by the specialized infectious diseases wards in certain hospitals only, in addition to which there were very few COVID-19 patients within this 6-month period in Shanghai.

In conclusion, our data demonstrate some of the key parameters that were affected by the impact of COVID-19 on GPs and patients within Shanghai. Substantially reduced outpatient visits, especially among respiratory patients, were observed, probably due to general social distancing and the wearing of face masks. Of particular importance was our observations concerning the acute psychological impact on the general population and the need for GPs to be aware of this issue and proactively develop strategies to reduce associated morbidity in this area, particularly among those with a preexisting disorder, such as depression, during the outbreak of COVID-19, and in the future during similar pandemics. Telephone or online consultation may be an effective alternative approach during the outbreak of COVID-19 and future pandemics.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of the hospital (No. 2020-079-01). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZX designed the experiments, collected data, performed and analyzed the experiment, and wrote the manuscript. JF designed the experiments, analyzed data, and wrote the manuscript. JD, XF, ST, and LQ collected and analyzed the data. KT and BH designed the experiments and revised the manuscript. SB designed the experiments and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Economic Evaluation of First-Line Atezolizumab for Extensive-Stage Small-Cell Lung Cancer in the US

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Introduction: This study evaluated the cost-effectiveness of atezolizumab + chemotherapy vs. chemotherapy as first-line treatment for extensive-stage small-cell lung cancer (SCLC) in the United States (US).

Methods: The three health states partitioned survival (PS) model was used over the lifetime. Effectiveness and safety data were derived from the IMpower133 trial. The parametric survival model and mixture cure model were used for the atezolizumab + chemotherapy group to explore the long-term uncertainty of the effect of immunotherapy, and the parametric survival model was used for the chemotherapy group. Costs were derived from the pricing files of Medicare and Medicaid Services, and utility values were derived from previous studies. Sensitivity analyses were performed to observe model stability.

Results: If the mixture cure model was considered for the intervention group, compared with chemotherapy alone, atezolizumab + chemotherapy yielded an additional 0.11 quality-adjusted life-years (QALYs), with an incremental cost of US$84,257. The incremental cost-utility ratio (ICUR) was US$785,848/QALY. If the parametric survival model was considered for the intervention group, atezolizumab + chemotherapy yielded an additional 0.10 QALYs, with an incremental cost of US$84,257; the ICUR was US$827,610/QALY. In the one-way sensitivity analysis, progression-free (PF) and postprogression (PP) utilities were the main drivers. In the scenario analysis (PF utility = 0.673, PP utility = 0.473), the results showed that the ICUR was US$910,557/QALY and US$965,607/QALY when the mixture cure model and parametric survival model was considered for the intervention group, respectively. In the PSA, the probabilities that atezolizumab + chemotherapy would not be cost-effective were 100% if the willingness-to-pay threshold was US$100,000/QALY.

Conclusions: The findings of the present analysis suggest that atezolizumab + chemotherapy is not cost-effective in patients receiving first-line treatment for extensive-stage SCLC in the US.

Keywords: small-cell lung cancer, cost-effectiveness, atezolizumab, chemotherapy, extensive stage

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INTRODUCTION

Lung cancer is currently the second most common cancer classified by sex; after prostate cancer in men and breast cancer in women, lung cancer accounts for 14% of new cancers in American men and 13% of new cancers in American women (1). Extensive-stage small-cell lung cancer (SCLC) accounts for ∼15% of all lung cancers (2). The prognosis of SCLC is usually poor. It has been reported that the median overall survival (OS) of patients with SCLC is 8–12 months, and the annual OS rate is ∼5%. Three first-line treatment options are currently recommended for extensive-stage SCLC: (1) carboplatin + etoposide + atezolizumab, (2) carboplatin + etoposide + durvalumab, and (3) cisplatin + etoposide + durvalumab (3).

Atezolizumab is a humanized monoclonal antibody designed to bind to the PD-L1 protein expressed on tumor cells and tumor-infiltrating immune cells, blocking its interaction with the PD-1 and PD-L1–B7- 1 receptors (4). By inhibiting PD-L1, atezolizumab can activate T cells, allowing them to kill cancer cells. Atezolizumab was approved by the Food and Drug Administration FDA for the first-line treatment of SCLC, based on the IMpower133 trial (NCT02763579), which was a randomized, multicenter, double-blind, placebo-controlled phase III trial (5). This trial studied 403 patients who had not previously received chemotherapy and had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1. The patients were randomly divided into two groups: the intervention group received carboplatin + etoposide + atezolizumab, and the control group received carboplatin + etoposide + placebo. The primary outcomes were OS and progression-free survival (PFS).

The trial showed that atezolizumab combined with chemotherapy could significantly prolong survival time [median OS = 12.3 vs. 10.3 months; hazard ratio (HR) = 0.70, 95% confidence interval (CI): 0.54–0.91; $p = 0.0069$], which meant that the risk of death was reduced by 30%, and patients receiving atezolizumab were more likely to survive within 1 year (1-year survival rate = 51.7%) than patients in the control group (1-year survival rate = 38.2%). Compared with chemotherapy alone, the median PFS of patients receiving atezolizumab combined with chemotherapy also improved (median PFS = 5.2 vs. 4.3 months in the placebo group; HR = 0.77; 95% CI: 0.62–0.96; $p = 0.017$), significantly reducing the risk of disease deterioration or death. Serious adverse reactions occurred in 37% of patients receiving atezolizumab combined with chemotherapy, compared with 35% of patients receiving chemotherapy alone. Although the addition of atezolizumab to chemotherapy resulted in significantly clinical efficacy, the immunotherapy causes enormous medical expenditure which brings economic burden to patients and governments. According to the statistics, biologic therapies are among the most expensive drugs, accounting for 40% of total US spending on prescription drugs despite only 2% of patients using biologics (6). Therefore, the economic evaluation is required to explore the clinical effectiveness and the cost-effectiveness of the new intervention showing whether it is available to patients.

In the economic evaluation of tumor drugs, we usually need to fit the curves from the clinical trials to construct a Markov model or a partitioned survival (PS) model (7). Even when the data for OS and PFS curves are immature, we still need to extrapolate them based on the fit results. In many previously published studies, standard parametric models were used. The commonly used fitting distributions include the exponential distribution, Weibull distribution, Gompertz distribution, lognormal distribution, etc. The reason for the selection of a parameter distribution was explained in some (8–10) but not all studies (11). However, many researchers overlooked a problem: the premise for the application of the standard parametric model was that all observed subjects would have an expected event at a certain point in time within a defined sufficient follow-up time. Obviously, this would not be suitable for data analysis of long-term survival analyses. Some immunotherapies, such as PD-1/PD-L1 or CAR-T, might keep the patient alive for a longer time or even cure the patient; therefore, the Kaplan–Meier (KM) curve showed an obvious plateau. For this case, the mixed cure model was also an important alternative method in addition to the standard parameter model, and it would be more suitable under certain circumstances. We can also see that an increasing number of studies are trying to use the mixture parametric model instead of the standard parametric model (12, 13). For example, Roth et al. (12) used a cure model to estimate the proportion achieving long-term survival.

Information on the cost-effectiveness of immunotherapy PD-L1 is required by decisionmakers in the health care system to determine the value of these novel treatment in extensive-stage SCLC in the world, for example NICE had already released Technology appraisal guidance [TA638] (https://www.nice.org.uk/guidance/ta638). The objective of this study was to explore the cost-effectiveness of atezolizumab in the United States (US). Besides, our research also explored how the use of the standard parametric model vs. the mixture parametric model would affect the incremental cost-utility ratio (ICUR) and incremental cost-effectiveness ratio (ICER) results.

METHODS

Patient Cohort and Treatment Duration

The patients included in the cohort were those who were adults with extensive-stage SCLC who had not previously received chemotherapy, which was consistent with the IMpower133 trial (5). We assumed that all patients were in the progression-free (PF) health state, and they received one of the following two treatments at the beginning of the model:

1. The patients in the intervention group received four 21-day cycles of carboplatin (area under the curve of 5 mg per milliliter per minute) and etoposide (100 mg per square meter of body surface area). In addition, they received atezolizumab (1,200 mg) in each 21-day cycle until disease progression or death.
2. The patients in the control group received four 21-day cycles of carboplatin (area under the curve of 5 mg per milliliter per minute) and etoposide (100 mg per square meter of body surface area).

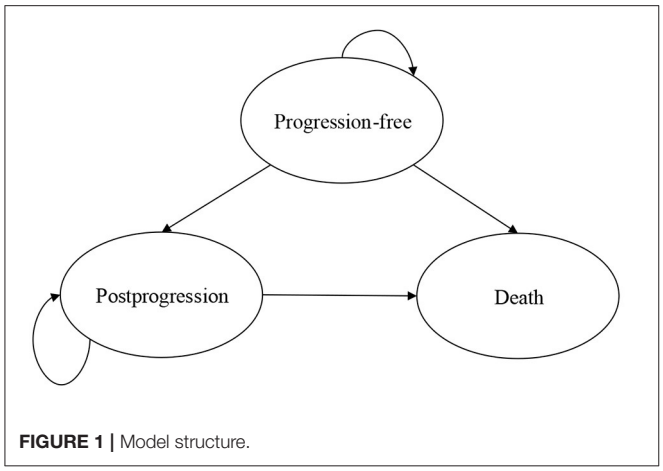


FIGURE 1 | Model structure.

Model Overview

A PS model with three mutually exclusive health states was developed to estimate the costs and outcomes of the first-line treatment of patients with extensive-stage SCLC in Microsoft Excel (**Figure 1**). The proportion of patients in the postprogression (PP) state in each cycle was calculated as the difference between OS and PFS based on data from the IMpower133 trial. Each cycle lasted 3 weeks, which was consistent with the IMpower133 trial. A lifetime horizon (2.5 years) was chosen, and ≥95% of patients in the control group died. We examined the following outcomes: quality-adjusted life-years (QALYs), life-years gained (LYGs), and costs. All of them were discounted by 3%. The US payer perspective was taken; therefore, only the direct medical care costs were included.

Model Approaches

Standard Parametric Models

There are a wide range of parametric models available, and each have their own characteristics which make them suitable for different data sets. Standard models considered in our studies were the proportional hazards-based exponential, Weibull, Gompertz, and the accelerated failure time-based log-normal, log-logistic. In fact, the standard models have been commonly used in National Institute for Health and Care Excellence appraisals (14).

Cure Models

This model was first proposed by Boag et al. in 1949 (15). Their study showed that in the survival analysis of tumor data, the existence of "long-term survival" needed to be considered. The key to the cure model is to determine how many patients are "cured," that is, there exists a long-term survival situation in them (16). In this model, Logistic regression and Probit regression are usually used to predict whether the patient is "cured" (17). The death risk of cured patients is generally assumed to be similar to the background population, while the death risk of uncured patients is the mortality of the diseased population.

There are currently two main types of cure models: mixture cure model and non-mixture cure model. In the mixture cure model, the population is divided into two groups, namely the uncured group and the cured group, and the population is analyzed as the mixed distribution of the two groups. In contrast, it is assumed that all patients are in the same group in the non-mixture cure model, but the risk of the event decreases to 0 over time changes over time.

The survival function of the mixture cure model can be written as shown in Equation (1) (18):

$$\begin{aligned} \text{Survival}_{\text{population}} &= \text{Survival}_{\text{generalpopulation}} * (p_{\text{cured}} + \\ &(1 - p_{\text{cured}}) * \text{Survival}_{\text{uncured}}) \end{aligned} \quad (1)$$

The survival function of the mixture cure model can be written as shown in Equation (2) (18):

$$\begin{aligned} \text{Survival}_{\text{population}} &= \text{Survival}_{\text{generalpopulation}} * \exp(\text{Ln} \\ &(p_{\text{cured}}) * (1 - S)) \end{aligned} \quad (2)$$

S is a standard extrapolation distribution that decreases to 0 over time

It should be noted that the premise of non-mixture cure model is: survival data should meet the proportional hazard assumption, because the non-mixture cure model is a proportional hazards model of cure (19).

Overall Survival and Progression-Free Survival

Long-term OS and PFS were estimated by fitting parametric survival distributions to pseudo-individual participant data (IPD) derived from digitized KM curves from the IMpower133 trial, and the pseudo-IPD data were extracted with Engauge Digitizer software (http://markummitchell.github.io/engauge-digitizer/). To extrapolate the probability of survival to cover the lifetime horizon, we considered five standard parametric models in Microsoft Excel to fit two curves: exponential distribution, the Weibull distribution, the Gompertz distribution, loglogistic distribution, and lognormal distribution. For the special mechanism of PD-L1 and the obvious plateau at the end of the curve, the mixture cure model was also considered for the intervention group (carboplatin + etoposide + atezolizumab), which was conducted in R 3.6.0. The OS and PFS curves were found to be inconsistent with the proportional hazard (PH) assumption; therefore, the non-mixture cure model was not considered (20). Parametric survival models and mixture cure models were selected based on Akaike's information criterion (AIC) statistic and visual inspection of survival distributions. The lowest AIC values were considered as goodness-of-fit statistics, and visual inspection was to check whether the distribution was fit to KM curve. External data were also used to validate the long-term extrapolations of the control group (21). When few data were available about long-term extrapolations of atezolizumab in SCLC, two kinds of models (standard parametric models and mixture cure models) were used to extrapolate the intervention group, which is explained in the discussion section. The Gompertz distribution was used to estimate OS for the atezolizumab + chemotherapy group and chemotherapy group based on its good statistical and visual

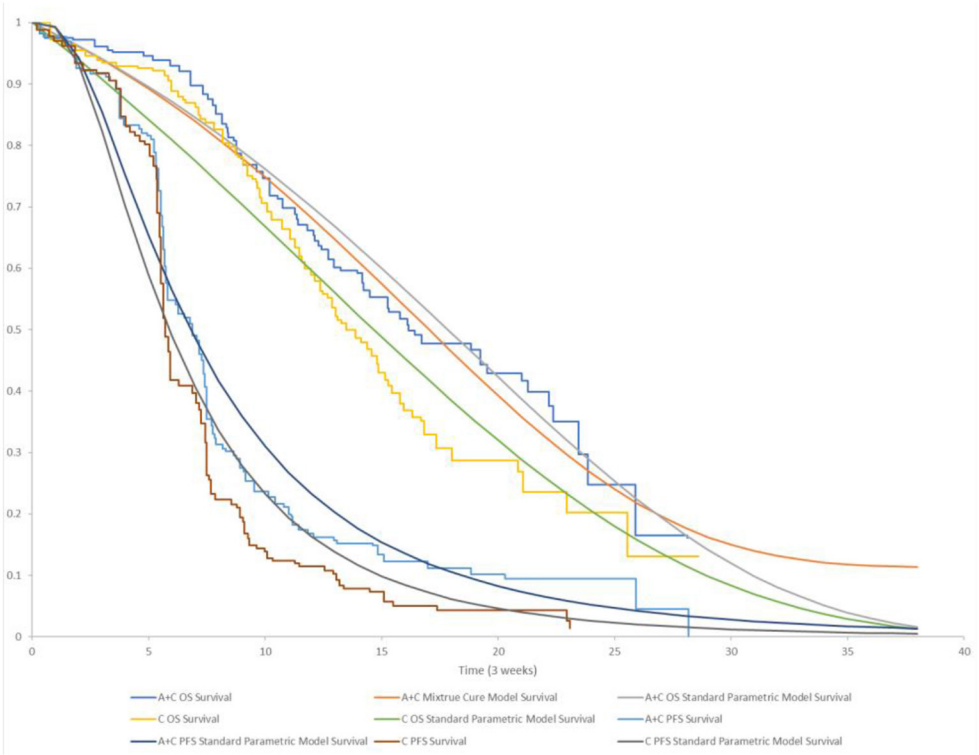


FIGURE 2 | KM and parametric survival distributions for OS and PFS. A + C, atezolizumab + chemotherapy; C, chemotherapy.

inspection. For the mixture model, the Gompertz (restricted) distribution was used to estimate OS for the atezolizumab + chemotherapy group based on its good statistical and visual fit.

PFS curves were estimated based on the lognormal distribution fit to pseudo-IPD. Age- and sex-adjusted US general population mortality rates were additively applied to the estimated parametric survival distributions for PFS and OS to account for natural mortality, which was referred to background population in the cure model (22). While the death risk of the diseased population was derived from the OS curve. KM and parametric survival distributions for OS and PFS used in the model are shown in **Figure 2**. Additional details regarding the selection of parametric survival models and mixture cure models are provided in the **Supplementary Material**.

Utility Values

Because little information on the quality of life of SCLC patients was collected in the IMpower133 trial and other published studies, utilities of each health state were obtained from previously published studies about NSCLC (0.840 for PF, 0.473 for PP and 0 for death) (23).

Disutilities for adverse events (AEs) whose values were taken from published sources were also included for patients receiving treatment (i.e., atezolizumab + chemotherapy and chemotherapy) (23–25). The duration of AEs was derived from the published clinical expert opinion (10).

Cost

Direct medical costs include drugs, administration, and costs for the management of adverse reactions. We found that in the IMpower133 trial, ∼40.3% of patients in the atezolizumab + chemotherapy group received subsequent chemotherapy, but the trial did not describe detailed second-line treatment options; therefore, we consequently assumed that 40.3% of patients who progressed while receiving atezolizumab + chemotherapy group received topotecan (0.1 mg, at 1.5 mg/m^2 daily on days 1–5 of each 21-day cycle) and 15.4% of patients received CAV (cyclophosphamide, 25 mg, 1,000 mg/m^2 on day 1; doxorubicin, 10 mg, 45.0 mg/m^2 on day 1; vincristine, 1 mg, 2.0 mg on day 1 of each 21-day cycle) (26) as their second-line treatment according to the National Comprehensive Cancer Network (NCCN) guideline (27). Similarly, we assumed that 43.6% of patients who progressed while receiving chemotherapy received topotecan and 22.8% of patients received CAV as their second-line treatment. A body weight of 70 kg, a body surface area of 1.86 m^2, and a creatinine clearance of 70 mL/min were assumed in the model from the published literature (28). The 2019 average sale price from the Centers for Medicare and Medicaid Services and administration costs were estimated according to the Medicare Physician Fee schedule for 2018. The impact of grade 3 or 4 AEs was considered in the model.

TABLE 1 | Key inputs for the partitioned survival model.

	Deterministic	Distribution	Low	High	Source
QoL utility (per year)					
PF	0.840	BETA	0.672	0.883	(23)
PP	0.473	BETA	0.166	0.568	
Units for costs					
Cost of atezolizumab/10 mg	77.46	GAMMA	77.01	77.76	(29)
Cost of etoposide/10 mg	0.66	GAMMA	0.56	0.74	
Cost of carboplatin/50 mg	3.09	GAMMA	2.89	3.25	
Cost of topotecan/0.1 mg	0.94	GAMMA	0.87	1.01	
Cost of cyclophosphamide/100 mg	3.91	GAMMA	3.31	4.54	
Cost of doxorubicin/10 mg	3.08	GAMMA	2.89	3.73	
Cost of vincristine/1 mg	4.88	GAMMA	4.79	5.00	
Supportive care cost	478	GAMMA	359	597	(9)
Death cost	9,433	GAMMA	7,075	11,791	
Administration cost					
First	144.72	GAMMA	115.78	173.66	(29)
Additional	31.68	GAMMA	25.34	38.02	
Costs of MAEs					
Neutropenia	17,181	GAMMA	13,745	20,617	(30)
Anemia	20,260	GAMMA	16,208	24,312	
Decreased neutrophil count	17,181	GAMMA	13,745	20,617	
Thrombocytopenia	22,698	GAMMA	20,289	25,377	
Leukopenia	17,181	GAMMA	13,745	20,617	
Risk of AEs in A + C					
Neutropenia	0.23	BETA	0.19	0.28	(5)
Anemia	0.14	BETA	0.11	0.17	
Decreased neutrophil count	0.14	BETA	0.11	0.17	
Thrombocytopenia	0.10	BETA	0.08	0.12	
Leukopenia	0.05	BETA	0.04	0.06	
Risk of AEs in C					
Neutropenia	0.25	BETA	0.20	0.29	(5)
Anemia	0.12	BETA	0.10	0.15	
Decreased neutrophil count	0.17	BETA	0.13	0.20	
Thrombocytopenia	0.08	BETA	0.06	0.09	
Leukopenia	0.04	BETA	0.03	0.05	
Discount rate	0.03	Fixed	0	0.05	(31)
Disutilities of AEs					
Neutropenia	−0.09	BETA	−0.122	−0.062	(23–25)
Anemia	−0.09	BETA	−0.133	−0.055	
Decreased neutrophil count	−0.09	BETA	−0.122	−0.062	
Thrombocytopenia	−0.108	BETA	−0.128	−0.089	
Leukopenia	−0.09	BETA	−0.122	−0.062	
AEs duration					
Neutropenia	2	Normal	2	2	(10)
Anemia	21	Normal	17	25	
Decreased neutrophil count	4	Normal	3	5	
Thrombocytopenia	24	Normal	19	28	
Leukopenia	2	Normal	2	2	

A + C, atezolizumab + chemotherapy; C, chemotherapy; MAE, main adverse event; QoL, quality of life.

Sensitivity Analysis

To explore the uncertainty, one-way sensitivity analyses, probabilistic sensitivity analyses and scenario analyses were performed separately when using the mixture cure model or standard parametric model. The upper and lower limits of the inputs were derived from the original literature. For those inputs without upper and lower limits, the method of floating by 20% of the default input was used. In the probabilistic sensitivity analysis (PSA), we used visual basic programming to run 1,000 Monte Carlo simulations. Cost-effectiveness acceptability curves were then calculated.

For scenario 1, we assumed the utilities were from the other published literature, which were used in some other studies (11).

All parameters included in DSA/PSA and their variations are listed in **Table 1**.

Ethics

The data of the PFS/OS curve was based on previously published trial, not from the database or the medical records. We used the Engauge Digitizer software to get the survival information from the figures in the paper and reconstructed data by ourselves, which was explained in the Section "Overall Survival and Progression-Free Survival." Besides, the utilities and costs were derived from the published literatures, so ethics approval or specific consent procedures were not required for this study.

RESULTS

Base-Case Results

In order to facilitate the identification of the models using the two extrapolation methods, we defined the model using the mixture cure model as model 1, and the model using the standard parametric model as model 2.

If the mixture cure model was considered for the intervention group, atezolizumab + chemotherapy was estimated to result in 0.73 QALYs, which was 0.11 QALYs higher than chemotherapy alone. In terms of LYGs, atezolizumab + chemotherapy was estimated to result in 1.12 LYGs, while chemotherapy alone was estimated to result in 1.1 LYGs. The total cost was higher in the atezolizumab + chemotherapy group, and atezolizumab + chemotherapy resulted in an average increase in patient lifetime costs of US$83,484. If the standard parametric model was considered for the intervention group, atezolizumab + chemotherapy was estimated to result in 0.73 QALYs, which was 0.15 QALYs higher than chemotherapy alone. In terms of LYGs, atezolizumab + chemotherapy was estimated to result in 1.12 LYGs, while chemotherapy alone was estimated to result in 1.11 LYGs. In comparing the results from the mixture cure model and standard parametric model, similar expected costs, expected outcomes and ICUR/ICER results could be seen by using either extrapolating approach. In the base-case analysis with a lifetime horizon, the costs and health outcomes calculated using the mixture cure model and standard parametric model are presented in **Table 2**.

We found that the ICUR when using the standard parametric model was slightly higher than that when using the mixture cure model, with a difference of US$41,761/QALY. Similarly, the ICER when using the standard parametric model was slightly higher than that when using the mixture cure model, with a difference of US$38,679/LYG.

TABLE 2 | Results for the cost-effectiveness analysis in model 1 and model 2.

Model	Group	Total Cost US$	Outcomes	
			Total QALYs	Total LYGs
Model 1 (mixture cure model for A + C)	A + C	109,051	0.73	1.12
	C	25,556	0.63	0.96
	Incremental	83,484	0.11	0.16
	ICUR/ICER		US$785,848/QALY	US$529,888/LYG
Model 2 (standard parametric model for A+C)	A + C	109,824	0.73	1.11
	C	25,556	0.63	0.96
	Incremental	84,257	0.10	0.15
	ICUR/ICER		US$827,610/QALY	US$568,567/LYG

A + C, atezolizumab + chemotherapy; C, chemotherapy.

Sensitivity Analysis

One-Way Sensitivity Analysis

According to the results of the one-way sensitivity analysis, we found that PP utility and PF utility were the main model drivers in both models (**Figures 3**, **4**). The range of the one-way sensitivity analysis was from US$739,289/QALY to US$986,655/QALY in model 1, and the range of the one-way sensitivity analysis was from US$782,990/QALY to US$1,014,415/QALY in model 2.

Probabilistic Sensitivity Analysis

Figure 5 shows the PSA results when the mixture cure model was used for the atezolizumab + chemotherapy group and the standard parametric model was used for the chemotherapy group. The cost-effectiveness threshold of US$100,000 per QALY was used as willingness to pay according to the recommendation of literature (32). The results demonstrated that atezolizumab + chemotherapy was associated with a 100% probability of being not cost-effective at the threshold of US$100,000 per QALY gained vs. chemotherapy alone. The same result was found when the standard parametric model was used for both the atezolizumab + chemotherapy group and the chemotherapy group (**Figure 6**).

Scenario Analysis

In the first scenario analysis in which we used the PF utility of 0.673 and the PP utility of 0.473, the result showed that the ICUR was US$910,557/QALY when the mixture cure model was used for the atezolizumab + chemotherapy group and the standard parametric model was used for the chemotherapy group. The ICUR was US$965,607/QALY when the standard parametric

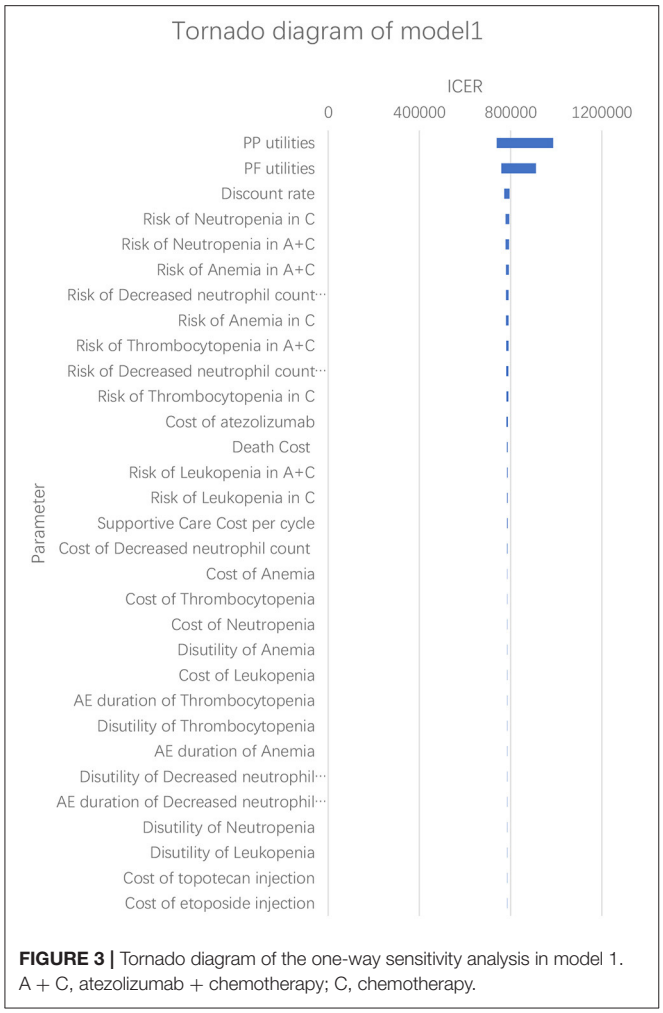


FIGURE 3 | Tornado diagram of the one-way sensitivity analysis in model 1. A + C, atezolizumab + chemotherapy; C, chemotherapy.



FIGURE 4 | Tornado diagram of the one-way sensitivity analysis in model 2. A + C, atezolizumab + chemotherapy; C, chemotherapy.

model was used for both the atezolizumab + chemotherapy group and the chemotherapy group.

DISCUSSION

This study evaluated the cost-effectiveness of atezolizumab + chemotherapy vs. chemotherapy alone in adult patients with SCLC from a US payer perspective based on data from the IMpower133 trial. The results of this economic evaluation indicated that atezolizumab + chemotherapy was more costly and more effective than chemotherapy alone for first-line treatment of extensive-stage SCLC. The estimated ICUR of US$785,848/QALY in model 1 and US$827,610/QALY in model 2 was much higher than the willing-to-pay threshold in US, which indicated that atezolizumab + chemotherapy was not cost-effective for first-line treatment of extensive-stage SCLC in US.

There existed one cost-effectiveness analysis based on IMpower133 trial data by Zhou K et.al. and we thought there were four deficiencies in that research. We supplemented and discussed these four points in this research: (1) That study only used exponential function for curve fitting, which could not reveal the delay effect in tumor immunotherapy. We used five standard parametric models and cure models to explore the most suitable fitting method. (2) The curve fitting did not discuss the potential long-term survival of tumor immunotherapy in that study, while we used the mixture cure model to assess the long-term uncertainty; (3) The previous literature only assumed the patients received the topotecan alone as second-line chemotherapy, which was inconsistent with the Impower133 experiment, while we used the follow-up therapy which was consistent with the Impower133 experiment; (4) PSA was not done in the previous literature, which is very important for the final conclusion and judgment, while we have done it.

For the special mechanism of PD-L1 and the obvious plateau at the end of the curve, the mixture cure model was also considered for the intervention group (carboplatin + etoposide + atezolizumab) to assess the long-term uncertainty, which was innovative to our best knowledge. It could be found that the intervention group would bring greater long-term survival benefits to patients when using the mixture cure model than when using the standard parametric model. Therefore, the total cost in model 1 was lower and the total QALYs and LYGs

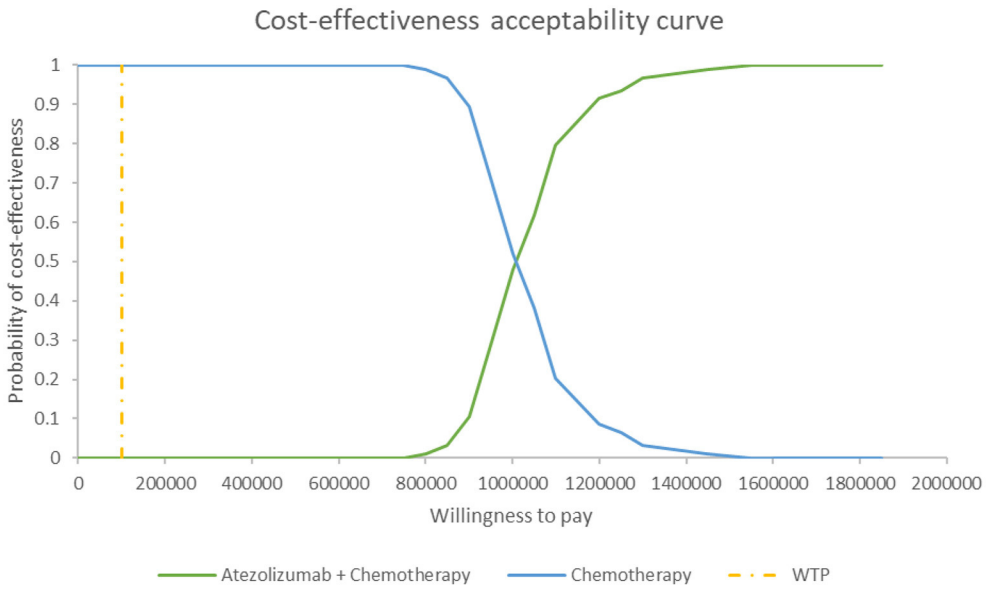


FIGURE 5 | Cost-effectiveness acceptability curve at different thresholds of willingness to pay in model 1. WTP, willingness to pay.

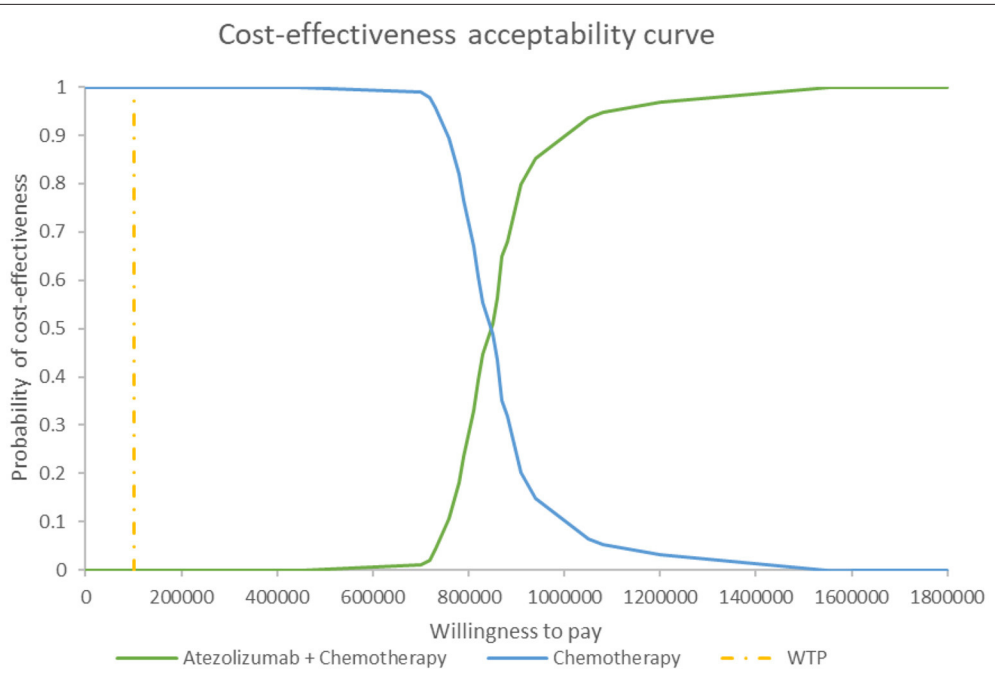


FIGURE 6 | Cost-effectiveness acceptability curve at different thresholds of willingness to pay in model 2. WTP, willingness to pay.

were higher and the ICER in model 1 was lower than that in model 2. We could see that when the willingness to pay was US$100,000/QALY, the results from both models demonstrated that atezolizumab + chemotherapy was not more cost-effective than chemotherapy alone in the US patients with SCLC.

Although there were certain differences in the results obtained by different extrapolation methods, it did not change the conclusion, which did not mean that the same conclusion would be reached using other data because it was associated with other factors, such as the length of the plateau period which might herald that there existed more "cured" patients.

Besides, difference in efficacy and safety of different chemotherapies would affect the results of this study. In the Impower133 experiment, the carboplatin + etoposide was used

as the chemotherapy, but there are other chemotherapies such as cisplatin + etoposide, carboplatin + irinotecan and cisplatin + irinotecan which were recommended in NCCN Guidelines Small Cell Lung Cancer. Existing evidence shows that there is no huge difference in the efficacy and safety of these chemotherapy (33–36), but the irinotecan was much more expensive than other chemotherapy drugs. Therefore, if irinotecan was used as the chemotherapy, the results of this study might be more cost-effective.

In addition to atezolizumab, durvalumab was also recommended for the first-line treatment of extensive-SCLC according to NCCN Guidelines Small Cell Lung Cancer. It was found that one published literature explored the cost-effectiveness of durvalumab as a first-line treatment for extensive-SCLC https://doi.org/10.3389/fonc.2020.602185, which found that under a willingness-to-pay threshold of $100,000, durvalumab does not have a cost-effective comparative advantage in the US. Therefore, the existing evidence confirms that PD-L1 immunotherapies + chemotherapies were not cost-effective.

There were other shortcomings in our analyses. First, since the OS curve from the clinical trials did not meet the PH assumption, the non-mixture cure model could not be used, and it was impossible to detect the impact of the non-mixture cure model. According to the external data (21), we found that the standard parametric model was more authentic than the mixture cure model for the chemotherapy group. Therefore, for the chemotherapy group, we used a standard parametric model, which is different from the previous article. Due to the lack of external data about the atezolizumab + chemotherapy group, there was uncertainty in the exploration of the atezolizumab + chemotherapy group; therefore, we used two different methods to assess the uncertainty. Which model reflects the real treatment situation remains to be verified by long-term real-world data. Second, the utilities used in our study were not from the US SCLC patients. Therefore, we conducted scenario analysis and one-way sensitivity analysis to explore the uncertainty. Third, the adverse reactions included in the article were mainly grade 3 or higher adverse reactions with an incidence of more than 10% mentioned in clinical trials. However, clinical trials might not cover all the adverse reactions caused by atezolizumab + chemotherapy and chemotherapy alone due to the small sample size. In addition, because the dosages and usages we used were derived from clinical trials, there might be differences between clinical trials and real-world data. Therefore, the generalizability of study findings should be also a limitation of this study. Besides, many factors, especially PD-L1 expression might have a great impact on the effect of PD-1/L1 drugs. One published study revealed that when the expression of PD-L1 was different, PFS and OS of atezolizumab was obviously different for extensive-stage SCLC (37). It can be seen that when atezolizumab is used to treat SCLC patients with high PD-L1 expression, there exists an obvious plateau on the survival curves. Therefore, it might be more cost-effective for patients with high PD-L1 expression.

CONCLUSIONS

With various approaches for estimating the relative effectiveness of atezolizumab + chemotherapy vs. chemotherapy alone, atezolizumab + chemotherapy was not found to be cost-effective compared with chemotherapy alone in adult patients with SCLC from a US payer perspective.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants, in accordance with the local legislation and institutional requirements.

AUTHOR CONTRIBUTIONS

MR, AM, and HL contributed to the study conception and design. Material preparation and data collection were performed by YW, LY, XW, and MR, and analysis were performed by HL and AM. The first draft of the manuscript was written by MR and YS. All authors commented on subsequent versions of the manuscript and read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.650392/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SYSTEMATIC REVIEW
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An Overview of Systematic Reviews of Acupuncture for Infertile Women Undergoing *in vitro* Fertilization and Embryo Transfer

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Background: Currently, more and more subfertility couples are opting for combined acupuncture to improve the success rate of *in vitro* fertilization and embryo transfer (IVF-ET). However, the efficacy and safety of acupuncture in IVF-ET is still highly controversial.

Objectives: The purpose of this overview is to summarize evidence of essential outcomes of systematic reviews (SRs) of acupuncture in IVF-ET and evaluate their methodological quality.

Methods: We conducted a comprehensive literature search for relevant SRs in eight databases from inception to July 31, 2020, without language restriction. We evaluated the methodological quality of the included SRs by using A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR-2), which was the latest available assessment tool. The Risk of Bias in Systematic Review (ROBIS) tool was used to assess the risk of bias in SRs. We assessed the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) score to determine the strength of evidence. We excluded the overlapping randomized controlled trials (RCTs) and performed a re-meta-analysis of the primary RCTs.

Results: This review included 312 original RCT studies and 65,388 participants. By using AMSTAR-2, we found that the methodological quality of 16 SRs was critically low, because they had more than one critical weakness. Our reviews showed that although the GRADE for quality of evidence profile was suboptimal, acupuncture seemed to be beneficial in increasing the pregnancy rate. Our re-meta-analysis suggested that acupuncture was superior to sham acupuncture in improving the clinical pregnancy rate (CPR) of IVF-ET with substantial heterogeneity (RR = 1.31, 95% CI: 1.13–1.52, p = 0.0004, I^2 = 66%). No statistical difference was observed regarding the outcomes of live birth rate (LBR), ongoing pregnancy rate (OPR), biochemical pregnancy rate (BPR), and miscarriage rate (MR) between two groups. When compared with no adjunctive treatment groups, acupuncture improved CPR (RR = 1. 25, 95% CI: 1.11–1.42, p = 0.0003) and OPR (RR = 1. 38, 95% CI: 1.04–1.83, p = 0.03). Acupuncture was more superior than no adjunctive treatment in reducing MR (OR = 1.42, 95% CI: 1.03–1.95, p = 0.03) and BPR (RR = 1.19, 95% CI: 1.02–1.37, p = 0.02).

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Conclusions: Although the evidence of acupuncture in IVF-ET is insufficient, acupuncture appears to be beneficial to increase the clinical pregnancy rate in women undergoing IVF-ET. However, there are severe heterogeneity and methodological quality defects, which limit the reliability of results. Further, high-quality primary studies are still needed.

Keywords: acupuncture, *in vitro* fertilization, systematic reviews, overview, methodological quality

INTRODUCTION

Infertility is defined as failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse (1, 2). The prevalence rate of infertility is 15% in the reproductive period (3). Among couples who are trying to conceive at reproductive age in China, 25% may encounter infertility (4). According to the report, female factors account for 40% of overall infertility (5). *In vitro* fertilization and embryo transfer (IVF-ET) is an effective treatment method for subfertility couples (6, 7). Worldwide, 7,079,145 cycles were carried out between 2004 and 2013, and successfully resulted in the birth of approximately 1.45 million children (8). Currently, the average success rates per IVF cycle remain low, although live birth rate gradually improved in most regions, some demonstrated declines. Fresh cycle live birth rate was highest in the USA (29%) and lowest in Japan (5%) between 2012 and 2013 (8). For many women, cycles need to be repeated to succeed. The IVF-ET cycle is time-consuming and costly. The direct and indirect costs of one cycle of IVF-ET are equivalent to $10,000 to 25,000 (9, 10), so it is essential to enhance the success rate of IVF-ET. Therefore, many patients try to seek alternative therapies to improve IVF-ET outcomes, including acupuncture. Acupuncture involves the insertion of metallic needles into the body. The application of acupuncture through stimulating certain acupoints on the human body is to activate the meridians and to regulate the function of qi and blood so as to prevent and treat disease. In the USA, 47% of infertile women engaged in acupuncture during IVF-ET treatment (11). The mechanisms of acupuncture in IVF-ET have been reported to enhance hormonal balance (12), inhibit uterine motility (13), increase blood flow to uterine and ovarian areas (14), and downregulate various stress responses (15–17).

Nowadays, some systematic reviews (SRs) of acupuncture in IVF-ET have been published to evaluate its effectiveness and safety. However, no consensus has been reached. Some reviews indicated that acupuncture might provide benefits in improving reproductive outcomes (18–29). Others found no statistically significant difference in clinical pregnancy or live birth when compared with a control (30–33). The quality of evidence is unclear. Therefore, our study aims to assess the methodological and reporting quality of SRs concerning the effectiveness of acupuncture for infertile women undergoing IVF-ET, and to provide beneficial recommendations for the implementation of SRs.

METHOD

Protocol and Registration

The protocol of this study was registered in PROSPERO with the registration number CRD42020201238 (https://www.crd.york.ac.uk/PROSPERO/).

Search Strategy for Identification of Studies

Electronic literature was searched in the following databases from inception to July 31, 2020, without language restrictions: including four international electronic databases (Pubmed, EMBASE, Cochrane Library, and Web of Science) and four Chinese electronic databases (CNKI, Sino, Wan Fang, and VIP database). Unpublished conference proceedings relevant to infertile women undergoing IVF-ET were reviewed, if available. MeSH items or free words included: (*In vitro* fertilization OR Intracytoplasmic sperm injection OR Embryo transfer OR Assisted reproductive techniques) AND (systematic review OR Meta-analysis) AND (Acupuncture OR Acupuncture therapy OR Acupuncture points OR Electroacupuncture OR Acupuncture Analgesia). The search strategy of EMBASE is shown in **Appendix** and modified to suit other databases.

Inclusion and Exclusion Criteria

Study Participants

Female patients diagnosed with infertility and undergoing IVF-ET would be included. There were no restrictions in diagnosis criteria or participant age. IVF-ET with intracytoplasmic sperm injection (ICSI) was allowed.

Study Intervention

Treatment with acupuncture must be used as the primary intervention measure. All types of acupuncture (i.e., traditional acupuncture, electro-acupuncture, auricular acupuncture, laser acupuncture) were included. It could be treated with acupuncture alone, or combined with medicine, or with other treatments, regardless of the frequency or duration of the treatment.

Study Comparison

The control interventions included placebo (sham) acupuncture or no adjunctive treatment, or western medicine treatment, or rehabilitation exercise, or Chinese herb medicine, or Tui-na massage, or other convenient controls. Systematic reviews comparing different types of needle were excluded.

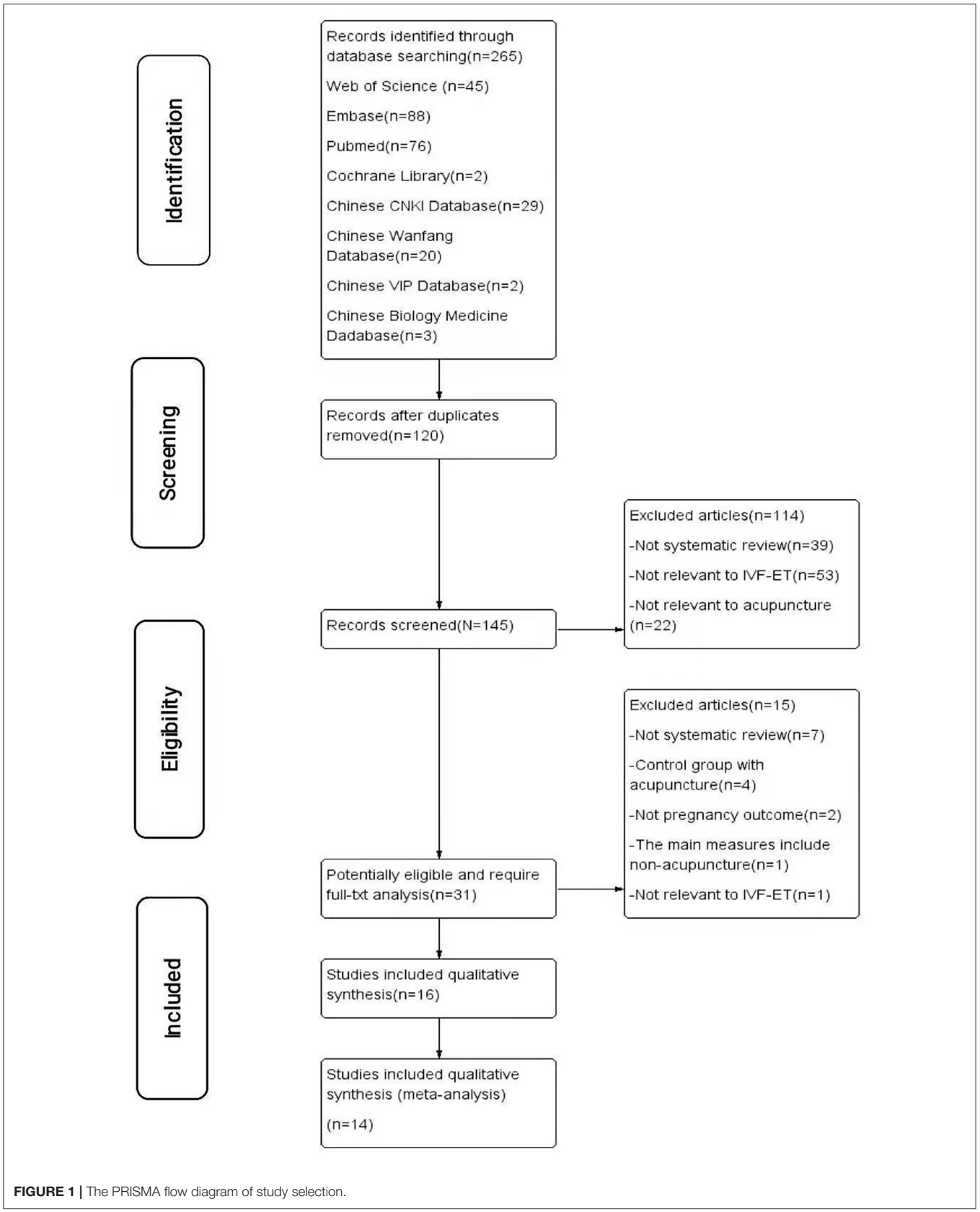


FIGURE 1 | The PRISMA flow diagram of study selection.

TABLE 1 | Basic characteristics of the included SRs.

Study	Language	Number of studies (total sample)	Nature of acupuncture	Nature of control interventions	Time of acupuncture	Primary outcome	Methodological evaluation tool	Data analysis methods
Jang et al. (18)	English	3 (400)	MA/EA	Sham acupuncture or no treatment or other active control	Menstrual and ovulatory cycles	CPR	Cochrane handbook	Not applicable
Smith et al. (19)	English	20 (5,130)	MA/EA	Invasive sham control and no adjunctive treatment	Before and immediately after ET	CPR	Cochrane handbook	Meta-analysis
Gu et al. (20)	English	31 (4,450)	TA/EA/AA/TEAS	No adjunctive treatment or sham acupuncture or western medication	During COH, during the pre-embryo transfer treatment, before and immediately after ET	CPR	Cochrane handbook	Not applicable
Xie et al. (21)	English	27 (6,166)	MA/EA/AA	No adjunctive treatment or sham acupuncture	During COH, during the pre-embryo transfer treatment, before and immediately after ET	CPR/LBR	Cochrane handbook	Meta-analysis
Zhang et al. (22)	English	31 (6,098)	TA/EA/AA/TEAS	No adjunctive treatment or sham acupuncture	Not reported	CPR/LBR/ BPR/OPR/MR	Cochrane handbook	Meta-analysis
Schwarze et al. (30)	English	6 (2,376)	TA	Sham acupuncture	25 or 30 min before and after ET	CPR	Cochrane handbook	Meta-analysis
Jo and Lee (23)	English	4 (430)	MA/EA	Sham acupuncture or no adjunctive treatment	Not reported	CPR/LBR	Cochrane handbook	Meta-analysis
Yang et al. (24)	Chinese	32 (4,815)	MA/EA	No adjunctive treatment or sham acupuncture	Not reported	CPR/LBR	Cochrane handbook	Meta-analysis
Qian et al. (25)	English	30 (6,344)	TA/EA/AA	No adjunctive treatment or sham acupuncture	Before and after ET, or around the time of oocyte aspiration	CPR/LBR/ BPR/ OPR	Cochrane handbook	Meta-analysis
Shen et al. (26)	English	21 (5,428)	MA/LA/EA	No adjunctive treatment or sham acupuncture	The time of ET, or 25 or 30 min before and after ET	CPR	Not reported	Meta-analysis
Manheimer et al. (31)	English	16 (4,021)	TA	No adjunctive treatment or sham acupuncture	Before and after ET	CPR	Cochrane handbook	Meta-analysis
Qu et al. (32)	English	17 (3,713)	TA/AA/EA/LA	No adjunctive treatment or sham acupuncture	Before and after ET	CPR/LBR/BPR/ OPR/MR	Cochrane handbook	Meta-analysis
Zheng et al. (27)	English	24 (5,807)	MA/EA/LA	No adjunctive treatment or sham acupuncture	Before and after ET, or around the time of oocyte aspiration	CPR/LBR	Not reported	Meta-analysis
Yu (28)	Chinese	10 (2,046)	TA/AA/EA	No adjunctive treatment or sham acupuncture	25 or 30 min before and after ET	CPR/LBR/OPR	Jadad	Meta-analysis
Manheimer et al. (29)	English	7 (1,366)	TA	Sham acupuncture or no adjunctive treatment	Before and after ET	CPR/LBR/OPR	Cochrane handbook	Meta-analysis
El-Toukhy et al. (33)	English	13 (2,500)	MA/AA	No adjunctive treatment or sham acupuncture	25 or 30 min before and after ET	CPR/ LBR	Cochrane handbook	Meta-analysis

TA, traditional acupuncture; EA, electrical acupuncture; MA, manual acupuncture; AA, auricular acupuncture; TEAS, transcutaneous electrical acupoint stimulation; LA, laser acupuncture; CPR, clinical pregnancy rate; LBR, live birth rate; BPR, biochemical pregnancy rate; OPR, ongoing pregnancy rate; MR, miscarriage rate; COH, controlled ovarian hyperstimulation.

TABLE 2 | AMSTAR-2 for methodological quality of the included SRs.

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Ranking of quality
Jang et al. (18)	Y	Y	N	PY	Y	Y	N	Y	Y	N	N/A	N/A	Y	Y	N/A	Y	Critically low
Smith et al. (19)	Y	N	Y	Y	Y	Y	N	PY	Y	N	Y	Y	Y	Y	Y	N	Critically low
Gu et al. (20)	Y	N	N	PY	Y	Y	N	Y	Y	N	N/A	N/A	Y	Y	N/A	N	Critically low
Xie et al. (21)	Y	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Critically low
Zhang et al. (22)	Y	N	N	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	N	Y	Critically low
Schwarze et al. (30)	Y	N	N	PY	Y	Y	N	PY	Y	N	Y	Y	Y	Y	Y	N	Critically low
Jo and Lee (23)	Y	N	N	Y	Y	Y	N	PY	Y	N	Y	Y	Y	Y	N	N	Critically low
Yang et al. (24)	Y	N	N	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Critically low
Qian et al. (25)	Y	N	N	Y	Y	Y	N	Y	Y	N	N	Y	Y	Y	N	Y	Critically low
Shen et al. (26)	Y	N	N	PY	Y	Y	N	PY	N	N	Y	N	Y	Y	N	N	Critically low
Manheimer et al. (31)	Y	Y	N	Y	Y	Y	N	PY	Y	N	Y	Y	Y	Y	Y	Y	Critically low
Qu et al. (32)	Y	N	N	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	N	N	Critically low
Zheng et al. (27)	Y	N	N	Y	Y	Y	N	PY	N	N	Y	N	Y	Y	Y	N	Critically low
Yu (28)	Y	N	N	Y	Y	Y	N	PY	Y	N	Y	N	Y	Y	Y	N	Critically low
Manheimer et al. (29)	Y	N	N	Y	Y	Y	N	PY	Y	N	Y	Y	Y	Y	Y	Y	Critically low
El-Toukhy et al. (33)	Y	N	N	Y	Y	Y	N	PY	PY	N	Y	Y	Y	Y	Y	N	Critically low

Study Outcome Measures

The primary outcomes were clinical pregnancy rate (CPR), live birth rate (LBR), biochemical pregnancy rate (BPR), ongoing pregnancy rate (OPR), and miscarriage rate (MR). The secondary outcomes were adverse events.

Study Design

Systematic reviews containing more than one randomized controlled trial (RCT) were included. Non-RCT SRs, review comments, overviews of SRs, editorials, and guidelines were excluded.

Selection of Studies and Data Extraction

According to the intended inclusion and exclusion criteria, the articles were screened independently by two reviewers (XW and YW). Another reviewer (SBW) was involved and made a decision when two authors showed a difference of opinion. One reviewer (XW) used a standardized form to extract the following information from the included articles; another author (YW) reviewed the extracted document. Data extraction included researcher, publication time, number of RCTs enrolled, data synthesis methods, quality assessment tool for RCTs, adverse effects, characteristics of interventions and control groups, primary and secondary outcomes, evaluation criteria of methodology, main results, and conclusions.

Assessment of Systematic Reviews

Two independent reviewers (XW and YW) evaluated the quality of the included SRs. Before the evaluation, each topic of the assessment tools was intensively discussed to reach a consensus.

Assessment of Methodological Quality

The methodological quality of the included reviews was assessed by using A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR-2), which was the latest available assessment tool. The AMSTAR-2 contains 16 domains, of which domains 2, 4, 7, 9, 11, 13, and 15 were the critical items, and the items should not be used to derive an overall score (34). We adopted the rating process based on the identification of critical domains. AMSTAR-2 domains are shown in **Supplementary Figure 2**.

Assessment of Bias

Risk of Bias in Systematic Review (ROBIS) is a new tool for assessing the risk of bias in systematic reviews (35). The four critical elements were "study eligibility criteria," "identification and selection of studies," "data collection and study appraisal" and "synthesis and findings." Each domain was evaluated as "high risk," "low risk," or "unclear risk."

The Quality of Evidence

For each significant result, we gave a score of 4 because these were based on randomized trials and assessed limitations that might have reduced the evidence's quality (36). We deducted points if there were: study limitations; sparse data on an outcome of interest, inconsistent results, indirectness of evidence, or imprecision. According to the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) score, the quality of evidence was classified into high, moderate, low, and very low (36, 37).

Strategy for Data Synthesis

To assess the combined effects of the included reviews, we performed a re-meta-analysis of the main outcomes. The effects of acupuncture on CPR, LBR, BPR, OPR, and MR were observed in women undergoing IVF-ET. Considering the overlap of some primary RCTs, the two reviewers listed the trials for each SR and then excluded the overlapping trials. All data were dichotomous. When no significant heterogeneity could be observed ($I^2 < 50\%$), a fixed-effects model was applied and results were pooled. If there

TABLE 3 | Suggested tabular presentation for ROBIS results.

Review	Phase 2				Phase 3
	1. Study eligibility criteria	2. Identification and selection of studies	3. Data collection and study appraisal	4. Synthesis and findings	Risk of bias in the review
Jang et al. (18)	☺	☺	☺	?	☺
Smith et al. (19)	☺	☺	☺	☺	☺
Gu et al. (20)	☺	☹	☺	?	☹
Xie et al. (21)	☺	☺	☺	☺	☺
Zhang et al. (22)	☹	☺	☺	☺	☹
Schwarze et al. (30)	☹	☹	☹	☺	☹
Jo and Lee (23)	☺	☺	☺	☺	☺
Yang et al. (24)	☺	☺	☺	☺	☺
Qian et al. (25)	☺	☺	☹	☺	☺
Shen et al. (26)	☺	☹	☹	☹	☹
Manheimer et al. (31)	☺	☺	☺	☺	☺
Qu et al. (32)	☹	☺	☹	☹	☹
Zheng et al. (27)	☺	☹	☹	☹	☹
Yu (28)	☹	☺	☺	☹	☹
Manheimer et al. (29)	☺	☺	☹	☺	☺
El-Toukhy et al. (33)	☺	☺	☹	☺	☺

☺, *low risk;* ☹, *high risk; ?, unclear risk.*

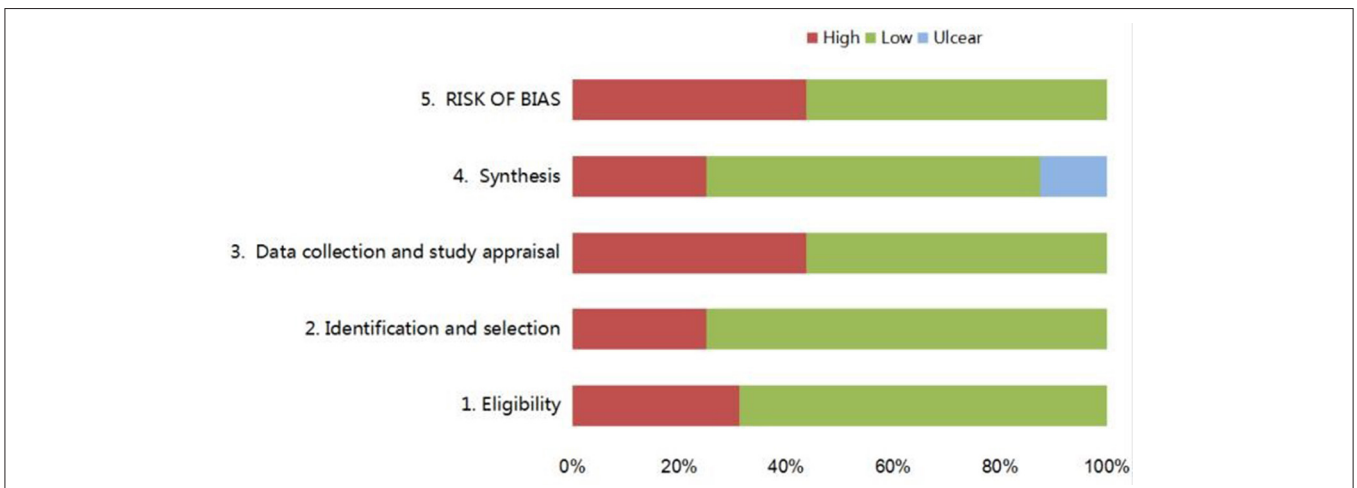


FIGURE 2 | Graphical presentation of risk of bias of the included SRs.

was significant heterogeneity ($I^2 \geq 50\%$), the random-effects model was applied correctly, and expressed as relative risk (RR). The Forest plots were performed with RevMan5.3 software.

We also performed a subgroup analysis of several factors that might influence the CPR of acupuncture. This included: (1) age (≥35 or <35 years); (2) duration of infertility (≥4 or <4 years); (3) number of embryos transferred (≥2 or <2); (4) type of sham (invasive vs. non-invasive); and (5) sham points (yes or no). The information of the variables for subgroup analysis are shown in **Supplementary Table 1**. Sensitivity analysis

TABLE 4 | GRADE for quality of evidence profile.

Outcomes	Study	Number of studies	Effect (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence
CPR	Smith et al. (19)	20	RR 1.32 (1.07, 1.62)	Not serious	Not serious	Not serious	Not serious	None	High
	Xie et al. (21)	27	RR 1.21 (1.07, 1.38)	Serious	Not serious	Not serious	Not serious	None	Moderate
	Zhang et al. (22)	31	RR 1. 19 (1.06, 1.34)	Serious	Not serious	Not serious	Not serious	None	Moderate
	Schwarze et al. (30)	6	RR 0. 87 (0.77, 0.98)	Not serious	Not serious	Not serious	Not serious	None	High
	Jo and Lee (23)	4	RR 1.35 (1.05, 1.74)	Serious	Not serious	Not serious	Serious	None	Low
	Yang et al. (24)	14	RR 1.43 (1.15, 1.77)	Serious	Not serious	Not serious	Not serious	Reporting bias	Low
	Qian et al. (25)	30	OR 1.26 (1.06, 1.50)	Serious	Not serious	Not serious	Serious	Reporting bias	Very low
	Shen et al. (26)	10	RR 1.24 (1.02, 1.50)	Serious	Not serious	Not serious	Not serious	Reporting bias	Low
	Manheimer et al. (31)	7	OR 1.65 (1.27, 2.14)	Serious	Not serious	Not serious	Not serious	None	Moderate
	Qu et al. (32)	17	RR 1. 09 (0.94, 1.26)	Serious	Not serious	Not serious	Serious	Reporting bias	Very low
	Zheng et al. (27)	23	OR 1.22 (1.01, 1.47)	Serious	Not serious	Not serious	Not serious	None	Moderate
	Yu (28)	11	RR 1.34 (1.09, 1.66)	Serious	Not serious	Not serious	Not serious	Reporting bias	Low
	Manheimer et al. (29)	7	OR 1.65 (1.27, 2.14)	Not serious	Not serious	Not serious	Not serious	Reporting bias	Moderate
	El-Toukhy et al. (33)	8	RR 1.23 (0.96, 1.58)	Not serious	Not serious	Not serious	Serious	None	Moderate
LBR	Zhang et al. (38)	12	RR 1.36 (1.09, 1.69)	Not serious	Not serious	Not serious	Not serious	None	High
	Jo and Lee (23)	1	RR 1.61 (0.73, 3.58)	Not serious	Not serious	Not serious	Serious	Reporting bias	Low
	Yang et al. (24)	8	RR 1.18 (0.89, 1.58)	Not serious	Not serious	Not serious	Serious	Reporting bias	Low
	Qian et al. (25)	9	OR 1.17 (0.80, 1.72)	Serious	Not serious	Not serious	Serious	Reporting bias	Very low
	Qu et al. (32)	6	RR 1.42 (0.92, 2.20)	Serious	Not serious	Not serious	Serious	Reporting bias	Very low
	Zheng et al. (27)	6	OR 1.09 (0.74, 1.60)	Serious	Not serious	Not serious	Serious	Reporting bias	Very low
	Manheimer et al. (29)	4	OR 1. 91 (1.39, 2.64)	Not serious	Not serious	Not serious	Not serious	Reporting bias	Moderate
	El-Toukhy et al. (33)	5	RR 1.34 (0.85, 2.11)	Not serious	Not serious	Not serious	Serious	None	Moderate
	Yu (28)	6	RR 1.28 (0.91, 1.79)	Serious	Not serious	Not serious	Serious	Reporting bias	Very low
BPR	Zhang et al. (38)	12	RR 1.12 (0.92, 1.35)	Serious	Not serious	Not serious	Serious	None	Low
	Qian et al. (25)	17	OR 1.06 (0.82, 1.37)	Serious	Not serious	Not serious	Serious	Reporting bias	Very low
	Qu et al. (32)	9	RR 1.01 (0.84, 1.20)	Not serious	Not serious	Not serious	Serious	Reporting bias	Low
OPR	Zhang et al. (22)	9	RR 1.21 (0.95, 1.55)	Serious	Not serious	Not serious	Serious	None	Low
	Qian et al. (25)	10	OR 1.14 (0.87, 1.48)	Serious	Not serious	Not serious	Serious	Reporting bias	Very low
	Qu et al. (32)	8	RR 1.20 (0.93, 1.56)	Serious	Not serious	Not serious	Serious	Reporting bias	Very low
	Manheimer et al. (29)	5	OR 1.87 (1.40, 2.49)	Not serious	Not serious	Not serious	Not serious	Reporting bias	Moderate
	Yu (28)	6	RR 1.28 (0.91, 1.79)	Serious	Not serious	Not serious	Serious	Reporting bias	Very low
MR	Zhang et al. (22)	12	RR 0.89 (0.67, 1.20)	Serious	Not serious	Not serious	Serious	None	Low
	Qu et al. (32)	5	RR 0.94 (0.67, 1.33)	Serious	Not serious	Not serious	Serious	Reporting bias	Very low

was performed to explore whether the overall conclusions were affected.

RESULTS

Results on Literature Search and Selection

A total of 265 records were collected from electronic databases. In total, 120 duplicates were excluded by filtration; 114 of the remaining citations were excluded by title and abstract screening, and 31 studies were assessed through the full texts. After being reviewed by two reviewers independently, 16 SRs about acupuncture for infertile women undergoing IVF-ET were included (**Figure 1**). The reasons for exclusion are shown in **Supplementary Figure 2**.

Characteristics of Included Reviews

The sixteen included reviews (18–33) were published between 2008 and 2020. Fourteen reviews were published in English, two in Chinese. This overview included 312 original RCTs and 65,388 participants. The number of RCTs of included SRs ranged from 3 to 32 studies. As for intervention, all reviews compared acupuncture with no adjunctive treatment or sham

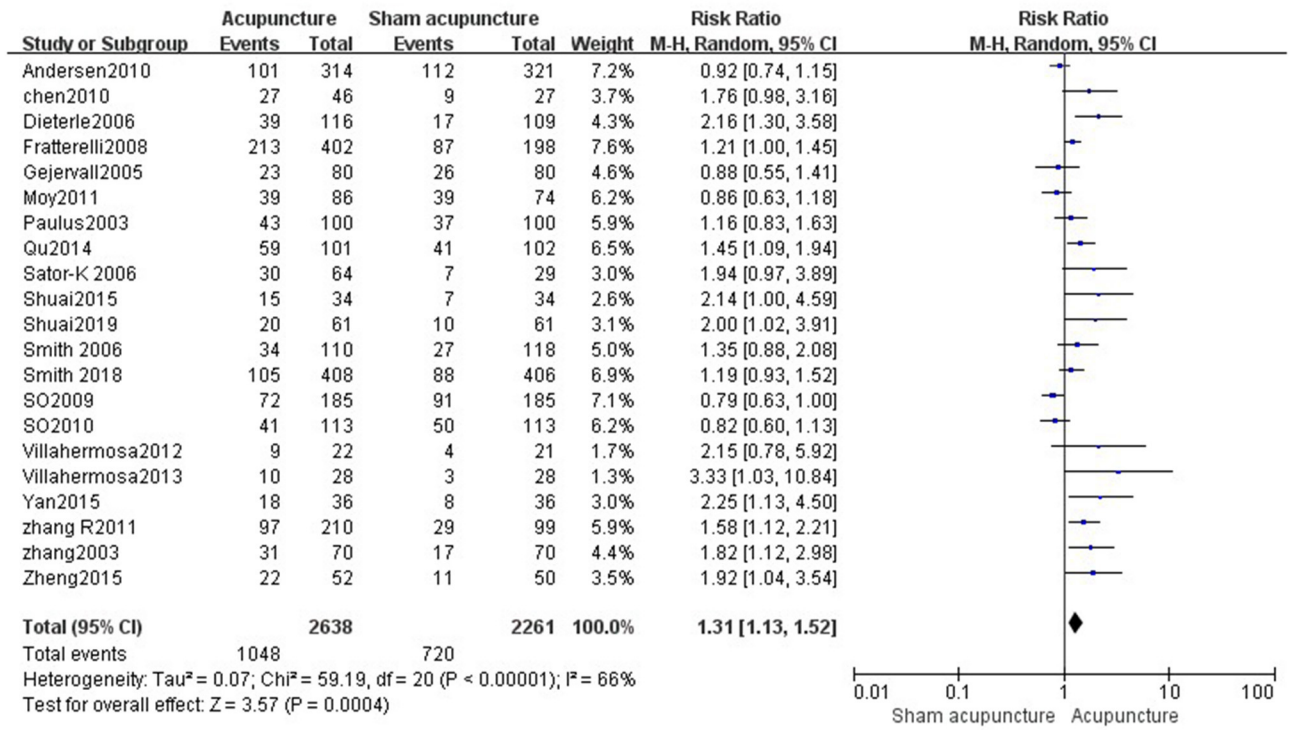


FIGURE 3 | Acupuncture vs. sham acupuncture on the clinical pregnancy rate.

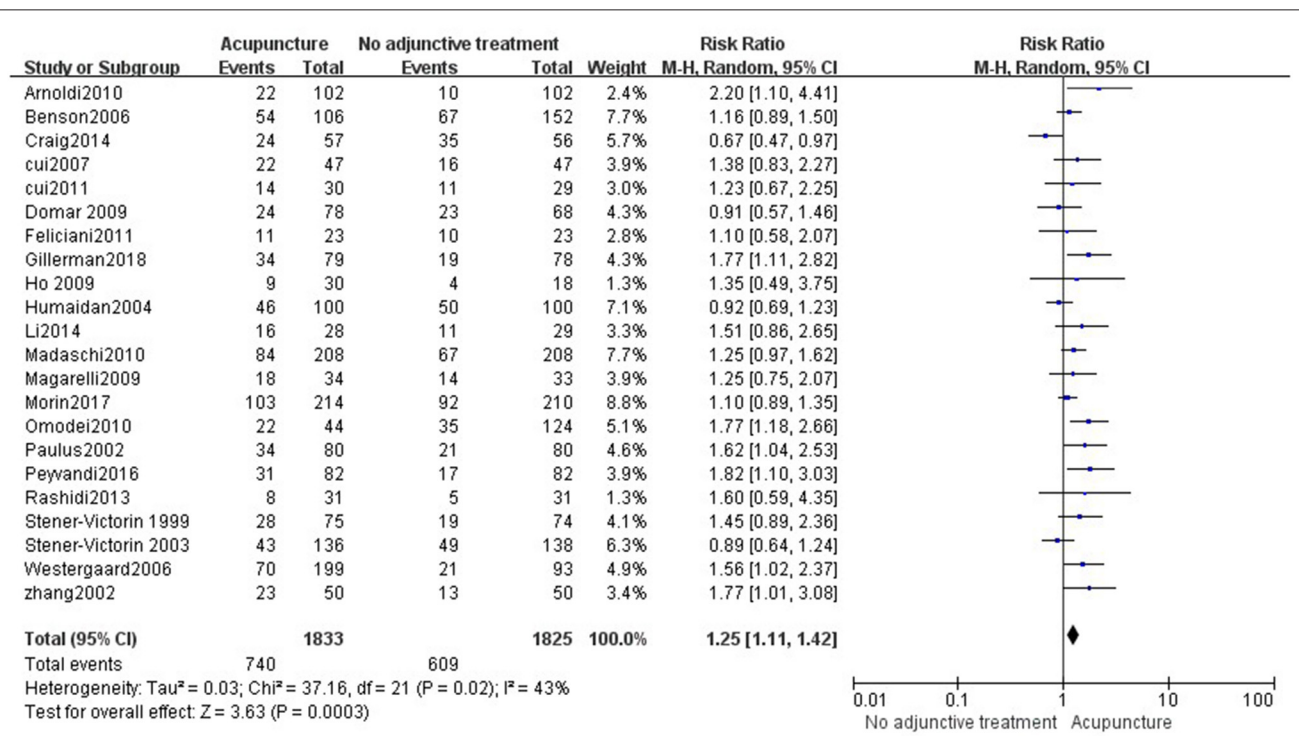


FIGURE 4 | Acupuncture vs. no adjunctive treatment on the clinical pregnancy rate.

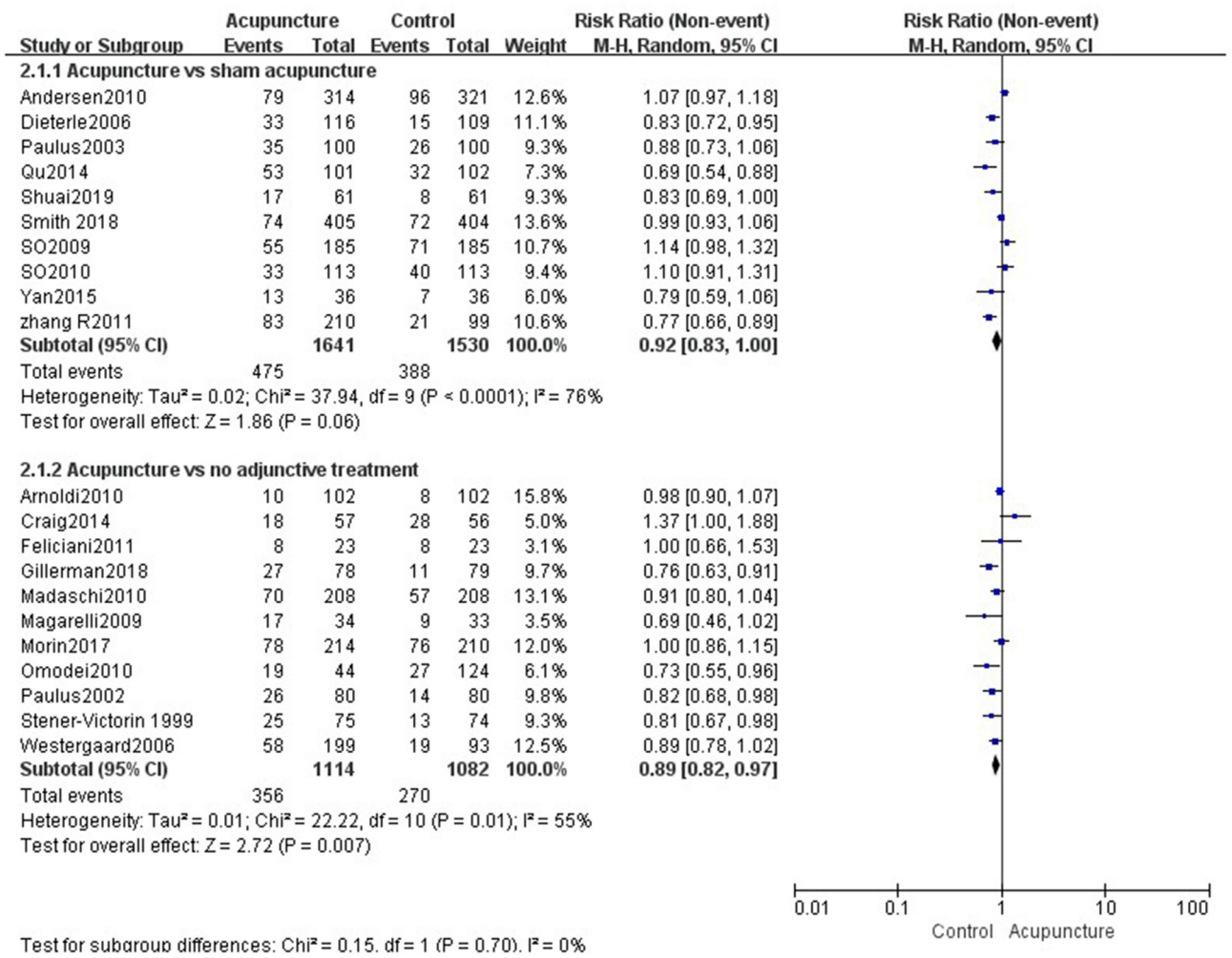


FIGURE 5 | Effects of acupuncture on the live birth rate.

(placebo) acupuncture. Eight reviews (20, 22, 25, 28–32) included traditional acupuncture as the main intervention. Twelve reviews (18–28, 32, 33) used electroacupuncture as an intervention measure. Eight SRs (18, 19, 21, 23, 24, 26, 27, 33) used manual acupuncture as a therapeutic intervention. Five SRs (20, 22, 26, 27, 32) included auricular acupuncture as an intervention measure. Five reviews (20–22, 25, 32) used transcutaneous electrical acupoint stimulation or laser acupuncture as the intervention. One review (30) used sham acupuncture as the control group, while others used sham acupuncture or no adjunctive treatment. Only one review (28) applied the Jadad scale for methodological quality assessment of original RCTs, and thirteen SRs (18–25, 29–33) used the Cochrane Handbook, but two reviews (26, 27) did not report the methodological tool. **Table 1** shows the basic characteristics of the included SRs.

Methodological Appraisal

AMSTAR-2 was used to assess the methodological quality of studies. The qualities of sixteen reviews were considered critically low, because they had more than one critical flaw (items 2, 4, 7, 9, 11, 13, and 15) with multiple non-critical weaknesses. Fourteen SRs (19–30, 32, 33) were not registered in advance, and we could not judge whether the review methods were established in advance. Only one author (19) explained their selection of the study designs for inclusion in the review. Eleven reviews (19, 22–25, 27–29, 31–33) described a comprehensive literature search strategy. Only one review (21) provided a list of excluded studies. None of the SRs described the funding sources of included RCTs. Fourteen reviews (19, 21–33) applied meta-analytical methods, and all of them explained reasons for heterogeneity reasonably. Nine studies did not declare the conflicts of interest or provide a source of funding. The details of the assessment of the quality of the included SRs are shown in **Table 2**.

Risk of Bias of Included Systematic Reviews

The assessment of the risk of bias of each review is shown in **Table 3** and **Figure 2**. The final phase considered the overall risk of bias of SRs, and nine SRs (56.25%) were rated with a low-risk of bias. Seven SRs (43.75%) were rated with a high-risk of bias,

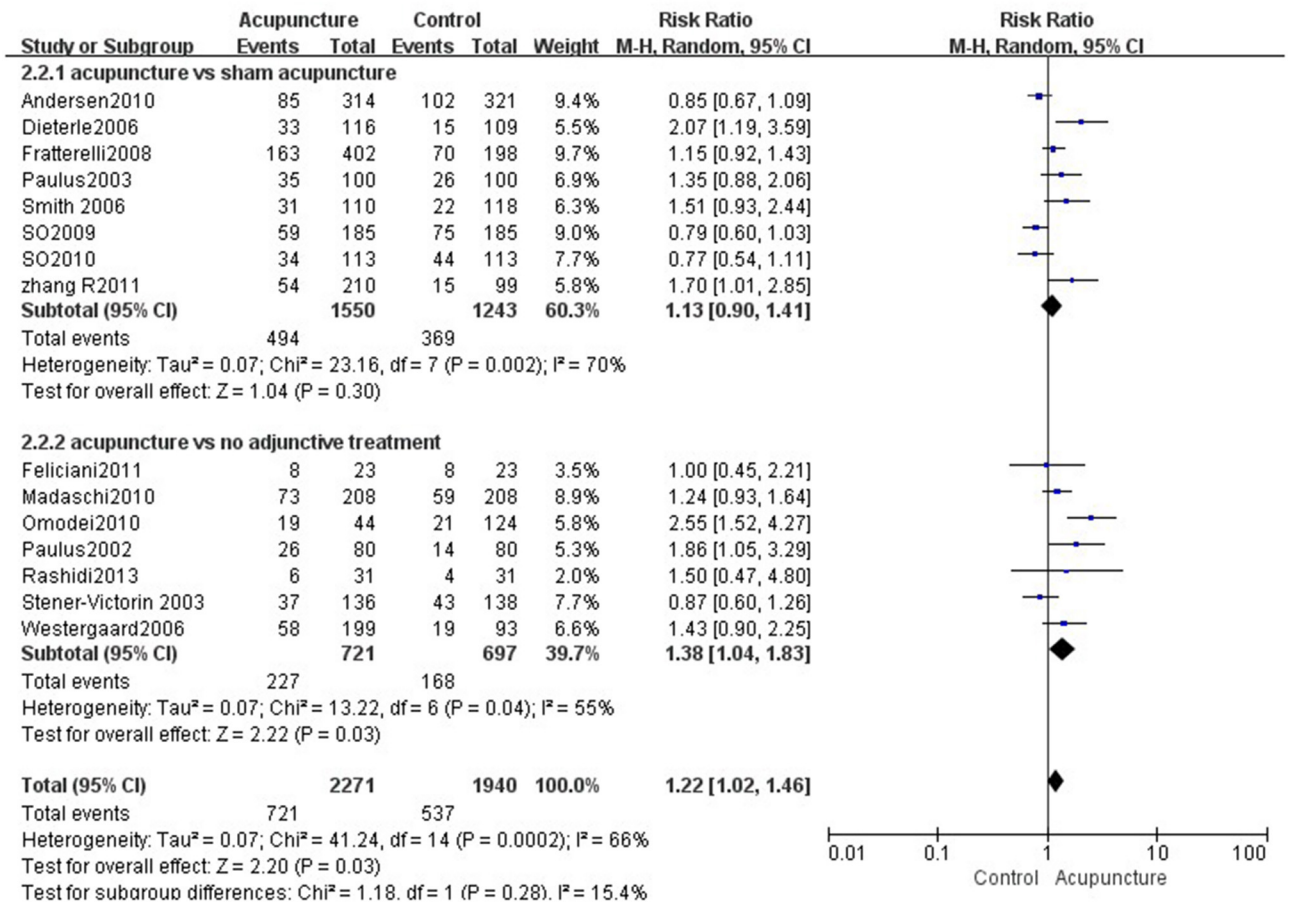


FIGURE 6 | Effects of acupuncture on the ongoing pregnancy rate.

and the main reason for the risk of bias in SRs was the failure to adequately explain and deal with the risk of bias in their results.

GRADE for Quality of Evidence Profile

Fourteen reviews (19, 21–33) included 35 outcomes that were related to the effectiveness of acupuncture for IVF-ET. The risk of bias, imprecision, and reporting bias were the main reasons for downgrading. There was high or moderate or low or very low-grade evidence to indicate that acupuncture might improve the CPR and LBR when acupuncture was performed on the day of ET. The qualities of the evidence are shown in **Table 4**.

Effect of the Interventions

Acupuncture vs. Sham Acupuncture

Fourteen reviews (19, 21–33) encompassing 21 primary RCTs (4,899 participants) suggested that acupuncture was superior to sham acupuncture in increasing the CPR of IVF-ET (RR = 1.31, 95% CI: 1.13–1.52, $p = 0.0004$). However, there was substantial heterogeneity for the CPR ($I^2 = 66\%$) (**Figure 3**). There was no statistical difference between the acupuncture and sham acupuncture groups for improving LBR (RR = 0.92, 95% CI: 0.83–1.00, $p = 0.06$, 10 RCTs, 3,171 participants) or OPR (RR = 1.13, 95% CI: 0.90–1.41, $p = 0.30$, 8 RCTs, 2,793 participants) (**Figures 5**, **6**). The benefits for reducing MR (OR = 1.20, 95% CI: 0.87–1.65, $p = 0.28$, 7 RCTs, 2,698 participants) or BPR (RR = 1.08, 95% CI: 0.87–1.32, $p = 0.49$, 8 RCTs, 2,581participants) were not significant between the acupuncture and control groups (**Figures 7**, **8**).

Acupuncture vs. No Adjunctive Treatment

Data were obtained from 22 RCTs (3,658 participants) out of the 14 included reviews. When using the random-effects model, the pooled results showed that acupuncture groups were significantly better than no adjunctive treatment group in improving the CPR (RR = 1.25, 95% CI: 1.11–1.42, $p = 0.0003$; **Figure 4**). The results of 11 RCTs (2,196 participants) suggested that acupuncture was not better than no adjunctive treatment in the LBR (RR = 0.89, 95% CI: 0.82–0.97, $p = 0.007$; **Figure 5**). OPR data from 7 RCTs out of the 14 included reviews were available (1,418 participants). A significant difference in the OPR was observed when the random-effects model was used (RR = 1.38, 95% CI: 1.04–1.83, $p = 0.03$; **Figure 6**). Moreover, acupuncture was more superior than no adjunctive treatment on MR reduction (OR = 1.42, 95% CI: 1.03–1.95, $p = 0.03$, 12 RCTs, 2,465 participants)

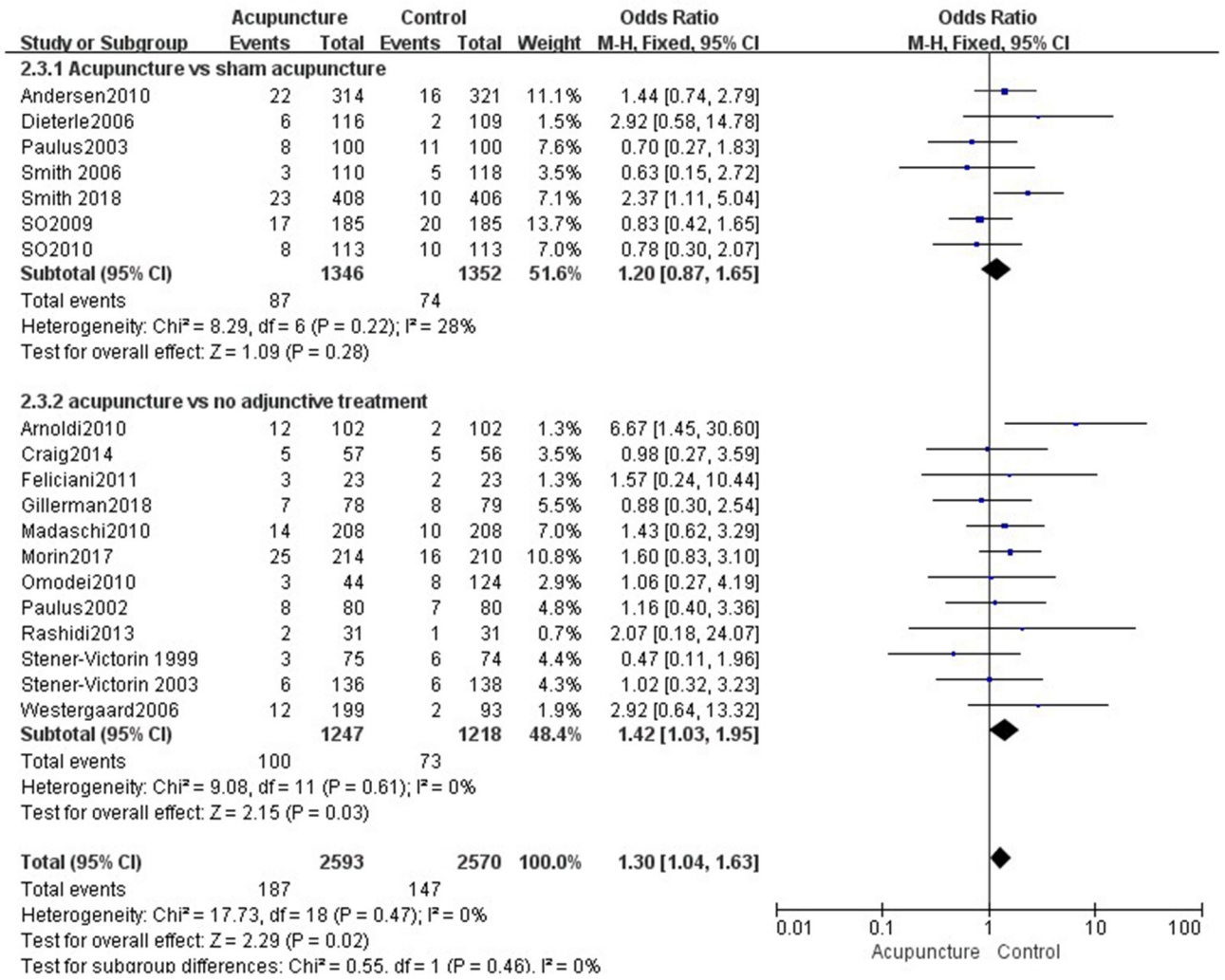


FIGURE 7 | Effects of acupuncture on the miscarriage rate.

(**Figure 7**). The pooled results showed a significant difference in reducing the BPR (RR = 1.19, 95% CI: 1.02–1.37, $p = 0.02$) between acupuncture groups and no adjunctive treatment groups (**Figure 8**).

Subgroup Analysis on Clinical Pregnancy Rate

Sensitivity analysis was conducted by examining individual studies, the pooled results were not affected. Age below 35 years was a significant factor in the CPR (RR = 1.41, 95% CI: 1.15–1.74). Studies that used the invasive sham control showed a significant difference in the CPR (RR = 1.77, 95% CI: 1.09–2.86), and non-invasive sham control also significantly improved the CPR (RR = 1.28, 95% CI: 1.06–1.53). The duration of infertility over 4 years was not conducive to improving the CPR (RR = 0.81, 95% CI: 0.71–0.93). The number of transplanted embryos more than two (RR = 0.79, 95% CI: 0.70–0.88) and the absences of sham acupoint controls (RR = 0.82, 95% CI: 0.74–0.92) were detrimental to the CPR. Age over 35 years, duration of infertility <4 years, and sham points were not significant modifiers of the CPR. **Table 5** shows the results of the subgroup analysis of outcomes regarding the CPR.

Adverse Effects

A total of five reviews (18, 19, 22, 29, 31) mentioned adverse events. Only three SRs (18, 19, 22) reported adverse events, including mild allergy, nausea, drowsiness, headache, chest pain, dizziness, and fatigue, while the other two SRs (29, 31) reported no serious adverse events.

DISCUSSION

Summary of Main Findings

This updated overview of 16 SRs summarized the clinical evidence on the effectiveness and safety of acupuncture for infertile women undergoing IVF-ET from 312 primary studies that included 65,388 participants, and evaluated the

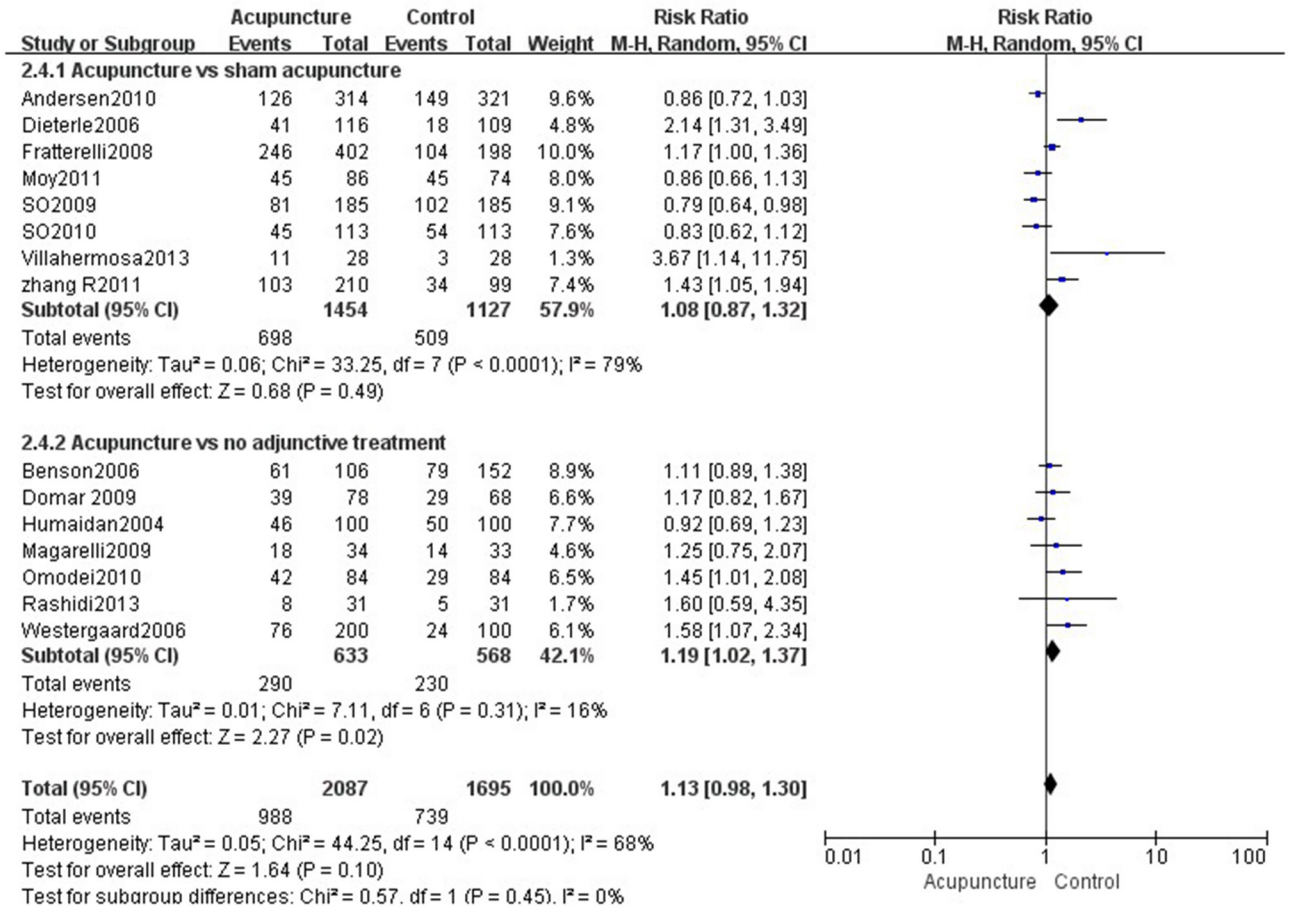


FIGURE 8 | Effects of acupuncture on the biochemical pregnancy rate.

methodological quality and quality of evidence. The current evidence indicated that acupuncture appeared to be superior to the control group in improving the CPR of IVF-ET. However, the methodological qualities of SRs were critically low, and the GRADE for the quality of evidence profile was suboptimal. By using the ROBIS tool, seven SRs were rated with a high-risk bias. Some SRs showed that acupuncture might be increasing LBR and OPR, but the sample was insufficient. No significant difference was found in reducing BPR and MR between groups. High-quality RCTs with large sample sizes were necessary to demonstrate the clinical effectiveness of acupuncture for IVF-ET.

In this overview, we used AMSTAR-2 to assess the methodological quality of SRs. The confidence of the overview was critically low. In some reviews using AMSTAR-2, we also found that the overall confidence in the results was rated as critically low (38–40). AMSTAR-2 was updated in 2017, so previous SRs might not have covered some items of AMSTAR-2. It might be one reason why most of the SRs were critically low as assessed by AMSTAR-2. The methodological quality of SRs was limited by the lack of data on registration and funding, comprehensive search strategy, a list and justification of excluded articles, and explanation of the risk of bias. Future research should pay attention to the above issues. The GRADE system was used to assess the evidence quality of the included SRs. The strength of evidence was moderate or low or very low for most outcomes. Most of the outcome indicators were demoted because of the bias in random, distributive hiding, or blind studies. Due to the characteristics of acupuncture, it was difficult for patients to achieve blinding, so it was important to separate researchers.

Our re-meta-analysis finds that acupuncture in IVF-ET trials appears to increase CPR, OPR, and LBR compared with no adjunctive treatment. The differences are not significant compared with sham acupuncture in increasing OPR and LBR. Since the quality of the methodology of all the SRs included is critically low, there is a high probability that the result of the re-meta-analysis is biased. There is significant heterogeneity in these clinical studies of acupuncture. Almost every trial has a different approach design in terms of interventions, the timing of treatments, controls, and outcome measures. Subgroup analysis is used to explore the factors that may affect the CPR of acupuncture. Age below 35 years is a significant factor on reproductive outcomes. Non-invasive

TABLE 5 | Subgroup analysis on clinical pregnancy rate.

Characteristic	Subgroup analyses				Heterogeneity	
	No. of subjects	No. of studies	RR (95% CI)	*P*-value	I^2	*P*
Age						
≥35 years	1,796	6	1.15 (0.85, 1.54)	0.36	72%	0.003
<35 years	2,430	13	1.41 (1.15, 1.74)	0.001	65%	0.0007
Duration of infertility						
≥4 years	1,627	11	0.81 (0.71, 0.93)	0.003	69%	0.0004
<4 years	863	2	0.98 (0.84, 1.13)	0.76	58%	0.13
No. of embryos transferred						
≥2	1,093	6	0.79 (0.70, 0.88)	<0.0001	33%	0.19
<2	2,307	6	1.02 (0.92, 1.13)	0.07	61%	0.02
Type of sham						
Invasive	629	6	1.77 (1.09, 2.86)	0.02	72%	0.003
Non-invasive	3,510	13	1.28 (1.06, 1.53)	0.009	69%	0.0001
Sham points						
Yes	1,245	4	0.94 (0.86, 1.03)	0.16	18%	0.30
No	2,894	15	0.82 (0.74, 0.92)	0.0004	71%	<0.0001

sham control also shows a significant difference, so it is also important to estimate the placebo effect of sham acupuncture in acupuncture IVF-ET trials. Currently, most trials adopt the protocol of Paulus (41), involving acupuncture treatments before and after ET. However, the quality of the embryo is essential, but acupuncture only before and after ET has significant limitations.

Strengths and Limitations

To reduce the risk of bias, we only included the SRs of randomized trials. We evaluated the methodological quality of the included SRs by using the AMSTAR-2 tool, which was the latest available assessment tool. We assessed the GRADE score to determine the strength of evidence. We excluded the overlapping RCTs and performed a re-meta-analysis of the primary RCTs. To minimize potential bias in the overview process, we used more than two reviewers in the literature screening, data extraction, and quality assessment.

The latest RCTs were unlikely to be included in the recently published SRs, so there was some publication bias. Almost every IVF-ET trial had a different methodological design, which tended to cause severe heterogeneity, which limited the ability to interpret aggregate estimates. We collected evidence for acupuncture in IVF-ET, but we could not separate the different types of acupuncture intervention and timing of treatments.

Opportunities for Future Research

There is some debate about the effectiveness of acupuncture to treat infertile women undergoing IVF-ET. Acupuncture appears to be superior to the control group in improving the CPR of IVF-ET, but the evidence should be treated cautiously because of the methodological flaws. Recommendations for further studies are as follows: ① Most RCTs are considered to have an unclear risk of bias in the domains of allocation concealment and selective outcome reporting due to poor reporting, so RCTs should comply with the relevant guidelines. ② In most of the included studies, acupuncture was performed within a few days or hours before and after ET. So we can perform acupuncture during COH to observe the effect of acupuncture on the number of eggs obtained and oocyte quality. ③ The duration of acupuncture may also influence the efficacy of acupuncture. Increasing the duration of insertion may increase the cumulative effect of acupuncture. ④ Some reviews found that women with a history of multiple IVF-ET failures would benefit more from the effect of acupuncture, so more relevant RCTs should be conducted to estimate the effectiveness of acupuncture in the future. ⑤ Acupuncture and placebo acupuncture touching the skin would evoke activity in cutaneous afferent nerves and leading to the "limbic touch response," so they were equally effective (42). Therefore, it is also necessary to estimate the clinical effects of sham acupuncture in acupuncture IVF-ET trials. The difference of non-specific effect between acupuncture and sham acupuncture can be reduced to the maximum extent through the effective blind and random method. ⑥ An advance registration contributes to improving transparency and minimizes potential bias. Only two SRs reported the protocol or registration number, so advance registration should be encouraged.

CONCLUSION

This study reviews the SRs of acupuncture for infertile women undergoing IVF-ET. Based on the current evidence, acupuncture appears to be beneficial to increase the CPR in women undergoing IVF-ET. However, there are severe heterogeneity and methodological quality defects, which limit the reliability of results. Further, high-quality primary studies are still needed.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

XW and YW participating in study design, critical dialogue, data analysis, and article writing. SW contributed to the design of this study, participated in critical dialogue, and revised the manuscript. BH, YC, and NZ contributed to the literature search and extracted data. ML proofread the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.651811/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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APPENDIX

The following search strategy was used for EMBASE and was modified to suit other databases.
#1. "*in vitro* fertilization"/exp OR "*in vitro* fertilization" (94,173)
#2. "intracytoplasmic sperm injection" (22,292)
#3. "embryo transfer" (34,983)
#4. "assisted reproductive techniques" (2,769)
#5. #1 OR #2 OR #3 OR #4 (9,7692)
#6. acupuncture (51,982)
#7. "acupuncture therapy" (1,780)
#8. "acupuncture points" (2,067)
#9. "electroacupuncture" (8,057)
#10. "acupressure" (2,405)
#11. "acupuncture analgesia" (2,164)
#12. #6 OR #7 OR #8 OR #9 OR #10 OR #11 (54,401)
#13. "review it" (2,912)
#14. "systematic review" (330,910)
#15. "meta analysis" (290,000)
#16. "systematic∗ review∗" (357,380)
#17. "meta analy∗" (307,640)
#18. #13 OR #14 OR #15 OR #16 OR #17 (504,371)
#19. #5 AND #12 AND #18 (88).

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Comparative Utility of Genetic Determinants of Drug Resistance and Phenotypic Drug Susceptibility Profiling in Predicting Clinical Outcomes in Patients With Multidrug-Resistant *Mycobacterium tuberculosis*

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Setting: Programmatic management of drug-resistant tuberculosis in Ningbo, China.

Objective: To assess whether data-driven genetic determinants of drug resistance patterns could outperform phenotypic drug susceptibility testing in predicting clinical meaningful outcomes among patients with multidrug-resistant tuberculosis (MDR-TB).

Design: We conducted a prospective cohort study of 104 MDR-TB patients. All MDR-TB isolates underwent drug susceptibility testing and genotyping for mutations that could cause drug resistance. Study outcomes were time to sputum smear conversion and probability of treatment success, as well as time to culture conversion within 6 months. Data were analyzed using latent class analysis, Kaplan–Meier curves, and Cox regression models.

Results: We report that latent class analysis of data identified two latent classes that predicted sputum smear conversion with $P = 0.001$ and area under receiver-operating characteristic curve of 0.73. The predicted latent class memberships were associated with superior capability in predicting sputum culture conversion at 6 months and overall treatment success compared to phenotypic drug susceptibility profiling using boosted logistic regression models.

Conclusion: These results suggest that genetic determinants of drug resistance in combination with phenotypic drug-resistant tests could serve as useful biomarkers in predicting treatment prognosis in MDR-TB.

Keywords: genetic determinant, resistance, multidrug, mycobacterium tuberculosis, phenotypic drug susceptibility test

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INTRODUCTION

According to World Health Organization (WHO) report, there were approximately half a million new cases of rifampicin-resistant tuberculosis (TB) worldwide, of which 78% had multidrug-resistant TB in 2019. China is among the countries with the highest burden of multidrug-resistant tuberculosis (MDR-TB), with prevalence rate of MDR-TB at 5.7 and 25.6% among new and previously treated cases, respectively (1, 2).

Early detection of MDR-TB is essential to worldwide TB eradication efforts, as MDR-TB continues to be a great public health threat (3, 4). While drug susceptibility testing (DST) for culture-positive TB patients is recommended by the national guidelines on TB management, there is a growing evidence in the literature that phenotypic DST is not only time consuming but also oftentimes fails to detect mutations that confer poor clinical outcomes (5, 6). The effect of drug resistance on treatment outcomes has not been studied adequately. In addition, it is unclear if genotypic DST results could supplement first- and second-line phenotypic drug susceptibility profiling to better predict treatment outcomes among patients with MDR-TB.

We aimed to identify subgroups of MDR-TB patients who share similar patterns of genetic determinants of drug resistance using latent class analysis (LCA). We compared demographic and clinical characteristics associated with genotypic DST latent classification. Finally, we investigated the comparative utility of genetic mutation profile and the drug-resistant phenotype in predicting clinical important outcomes of MDR-TB.

MATERIALS AND METHODS

Study Population

We conducted the present study in Ningbo, China, where the estimated incidence of TB was 43.77 per 100,000 residents in 2019. We conducted a prospective cohort study between 2015 and 2017 in Ningbo, China. All subjects were followed until cure, treatment completion, death, end-of-study period (31 December 2019), loss to follow-up, whichever came first. MDR-TB [defined as resistant to at least isoniazid (INH) and rifampin (RFP)] was identified by a laboratory at Ningbo Tuberculosis Control Institute using the conventional DST. Study participants signed an informed consent form and were enrolled. Their demographic characteristics and clinical information were obtained from patients' medical record at local TB dispensaries. Patients were included if they were diagnosed as MDR-TB and if they gave informed consent. Exclusion criteria included pregnancy, age below 18 years old at TB diagnosis, and serious liver or renal dysfunction.

This study was approved by the Ethics Committee of Ningbo Municipal Center for Disease Control and Prevention. Written informed consent was obtained from all participants. This study was conducted in accordance with the Declaration of Helsinki.

Drug Susceptibility Testing and Strain Identification

The isolates were cultured on Lowenstein–Jensen (L–J) medium for 4–8 weeks, and the culture with growing colonies were further evaluated for drug susceptibility testing at regional reference laboratories. Testing for susceptibility to four first-line anti-TB drugs and seven second-line drugs was performed with the proportional method recommended by WHO (7). The concentrations of drugs in L–J medium were as follows: isoniazid (INH), 0.2 μg/ml; rifampicin (RFP), 40 μg/ml; ethambutol (EMB), 2 μg/ml; streptomycin (SM), 4 μg/ml; ofloxacin (OFX), 2 μg/ml; levofloxacin (LFX), 2 μg/ml; kanamycin (KM), 30 μg/ml; amikacin (AMK), 30 μg/ml; capromycin (CM), 40 μg/ml; protionamide (PTO), 40 μg/ml, and p-aminosalicylic acid (PAS), 1 μg/ml (7). The pyrazinamide (PZA) drug susceptibility testing was performed with a Bactec MGIT 960 system, and critical concentration was 100 μg/ml (8). Quality control was performed during DST using the H37RV reference strains. Members of the Beijing family of strains were identified by the RD105 multiplex PCR (9).

DNA Extraction and Sequencing of Drug-Resistance-Related Genes

The crude DNA was extracted from freshly harvested bacteria as reported (10). The cultured bacteria that were extracted from the surface of L–J medium were suspended in 500 μl Tris-EDTA (TE) buffer and heated in a 95°C water bath for 30 min. The genomic DNA was used as template for amplification. Expected fragments were amplified. Each 30 μl PCR mixture contained 15 μl 2×GoldStar MasterMix (CWBio, Beijing, China), 1 μl (each) of the forward and reverse primers (5 μM), 12 μl distilled H_2O, and 1 μl of genomic DNA. The reaction conditions consisted of a denaturation step of 5 min at 95°C followed by 35 cycles of 30 s at 94°C, 30 s at 60°C, and 45 s at 72°C, with a final extension step of 5 min at 72°C. PCR products were carried out at Personalbio Company (Shanghai, China). Gene polymorphisms were aligned with pncA of reference strain H37RV (ATCC) using DNAstar MegAlign (version 7.1) software.

Definitions of DR-TB Types and Outcomes

MDR-TB were defined as those resistant to both isoniazid and rifampicin. Pre-XDR TB was defined as MDR-TB additionally resistant to either quinolone family or second-line anti-TB injectable drugs, but not both. XDR-TB was defined as MDR-TB resistant to any member of the quinolone family and at least one of the remaining second-line anti-TB injectable drugs (11).

All patients were followed for the treatment outcomes. Sputum smear and culture were performed in accordance of the national TB guidelines. We assessed time to sputum conversion as time-to-event endpoint while time to culture conversion at month 6 after treatment initiation as binary outcomes. We further used standard WHO outcomes definitions for MDR tuberculosis: cure, treatment completion, treatment failure, death from any case, default, and transfer out (12, 13). We defined successful outcomes as cure or completion of treatment and poor outcomes as failure or death. Collectively, these were considered favorable outcomes, whereas unfavorable outcomes included default, transfer, or continuing treatment.

Statistical Analysis

We performed latent class analysis models to estimate patterns of genotypic markers in the sample of MDR-TB isolates (14). Seven genetic determinants comprising *pnc*A, *rrs*, *rpsL*, *gyr*A, *gyr*B, *emb*B, and Beijing genotype were included as explanatory latent class indicators. Model fit indices such as Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) were calculated to determine the best-fitting subclass structure, with smaller values indicating better fit (15). A series of models with increasing number of classes ranging from 2 to 7 were assessed to determine the optimal number of latent classes using model fit indices, interpretability, theoretical justification, and parsimony considerations. The final LCA model selection was based upon these measures varied within a plausible range and clinical judgment.

Descriptive and inferential statistics were used to compare baseline demographic and clinical characteristics across latent classes within MDR-TB cohort. Continuous variables were summarized as means and standard deviations. Categorical variables were summarized as counts and percentages. Statistical comparisons between groups were performed using Student's *t*-test for continuous variables and χ^2 test for categorical variables.

Once the optimal number of latent classes was defined, we used univariate logistic regression models to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for associations between latent class membership, baseline demographic, clinical characteristics, and DST-related covariates with binary outcomes. We used multivariable Cox regression models to estimate hazard ratios (HRs) and 95% CIs for associations between pretreatment characteristics and sputum smear conversion in time-to-event analysis.

We then assessed the performance of both genotypic latent class and phenotypic DST results as predictors in fully adjusted multivariable analyses on all three clinical outcomes. LogitBoost classification algorithm with built-in feature selection was applied on the analytical dataset using the popular open-source R package caret. In predictive model, the learning objective function was binary logistic. Overfitting was minimized by introducing log-likelihood loss function to reduce the sensitivity to noise and outliers. Its performance is further enhanced by performing classification via combining many weak classifiers into a more robust classifier (16). All classifiers were run on the dataset in a 10-repeated nested 5-fold cross-validation with hyperparameter tuning. Performance metrics [area under the curve (AUC) and accuracy] were computed.

All statistical tests were two-tailed, and a $p < 0.05$ was defined *a priori* as statistically significant. Analyses were conducted using open-source software R 4.0.2 including the poLCA and caret packages (https://CRAN.R-project.org).

RESULTS

Demographic and Clinical Characteristics of Study Participants

During the study period, a total of 332 patients were diagnosed with MDR-TB, of which 225 consecutive MDR-TB patients with full medical and microbiological information were assessed for study eligibility. After excluding patients who failed to meet the selection criteria, 104 MDR-TB patients with complete genotypic markers profiles were included in the final analysis (**Figure 1**).

The baseline characteristics for the eligible patients with MDR-TB according to genetic determinants of drug resistance patterns are presented in **Table 1**. The majority of patients were male (71.2%), permanent resident (54.8%), and have a previous history of tuberculosis treatment (61.5%). Cavity disease was present in 60 patients (57.7%). With regard to the treatment history among MDR-TB cases, the percentage of retreated MDR-TB patients in the class 2 group was significantly higher than in the class 1 group ($P < 0.05$). Additionally, we found that no statistically significant difference between the class 1 and class 2 group in age, gender, permanent resident, and cavity. Model fit statistics are shown in **Supplementary Table 1**.

Characteristics of Genotypic Markers

Totally, 53 out of 104 (51.0%) MDR-TB isolates observed a mutation located in the *pnc*A gene, including 48 (90.6%, 48/53) of single nucleotide substitutions and 5 (9.4%, 5/53) of frame-shift mutation. As shown in **Supplementary Table 2**, we found a great mutant diversity in *pnc*A gene (17–19). The gene mutation percentage of *rrs*, *rpsL*, *gyrA*, *gyrB*, and *embB* in MDR-TB isolates were (7.7%, 8/104), (50.0%, 52/104), (33.7%, 35/104), (2.9%, 3/104), and (56.7%, 59/104). We found the gene mutation percentage of *pnc*A, *rps*L, *gyr*A, and *emb*B in class 1 group was significantly higher than in class 2 group ($P < 0.05$) (**Supplementary Figures 1, 2**).

Drug Susceptibility Profiles

We analyzed the resistance phenotypic of anti-TB drugs between class 1 and class 2 groups. We found that the resistance of ofloxacin (57.4 vs. 7.0%, $P < 0.001$), levofloxacin (55.3 vs. 8.8%, $P < 0.001$), and pre-XDR (55.3 vs. 8.8%, $P < 0.001$) were more frequently detected among class 1 groups compared with class 2 groups. Additionally, we also found that the drug resistance pattern (INH + RFP + SM + EMB) has significant difference between class 1 and class 2.

Treatment Outcomes

Successful treatment outcome occurred in 43 (41.3%) of the 104 patients. Forty-two (40.4%) treatment interrupted due to ADR, 10 (9.6%) died, and 9 (8.7%) lost to follow-up. It showed that no statistically significant difference between the class 1 and class 2 group in treatment outcome. Among the sputums of 104 patients, 76 (73.1%) were negative at 2 months, 76 (73.1%) negative at 6 months, and 82 (78.8%) converted to negative. There was no significant difference between class 1 and class 2 in sputum conversion at 2 or 6 months and no difference in culture conversion at 6 months after TB diagnosis.

In this study, MDR-TB treatment was administered daily, in accordance with WHO guidelines. The recommended treatment course comprises a 6-month intensive phase and 18-month continuation phase using the regimen: 6ZKmLfxPtoPAS (Z = PZA; Km = Kanamycin, Lfx = levofloxacin; Pto = ethionamide; PAS = para-aminosalicylic acid).

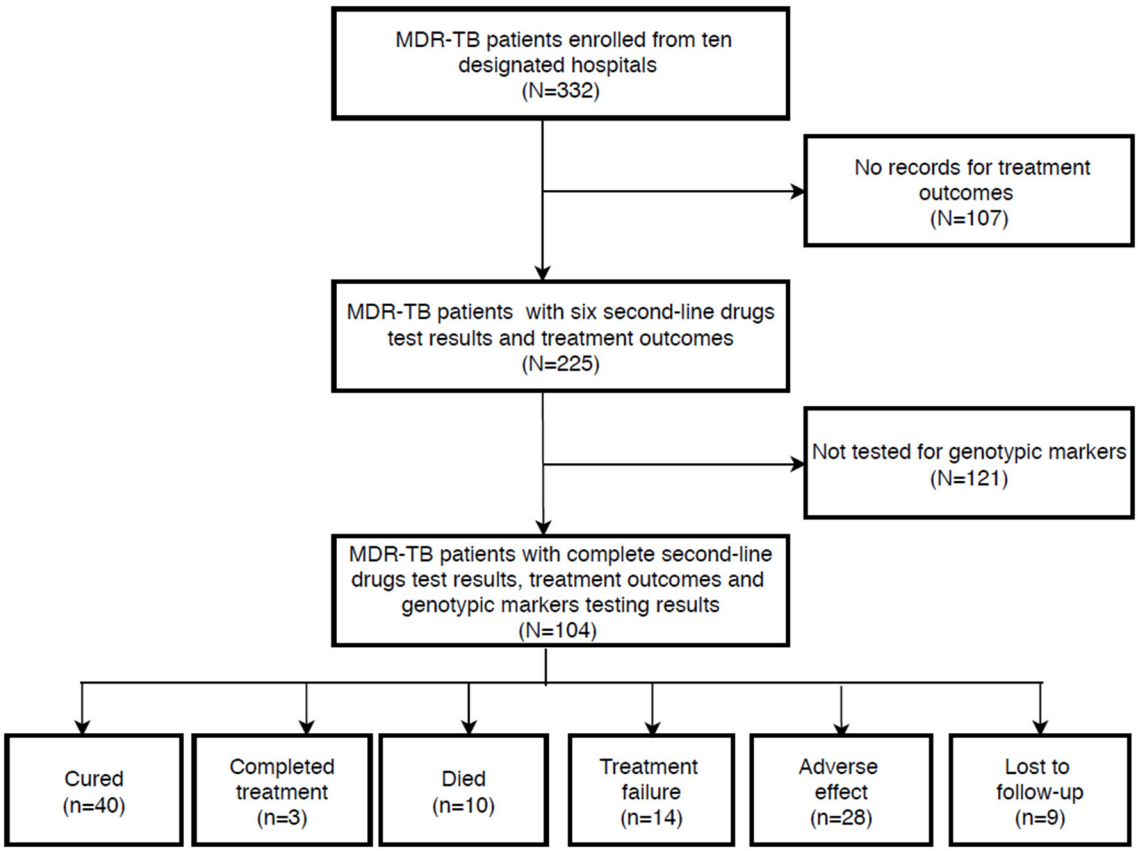


FIGURE 1 | Schematic presentation of patient flow diagram.

Factors Related With Sputum Conversion, Treatment Success, and 6-Month Sputum Culture Conversion

As showed in **Table 2**, in univariate analysis, the latent class membership was associated with overall sputum smear conversion (HR = 2.18; 95% CI, 1.36–3.50). While our results failed to confirm statistically significant association between overall treatment success, in relation to LCA membership (OR = 1.48; 95% CI, 0.67–3.26), we failed to demonstrate statistically significant association between LCA membership and culture conversion by the end of 6 months from TB diagnosis (OR = 2.18; 95% CI, 0.87–5.47, $p = 0.10$). We also found that *pnc*A, *rpsL*, and *gyr*A mutations were associated with poor clinical outcomes. As shown in **Figure 2**, the time-to-event analyses evaluated the association between LCA membership and meaningful clinical outcomes.

Association Between Latent Class Membership and Outcomes

After adjusting for potential confounding factors based on multivariable regression models, we found that latent class memberships were positively associated with sputum smear conversion (AUC-ROC = 0.73), compared to the model using phenotypic DST findings (AUC-ROC = 0.69). On the other hand, the LCA membership performed better than the phenotypic DST in predicting overall treatment success (AUC-ROC 0.63 vs. 0.57) (**Supplementary Figure 3**).

DISCUSSION

We performed a latent class analyses in predicting clinical meaningful outcomes among patients with MDR-TB. We developed and evaluated the association between latent class membership and treatment outcomes at 2 and 6 months following systemic TB treatment. We found that the latent class membership based on genetic features outperformed traditional DST approach in predicting sputum conversion events.

To our knowledge, we were among the few investigators using LCA in evaluating prognosis of MDR-TB patients in combination with parallel culture-based DST findings, using over 2 years follow-up data in the majority of patients. After adjusting for potential confounding factors, we found that the LCA-derived membership status was statistically significantly associated with overall sputum conversion events. However, due to limited sample size, our analysis was underpowered to conclusively demonstrate association between LCA membership and overall treatment success at the standard alpha level of 0.05.

TABLE 1 | Baseline characteristics for the eligible patients with MDR-TB according to genetic determinants of drug resistance patterns.

Patient characteristic	Overall of isolates		No. (%) of isolates class 1		No. (%) of isolates class 2		*P*-value
	N	%	*N*	%	*N*	%	
	N = 104		*N* = 47		*N* = 57		
Male sex	74	71.2%	35	74.5%	39	68.4%	0.50
Female sex	30	28.8%	12	25.5%	18	31.6%	
Age at TB diagnosis							
(Median, IQR)	44	33–59	43	33–59	45	33–59	0.66
Permanent resident	57	54.8%	27	57.4%	30	52.6%	0.62
Treatment history							
New case	40	38.5%	10	21.3%	30	52.6%	< 0.01
Re-treated	64	61.5%	37	78.7%	27	47.4%	
Cavity	60	57.7%	28	59.6%	32	56.1%	0.72
***M. tuberculosis* type**							
Beijing family	83	79.8%	37	78.7%	46	80.7%	
Non-*Beijing* family	21	20.2%	10	21.3%	11	19.3%	0.80
PncA gene mutation	53	51.0%	45	95.7%	8	14.0%	0.00
rrs gene mutation	8	7.7%	5	10.6%	3	5.3%	0.31
rpsL gene mutation	52	50.0%	29	61.7%	23	40.4%	0.03
gyrA gene mutation	35	33.7%	30	63.8%	5	8.8%	< 0.01
gyrB gene mutation	3	2.9%	2	4.3%	1	1.8%	0.87
embB gene mutation	59	56.7%	41	87.2%	18	31.6%	< 0.01
MDR	104	100.0%	47	100.0%	57	100.0%	
Pre-XDR	31	29.8%	26	55.3%	5	8.8%	< 0.01
XDR	6	5.8%	4	8.5%	2	3.5%	0.51
Resistance to							
SM	61	58.7%	32	68.1%	29	50.9%	0.08
EMB	49	47.1%	27	57.4%	22	38.6%	0.06
OFX	31	29.8%	27	57.4%	4	7.0%	< 0.01
LFX	31	29.8%	26	55.3%	5	8.8%	< 0.01
KM	8	7.7%	5	10.6%	3	5.3%	0.51
AMK	7	6.7%	4	8.5%	3	5.3%	0.79
CM	3	2.9%	0	0.0%	3	5.3%	0.31
PTO	5	4.8%	3	6.4%	2	3.5%	0.83
PAS	20	19.2%	8	17.0%	12	21.1%	0.60
Drug resistance pattern							
SM, INH, RFP, and EMB	32	30.8%	21	44.7%	11	19.3%	0.01
INH and RFP	26	25.0%	9	19.1%	17	29.8%	0.21
INH, RFP, and SM	29	27.9%	11	23.4%	18	31.6%	0.36
INH, RFP, and EMB	17	16.3%	6	12.8%	11	19.3%	0.37
Treatment outcomes							
Sputum negative at month 2	76	73.1%	33	70.2%	43	75.4%	0.55
Sputum negative at month 6	76	73.1%	31	66.0%	45	78.9%	0.14
Culture negative at month 6	76	73.1%	31	66.0%	45	78.9%	0.14
Sputum converted to negative	82	78.8%	34	72.3%	48	84.2%	0.14
Cured	40	38.5%	16	34.0%	24	42.1%	0.40
Treatment completed	3	2.9%	1	2.1%	2	3.5%	1.00
Treatment success	43	41.3%	17	36.2%	26	45.6%	0.33
Death	10	9.6%	5	10.6%	5	8.8%	0.75
Treatment interrupted due to ADR	42	40.4%	19	40.4%	23	40.4%	0.99
Lost to follow-up	9	8.7%	6	12.8%	3	5.3%	0.18

IQR, inter quantile range; INH, isoniazid; RFP, rifampicin; SM, streptomycin; EMB, ethambutol; OFX, ofloxacin; LFX, levofloxacin; KM, kanamycin; AMK, amikacin; CM, capreomycin; PTO, protionamide; PAS, paza-aminosalioylate; MDR, multi drug resistance; Pre-XDR, pre-extensively extensive drug resistance; XDR, extensive drug resistance.

TABLE 2 | Univariate association between molecular/phenotypic drug susceptibility tests findings and clinical outcomes.

	Sputum smear conversion (HR, 95%CI)	*P*	Treatment success (OR, 95%CI)	*P*	Culture conversion at month 6 (OR, 95%CI)	*P*
Latent class membership 2 vs. 1	2.18 (1.36–3.50)	<0.01	1.48 (0.67–3.26)	0.33	2.18 (0.87–5.47)	0.10
pncA mutation	0.55 (0.35–0.87)	0.01	0.74 (0.34–1.61)	0.45	0.51 (0.20–1.29)	0.15
rrs mutation	0.55 (0.20–1.51)	0.25	1.46 (0.35–6.20)	0.61	0.29 (0.07–1.27)	0.10
rpsL mutation	0.55 (0.34–0.86)	0.01	0.57 (0.26–1.26)	0.17	0.48 (0.19–1.22)	0.12
gyrA mutation	0.52 (0.32–0.86)	0.01	1.31 (0.58–2.98)	0.52	0.69 (0.27–1.76)	0.44
gyrB mutation	1.44 (0.35–5.96)	0.61	0.000 (0.000)	1.00	0.65 (0.06–7.47)	0.73
embB mutation	0.60 (0.38–0.95)	0.03	0.94 (0.43–2.06)	0.87	0.82 (0.33–2.07)	0.68
Beijing genotype	1.14 (0.63–2.09)	0.66	0.93 (0.35–2.44)	0.88	1.11 (0.36–3.46)	0.86
Phenotypic DST tests	1.64 (1.04–2.59)	0.03	0.70 (0.32–1.54)	0.37	0.48 (0.18–1.28)	0.14
SM						
EMB	1.30 (0.82–2.05)	0.26	0.70 (0.32–1.53)	0.37	0.64 (0.26–1.58)	0.33
KM	1.16 (0.42–3.20)	0.77	0.45 (0.09–2.33)	0.34	0.29 (0.07–1.27)	0.10
CM	0.28 (0.08–0.92)	0.04	1.07 (0.23–5.04)	0.93	0.41 (0.09–1.96)	0.26
OFX	1.34 (0.81–2.24)	0.26	1.25 (0.54–2.92)	0.61	0.87 (0.33–2.30)	0.77
LFX	1.40 (0.84–2.31)	0.20	1.04 (0.44–2.43)	0.94	0.87 (0.33–2.30)	0.77
MFX	1.29 (0.62–2.72)	0.50	0.94 (0.25–3.56)	0.93	1.35 (0.27–6.84)	0.72
PTO	1.16 (0.36–3.69)	0.80	0.94 (0.15–5.90)	0.95	0.99 (0.10–9.93)	0.99
PAS	1.23 (0.71–2.15)	0.46	1.99 (0.74–5.32)	0.17	0.98 (0.32–3.05)	0.98

HR, hazard ratio; CI, confidence interval; OR, odds ratio; DST, drug susceptibility test; SM, streptomycin; EMB, ethambutol; KM, kanamycin; CM, capreomycin; OFX, ofloxacin; LFX, levofloxacin; MFX, moxifloxacin; PTO, protionamide; PAS, paza-aminosalioylate.

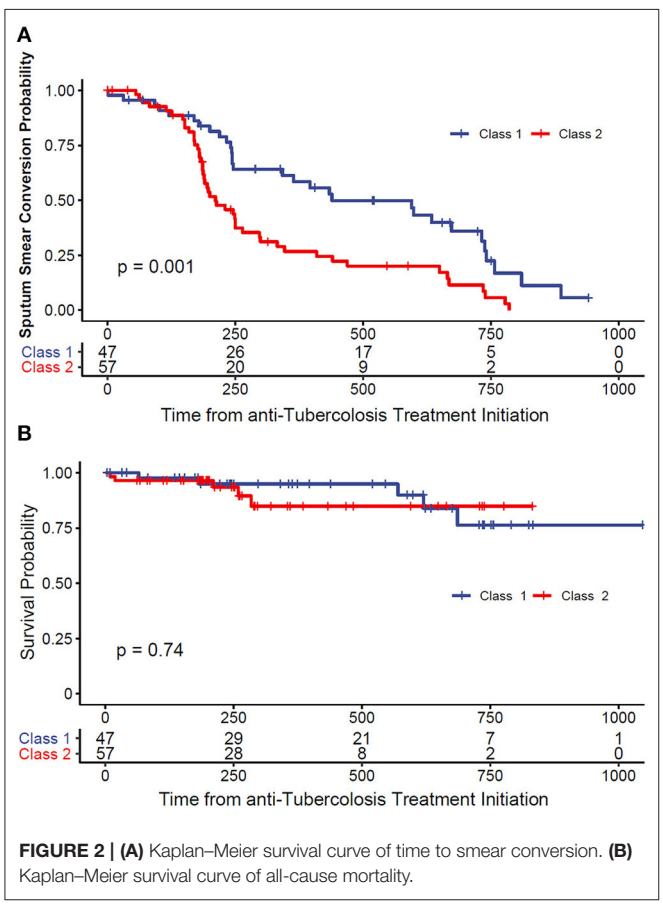


FIGURE 2 | (A) Kaplan–Meier survival curve of time to smear conversion. **(B)** Kaplan–Meier survival curve of all-cause mortality.

Our results are in agreement with those from preexisting reports. We found that ∼17% of patients with MDR-TB had discrepancies between molecular and phenotypic DST tests for susceptibility to PZA treatment. A recent study in China demonstrated the usefulness of *pncA* gene mutation in predicting clinical outcomes, when combined with clinical information such as treatment regimen and age (20). Other multinational cohort studies suggested that *gyrA* mutations were associated with increased mortality risks among patients with MDR/XDR-TB (21, 22). However, these studies were limited in restricting molecular tests findings to single gene mutations and failed to evaluate predictive models using all available genetic test results in a comprehensive manner. Using our data-driven approach, we were capable of combining important clinical characteristics extracted from TB registries and medical charts to build user-friendly clinical decision support tools.

Our study has a number of important policy and clinical implications worth mentioning. Prognosis prediction is challenging in MDR-TB management, and DST evaluation remains problematic due to long turnaround time. While confirmatory drug resistance profiling based on genetic tests is time saving and less ambiguous, the multiple combinations of molecular mutation status prohibits more straightforward evaluation of DST findings.

Despite the fact that our LCA model has been carefully designed, we acknowledge that our results might be limited, as the interpretation of these findings depends on a number of assumptions. One of the strength of our study was that we used treatment outcomes to validate the results of both phenotypic and genotypic DST to directly compare the predictive values of the two approaches. Since poor prognosis is associated with other risk factors such as HIV infection, malnutrition, medication

adherence, and other comorbidities not routinely measured in clinical practice, this explains the imperfect correlation between LCA membership and *in vitro* susceptibility tests. Here, our data-driven LCA models achieved more accurate prognosis prediction in overall sputum conversion, highlighting the clinical utility of this method.

Future study should aim to further improve the performance of molecular testing by incorporating mode detailed specific mutations of genes that are confirmed to associate with poor outcomes. We also hypothesize that inclusion of more host-related socioeconomic risk factors for poor clinical outcomes could improve the accuracy of prognostic prediction among MDR-TB patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Ningbo Municipal Center for Disease Control and Prevention. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YC conceived the study and was involved in the design, analysis, report writing, and drafting the manuscript. TY, LL, YX, FJ, YChe, and TC were involved in the conception, design, and supervised the work. JZ was involved in manuscript review. All authors contributed to and approved the final draft.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.663974/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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STUDY PROTOCOL
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Development of a Core Outcome Set for the Benefits and Adverse Events of Acute Heart Failure in Clinical Trials of Traditional Chinese Medicine and Western Medicine: A Study Protocol

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Aims: To identify a minimum set of efficacy and adverse events for patients with acute heart failure (AHF) among different stakeholders in clinical trials of traditional Chinese medicine and Western medicine.

Methods and Analysis: First, we will develop a preliminary long list of outcomes that includes efficacy and adverse events/reactions via three steps: (i) systematic reviews of efficacy and safety outcomes for clinical trials of AHF; (ii) drugs included in the National Medical Insurance Catalog, the National Essential Medicines Catalog, and the WHO Essential Medicines List will be collected and safety outcomes extracted from the package inserts; and (iii) patients' or caregivers' semi-structured interviews will be carried out to add new viewpoints to the list. Second, after merging outcomes and grouping them under different outcome domains, questionnaires for health professionals and patients will be separately developed. Further, two rounds of Delphi survey for health professionals and a survey for patients and the public will be carried out. Third, different stakeholders will discuss and determine the final core outcome set (COS) for AHF in a consensus meeting.

Ethics and Dissemination: The entire project has been approved by the Ethics Committee of the main institution. After the final COS is developed, it will be published and discussed widely in conferences.

Clinical Trial Registration: This study is registered with the Core Outcome Measures in Effectiveness Trials database as study 1566 (available at: https://www.cometinitiative.org/Studies/Details/1566).

Keywords: acute heart failure, core outcome set, integrative medicine, methodology, safety and efficacy, study protocol

INTRODUCTION

Acute heart failure (AHF) is a life-threatening condition associated with a high risk of mortality and readmission. Therapies for AHF include intravenous diuretics with adjunctive vasodilators and inotropes. However, studies have failed to prove the long-term efficacy obtained from new therapies or drugs in the past decades for patients with AHF (1, 2).

In China, traditional Chinese medicine (TCM), which is proven to be effective in protecting the myocardium, has been used to treat cardiovascular diseases, including AHF (3). It is important to merge data or compare outcomes between randomized controlled trials (RCTs) that employ different interventions. However, a large number of trials were excluded because no important outcomes were reported, and comparison and meta-analyses were hampered because of the heterogeneity of outcome reporting in systematic reviews (4–6). This could reduce the value of clinical trials and increase waste. To improve the consistency of outcomes in future clinical trials, it is necessary to develop a core outcome set (COS).

A COS is an agreed minimum set of outcomes that should be measured and reported in all clinical trials of a particular disease or health condition (7). Researchers are also encouraged to report other outcomes that are not included in a COS (8). Using a COS has potential benefits such as reducing the heterogeneity of outcomes reporting in different clinical trials as well as reducing outcome reporting bias when all clinical trials report predetermined outcomes.

The sixth annual update of a systematic review of COS showed that there were 370 published (1981–2019) COS studies documenting clinical research (9). A research assessed the uptake of COS in RCTs or systematic reviews, and the results showed that the uptake rates reported for RCTs varied from 0% RCTs (gout) to 82% RCTs (rheumatoid arthritis) (10).

There is no specific defined COS for AHF that can be used in clinical trials of pharmacotherapy (including TCM and Western medicine). After searching the Core Outcome Measures in Effectiveness Trials (COMET) database, we identified four related COS for heart failure (HF). The COS for acute heart failure syndromes (AHFS) recommended potential endpoints that should be considered in clinical trials of mechanical circulatory support devices for AHFS (COS for AHFS-MCS), which is developed in 2006 (11). The European Society of Cardiology Heart Failure Association recommended clinical outcome endpoints in HF trials in 2012 (COS for HF trials) (12). Another study represents the perspectives of a workshop held in 2014, which recommended endpoints selection that should be considered for future clinical trials of HF with preserved ejection fraction (HFpEF) in targeted therapies (COS for HFpEF) (13). To our knowledge, thus far, only one international consortium has developed a standardized outcome measurement set for patients with HF, dedicated to increase quality and value in HF care (COS for HF practice) (14).

All of these related COS include stakeholders from Europe and America. Two studies include stakeholders from Asia (Singapore) and Oceania (Australia) (13, 14). The results missed the views of stakeholders from middle- and low-income areas and stakeholders that provide and accept herbs or complementary and alternative medicine. The characteristics of these related COS are shown in **Table 1**. The number of outcomes in different COS ranged from 6 to 24. All of these COS recommended mortality, symptoms, quality of life/patient-reported outcomes, and functional/exercise capacity/status. The outcomes of these COS are shown in **Figure 1**.

To improve the consistency of outcome reporting and reduce potential outcome reporting bias, especially for safety outcome reporting in clinical trials of AHF, and add the perspectives of stakeholders from China, we plan to develop a specific COS for AHF. In China, a large number of patients have received TCM or integrative medicine (combined TCM and Western medicine); therefore, this specific COS will be used both in clinical trials of TCM and Western medicine.

First, we will conduct systematic review, Package Inserts review, and qualitative interviews to develop a long list of outcomes (including efficacy and adverse events) for AHF. Second, we will carry out two rounds of the Delphi survey with different stakeholders to determine the importance and priority of outcomes that should be measured and reported in all clinical trials. Third, we will hold a consensus meeting to decide the final COS. This COS will be published and widely discussed in national and international conferences to encourage researchers to use it in future clinical trials of AHF. This research will be conducted in China.

The objective of this study is to identify what efficacy and adverse events should be measured in clinical trials of integrative medicine for AHF. After the COS completed, we intend to consider when and how to measure these outcomes. This protocol will be reported following the Core Outcome Set Standards for Protocol Items (COS-STAP) statement, which is shown in **Supplementary Material 1** (15).

The scope of the COS is as follows:

1. Health condition: AHF, including classified as an acute first presentation or as an acute decompensation of chronic heart failure.
2. Population: patients aged between 18 and 80 years.
3. Interventions: TCM, Western medicine (pharmacotherapy) or integrated medicine.
4. Context of use: RCTs.

The study is registered in the COMET database as study 1566 (available at: http://www.comet-initiative.org/Studies/Details/1566).

METHODS AND ANALYSIS

Steering Committee

We will form a national Steering Committee to support the development of the COS for AHF. The Steering Committee will include five experts, including two TCM/integrated medicine experts in cardiology, a Western medicine expert in cardiology, a nurse and a methodologist. The Steering Committee will review and confirm the research protocol, identify the preliminary checklist of outcomes, make decisions when there is confusion and attend the consensus meeting to facilitate COS development.

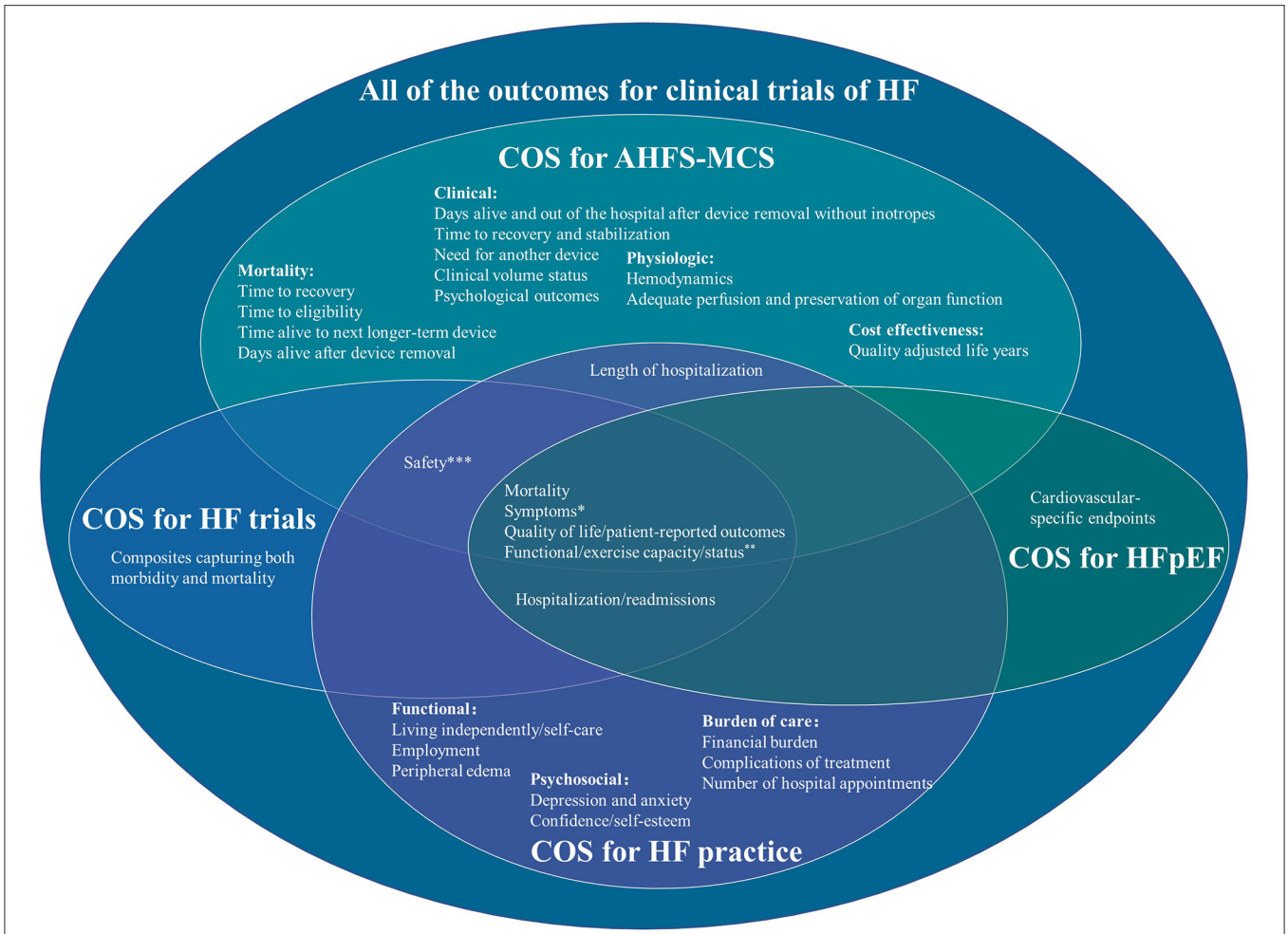


FIGURE 1 | Outcomes in different core outcome sets of heart failure. *COS for AHFS-MCS: dyspnea and fatigue, COS for HF practice: shortness of breath, fatigue and tiredness, and disturbed sleep. **COS for AHFS-MCS: VO2, 6-min walk, and NYHA Class, COS for HF practice: maximum level of physical exertion. ***COS for AHFS-MCS: infection, stroke, bleeding, device failure or malfunction, procedural complications, need for device repair/removal/re-implantation. COS for HF practice: medication side-effects.

Patient and Public Involvement

We will recruit patients and the public (caregivers and journal editors) to participate in semi-structured interviews or a questionnaire-based survey.

Design

This COS will be developed in four phases.

Phase 1: Developing a long list of efficacy and adverse events for AHF

Phase 2: Delphi survey for health professionals

Phase 3: Survey for patients and the public

Phase 4: Consensus meeting.

The details of the process are as follows:

Phase 1: Developing a Long List of Efficacy and Adverse Events for AHF

There are three steps to develop a long list of efficacy and adverse events for AHF, namely: systematic reviews, Package Inserts review and semi-structured interviews.

Systematic Reviews

To obtain a preliminary long list of outcomes, we will conduct two systematic reviews, one is for developing a list of efficacy outcomes, and the other is for developing a list of adverse events. We will search three English databases and three Chinese databases: PubMed, the Cochrane Library, Embase, Wanfang Database, the China National Knowledge Infrastructure (CNKI) and SinoMed. Studies published from January 1, 2010 to August 1, 2020 will be retrieved. The English search strategy is presented in **Supplementary Material 2**. The language of publication will be restricted to English and Chinese.

The inclusion and exclusion criteria for the systematic reviews are shown in **Table 2**. We will extract the first author's name; number of participants; characteristics of the study; classification of HF with regard to age, sex, interventions, comparisons; and outcomes (including primary outcomes, secondary outcomes and safety outcomes); definition of outcomes/outcome measurement instruments; and outcome

TABLE 1 | The characteristics of related core outcome set (COS) for heart failure.

Study ID	Indication	Intervention	Study method	Study type	Stakeholders	Geographical location
O'Connell 2009 (11)	Acute heart failure syndromes	Mechanical circulatory support devices	-Semi–structured discussion	-COS for clinical trials or clinical research	-Clinical experts -Other (unknown)	International -Europe (France, Greece) -North America (USA)
Zannad 2013 (12)	Heart failure	/	-Semi–structured discussion	-COS for clinical trials or clinical research	-Members of a clinical trial network. -Pharmaceutical industry representatives -Regulatory agency representatives -Statisticians	International Europe (Austria, France, Germany, Greece, Italy, Norway, Poland, Spain, Sweden, Switzerland, the Netherlands, UK) -North America (Canada, USA)
Senni 2014 (13)	Heart failure with preserved ejection fraction	Targeted therapies	-Semi–structured discussion	-COS for clinical trials or clinical research	-Health professionals	International -Europe (Germany, Greece, Italy, the Netherlands, Norway, Spain, UK) -North America (USA) -Asia (Singapore) -Oceania (Australia)
Burns 2019 (14)	Heart failure	Pharmacotherapy, invasive therapies, rehabilitation	-Delphi survey -Patient focus groups -Online patient surveys -Systematic research -Teleconferences	-COS for practice	-Clinical heart failure experts Researchers Patient representatives	International -Europe (Greece, Spain, Sweden, the Netherlands, UK) -North America (USA) -South America (Brazil) -Asia (Singapore) -Oceania (Australia)

TABLE 2 | The inclusion and exclusion criteria of systematic reviews for reported outcomes.

Inclusion criteria	Exclusion criteria
Patients with acute heart failure	The main objectives of the study were to assess the mechanisms or pharmacokinetics of interventions
Interventions include Western medicine, TCM, and integrated medicine	Outcome measurement time or outcome definition/measurement instruments cannot be extracted
The systematic review for efficacy will include randomized controlled trials, the systematic review for safety outcomes will include any type of trials, such as randomized controlled trials, case reports and observational studies	No information on ethical approval/funding/trial registration
The clinical trials were published in Chinese or English only	Full-text cannot be obtained

measurement time (intervention time/follow-up time). If TCM syndromes are reported in clinical trials of TCM/integrated medicine, TCM syndrome names and diagnostic criteria will also be extracted. In addition, we will use the MOMENT scoring system to assess the quality of outcomes reporting (16), the Risk of Bias tool to assess the quality of RCTs (17), the Newcastle-Ottawa Scale to assess the quality of cohort studies (18), and the tool developed by the Canadian Institute of Health Economics to assess the quality of case series studies (19).

Two researchers will independently extract the information and assess the quality of each study. After cross-checking, any disagreement will be resolved by discussion or via consulting with the third investigator.

Drug Package Inserts Review

Interventions of AHF will be extracted based on the newest clinical practice guideline. Then, two researchers will choose drugs from the National Medical Insurance Catalog, the National Essential Medicines Catalog, and the WHO Essential Medicines List. One investigator will extract adverse events/effects from drug package inserts. The other investigator will check the results. New adverse events/effects will be added to the list.

Semi-structured Interviews

We will recruit patients with AHF (or their caregivers) to participate in semi-structured interviews. The inclusion and exclusion criteria for the semi-structured interview are presented in **Table 3**. We will recruit at least 30 patients or caregivers, which we believe will achieve sufficient saturation in the semi-structured interview, that means no new ideas occur (20). Data will be analyzed upon completion of the interview. When there is a new point of view in the final interview, we will recruit more patients or caregivers to participate, until no new point of view is generated. We will recruit patients or caregivers by simple sampling.

TABLE 3 | The inclusion and exclusion criteria for semi-structured interview.

Inclusion criteria	Exclusion criteria
Patients with acute first presentation of heart failure or acute decompensation of chronic heart failure	Patients with severe mental disease, cancer, and other life-threatening diseases
Patients who are 18–80 years old	
Caregivers who are taking care of patients with AHF	
Patients/caregivers who signed the informed consent forms	

We will approach potential participants in Dongzhimen Hospital, Beijing University of Chinese Medicine. An investigator experienced in qualitative research will explain the study to the patients. All patients or caregivers will have the chance to read separate written information sheets, and informed consent forms will be signed by the ones who agree to participate in the interview. Then, a semi-structured interview will be conducted by themselves or their caregivers. The investigator will collect patients' socioeconomic, demographic, and other information in the interview.

The outline of the semi-structured interviews is as follows:

1. When did you/the patient experience AHF for the first time?
2. What inconveniences have you experienced after being diagnosed with AHF/after taking care of the patient?
3. What therapies have you/the patient received because of AHF?
4. What effect do you/the patient hope to achieve after treatment?
5. What inconveniences have you/the patient experienced from the current treatment?

The results of the semi-structured interviews will be analyzed concurrently with data collection. All interviews will be transcribed verbatim and imported into qualitative analysis software. We will use framework methodology, including familiarization, for developing a thematic framework, indexing, devising thematic charts, mapping and interpreting, to further analyze the data (21). Narrative explanations of the effects of AHF and treatments on the patients' lives will be interpreted by the process of constant comparison to identify outcomes that are important to patients (22). Then, two researchers will identify whether these outcomes are new. Any inconsistency will be discussed and consensus achieved. After review by the Steering Committee, the new ones will be added to the long list of outcomes.

Merging Outcomes and Grouping Under Outcome Domains

After the reviews and interviews are completed, two researchers will merge the outcomes and independently group them under outcome domains. The methods of merging outcomes and grouping under different outcome domains have been used in our previous research (23):

TABLE 4 | The inclusion and exclusion criteria for health professionals in the Delphi survey.

Inclusion criteria	Exclusion criteria
Health professionals with at least a bachelor's degree	None
Health professionals who have at least 1 year of work experience	
Clinicians and nurses who work in tertiary hospitals in China	
Researchers who have participated in the design, implementation, management or statistical analysis in clinical trials of AHF, or conducted systematic reviews of AHF in the past 10 years	
There will be no restriction on the professionals' geographical area.	

1. English will be translated into Chinese according to the terminology formulated by the national science and technology terminology committee. If there is no relevant term, the appropriate translation will be determined by two researchers.
2. Composite outcomes will be extracted as individual outcomes.
3. The overlapping outcomes will be merged into one according to the definition of the outcomes. For example, death, death from any cause, mortality, over-all mortality, total mortality, all causes of death and all causes of mortality will be aggregated as "all-cause mortality."
4. Those outcomes without definition or measurement instrument will be dropped.
5. The outcomes will be grouped into different outcome domains according to the taxonomy that has been developed by the COMET initiative (24).

Two researchers will cross-check the results. Any inconsistency will be further discussed by the two researchers until a consensus is reached.

Phase 2: Delphi Survey for Health Professionals

Stakeholder Selection

We will invite health professionals, such as TCM/integrated medicine experts (clinicians and researchers) in cardiology, Western medicine experts (clinicians and researchers) in cardiology, nurses, and methodologists in evidence-based medicine to participate in the two rounds of Delphi survey. The inclusion and exclusion criteria for health professionals in the Delphi survey are given in **Table 4**.

The original information of the health professionals will be identified from the Department of Cardiology in Dongzhimen Hospital, Beijing University of Chinese Medicine; the membership lists of the Alliance of Chinese and Western Medicine Clinical Research, Clinical Research Method of Cardiovascular Disease of Professional Committee of Chinese Association of Integrative Medicine; and the China Research Institute of China, Information Association for Traditional Chinese Medicine and Pharmacy.

Sampling Strategy

There is no standard sample size calculation method in the Delphi survey in the development of COS. In previous studies, the sample size of health professionals ranged from 12 to 174 (25). In this research, we will try to invite every eligible participant from the aforementioned institutions to participate in the Delphi survey. We will encourage participants to forward the online survey to their colleagues who are eligible. The sample size for each stakeholder will be at least 15.

Development of Questionnaire for Round 1 of the Delphi Survey

The questionnaire for round 1 of the Delphi survey will include all candidate outcomes in different outcome domains and scoring. A nine-point scoring system will be used in the questionnaire, wherein "1–3" indicates that the outcome is not important in the COS, "4–6" indicates that the outcome is important but not critical in the COS, and "7–9" indicates that the outcome is critical in the COS (23, 26). Participants will also have the option to choose "unclear" for each outcome, if they find it difficult to score in terms of importance. At the end of the questionnaire, there will be one open-ended question: which outcomes do you think are important but are not included in the questionnaire?

Round 1 of the Delphi Survey

Round 1 of the Delphi survey will last for 3 weeks. The questionnaire will be sent by email or smartphone APP to potential participants. The participants will be asked to forward the questionnaire to their colleagues. We will send emails or messages to remind potential participants to complete the Delphi survey at the end of the 2nd weekend.

Data Analysis for Round 1 of the Delphi Survey

Data analysis for round 1 of the Delphi survey will include the frequencies of the response options for each outcome. If an outcome is scored as 7–9 by no more than 10% participants who complete the questionnaire, it will be excluded from round 2 of the Delphi survey. If participants recommend outcomes that are not included in round 1 of the Delphi survey, two researchers will identify if they are new ones. New outcomes will be included in round 2 of the Delphi survey.

Round 2 of the Delphi Survey

Round 2 of the Delphi survey will be sent to participants who complete round 1 of the Delphi survey. In the questionnaire, the participants will receive their score from round 1 of the Delphi survey and the score distribution of their own stakeholders. They will be asked to re-score the outcomes within 3 weeks. We will send emails or messages to remind participants to complete the Delphi survey at the end of the 2nd weekend. If the response rate is <80%, we will keep the Delphi survey open longer, or invite other eligible people to participate in the survey.

Data Analysis for Round 2 of the Delphi Survey

Data analysis for round 2 of the Delphi survey will include the response rate; the frequencies of the response options for each outcome from different stakeholders; the number of participants who score differently among those who complete both round 1 and round 2; the outcomes that achieve "consensus in," "consensus out" and "no consensus;" and the potential attrition bias. The attrition bias will be calculated by the mean score in participants who complete or do not complete the two rounds of the survey. If the attrition bias is because of the participants that do not complete round 2 of the Delphi survey, we will calculate the mean score for each outcome in participants who complete or do not complete the two rounds of the survey. The statistically significant outcomes will be discussed in the consensus meeting.

The consensus definitions are as follows, which have been used in previous research (23, 27):

Consensus in (the outcome that should be included in the COS): 70% or more of the participants scored outcome as 7–9, and <15% of the participants scored the outcomes as 1–3.

Consensus out (the outcome that should not be included in the COS): 50% or less of the participants scored the outcome as 7–9.

No consensus (the importance of the outcome remains uncertain): anything else.

TABLE 5 | The inclusion and exclusion criteria for patients and the public survey.

Inclusion criteria	Exclusion criteria
Patients with acute first presentation of heart failure or acute decompensation of chronic heart failure	Patients with severe mental disease, cancer, and other life-threatening diseases
Patients who are 18–80 years old	Participants who cannot communicate with others
Patient caregivers should have the experience of caring for patients with AHF, including care workers and family members	Participants who cannot read and write
Journal editors should have at least 3 years' work experience	
Participants who signed the informed consent forms	

Phase 3: Survey for Patients and the Public

Stakeholder Selection

We will invite patients to participate in the survey for patients and the public.

The inclusion and exclusion criteria are given in **Table 5**.

We will approach potential patients in Dongzhimen Hospital, Beijing University of Chinese Medicine. An investigator will explain the study to the patients. The patients will have chance to read separate written information sheets, and an informed consent form will be signed by the ones who agree to participate in the survey. Then, the patients will get a printed questionnaire or online questionnaire that is sent by smartphone. They can complete the questionnaire with the help of the investigator.

Sampling Strategy

From the previous COS studies, the number of patients ranged from 32 to 185 (25). In this research, we will recruit at least 32 patients and the public.

TABLE 6 | The inclusion and exclusion criteria for health professionals in consensus meeting.

Inclusion criteria	Exclusion criteria
The health professionals should have at least a Sino Med master's degree	None
The health professionals should have more than 5 years of work experience.	
The clinicians and nurses should have work experience in tertiary hospitals.	
There will be no restriction on the professional's geographical area.	
The researchers should have participated in the design, implementation, management or statistical analysis in clinical trials of AHF, or conducted systematic reviews of AHF in the past 10 years.	
There will be no restriction on whether the health professionals participate in the Delphi survey	

Development of Questionnaire for Patients and the Public

From the experience of the previous COS studies, we found that it is difficult for patients to score the importance of outcomes, either because they do not understand the significance of clinician-reported outcomes such as laboratory/biomarkers and outcomes that can be observed/measured by trained professionals or because they believe that all outcomes are important and should be measured.

In this research, we will develop a simple questionnaire with understandable language for patients and the public. The outcome domains will be listed in the questionnaire. If the outcome domains include individual subjective outcomes that can be observed (e.g., vomiting) or primarily observable outcomes with subjective components (e.g., nail discoloration), the outcomes will be listed under the outcome domains.

In the questionnaire for patients and the public, participants will be asked to vote on which outcomes/outcome domains are important to them and should be measured in all clinical trials. At the end of the questionnaire, there will be one open-ended question: which outcomes do you think are important but are not included in the questionnaire?

Data Analysis of Questionnaire for Patients and the Public

The frequencies of outcomes/outcome domains voted by each stakeholder will be calculated. If an outcome/outcome domain is voted by $\geq$70% participants, it will be defined as "consensus in." If an outcome/outcome domain is voted by $<$50% participants, it will be defined as "consensus out." If an outcome/outcome domain is voted by 50–70% participants, it will be defined as "no consensus."

If there are new outcomes recommended by patients and the public, two researchers will identify if they are new ones. The new ones will be discussed if measurable. If so, they will be included in the consensus meeting.

Phase 4: Consensus Meeting

Stakeholder Selection

We will hold a face-to-face consensus meeting after analyzing the data of the surveys. The Steering Committee will be included in the consensus meeting. We will also invite different stakeholders to participate. For the health professionals, the inclusion and exclusion criteria are as listed in **Table 6**. For the patients and the public, we will respectively invite one participant who completes the questionnaire from each stakeholder to attend the meeting.

Sampling Strategy

There is no standard sample size calculation method for the process of the consensus meeting. To obtain different stakeholders' perspectives, as well as to improve consensus achievement, we will invite at least two participants from each stakeholder to attend the consensus meeting.

Consensus Meeting Process

The consensus meeting will be held in China. It will last at least 1 day. In the consensus meeting, we will report the results of round 2 of the Delphi survey for health professionals and the results of the survey for patients and the public. The outcomes which are achieved "consensus out" by all stakeholders will be excluded. The outcomes which are achieved "consensus in" by all stakeholders will be sent to the Steering Committee and participants on the day before the consensus meeting.

In the consensus meeting, if the participants disagree with any outcome that achieved "consensus in" by all stakeholders to include in the COS, they will further discuss it. No consensus outcomes will be discussed one by one. Then, all of the participants in the consensus meeting will be anonymously asked to vote as "controversial" or "no consensus" outcomes reached. The ones which are voted by $\geq$70% participants will be included in the final COS.

The final COS will recommend efficacy and safety outcomes that should be measured by all RCTs of AHF, including different classification of HF, such as HF with reduced EF (HFrEF), HF with mid-range EF (HFmrEF), and HFpEF.

The flowchart of this research is shown in **Figure 2**.

DISCUSSION

At present, there are four related COS for HF (11–14). After identifying the COS, mortality, symptoms, quality of life/patient-reported outcomes, and functional/exercise capacity/status are important outcomes/outcome domains in all of the recommendations. However, there are still minor difference in individual outcomes between different COS, as well as the difference in how to measure and when to measure these outcomes. According to the scope and methods of these COS, it appears that the researchers can choose the four outcomes/outcome domains for clinical trials of AHF that are treated by pharmacotherapy when there is no specific COS.

We believe that it is necessary to develop a specific COS for AHF. There is a specific COS for mechanical circulatory support devices. This COS will only consider pharmacotherapy that include TCM and Western medicine. Only the COS for HF practice was developed by mixed methods (12), while the others were developed by qualitative research. It is unclear whether all candidate outcomes were considered in the semi-structured discussion. In this COS development, we will conduct a mixed-methods research to achieve consensus in different stakeholders.

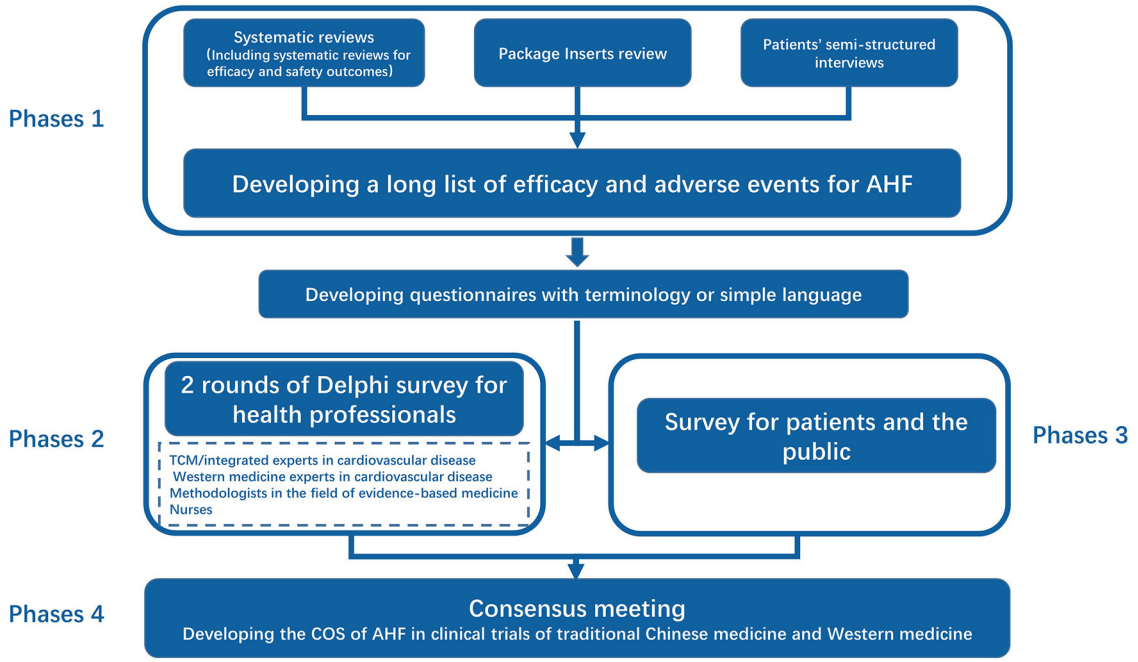


FIGURE 2 | The flowchart of the study.

In previous research, it is difficult to recommend safety outcomes except for surgery therapy. When the drugs for AHF are known, the adverse events/effects of these drugs could be obtained, and it is feasible to standard the adverse events/effects that should be reported in RCTs of AHF. Maybe, the adverse events/effects would not occur, and it will reduce selective reporting bias when all RCTs report common adverse events/effects.

In previous COS for HF, although different studies have recommended the same outcomes/outcome domains, the definitions, measurement instruments or measurement times are different for the same outcomes/outcome domains. These differences will also result in heterogeneity. In addition, the poor quality of the measurement properties of the measurement instruments may exaggerate or decrease the efficacy of interventions. Selecting unsuitable or poor quality of outcome measurement instruments may introduce bias and lead to a waste of resources and be unethical (28). After the final COS for AHF is completed, we will recommend one measurement instrument for one outcome on the basis of "how to select outcome measurement instruments for outcomes included in a 'core outcome set'—a practical guideline" (29). We will also invite different stakeholders to discuss when to measure each outcome that is included in the COS.

ETHICS AND DISSEMINATION

The entire project has been approved by the Ethics Committee of Dongzhimen Hospital, Beijing University of Chinese Medicine (DZMEC-KY-2020–65). We will obtain informed consent from patients and the public who participate in the semi-structured interviews or questionnaire survey.

After the final COS is completed, we will publish this research in a journal, report the results at national and international conferences and disseminate our findings on Wechat Official Accounts Platform of China Information Association for Traditional Chinese Medicine and Pharmacy Clinical Research Information Association. We will also send the publication to researchers who participated in the Delphi surveys and the consensus meeting, so that the researchers can use it in their research.

AUTHOR CONTRIBUTIONS

RQ, JC, and HS drew up the research design. RQ drafted the protocol and wrote the manuscript in English. CZho, XW, and CZha participated in the design amendment and helped with project coordination. SH participated in the design of systematic review. JH, ML, and PW revised the details and the language. RQ and HS are the principal investigators of the project. All authors reviewed the manuscript content and approved the final version for submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.677068/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Prediction Models for Prognosis of Cervical Cancer: Systematic Review and Critical Appraisal

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Objective: This work aims to systematically identify, describe, and appraise all prognostic models for cervical cancer and provide a reference for clinical practice and future research.

Methods: We systematically searched PubMed, EMBASE, and Cochrane library databases up to December 2020 and included studies developing, validating, or updating a prognostic model for cervical cancer. Two reviewers extracted information based on the CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modeling Studies checklist and assessed the risk of bias using the Prediction model Risk Of Bias ASsessment Tool.

Results: Fifty-six eligible articles were identified, describing the development of 77 prognostic models and 27 external validation efforts. The 77 prognostic models focused on three types of cervical cancer patients at different stages, i.e., patients with early-stage cervical cancer (n = 29; 38%), patients with locally advanced cervical cancer (n = 27; 35%), and all-stage cervical cancer patients (n = 21; 27%). Among the 77 models, the most frequently used predictors were lymph node status (n = 57; 74%), the International Federation of Gynecology and Obstetrics stage (n = 42; 55%), histological types (n = 38; 49%), and tumor size (n = 37; 48%). The number of models that applied internal validation, presented a full equation, and assessed model calibration was 52 (68%), 16 (21%), and 45 (58%), respectively. Twenty-four models were externally validated, among which three were validated twice. None of the models were assessed with an overall low risk of bias. The Prediction Model of Failure in Locally Advanced Cervical Cancer model was externally validated twice, with acceptable performance, and seemed to be the most reliable.

Conclusions: Methodological details including internal validation, sample size, and handling of missing data need to be emphasized on, and external validation is needed to facilitate the application and generalization of models for cervical cancer.

Keywords: cervical cancer, prediction model, predictors, risk of bias, statistical analysis

INTRODUCTION

Cervical cancer is one of the leading causes of cancer-related death among women and ranks fourth among the most common malignancy in women in 2020 worldwide (1, 2). In 2020, there were an estimated 604,127 new cases and more than 341,831 deaths from cervical cancer, representing 7.7% of all female cancer deaths around the world (2). Cervical cancer patients have a poor prognosis in developing countries (3, 4). Improvement in survival remains the ultimate goal of treatment in the clinical setting, and treatment varies according to the stage, metastasis, or recurrence (5, 6). The physician can use known factors to check the personal prognosis and predict the clinical outcomes after a specific therapy such as radical hysterectomy or radiotherapy (7, 8). The prediction of potential personal prognosis facilitates the clinicians to decide the subsequent therapies or follow-up examinations (9, 10). For example, an American study indicated that clinicians could get a net benefit of 0.35 (the benefit from treating true positive patients minus the harm from treating those who do not need treatment) with only delivering intensive therapy to patients with a high risk of 3-year survival (threshold probability: about 0.76) based on the prognostic model, compared with delivering therapy to all patients (11).

A prognostic model, combining a few known factors to predict the individual risk of occurrence, progression, and clinical outcome of cervical cancer, is critical in practice (12). A couple of models have shown great positive net benefits across wide ranges of risk, indicating their favorable clinical utility (11, 13, 14). A prognostic model is a formal combination, usually a statistical equation, of multiple predictors, from which risks of a specific outcome can be calculated for individuals (15–17). As for cervical cancer patients, due to the limited predictive value for the classification of the International Federation of Gynecology and Obstetrics (FIGO) alone, a couple of prognostic models have been proposed to predict and guide treatments based on different tumor and demographic characteristics (13, 18). However, the uneven quality and the diversity of the clinical settings, outcomes, and predictors may limit the practicality of models, and systematic reviews on prognostic models of other diseases also suggested that the methodological features of existing studies varied (19–21). No comprehensive evaluation of prognostic models for cervical cancer has been done. Therefore, in order to help clinicians and the public to select the most appropriate models in practice, there is an urgent need to systematically summarize these models, map their characteristics, and examine their performance.

In this study, we conducted a systematic review to identify and summarize these prognostic models for cervical cancer patients and assess their qualities based on the guideline of the CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modeling Studies (CHARMS) and the Prediction model Risk Of Bias ASsessment Tool (PROBAST) (22, 23) in order to provide evidence for determining reliable models and to provide a methodology reference for future research within this field.

MATERIALS AND METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines guided this systematic review. **Supplementary Material 1** shows the PRISMA checklist.

Information Sources and Search Strategy

We systematically searched PubMed, EMBASE, and Cochrane library databases from their inception to December 31, 2020 for relevant articles. We combined the following search terms which were used in referring to prediction models (predict*, progn*, risk score, risk calculation, risk assessment, c statistic, discrimination, calibration, AUC, area under the curve, area under the receiver operator characteristic curve) and the disease (cervical, cervix; cancer*, carcinoma*, neoplasm*, and tumor*) based on previous research (19, 24) (* means asterisk wildcard). No other filters were applied. Details of the search strategy are given in **Supplementary Material 2**.

Eligibility Criteria

Studies were included if they reported the development, the update, or the external validation of at least one multivariable prognostic model based on individual characteristics, and the outcome of the prognostic model was any clinical outcome (recurrence, metastasis, death, *etc*.) in patients diagnosed with cervical cancer (**Table 1**). Only published studies were considered.

Studies were not eligible for inclusion if they (1) were conference abstracts, letters, and editorials or non-original studies such as reviews, (2) only examined independent prognostic factors, (3) focused on methodology, (4) developed or validated diagnostic or screening models, (5) did not construct a model to estimate individual risks, and (6) did not have a full text in English or available full text.

Study Selection

Study selection was conducted using EndNote X9. Duplicates were found and removed automatically and manually. Preliminary screening was performed through reviewing of the titles and abstracts by two independent reviewers with

TABLE 1 | Key items for framing the aim, search strategy, and study inclusion and exclusion criteria for systematic review.

Item	Definition
Population	Patients diagnosed as having cervical cancer
Intervention	Any prognostic model to predict clinical outcomes (recurrence, metastasis, death, *etc*.) in cervical cancer patients
Comparator	Not applicable
Outcomes	Any outcome reported by prognostic models
Timing	No restriction
Setting	No restriction

backgrounds in obstetrics and gynecology and uniform training, using pre-defined eligibility criteria. The full texts of the included articles after preliminary screening were reviewed independently by two reviewers. Any disagreement between reviewers was resolved by consensus.

Data Extraction

For each relevant publication, two reviewers extracted information through a piloted standardized form based on the recommendations in the CHARMS checklist (22). The key items to be extracted from each primary study were grouped within 11 domains, including source of data, participants, outcome(s) to be predicted, candidate predictors, sample size, missing data, model development, model performance, model evaluation, results, interpretation, and discussion. In addition, we extracted the general characteristics of the studies, including title, author, publication year, and specific objective (i.e., to develop or to validate or both). Model performance is typically evaluated using measures of calibration and discrimination. Calibration reflects the disparity between predictions and observed outcomes. Discrimination reflects the ability of a prognostic model to distinguish between individuals who do or do not develop the outcome (25, 26). Discrimination metrics are usually represented by concordance index (C-index) or area under the receiver operator characteristic curve (AUROC). A discrimination metric of 0.5 describes a random prediction, whereas a perfectly predicting model would have a discrimination metric of 1.0. The methods used to assess model calibration and discrimination should be suitable for the corresponding model (25).

The included models can be divided into three categories based on the FIGO stage of the research population: models for patients with early-stage cervical cancer, models for patients with locally advanced cervical cancer, and models for all-stage (including early stage and locally advanced) cervical cancer patients.

Assessment of Risk of Bias

The PROBAST was used to assess the risk of bias (ROB) of each prognostic model identified from the included studies (23, 25). Two investigators assessed ROB for each model independently. Applicability is beyond the scope of this study due to the lack of specific questions in the population, predictors, or outcome. The assessment of ROB in PROBAST involved four domains (participants, predictors, outcome, and analysis), and 20 signaling questions covered the key aspects of prediction model studies. Each question was answered as "yes," "probably yes," "probably no," "no," or "no information" according to the indications provided by PROBAST, and the ROB of each domain was judged as low, high, or unclear based on the questions in the corresponding domains. The overall assessment of each model was classified as low or high ROB. When all domains were judged as low risk, the overall risk was classified as low ROB; as long as one domain was considered high risk, the overall risk was classified as high ROB.

Data Synthesis

We conducted a descriptive analysis of the characteristics of models and reported mean or median for continuous variables, with differences calculated using *t*-test or Kruskal–Wallis test, or percentages for categorical variables, with differences calculated using χ^2 test or Fisher's exact test. We compared the number of sample size and events and the proportion of methodological items and predictors used in the models across three categories. We used Stata15.0 for the statistical analysis.

RESULTS

Of the 52,591 screened articles, 56 articles describing the development of 77 prognostic models and the external validation of 24 prognostic models for cervical cancer patients were eligible (**Figure 1**). The number of prognostic models increased steadily in the past decade, tripling in annual growth in 2019. The prognostic models were mainly developed in the United States ($n = 25$; 32%), China ($n = 23$; 30%), and Korea ($n = 18$; 23%). External validation was performed only in Korea ($n = 10$; 37%), Spain ($n = 8$; 30%), China ($n = 8$; 30%), and the United States ($n = 1$; 4%). For the derivation cohorts, the median sample size and the median number of events were 549 (interquartile range, 203.5–843) and 77 (40.5–187), respectively. For the internal validation cohorts, the median sample size and the median number of events were 484.5 (234–833) and 95 (46–187), respectively.

The research population of eligible models covered all stages of cervical cancer, including patients with early-stage cervical cancer ($n = 29$; 38%), patients with locally advanced cervical cancer ($n = 27$; 35%), and all-stage cervical cancer patients ($n = 21$; 27%) (**Supplementary Material 3**). These models also focused on a wide range of clinical outcomes. The most common clinical outcomes were overall survival ($n = 34$; 44%), disease-free survival ($n = 12$; 16%), progression-free survival ($n = 9$; 12%), and disease-specific survival ($n = 7$; 9%). The predictors encountered most frequently were lymph nodes status ($n = 57$; 74%), the FIGO stage ($n = 42$; 55%), histological types ($n = 38$; 49%), and tumor size ($n = 37$; 48%) (**Figure 2**). There were at least six forms of lymph nodes included in the prognostic models. The version of FIGO stage used for patients was presented only in 19 (25%) models. Treatment was considered a predictor in 18 (23%) models.

The modeling method used most frequently in these models was Cox proportional hazard regression ($n = 68$; 88%), and machine learning was also used in five (6%) models. Model presentation was available for most prognostic models ($n = 67$; 87%), but only 16 (21%) models had a regression formula (**Table 2**).

Prognostic Models for Patients With Early-Stage Cervical Cancer

Twenty-nine models were developed for patients with early-stage cervical cancer. The sample size ($p = 0.011$), number of events ($p = 0.005$), and events per variable in models that were not based on machine learning ($p = 0.006$) were significantly

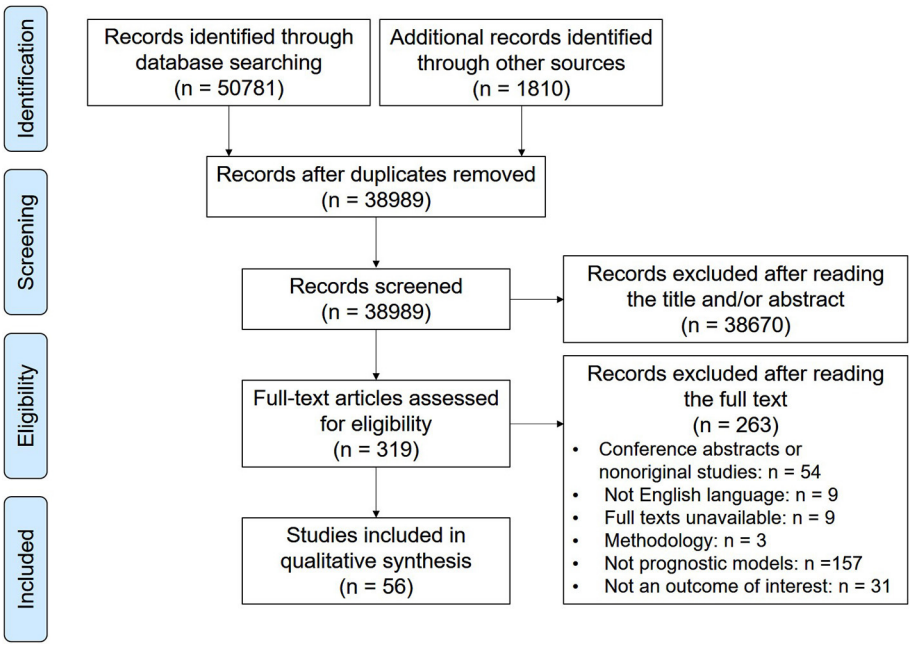


FIGURE 1 | Flow chart of the literature search for prognostic models related to cervical cancer.

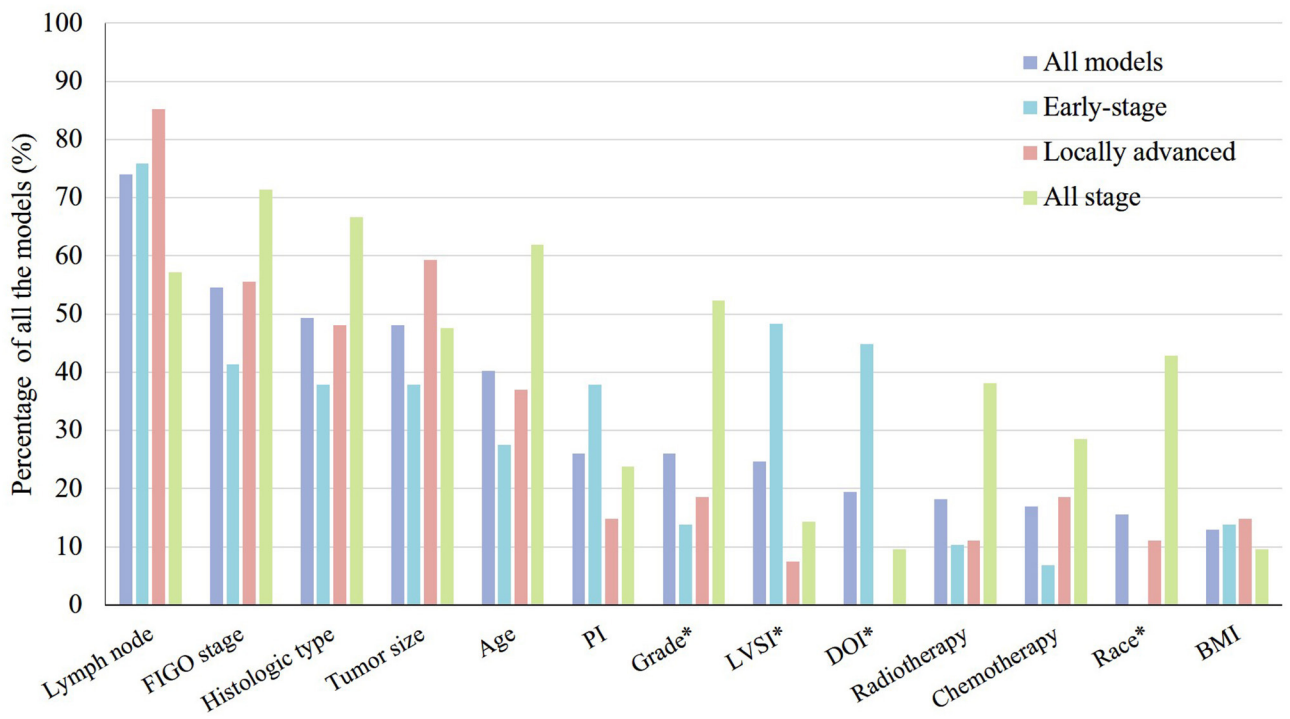


FIGURE 2 | Thirteen most frequently used predictors in 77 prognostic models for the prognosis of cervical cancer patients presented by clinical stage. PI, parametrium invasion; LVSI, lymph vascular space invasion; DOI, depth of stromal invasion; BMI, body mass index. *$p < 0.05$.

smaller in models for patients with early-stage cervical cancer. The predictors used most frequently in these models were lymph nodes status ($n = 22$; 76%), lymph vascular space invasion (LVSI) ($n = 14$; 48%), depth of stromal invasion (DOI) ($n = 13$, 45%), FIGO stage ($n = 12$; 41%), histological types ($n = 11$; 38%), tumor size ($n = 11$; 38%), and parametrium invasion ($n =$

11; 38%). LVSI ($p = 0.003$) and DOI ($p < 0.001$) were used significantly more frequently in the models for patients with early-stage cervical cancer (**Figure 2**).

A C-index or an AUROC was reported for 24 (83%) models, and the remaining five (19%) did not report any discrimination metric. The discrimination estimates ranged from 0.565 to 0.959. Less than half of the models ($n = 14$; 48%) performed internal validation. The calibration plot was used in 13 (45%) models, and the remaining models performed no calibration assessment. The relatively recommended prognostic model for patients with early-stage cervical cancer was the Je et al. model (27).

Prognostic Models for Patients With Locally Advanced Cervical Cancer

In terms of the 27 (35%) prognostic models developed for locally advanced cervical cancer, the predictors encountered most frequently also included lymph node status ($n = 23$; 85%), tumor size ($n = 16$; 59%), FIGO stage ($n = 15$; 56%), histological types ($n = 13$; 48%), and age ($n = 10$; 37%) (**Figure 2**). The differences of internal validation ($p < 0.001$), model presentation ($p < 0.001$), and discrimination evaluation ($p = 0.044$) were significant across three groups. Bootstrapping and nomogram were used more frequently in the models for patients with locally advanced cervical cancer compared to the others. A C-index or an AUROC was reported for 17 (81%) models, which was significantly higher than the other two types, and the discrimination estimates ranged from 0.62 to 0.86. Calibration was assessed properly for 20 (74%) models with a calibration plot. The Prediction Model of Failure in Locally Advanced Cervical Cancer (PREFACE) was the relatively recommended model (28).

Prognostic Models for All-Stage Cervical Cancer Patients

There were 21 (27%) models developed for the prognosis of all-stage cervical cancer patients. The predictors used commonly were FIGO stage ($n = 15$; 71%), histological type ($n = 14$, 67%), age ($n = 13$; 62%), lymph nodes status ($n = 12$; 57%), grade ($n = 11$, 52%), and tumor size ($n = 10$; 48%). Grade ($p = 0.014$) and race ($p < 0.001$) were used significantly more commonly in the models for all-stage cervical cancer patients (**Figure 2**). A C-index or an AUROC was reported for 17 (81%) models. The discrimination estimates ranged from 0.616 to 0.897. Two-thirds of the models ($n = 14$; 67%) had internal validation. More than a half of the ($n = 12$; 57%) models were assessed with a calibration plot. The Wang et al. model was relatively recommended (29).

External Validation Studies

Of all models included, 21 (27%) were externally validated once, and three (4%) were validated twice. The median sample size and the median number of events were 211 (101–653) and 39 (18.5–83.5), respectively. Two (7%) external validation studies did not report any discrimination metric, and that of the remaining 25 studies ranged from 0.52 to 0.88. Fifteen (56%) models were assessed with calibration. The prognostic models that were externally validated twice were the SNU/AM (30), KROG 12-08 (8), and PREFACE (28), and the PREFACE model had better performance, with good calibration and a C-index of 0.67. **Supplementary Material 4** presents detailed information on all the prognostic models.

Risk of Bias of the Included Studies

The PROBAST was used to assess the risk of bias of all studies developing or externally validating prognostic models. None of the models developed or validated were assessed as being at low ROB; the summary by domain is shown in **Figure 3**. As for the model development studies, 61 (79%), nine (11%), and 33 (47%) models were at low ROB for participants, predictors, and outcome, respectively, but none of the models were at low ROB for analysis. Similarly, among 27 external validation efforts, 15 (56%), four (15%), and five (19%) models were at low ROB for participants, predictors, and outcome, respectively, but none of the models were at low ROB for analysis. Specific signal questions and the result of the assessment are in **Supplementary Material 5**. The full risk of bias assessment table can be found in **Supplementary Material 6**.

The main problems with regards to the analysis domain included the inadequate number of events (68% for development and 93% for validation), the incomplete evaluation of model performance (64% for development and 74% for validation), the improper handling of missing data (86% for development and 89% for validation), and the incomplete procedure of internal validation (97% for development).

DISCUSSION

Our systematic review revealed the detailed characteristics of 77 prognostic models for the prediction of clinical outcomes in cervical cancer patients, but none of the models developed or validated were assessed as being at low ROB with PROBAST mainly because of the limitations in modeling methodology and model presentation. Relatively, the PREFACE model predicting 5-year distant recurrence in locally advanced cervical cancer patients appears to be the most reliable model.

In terms of the geographical distribution of the research population, most of the models were developed and externally validated in countries with high and very high human development index (HDI), especially in the United States, China, and Korea where the incidence of cervical cancer is relatively high rather than in less developed countries like Africa or Melanesia where the incidence and mortality were the highest (2). Prognostic models tailored to less developed countries and external validation are needed before the generalization and application. In addition, from the perspective of predictor choice, the most commonly used predictors in all eligible prognostic models were different types of tumor characteristics, which were also mentioned in the NCCN Clinical Practice Guidelines (31). The LVSI and DOI were more frequently used as predictors in the models for patients with early-stage cervical cancer. The recommended treatment for patients with early-stage cervical cancer is surgery, and these predictive factors can be obtained with more accurate results in postoperative pathological testing (31). Grade and race were also more frequently used as predictors in models for all-stage cervical cancer patients, mainly because of the generalization of these predictors for all cervical cancer

TABLE 2 | Methodological characteristics of the development of prognostic models for patients with cervical cancer by clinical stage.

Methodological items	All models (77 models)	Early stage (29 models)	Locally advanced (27 models)	All stage (21 models)	*P*-value
Sample size, median (IQR)	549 (203.5–843)	330 (119–788)	314 (234–833)	1,501 (371–4,220)	0.011
Number of events, median (IQR)	77 (40.5–187)	47 (19.5–96.5)	106 (52.5–246.75)	166 (45.25–696.75)	0.005
Events per variable					
Not machine learning					0.006
EPV <10	35 (49)	19 (70)	11 (41)	5 (28)	
EPV 10–20	3 (4)	1 (4)	0 (0)	2 (11)	
EPV >20	22 (31)	2 (7)	12 (44)	8 (44)	
No information	12 (17)	5 (19)	4 (15)	3 (17)	
Machine learning					1.000
EPV <100	5 (100)	2 (100)	0 (0)	3 (100)	
EPV ≥100	0 (0)	0 (0)	0 (0)	0 (0)	
Internal validation					<0.001
Bootstrapping	35 (45)	10 (34)	20 (74)	5 (24)	
Cross-validation	9 (12)	2 (7)	3 (11)	4 (19)	
Random split	6 (8)	0 (0)	1 (4)	5 (24)	
Resampling	1 (1)	1 (3)	0 (0)	0 (0)	
Not reported	1 (1)	1 (3)	0 (0)	0 (0)	
No internal validation	25 (32)	15(52)	3 (11)	7 (33)	
Modeling method					0.113
Cox hazard model	68 (88)	26 (90)	26 (96)	16 (76)	
Logistic regression	2 (3)	1 (3)	1 (4)	0 (0)	
Machine learning	5 (6)	2 (7)	0 (0)	3 (14)	
Discriminant analysis	1 (1)	0 (0)	0 (0)	1 (5)	
Not reported	1 (1)	0 (0)	0 (0)	1 (5)	
Missing data handling					0.092
Multiple imputation	4 (5)	1 (3)	3 (11)	0 (0)	
Complete case analysis	31 (40)	9 (31)	9 (33)	13 (62)	
No information	42 (55)	19 (66)	15 (66)	8 (38)	
Model presentation					<0.001
Full equation	9 (12)	8 (28)	0 (0)	1 (5)	
Nomogram	46 (60)	10 (34)	25 (93)	11 (52)	
Sum score	4 (5)	2 (7)	0 (0)	2 (10)	
CART	1 (1)	1 (3)	0 (0)	0 (0)	
More than one method	7 (9)	3 (10)	2 (7)	2 (10)	
None	10 (13)	5 (17)	0 (0)	5 (24)	
Discrimination					0.044
C-index or AUROC	68 (88)	24 (83)	27 (100)	17 (81)	
None	9 (12)	5 (17)	0 (0)	4 (19)	
Calibration					0.087
Calibration plot	45 (58)	13 (45)	20 (74)	12 (57)	
None	32 (42)	16 (55)	7 (26)	9 (43)	

Values are numbers (percentages[a]) unless stated otherwise.

[a]Some percentages do not add up to 100%, owing to rounding off.

IQR, interquartile range; EPV, events per variable; CART, Classification and Regression Tree; C-index, concordance index; AUROC, area under the receiver operating characteristic.

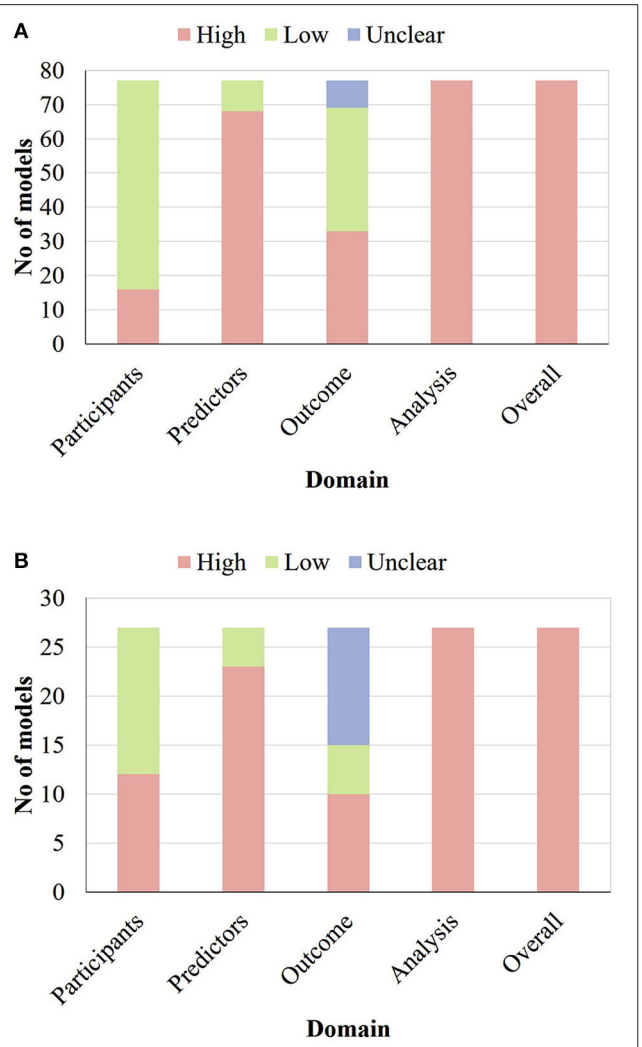


FIGURE 3 | Risk of bias assessment (using PROBAST) based on four domains across 77 prognostic model development studies related to cervical cancer **(A)** and across 27 external validation efforts of prognostic models related to cervical cancer **(B)**.

patients. Our research suggested that some issues related to predictors should be noted when developing, validating, or using prognostic models. First, the forms of predictors included in prognostic models are not consistent. For example, at least six forms of lymph node status were involved in existing models (29). A practical problem is that the effect of each form may be different, and which one is superior requires research to examine, which can help subsequent studies choose the appropriate one. Second, the FIGO stage is also crucial to the progression of cervical cancer, but the staging system has been revised at least three times during the past decades (32, 33). Researchers should confirm the version of FIGO stage they used ahead of model development or application. Third, the accuracy of measurement and the availability of predictors should be also considered. The tumor characteristics mentioned above are usually measured by different imaging evaluation and pathologic examination, which is subjective and may have inadequate accuracy (34). Therefore, parallel assessment and blindness are necessary during measurement procedures to ensure quality. Additionally, despite the increasing number of research on the predictive value of omics (35–37), the inclusion of omics into a conventional prediction model needs to be discussed considering the accessibility of these predictors and cost-effectiveness issues, especially in countries with middle or low income. Besides this, treatment is very important for the prognosis of cervical cancer patients, and different surgical methods may lead to different survival outcomes (38), but treatments were considered a predictor only in 18 models, which indicates that prognostic models tailored to different treatment modalities are needed.

Our systematic review showed several methodological pitfalls in the development or validation of the models, especially in the analysis domain which was the main cause of high ROB. Similar to reviews assessing the quality of prognostic models for other diseases including oropharyngeal cancer, chronic lymphocytic leukemia, and chronic obstructive pulmonary disease (19, 20, 39, 40), inadequate sample size, improper handling of missing data, and incomplete evaluation of model performance were the main problems in analysis domain and needed to be emphasized. Besides this, several other methodological details should also be noted. First, some common problems of internal validation exist, and the proportion of external validation was low. Only a half of the studies applied internal validation properly by using bootstrapping or cross-validation techniques to overcome overfitting; however, almost none of the bootstrapping or cross-validation techniques used in these studies were applied in all model development procedures such as variable selection, which was also consistent with other studies (41). It is one of the most overlooked technical aspects at present, but it violates the guidance and recommendations of PROBAST on internal validation (25, 42), indicating that the recommendation needs to be further strengthened. Additionally, only one third of the models have been externally validated, although the demonstration of the performance of a model in an independent population is a necessary step before recommending its widespread use (43). Researchers generally do not have access to multiple data, and external validation might be limited because of that. Data sharing can offer the possibility of making the most of all available data, which should be promoted in the future (44). Second, besides the most common Cox proportional hazard regression that was suitable for survival data, machine learning was also adopted for prognostic prediction in cervical cancer from 2019 (45). The discrimination parameter of the machine learning model was better than the traditional one (0.795 vs. 0.784) (45). The model performance could therefore be partially improved, but researchers should also attend to the difficulty of interpretation of algorithm and requirement of large sample size (46). In addition, it should be noted that different predicted outcomes have corresponding suitable modeling methods, and the same type of outcome also has alternative statistical models; therefore, researchers should consider the characteristics of different modeling methods when choosing one (47). Third, the model presentation was also inappropriate, with almost

one-seventh of the models having no presentation and only one-fifth providing the full model equation. Researchers should provide not only concise and proper presentation formats but also the full model equation to enable independent external validation, update, and recalibration (48). Compared with the above-mentioned two issues, this one is much easier to realize. Both authors and journals should pay attention to it to directly facilitate the validation and generalization of prognostic models.

In terms of the differences of methodological details across the three groups, the problem of adequate sample size was most severe in models for patients with early-stage cervical cancer. Early-stage patients have a better prognosis, leading to a fewer number of events. The methodological details (including internal validation, model presentation, and discrimination evaluation) of models for patients with locally advanced cervical cancer were generally better than the other two categories. We think that the reason for those differences might not be relevant to the features of patients in different stages. Indeed the all-stage cervical cancer patients included both patients with early-stage cancer and patients with locally advanced cancer. We think that the choice of method should be mainly related to the researchers. We added new analysis to compare the year of publication and the involvement of methodological experts across the three groups. We found that the publication years of the models were similar across the three groups, and the proportion of models involving methodological experts was not high in the locally advanced group (**Supplementary Material 3**). Although the current clues cannot easily explain the above-mentioned phenomenon, this result indicated that a couple of research teams did better at methodological details, and it also takes lead to improve the qualities of models in this field.

Although all of the existing models have high ROB, current research still inevitably needs the guidance of prognostic models on clinical intervention, therapeutic strategy, clinical trial, and so on. Clinicians need to choose the most appropriate and corresponding models to predict the prognosis of patients at different stages. Appropriate models should possess high quality, good model performance, strict validation, and available predictors. Before the development of new models with better quality, the Je et al. model (27), PREFACE model (28), and Wang et al. model (29) were relatively recommended for early stage, locally advanced, and all-stage cervical cancer patients, respectively. The Je et al. (27) model was recommended based on the relatively standardized measurement of predictors and outcome, large sample size, complete evaluation and good result of model performance, and internal validation. The PREFACE model was recommended based on the barely enough sample size and external validation in both Korea and Spain with acceptable performance. The Wang et al. (29) model was based on a large database with good data quality and enough sample size and was externally validated in an independent population with good performance. Of course, researchers should notice the high ROB and existing problems of these models when using them. The serum squamous cell carcinoma antigen, a predictor included in the PREFACE model, can only predict the prognosis of cervical squamous cell carcinoma (49, 50). The Je et al. (27) model still needs to be externally validated, and some analysis details including missing data were handled improperly in the Wang et al. (27) model. Therefore, external validation and more high-quality prognostic models tailored to different cervical cancer patients are needed before models can be implemented in clinical practice.

To get prognostic models with good predictive capability for clinical practice, researchers should pay attention to each detail in the modeling process. The larger value of discrimination and calibration does not always mean a better model; instead it is also important to assess the risk of bias of the model from multiple domains. Although these domains are very detailed, it is still recommended to pay attention and value to avoid misuse. On the basis of the aforementioned problems, besides some common issues including recruiting enough participants to obtain enough outcome events, applying imputation techniques to handle missing data, and providing complete model performance measures, the following recommendations could be stated to improve the research on prognostic models for cervical cancer. First, model development studies should apply internal validation to adjust for overfitting and include all model development procedures. Second, several modeling guidelines of methodology and reporting specific to machine learning have been developed recently (51, 52), and researchers should follow these guidelines to correctly apply machine learning for prediction in the future. Third, researchers should carefully consider the intended users, settings, and timing when choosing the format to present the model, and a final prognostic model equation should always be presented. Finally, research is mostly concentrated in countries with high and very high HDI now; similar studies in other populations are needed.

To our knowledge, this is the first systematic review to provide a comprehensive overview of available studies on prognostic models for different outcomes of cervical cancer according to the CHARMS and PROBAST tools. Nevertheless, it has some limitations. First, we only included studies published in English and did not search gray literature, but the missing models due to this are limited in usage and usually of relatively low quality. Second, a quantitative analysis was not conducted due to the heterogeneity of participants and outcomes.

CONCLUSION

The number of prognostic models for cervical cancer has increased steadily in the past decade, tripling in annual growth in 2019, and the performance of these models varies. However, all of them are at high risk of bias mainly because of unsatisfactory statistical analysis. High-quality prognostic models tailored to different stages of cervical cancer, external validation by an independent population, and head-to-head comparisons of existing models are needed to inform clinical practice better.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

BH, WC, LL, and SW designed the study. BH, WC, HZ, HC, and YZ did the literature search and the data extraction. BH and WC performed the initial analysis of data and wrote the first draft of the manuscript. ZH, SW, and SZ contributing to the interpretation of data. All the authors contributed to the critical revision of the manuscript for important intellectual content and approved the final version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.654454/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Etiology Exploration of Non-alcoholic Fatty Liver Disease From Traditional Chinese Medicine Constitution Perspective: A Cross-Sectional Study

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Background: From the traditional Chinese medicine (TCM) constitution theory perspective, the phlegm-dampness constitution is thought to be closely related to the occurrence of non-alcoholic fatty liver disease (NAFLD). However, this viewpoint still lacks rigorous statistical evidence. This study aimed to test the association between the phlegm-dampness constitution and NAFLD.

Methods: We conducted a cross-sectional study. Participants were residents living in Chengdu, China, undergoing health checkups at the health management center of Affiliated Hospital of Chengdu University of Traditional Chinese Medicine between December 2018 and September 2020. TCM constitution type was diagnosed by DAOSH four examinations instrument, NAFLD was diagnosed according to the liver ultrasonography and medical history. Multivariate logistic regression and propensity score matching (PSM) were used to analyze a total of 1,677 qualified data.

Results: 1,037 participants had biased constitution(s), 67.8% of which had mixed constitutions (with at least two constitutions). Among 1,677 participants, the phlegm-dampness constitution was associated with the yang-deficiency, yin-deficiency, dampness-heat, qi-depression, and blood-stasis constitutions. The correlation coefficients were 0.11, 0.32, 0.42, 0.20, 0.14, respectively. Between the phlegm-dampness constitution and NAFLD, the odds ratio (OR) and the 95% confidence interval (CI) was 2.05 (1.57–2.69) in the crude model. After adjusting for age, gender, Body mass index (BMI), other biased constitutions, smoking, high blood pressure, diabetes, and dyslipidemia, the OR reduced to 1.51 (1.04–2.18). The associations of seven other biased TCM constitutions and NAFLD were not statistically significant in the fully adjusted model. The PSM analysis showed consistent results with the logistic regression.

Conclusions: Among eight biased TCM constitutions, the phlegm-dampness constitution is independently associated with NAFLD. We speculate the phlegm-dampness constitution is a risk factor of NAFLD. Longitudinal studies are

needed to confirm this causal relationship in the future. In addition, inconsistent with some TCM practitioners' experience, we disagree that the blood-stasis constitution is associated with NAFLD.

Keywords: phlegm-dampness constitution, non-alcoholic fatty liver disease, traditional Chinese medicine, constitutional theory, propensity score matching

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the most commonly encountered liver disorders worldwide (1), prevalence accounting for 25.24% (2). Its epidemic is believed to be driven by unhealthy lifestyles, aging, and genetics (3). The disease spectrum extends from liver steatosis to non-alcoholic steatohepatitis (NASH); the latter may progress to advanced liver fibrosis, cirrhosis, or hepatocellular carcinoma (HCC) (4). To date, NAFLD has become a significant public health concern. Research showed that NASH is the second leading cause of liver transplantation in the USA (5, 6), while NAFLD is classified as the most common risk factor for the development of HCC (7).

Traditional Chinese medicine (TCM) constitution theory has its unique understanding of NAFLD. A specific TCM constitution named phlegm-dampness constitution is thought to be an important risk factor for the occurrence of NAFLD (8). In China, the TCM constitution is applied to evaluate a person's health status. It refers to the integrative and relatively stable inherent qualities on morphological structures, physiological function, and psychological state, formed on the basis of natural endowment and acquired elements in the process of life, which is the personal characteristic of the human body adapting to natural and social environment formed in the process of human growth and development (9). The standard of Classification and Determination of TCM Constitution was established, officially released by the China Association of Chinese Medicine in 2009, and incorporated into The State's Basic Public Health Services Specification (2009 ed) promulgated by the Ministry of Health, The People's Republic of China (9, 10). There are nine TCM constitution types: one balanced constitution (gentleness) and eight biased constitutions (qi-deficiency, yang-deficiency, yin-deficiency, phlegm-dampness, dampness-heat, qi-depression, blood-stasis, and special diathesis constitutions).

People with the phlegm-dampness constitution have a series of comprehensive syndromes and signs, including phlegm-dampness coagulation in the body, obesity, greasy and soft lower abdomen, oily skin in the face, sticky and sweet taste in the mouth, and slippery pulse. They often have a low ability to adapt to the rainy season and humid environments (11). Some TCM practitioners pointed out that phlegm and dampness are the pathological basis of NAFLD by experience (12, 13). Epidemiological data also showed the phlegm-dampness constitution is one of the most common constitutions in NAFLD patients (14, 15). Additionally, experimental studies found phlegm-resolving and dampness-dispelling formula could alleviate the liver injury of NAFLD rats and NASH mice (16, 17). However, without setting the control group and adjusting confounding variables, these research studies are still insufficient to prove the correlation between the phlegm-dampness constitution and NAFLD. To clarify this correlation, we conducted this analytical cross-sectional study.

MATERIALS AND METHODS

Study Sample

Participants included in this study were residents living in Chengdu, China, undergoing routine health checkups at the health management center of the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine between December 2018 and September 2020. Most participants only attended one health checkup during the study period. For the few participants who attended health checkups more than once, we only collected their first health reports for data analysis. The checkup included anthropometric and basic clinical assessment (weight, height, blood pressure), biochemical (such as, blood routine examination, hepatic function, renal function, trace elements test), and imaging tests (such as, chest radiography, abdominal ultrasonography). Inclusion criteria: (1) aged over 18; (2) completing the TCM constitution questionnaire; (3) completing the color ultrasound examination of liver and gallbladder. Exclusion criteria: (1) history of alcohol consumption (drink more than once a week in the past year); (2) infected with hepatitis B or C virus; (3) severe liver and kidney dysfunction; (4) pregnant women. After screening, 1,677 participants' data were qualified for the final analysis (**Figure 1**). The ethics committee of the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine approved the study (2018-KL050), and all participants provided written informed consent.

Assessment of TCM Constitution

The participants' TCM constitutional types were diagnosed by DAOSH four examinations instrument (Shanghai Food & Drug Administration approval No. 20202200060 for medical devices). Participants filled in a questionnaire on this instrument, then the system automatically assessed their TCM constitutions according to the Nine Basic Constitutions Classification and Criteria in Chinese Medicine (18). The questionnaire includes 60 items, in which items of nine subscales (each subscale consists of 7–8 items) are interspersed irregularly. For each item, an appropriate answer was selected from a Likert scale ("no," "occasionally," "sometimes," "often," and "always," scored 1–5). For each subscale, the original score was first calculated (original score = sum of the scores for each item) and then converted into the conversion score [(original score - number of subscale

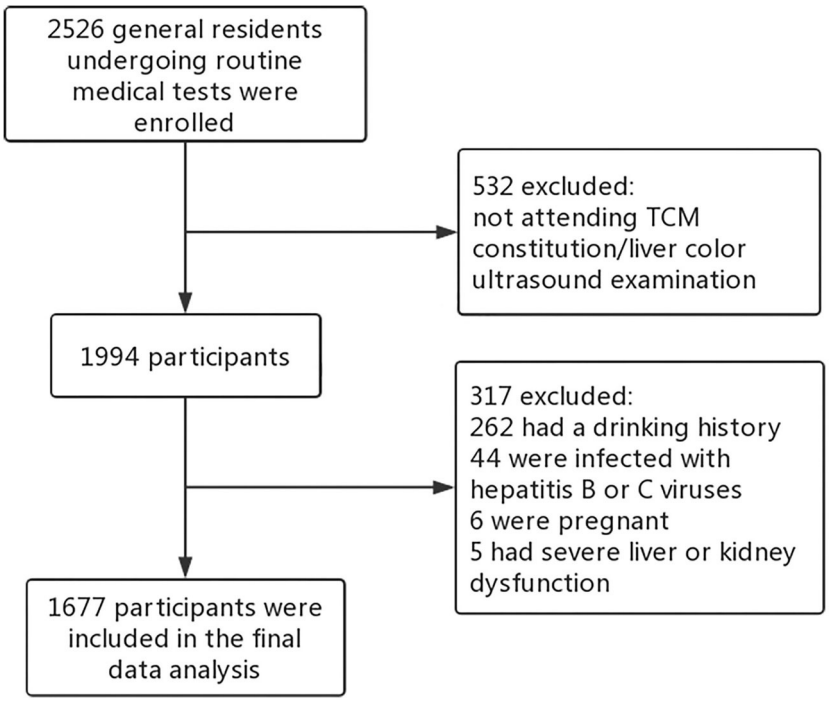


FIGURE 1 | The flow chart of the study sample selection.

items)/(number of subscale items × 4) × 100]. The conversion score of each subscale ranged from 0–100 points. Gentleness constitution referred to the participants with conversion scores of the eight biased constitutions being <30 points, and the conversion score of the gentleness constitution being ≥60 points. A biased constitution was diagnosed if the conversion score of any constitution was ≥40 points (see the TCM constitution questionnaire in the **Supplementary Material**).

Assessment of NAFLD

According to the definition of NAFLD, participants who met the following requirements were considered as NAFLD patients (19, 20): imaging evidence of hepatic steatosis; no excessive alcohol consumption (Alcohol consumption amounts to <30 g/d for men and <20 g/d for women); no specific diseases (such as, parenteral nutrition, viral hepatitis, drug hepatitis, and Wilson disease) that can lead to NAFLD. The diagnosis of fatty liver was assessed by experienced and trained radiologists who were blinded to the aim of the present study and the participants' clinical diagnosis. Ultrasonographic diagnosis of hepatic steatosis was determined by the presence of at least 2 of 3 abnormal findings on abdominal ultrasonography: diffusely increased echogenicity ("bright") liver with liver echogenicity greater than kidney or spleen, vascular blurring, and deep attenuation of the ultrasound signal (21).

Collection of Other Covariates

Other collected covariates included age, gender, height, weight, smoking history, previous medical history, blood pressure, blood glucose, and blood lipid. Experienced clinicians inquired about smoking history and previous medical history. Electronic instruments obtained standardized measurements of height, weight, and systolic and diastolic blood pressure. Body mass index (BMI) was calculated. Blood samples were collected from peripheral blood, and the laboratory department of the hospital detected blood glucose and blood lipid. A participant would be diagnosed as a diabetes patient if his/her concentration of fasting blood glucose ≥7.0 mmol/L or if he/she was currently taking any antidiabetic drugs. Hypertension was defined as the systolic blood pressure ≥140 mmHg or the diastolic blood pressure ≥90mmHg or who were currently undergoing antihypertensive treatments. Dyslipidemia was defined as an increase in plasma cholesterol (TC ≥ 6.2 mmol/L or LDL-C ≥ 4.1 mmol/L) or triglycerides (≥2.3 mmol/L), or a decrease in HDL cholesterol (≤1.0 mmol/L).

Statistical Analysis

Sample Size Estimate

In this study, 14 independent variables were included in the multivariate logistic regression equation, containing gender, age, BMI, smoking status, hypertension, diabetes, dyslipidemia, phlegm-dampness, qi-deficiency, yang-deficiency, yin-deficiency, dampness-heat, qi-depression, blood-stasis, and special diathesis constitutions. According to the 10 events per variable (EPV) principle (22), the study required 140 NAFLD patients. About 29.81% of China's population was reported to have NAFLD (23), so that the estimated sample size would be 470. Apart from TCM constitutions, since we also need to analyze the participants' tongue manifestation and pulse

condition in other studies. So we included participants as many as possible. This study eventually included 1,677 participants, and the sample size is big enough for logistic regression analysis.

Statistical Description and Inference

Continuous variables were expressed as mean ± standard deviation (normal distribution) or median (quartile) (skewed distribution), and categorical variables were expressed in frequency or as a percentage. The One-Way ANOVA (normal distribution), Kruskal-Wallis H (skewed distribution) test, and chi-square tests (categorical variables) were used to determine any statistical differences between the means and proportions of the groups. The polychoric correlation coefficient was calculated to determine the correlation between the phlegm-dampness constitution and other biased TCM constitutions. Logistic regression was used to evaluate the association between the phlegm-dampness constitution and NAFLD. According to the recommendation of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (24), we simultaneously showed the results of unadjusted, minimally adjusted analyses and those from fully adjusted analyses. In order to verify the stability of the results, we grouped participants according to whether they had the phlegm-dampness constitution, then used the PSM (propensity score matching) method to match the participants. Caliper was set to 0.01, with the proportion of 1:1, gender, age, BMI, smoking status, hypertension, diabetes, dyslipidemia, and other biased constitutions were matched. Subsequently, logistic regression was used to calculate the odds ratio and 95% confidence interval. All of the analyses were performed with the statistical software packages R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com,X&Y Solutions, Inc., Boston, MA). P-values <0.05 (two-sided) were considered statistically significant.

RESULTS

Baseline Characteristics of Participants

Among 1,677 participants, 365 (21.8%) were diagnosed with NAFLD. The average age of the participants was 48.3±10.4 years old, and about 57.4% of them are male. Compared with the non-NAFLD group, participants in the NAFLD group had a higher BMI, a higher proportion of male, phlegm-dampness, and dampness-heat constitutions, cigarette smoking, hypertension, diabetes and dyslipidemia, while a lower proportion of yang-deficiency, and blood-stasis constitutions (**Table 1**). In terms of TCM constitution distribution, the number of participants with the gentleness constitution was 640, accounting for 38.2%, while it with the biased constitution was 1,037, the proportion was 61.8%. Among participants with the biased constitution, 67.8% had mixed constitutions (with at least two constitutions). The majority of participants with the phlegm-dampness constitution had mixed constitutions, accounting for 89.5% (**Figure 2**).

TABLE 1 | Baseline characteristics of 1,677 participants according to non-alcoholic fatty liver disease status.

Characteristics	NAFLD			*P*-value
	Total	No	Yes	
Number	1,677	1,312	365	
Age (years, mean ± sd)	48.3 ± 10.4	48.4 ± 10.6	47.9 ± 9.6	0.43
Gender, male (*n*, %)	964 (57.4%)	676 (51.5%)	288 (78.9%)	<0.01
BMI (kg/m^2, mean ± sd)	24.5 ± 3.4	23.7 ± 3.0	27.1 ± 3.0	<0.01
Cigarette smoking (*n*, %)	304 (19.2%)	204 (16.5%)	100 (29.2%)	<0.01
Hypertension (*n*, %)	205 (12.2%)	135 (10.3%)	70 (19.2%)	<0.01
Diabetes (*n*, %)	66 (3.9%)	34 (2.6%)	32 (8.8%)	<0.01
Dyslipidemia (*n*, %)	793 (47.3%)	616 (45.5%)	177 (54.6%)	<0.01
TCM Constitutions (*n*, %)				
Phlegm-dampness	324 (19.3%)	218 (16.6%)	106 (29.0%)	<0.01
Gentleness	640 (38.2%)	507 (38.6%)	133 (36.4%)	0.44
Qi-deficiency	323 (19.3%)	247 (18.8%)	76 (20.8%)	0.39
Yang-deficiency	387 (23.1%)	332 (25.3%)	55 (15.1%)	<0.01
Yin-deficiency	275 (16.4%)	215 (16.4%)	60 (16.4%)	0.98
Dampness-heat	364 (21.7%)	263 (20.0%)	101 (27.7%)	<0.01
Qi-depression	227 (13.5%)	182 (13.9%)	45 (12.3%)	0.45
Blood-stasis	173 (10.3%)	155 (11.8%)	18 (4.9%)	<0.01
Special diathesis	105 (6.3%)	82 (6.2%)	23 (6.3%)	0.97

BMI, body mass index; NAFLD, non-alcoholic fatty liver disease.

Association Between the Phlegm-Dampness Constitution and Other Biased TCM Constitutions

Among 1,677 participants, chi-square and correlation analysis showed the phlegm-dampness constitution was positively associated with the yang-deficiency, yin-deficiency, dampness-heat, qi-depression, and blood-stasis constitution. The correlation coefficients were 0.11, 0.32, 0.42, 0.20, 0.14, respectively. In other words, participants with the phlegm-dampness constitution also tend to have the yang-deficiency, yin-deficiency, dampness-heat, qi-depression, or blood-stasis constitution (**Table 2**).

Relationship Between the Phlegm-Dampness Constitution, Seven Other Biased Traditional Chinese Medicine Constitutions, and NAFLD

We applied multivariate logistic regression to analyze the association between TCM biased constitutions and NAFLD. TCM biased constitutions were set as the exposures, NAFLD was set as the outcome. For the phlegm-dampness constitution, without adjusting for any confounding variables, the crude model showed the odds ratio (OR) and the 95% confidence interval (CI) was 2.05 (1.57–2.69). After adjusting for gender and age, the OR and the CI was 1.94 (1.46–2.58). In the fully adjusted model, we adjusted gender, age, BMI, smoking

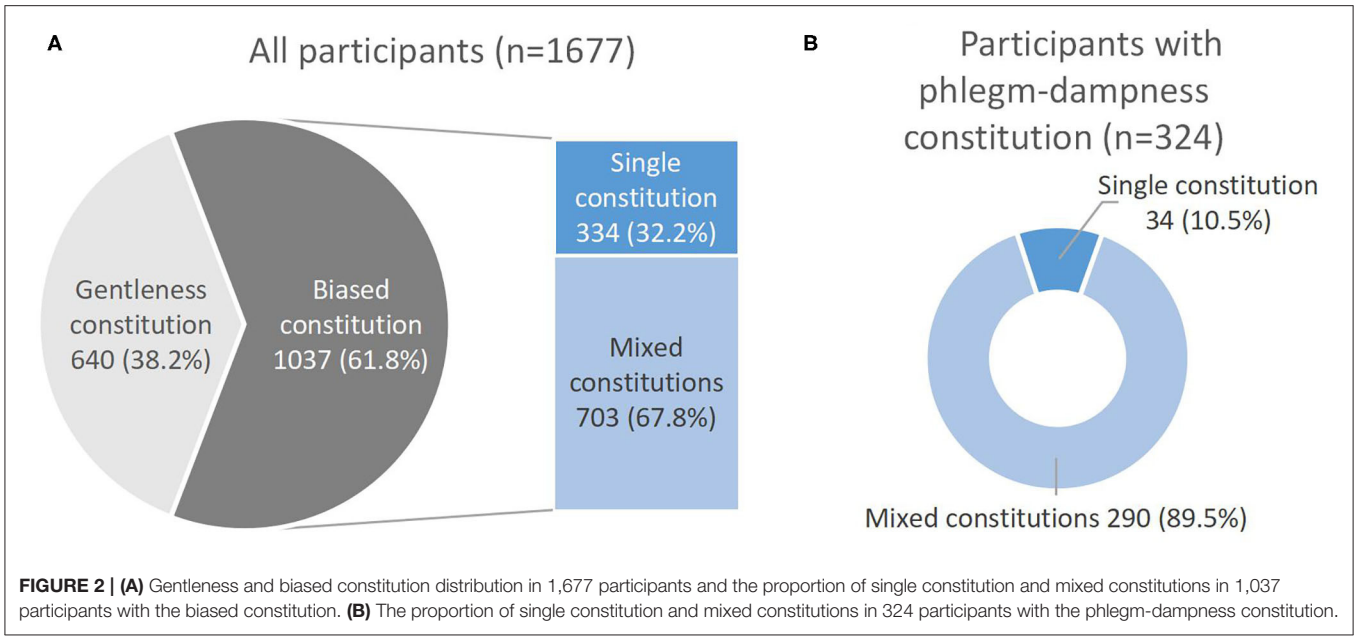


FIGURE 2 | (A) Gentleness and biased constitution distribution in 1,677 participants and the proportion of single constitution and mixed constitutions in 1,037 participants with the biased constitution. **(B)** The proportion of single constitution and mixed constitutions in 324 participants with the phlegm-dampness constitution.

TABLE 2 | Association between the phlegm-dampness constitution and seven other biased constitutions in 1,677 participants.

Seven other biased constitutions (*n*, %)	Phlegm-dampness constitution		Correlation coefficient	*P*-value
	No	Yes		
Qi-deficiency	254 (18.8%)	69 (21.3%)	0.05	0.30
Yang-deficiency	297 (22.0%)	90 (27.8%)	0.11	0.03
Yin-deficiency	181 (13.4%)	94 (29.0%)	0.32	<0.01
Dampness-heat	228 (16.9%)	135 (41.7%)	0.42	<0.01
Qi-depression	161 (11.9%)	66 (20.4%)	0.20	<0.01
Blood-stasis	127 (9.4%)	46 (14.2%)	0.14	0.01
Special diathesis	88 (6.5%)	17 (5.2%)	−0.06	0.40

status, hypertension, diabetes, dyslipidemia, qi-deficiency, yang-deficiency, yin-deficiency, dampness-heat, qi-depression, blood-stasis, and special diathesis constitutions. Although the OR reduced to 1.51 (1.04–2.18), there was still a statistical significance ($P = 0.029$). With the same analyzing process, the associations of seven other biased TCM constitutions and NAFLD were not statistically significant in the fully adjusted model (**Table 3**).

Sensitivity Analysis

Besides, the PSM analysis method was applied to match the participants. 260 pairs of participants were matched successfully in the phlegm-dampness constitution group and the non-phlegm-dampness constitution group. There was no statistically significant difference between the paired phlegm-dampness group and the non-phlegm-dampness group in terms of age, gender, BMI, other biased TCM constitutions, smoking status, hypertension, diabetes, and dyslipidemia (**Table 4**). The prevalence of NAFLD was 36.5% in the phlegm-dampness constitution group, compared with 26.2% in the non-phlegm-dampness constitution group. After adjusting for confounding variables, the OR was 1.59 (1.02–2.50) (**Table 5**), which was consistent with the result of multivariate logistic regression analysis.

DISCUSSION

Main Findings

Our study results demonstrated the TCM phlegm-dampness constitution is indeed associated with NAFLD. People with the phlegm-dampness constitution have a 50% increase in the odds of having NAFLD than those without this constitution. After adjusting for potential confounding variables such as age, gender, BMI, lifestyle, other biased TCM constitutions, and previous history of chronic diseases by logistic regression, the odds ratio directions of both univariate and multivariate analysis were consistent. Subsequent sensitivity analysis also showed accordant results using the PSM method to match the participants, which further supported that the association of the phlegm-dampness constitution and NAFLD is stable.

Besides, we also found that people tend to have at least two TCM constitutions, namely mixed constitutions. People

TABLE 3 | Relationship between the phlegm-dampness constitution, seven other biased traditional Chinese medicine constitutions and non-alcoholic fatty liver disease in different models among 1,677 participants.

	Crude model		Minimally adjusted model		Fully adjusted model	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Phlegm-dampness						
No	Reference		Reference		Reference	
Yes	2.05 (1.57, 2.69)	<0.001	1.94 (1.46, 2.58)	<0.001	1.51 (1.04, 2.18)	0.029
Qi-deficiency						
No	Reference		Reference		Reference	
Yes	1.13 (0.85, 1.51)	0.393	1.15 (0.85, 1.56)	0.379	1.32 (0.90, 1.94)	0.148
Yang-deficiency						
No	Reference		Reference		Reference	
Yes	0.52 (0.38, 0.72)	<0.001	0.58 (0.42, 0.81)	0.001	0.69 (0.46, 1.02)	0.064
Yin-deficiency						
No	Reference		Reference		Reference	
Yes	1.00 (0.73, 1.37)	0.981	1.12 (0.80, 1.56)	0.507	1.00 (0.66, 1.53)	0.982
Dampness-heat						
No	Reference		Reference		Reference	
Yes	1.53 (1.17, 2.00)	0.002	1.19 (0.89, 1.58)	0.244	0.93 (0.65, 1.35)	0.715
Qi-depression						
No	Reference		Reference		Reference	
Yes	0.87 (0.62, 1.24)	0.446	1.15 (0.79, 1.68)	0.465	1.00 (0.63, 1.60)	0.991
Blood-stasis						
No	Reference		Reference		Reference	
Yes	0.39 (0.23, 0.64)	<0.001	0.59 (0.35, 0.99)	0.048	0.58 (0.32, 1.05)	0.073
Special diathesis						
No	Reference		Reference		Reference	
Yes	1.01 (0.63, 1.63)	0.971	1.10 (0.66, 1.82)	0.725	1.34 (0.73, 2.45)	0.347

Crude model adjusted for none. Minimally adjusted model adjusted for gender, age. Fully adjusted model adjusted for gender, age, BMI, smoking status, hypertension, diabetes, dyslipidemia, other biased constitutions. OR, odds ratio; CI, confidence interval.

with the phlegm-dampness constitution often simultaneously have another TCM constitution, such as, the yang-deficiency, yin-deficiency, dampness-heat, qi-depression, or blood-stasis constitution. Because the coexisting biased constitution may also affect the diseases of the researchers' concern, therefore, when analyzing the relationship between a specific TCM constitution and a certain disease, other coexisting biased constitutions should be regarded as confounding variables for control. Otherwise, false positive or false negative results may be obtained. Among the published TCM constitution studies, the adjustment of other biased constitutions is often neglected. To promote the rigor and reliability of TCM constitution research, we hope that future researchers will pay attention to the confounding effect of other biased constitutions.

Comparison With Other Studies

In line with prior descriptive cross-sectional studies (14, 15), we also found the qi-deficiency, phlegm-dampness, dampness-heat, and gentleness constitution are the common TCM constitutions in NAFLD patients. Based on personal clinical experience and these cross-sectional surveys, many TCM practitioners and researchers believe that the internal retention of phlegm and dampness are the etiology and pathogenesis of NAFLD (12, 13). Although, our study results could not yet demonstrate this empirical theory, we have proved the correlation between the phlegm and dampness constitution and NAFLD for the first time. It sets the basis for the further casual relationship investigation.

In addition to phlegm and dampness, blood stasis is also regarded as NAFLD's etiology and pathogenesis (12, 13), suggesting the blood-stasis constitution is associated with

NAFLD. However, our data do not support this viewpoint. In our study, the association between the blood-stasis constitution and NAFLD neither has clinical significance or statistical significance. Since the theory released by TCM practitioners is a theoretical derivation and has not been tested before, according to our results, we think there is still no sufficient evidence to prove the blood-stasis constitution's causal effect on NAFLD.

Potential Explanations

Based on the expert opinion that the biased TCM constitution is the basis of diseases (11), we speculate that the phlegm-dampness constitution is a status appearing before the occurrence of NAFLD. The correlation between the phlegm-dampness constitution and NAFLD might be due to some common pathological basis they have at the genetic level. It was found that the PPARGC1A knockout mice exhibited marked hepatic steatosis due to a combination of reduced mitochondrial respiratory capacity and increased expression of lipogenic genes (25). Clinical study also showed a significant association between genetic variations in PPARGC1A and NAFLD, which suggested PPARGC1A polymorphism and lower expression of PPARGC1A mRNA in the liver are an important genetic contribution to the etiology of NAFLD (26). In addition, ABCA1 and ACSL4 genes are reported to be associated with NAFLD as well (27–29). Coincidentally, some people with the phlegm-dampness constitution are also accompanied by the abnormal expression of above genes (30–32). Thus, we hypothesize that PPARGC1A, ABCA1, ACSL4 genes express abnormally in some patients due to either congenital defect or acquired unhealthy lifestyles, afterwards the patients will get into a phlegm-dampness constitution state. If this pathological state continues for long, NAFLD may eventually occur.

TABLE 4 | Characteristics in non-phlegm-dampness and phlegm-dampness constitution groups after matching.

Characteristics	Phlegm-dampness constitution		*P*-value
	No	Yes	
Number	260	260	
Age (years, mean ± sd)	49.34 ± 10.30	48.07 ± 11.12	0.18
Gender, male (*n*, %)	153 (58.8%)	164 (63.1%)	0.37
BMI	24.98 ± 3.52	25.32 ± 3.50	0.26
Cigarette smoking (*n*, %)	73 (28.1%)	81 (31.2%)	0.50
Hypertension (*n*, %)	43 (16.5%)	45 (17.3%)	0.91
Diabetes (*n*, %)	11 (4.2%)	16 (6.2%)	0.43
Dyslipidemia (*n*, %)	161 (61.9%)	164 (63.1%)	0.86
TCM Constitutions (*n*, %)			
Qi-deficiency	66 (25.4%)	59 (22.7%)	0.54
Yang-deficiency	85 (32.7%)	72 (27.7%)	0.25
Yin-deficiency	70 (26.9%)	65 (25%)	0.69
Dampness-heat	106 (40.8%)	110 (42.3%)	0.79
Qi-depression	47 (18.1%)	52 (20%)	0.66
Blood-stasis	39 (15%)	37 (14.2%)	0.90
Special diathesis	21 (8.1%)	15 (5.8%)	0.39

Clinical Value

By revealing the correlation between the phlegm-dampness constitution and NAFLD, this study brings modern medicine community the TCM perspective on NAFLD, which could facilitate the communication between modern medicine and traditional medicine. It will also promote further longitudinal studies, which has certain guiding significance for the prevention and treatment of NAFLD. In terms of prevention, if future longitudinal studies prove that the phlegm-dampness constitution is a high-risk factor for the onset of NAFLD, intervention measures including some specific diet, exercise, drugs, and acupuncture will help prevent the disease by resolving phlegm and dispelling dampness. In terms of treatment, correcting patients' phlegm-dampness constituion through TCM therapy is expected to provide new ideas for modern medical treatment of NAFLD.

Strengths and Limitations

This study's strengths are that it has a large sample size, and the data analysis process is rigorous. Two statistical analysis methods were adopted to control the confounding variables, and consistent results were obtained, indicating that the results are stable and reliable. Also, within all the clinical studies on TCM constitutions, we first noticed the confounding effect of coexisting biased constitutions and controlled it.

Meanwhile, our study has the following four limitations: (1) this is a single-center study, and no random sampling was conducted, so participants in this study may not represent all the general population of China; (2) because of the cross-sectional nature, participants' TCM constitution and NAFLD status were evaluated at the same time point, which could only prove the correlation between the phlegm-dampness constitution and NAFLD, rather than the causal conclusion (33); (3) the diagnosis of NAFLD was based on the ultrasound examination instead of the pathological biopsy, CT, or MR examination, some cases might be missed. This would lower the prevalence of NAFLD and

TABLE 5 | Prevalence of non-alcoholic fatty liver disease in non-phlegm-dampness and phlegm-dampness constitution group after matching among 1,677 participants.

	Phlegm-dampness constitution		OR of paired sample	
	No	Yes	Adjusted OR (95% CI)	*P*-value
NAFLD (*n*, %)	68 (26.2%)	95 (36.5%)	1.59 (1.02, 2.50)	0.042

NAFLD, non-alcoholic fatty liver disease; OR, odds ratio; CI, confidence interval.

affect the estimated OR value; (4) without randomized grouping, some unknown confounding variables were not collected and might be distributed unevenly between the two groups.

CONCLUSIONS

Among eight biased TCM constitutions, the phlegm-dampness constitution is independently associated with NAFLD. Based on the TCM constitution theory, we speculate the phlegm-dampness constitution is a risk factor of NAFLD. Further longitudinal studies are needed to confirm this causal relationship. Additionally, inconsistent with some TCM practitioners' experience, we disagree that the blood-stasis constitution is associated with NAFLD. Besides, most people have mixed TCM constitutions, and the phlegm-dampness constitution is often accompanied by the yang-deficiency, yin-deficiency, dampness-heat, qi-depression, and blood-stasis constitution. Future clinical studies on the TCM constitution should notice the confounding effect of coexisting biased constitutions.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Affiliated Hospital of Chengdu University of Traditional Chinese Medicine. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KZ and YG collected the clinical data and conducted statistical analysis. CZ, SK, JL, JW, and ZT participated in the data collection and the establishment of the database. KZ wrote the original draft. BL and WL were responsible for designing the study and reviewing the draft. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.635818/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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BRIEF RESEARCH REPORT
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Mortality Rate and Characteristics of Deaths Following COVID-19 Vaccination

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Background: The emergency use authorization for coronavirus disease 2019 (COVID-19) vaccines brought both hopes and concerns to the Americans and others. We aimed to estimate the mortality rate of COVID-19 vaccination and presented characteristics of deaths following COVID-19 vaccination.

Methods: Data on deaths following COVID-19 vaccination were obtained from the Vaccine Adverse Event Reporting System (VAERS) from December 11, 2020 through January 8, 2021. The Centers for Disease Control and Prevention (CDC) COVID Data Tracker was used to identify the total number of people receiving COVID-19 vaccines during the same period to estimate the mortality rate. Stratified analysis was conducted by the location of vaccination.

Results: As of January 8, 2021, 55 deaths were reported, and the mortality rate of COVID-19 vaccination was 8.2 per million population. A total of 37 deaths were reported among long-term care facility residents, and the mortality rate was 53.4 per million population. Top reported comorbidities associated with deaths included hypertension, dementia, chronic obstructive pulmonary disease (COPD), diabetes, and heart failure. In addition, dementia was more likely to be associated with deaths vaccinated at long-term care facilities than at other locations.

Conclusion: The benefits of COVID-19 vaccines outweigh the potential risks in older frail populations, and our findings do not support actions to exclude older adults from being vaccinated. However, continued monitoring of COVID-19 vaccination is still warranted.

Keywords: COVID-19, vaccine, pharmacovigilance, safety, long-term care facility

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BACKGROUND

The emergency use authorization for coronavirus disease 2019 (COVID-19) vaccines brought both hopes and concerns to the Americans and others. Most recently, the Norwegian Medicines Agency reported 29 deaths following COVID-19 vaccines in very frail elderly patients, raising safety concerns for vaccination in older adults (1). Norwegian government has adjusted advice on who should receive COVID-19 vaccines which are based on novel messenger RNA (mRNA) technology.

TABLE 1 | Characteristics of deaths following COVID-19 vaccination in the U.S. ($N = 55$).

	All locations $N = 55$		Long-term care facilities $N = 37$		Other locations $N = 18$		P
	N	%	N	%	N	%	
Age							0.0003
18–64	9	16.4	1	2.7	8	44.4	
65–74	9	16.4	5	13.5	4	22.2	
75–84	12	21.8	9	24.3	3	16.7	
85+	25	45.5	22	59.5	3	16.7	
Sex							0.0444
Female	29	52.7	23	62.2	6	33.3	
Male	26	47.3	14	37.8	12	66.7	
Region							0.5464
Northeast	5	9.1	3	8.1	2	11.1	
Midwest	21	38.2	15	40.5	6	33.3	
South	17	30.9	13	35.1	4	22.2	
West	9	16.4	5	13.5	4	22.2	
Unknown	3	5.5	1	2.7	2	11.1	
Days to death							0.6989
0	14	25.5	11	29.7	3	16.7	
1–2	15	27.3	9	24.3	6	33.3	
3–6	16	29.1	11	29.7	5	27.8	
7+	10	18.2	6	16.2	4	22.2	

In contrast, the U.S. has prioritized people aged 65 years and older and long-term care facility residents to receive COVID-19 vaccines. However, COVID-19 vaccines have not been tested in clinical trials in these frail older adults (2). Pharmacovigilance examines adverse events of drugs or vaccines in populations but this information on COVID-19 vaccines is limited. This study estimated the mortality rate of COVID-19 vaccination and presented characteristics of deaths following COVID-19 vaccination and top reported comorbidities and medications associated with deaths in the U.S.

METHODS

Data on deaths following COVID-19 vaccination were obtained from the Vaccine Adverse Event Reporting System (VAERS), a national vaccine safety surveillance program (3). We searched VAERS for deaths associated with any COVID-19 vaccine from December 11, 2020 through January 8, 2021. To solve the common limitation of passive surveillance data of unknown denominator, we used the Centers for Disease Control and Prevention (CDC) COVID Data Tracker for the total number of people receiving COVID-19 vaccines during the same period to estimate the mortality rate (4). Stratified analysis was conducted by the location of vaccination.

RESULTS

Among 6,688,231 individuals who received COVID-19 vaccination, 55 deaths were reported as of January 8, 2021. The mortality rate of COVID-19 vaccination was 8.2 per million population (**Table 1**). A total of 37 deaths were reported in long-term care facilities when 693,246 residents are vaccinated. The COVID-19 vaccination mortality rate was 53.4 per million population among long-term care facility residents.

Adults aged 85 years and over accounted for half of the reported deaths ($N = 25$, 45.5%). Those vaccinated at long-term care facilities were more likely to be older and females than at other locations. A total of 14 individuals (25.5%) died on the same day and 45 individuals (81.8%) died within 1 week following vaccination. Top reported comorbidities associated with deaths were hypertension, dementia, chronic obstructive pulmonary disease (COPD), diabetes, and heart failure (**Table 2**). Dementia was more likely to be associated with deaths at long-term care facilities. Top medications associated with deaths were pain relievers, fever reducers, and antihypertensives.

DISCUSSION

COVID-19 vaccine is safe in younger groups. The majority of the reported deaths were in people aged 85 and older and vaccinated at long-term care facilities; these patients are frail older people with serious underlying health conditions such as dementia, hypertension, heart failure, COPD, diabetes, anemia, and fall. In addition, these vulnerable patients are polypharmacy users. Certain vaccine-disease and vaccine-drug interactions might have contributed to or have worsened health outcomes of those already vulnerable populations. It is essential to monitor the allergic reactions following the vaccination that mainly occur within a short period of time for preventable risks (5). However, the mortality rate of 53.4 per million following COVID-19

TABLE 2 | Top reported comorbidities and medications associated with deaths following COVID-19 vaccination by the location of vaccination.

	All locations *N* = 55		Long-term care facilities *N* = 37		Other locations *N* = 18		*P*
	N	%	*N*	%	*N*	%	
Comorbidities							
Hypertension	22	40.0	14	37.8	8	44.4	0.6390
Dementia	17	30.9	15	40.5	2	11.1	0.0267
COPD	13	23.6	9	24.3	4	22.2	1.0000
Diabetes	12	21.8	7	18.9	5	27.8	0.4993
Heart failure	10	18.2	9	24.3	1	5.6	0.1399
Hyperlipidemia	9	16.4	6	16.2	3	16.7	1.0000
Anemia	8	14.5	7	18.9	1	5.6	0.2497
CKD	7	12.7	4	10.8	3	16.7	0.6713
Stroke	7	12.7	5	13.5	2	11.1	1.0000
Atrial fibrillation	6	10.9	5	13.5	1	5.6	0.6514
Depression	6	10.9	5	13.5	1	5.6	0.6514
Fall	6	10.9	6	16.2	0	0.0	0.1621
GERD	6	10.9	4	10.8	2	11.1	1.0000
Medications							
Acetaminophen	9	16.4	8	21.6	1	5.6	0.2441
Aspirin	9	16.4	6	16.2	3	16.7	1.0000
Amlodipine	8	14.5	6	16.2	2	11.1	0.7079
Metoprolol	8	14.5	6	16.2	2	11.1	0.7079
Omeprazole	7	12.7	6	16.2	1	5.6	0.4058
Potassium	6	10.9	6	16.2	0	0.0	0.1621
Vitamin D	6	10.9	6	16.2	0	0.0	0.1621
Docusate	5	9.1	5	13.5	0	0.0	0.1603
Furosemide	5	9.1	5	13.5	0	0.0	0.1603
Lisinopril	5	9.1	4	10.8	1	5.6	0.6583
Mirtazapine	5	9.1	4	10.8	1	5.6	0.6583
Tamsulosin	5	9.1	3	8.1	2	11.1	1.0000

COVID-19, coronavirus disease 2019; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; GERD, gastroesophageal reflux disease.

vaccination among long-term care facility residents during the study period was much lower compared to the 2019 monthly all-cause mortality rate of 0.3% among adults aged 65 years or older (6), or the 30-day all-cause mortality rate of 21.5% among US nursing home residents with COVID-19 (7). Therefore, our data suggest that the benefits of COVID-19 vaccines far outweigh the potential risks in older frail populations (e.g., long-term care facilities), and our findings do not support actions to exclude older adults from being vaccinated as the Norwegian government did. Continued monitoring of COVID-19 vaccination among the older population, particularly those with comorbidities and medications reported in this study, however, is warranted.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found at: https://vaers.hhs.gov/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of Tennessee Health Science Center. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

GL and ML: concept and design. JY and ML: acquisition, analysis, or interpretation of data. GL, JY, XX, and ML: drafting of the manuscript and critical revision of the manuscript for important intellectual content. GL, JY, and ML: statistical analysis. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Ameliorative Effects of Component Chinese Medicine From *Curcumae Rhizoma* and *Sparganii Rhizoma*, a Traditional Herb Pair, on Uterine Leiomyoma in a Rat Model

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Uterine leiomyoma (UL), common benign tumors in women of child-bearing age, are believed to be caused mainly by Qi stagnation and blood stasis, according to a theory of traditional Chinese medicine. *Curcumae Rhizoma* and *Sparganii Rhizoma* (CRSR) is a classical herb pair that activates blood circulation to dissipate blood stasis. The purpose of this study was to explore the prevention and treatment effects of CRSR component compatibility on UL in rats. We randomly assigned adult female non-pregnant rats into three groups: a normal control (NC) group, a UL model group, and a CRSR treatment group. We administered to the UL and CRSR groups oral gavage diethylstilbestrol and injected them with progesterone (P) to establish UL for 5 weeks. The CRSR group received a CRSR medicinal solution after daily modeling. The uterus morphology of the UL group showed significantly more swelling than did that of the NC group, and we found no significant abnormalities in the morphology of the CRSR group. The pathological changes associated with UL were relieved in the CRSR group. CRSR improved the related parameters of the uterus and ovarian coefficients, significantly reducing the concentrations of P in the serum and the concentrations of estradiol, P, estrogen receptor, and P receptor in the uterus and ovary. In addition, CRSR significantly improved the abnormal blood conditions of UL, shown by decreases in plasma viscosity, the erythrocyte sedimentation rate equation *K* value, and erythrocyte aggregation index. Therefore, CRSR component compatibility may prevent and cure UL through the above ways.

Keywords: uterine leiomyoma, *Curcumae Rhizoma*, *Sparganii Rhizoma*, estrogen, progesterone, hemorheology, mechanism study

INTRODUCTION

Uterine leiomyoma (UL), or fibroids, are the most common tumors in women, caused by the proliferation of smooth muscle cells. Because of the difference in diagnostic methods and study participants, the prevalence rate varies from 4.5 to 68.6%, and the number of Black women with UL far exceeds that of white women (1). Although UL tumors are benign, they can cause symptoms such as dysmenorrhea, abnormal uterine bleeding, pelvic pain, and recurrent abortion, all of which may require medicine or surgery (2, 3).

UL are recognized as a hormone-dependent tumor, estrogen, progesterone (P), and their receptors can play an important role in its occurrence and development (3–5). Estradiol (E_2) can induce the expression of the progesterone receptor (PR) to directly affect human leiomyoma cells (6). P can promote the proliferation and complete development of leiomyoma cells (5). Thus, the current medical treatment of UL mainly is inhibiting steroid hormones (e.g., antiprogestins, aromatase inhibitors), but these can only reduce the size of a tumor, and after discontinuing use, the tumor will continue to grow (6). Although surgical resection is a relatively thorough method, it is not suitable for patients seeking to preserve their uterus or fertility, and the costs associated with surgical treatment can be an economic burden (7). Therefore, alternative economic and effective non-surgical treatment methods are needed.

Traditional Chinese medicine (TCM) has been used widely in the treatment of UL (8–10). Studies have shown that the surgical rate of patients with UL treated with TCM is significantly reduced (8), as are medication dosage and total medical expenses, as compared to conventional Western medicine (9). In TCM theory, UL is believed to be caused by stagnation of Qi and blood in the pelvic region over a certain time period (11). The prevention and treatment of hysteromyoma using TCM can normalize blood flow and unobstruct Qi. If Qi and blood do not accumulate in the uterus, tumors will not produce, so the treatment of UL mostly adopts the TCM formula of promoting blood circulation and removing blood stasis (10, 11).

Compare with TCM formula, herbal pairs, as the most basic form of TCM, can not only reflect the characteristics of TCM but also have simple ingredients, which is convenient for research (12). In general, a herbal pair is composed of two types of herbs.

CRSR, a classical herb pair used to promote blood circulation and remove blood stasis, is commonly used in the treatment of gynecological tumors (13–16). *Curcumae Rhizoma* has antitumor, antiplatelet aggregation, antithrombosis, hepatoprotective, antimicrobial, and other pharmaceutical activities. *Curcumae Rhizoma* essential oil also is widely used in China for the treatment of tumors (16). *Sparganii Rhizoma* has anti-estrogen, anticancer, and anti-angiogenic effects (14, 17). *Sparganii Rhizoma* can combine with *Curcumae Rhizoma* through its own antitumor activity compound (linear diarylheptanoids) to enhance the efficacy of CRSR (13). Xu et al. (15) also has found that the volatile oil of CRSR showed stronger antioxidant and anticancer activity, and its inhibitory effect on tumor cells was more significant than that of *Curcumae Rhizoma* oil or *Sparganii Rhizoma* oil alone.

Although CRSR has shown good effects on UL in clinical practice and experimental research, few have studied its prevention and treatment effects and its mechanisms of component compatibility. Therefore, in this study, we took CRSR intervention while making a UL model, from organ coefficients (ovary, uterus), histopathology, sex hormone levels (E_2, P, and their receptors), and hemorheology to explore the prevention and treatment effects of CRSR on UL.

MATERIALS AND METHODS

Reagents and Extract Preparation

Sparganii Rhizoma slices were obtained from Sichuan Hao-Bo Co., Ltd. (Lot no. 160301; China). Volatile oil of *Curcumae Rhizoma* was obtained from Shanxi Hao-Chen Biotechnology Co., Ltd. (Lot no. EZ150801; China). Diethylstilbestrol was provided by Chengdu West Asia Chemical Co., Ltd. (Lot no. K9212; China). P injections were manufactured by Zhejiang Xian-Ju Pharmaceutical Co., Ltd. (Lot no. 150610; China). Hematoxylin was purchased from Beijing Bailingwei Technology Co., Ltd. (Lot no. LM10N13; China). Eosin dye liquor was produced by Tokyo Chemical Industry Co., Ltd. (Lot no. GL01-GMPC; Japan).

ELISA kits for Rat E_2 (Lot no. XL-Er0478), P (Lot no. XL-Er0477), ER (Lot no. XL-Er1021), and PR (Lot no. XL-Er0474) were produced by Aimejie Technology Co., Ltd., and imported by Beijing Yonghui Biotechnology Co., Ltd., China.

Sparganii Rhizoma was smashed into coarse powder and passed through a no. 24 mesh sieve. The powder was soaked in 10× volume of 60% ethanol for 30 min. The reflux extraction was carried out twice by heating with an electric heating jacket for 1.5 h each time. After filtration with a vacuum pump, alcohol was recovered by decompression with a rotary evaporator, and the collected concentrated liquid was degreased with petroleum ether. Finally, polyamide column chromatography was performed. After chromatography, distilled water was used for elution, ethanol was used for elution and alcohol recovery. After placement in a constant-temperature drying oven, a solution of 1 g/mL was prepared with distilled water and stored at 4°C.

The volatile oil of *Curcumae Rhizoma* was emulsified with 1% tween −80, and a solution of 1 g/ml was prepared with distilled water. These two solutions were mixed at 1:1, configured as a CRSR solution, and stored at 4°C.

Construction of a UL Model in Rats and CRSR Treatment

All animal experimental protocols were reviewed and approved by the Animal Ethics Committee of Chengdu University of TCM. We obtained 27 non-pregnant female adult Sprague–Dawley rats (200 ± 20 g) from Jianyang Dashuo Experimental Animal Tech (Sichuan, China) with a license number SCXK (Chuan) 2013-24. Rats were kept in the Center of Laboratory Animals at Chengdu University of TCM. After 5 days of adaptive feeding, we divided the rats randomly into a normal control (NC) group ($n = 9$), a UL group ($n = 9$), and a CRSR group ($n = 9$).

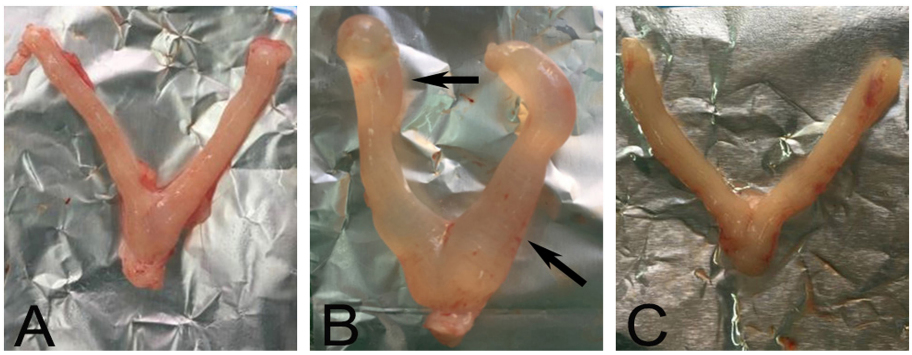


FIGURE 1 | Representative images of morphology of a rat uterus after CRSR treatment. The uterus of a NC rat **(A)** was bilaterally symmetrical, without swelling nodules and cysts. Significant swelling, nodules, and cysts (arrows) appeared in the UL group **(B)**. The CRSR uterus morphology **(C)** tended to match that of the NC group **(A)**. NC, normal control group; UL, uterine leiomyoma model group; CRSR, *Curcumae Rhizoma* and *Sparganii Rhizoma* treatment group.

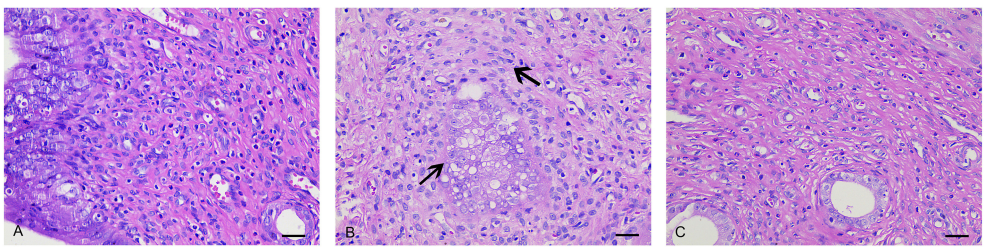


FIGURE 2 | Histopathologic examinations of uteruses from the NC, UL, and CRSR groups. The original magnification was 400×. Scale bar: 30 μm. **(A)** NC, normal control group; **(B)** UL, uterine leiomyoma model group; **(C)** CRSR, *Curcumae Rhizoma* and *Sparganii Rhizoma* treatment group.

We extracted the UL modeling method using our group's previous research (16). The UL and CRSR groups received a 1.35 mg/kg daily gavage of diethylstilbestrol, and 1.0 mg of progesterone intramuscularly injected every other day for 5 weeks. The CRSR group received medicine formulated from *Curcumae Rhizoma* and *Sparganii Rhizoma* (6.67 g/kg) 2 h after daily intragastric administration of the diethylstilbestrol. Meanwhile, the NC group received 2 ml of distilled water every day and 0.05 ml of normal saline injected intramuscularly every other day. We monitored the diet, weight, and general behavior of the rats weekly.

Sample Harvest

At the end of the experiment, the rats were sacrificed after an overnight fast, the rats were anesthetized by 10% chloral hydrate. We collected the blood samples (5 ml each) in vacutainer tubes from the femoral artery. The blood was allowed to clot before centrifugation at 3,500 rpm for 10 min at 6°C and then stored at −80°C until analysis. We peeled off the uterus and ovaries, removed the adipose tissue on the surface, and removed the blood stains with saline and then weighed and measured these separately. We measured the transverse diameter *(r)* and diameter *(R)* with vernier calipers. We calculated the uterine and ovarian coefficients using the following formula: coefficient = single organ weight (mg)/final body weight (g) × 100%. After taking the measurements, we stored half of the uteruses and ovaries in 4% paraformaldehyde fixative and the other half in liquid nitrogen.

Uterine Histopathologic Examination

We processed and stained the fixed uterine tissues with hematoxylin and eosin. The section images were acquired with a digital photographic microscope (BA400Digital; Mike Audi Industry Group Co., Ltd.).

Enzyme-Linked Immunosorbent Assay

ELISA kits determined the concentrations of serum E_2 and P, as well as the levels of E_2, P, ER, and PR in the uterine and ovarian homogenate tissues following the manufacturer's instructions.

Determination of Hemorheology

We determined the plasma viscosity (PV), the erythrocyte sedimentation rate equation *K*'s value (*K* value of ESR equation), and the erythrocyte aggregation index (EAI) in blood samples with an automatic blood rheometer (Sa-5600; Beijing Seksid Technology Development Co., Ltd.).

Statistical Analysis

All data were statistically analyzed by SPSS 21.0, reporting the results as mean ± SD. We used one-way analysis of variance (ANOVA) and the least significant difference (LSD) test if the variances are homogeneous; otherwise, used the Kruskal–Wallis H test. We considered $p < 0.05$ as statistically significant.

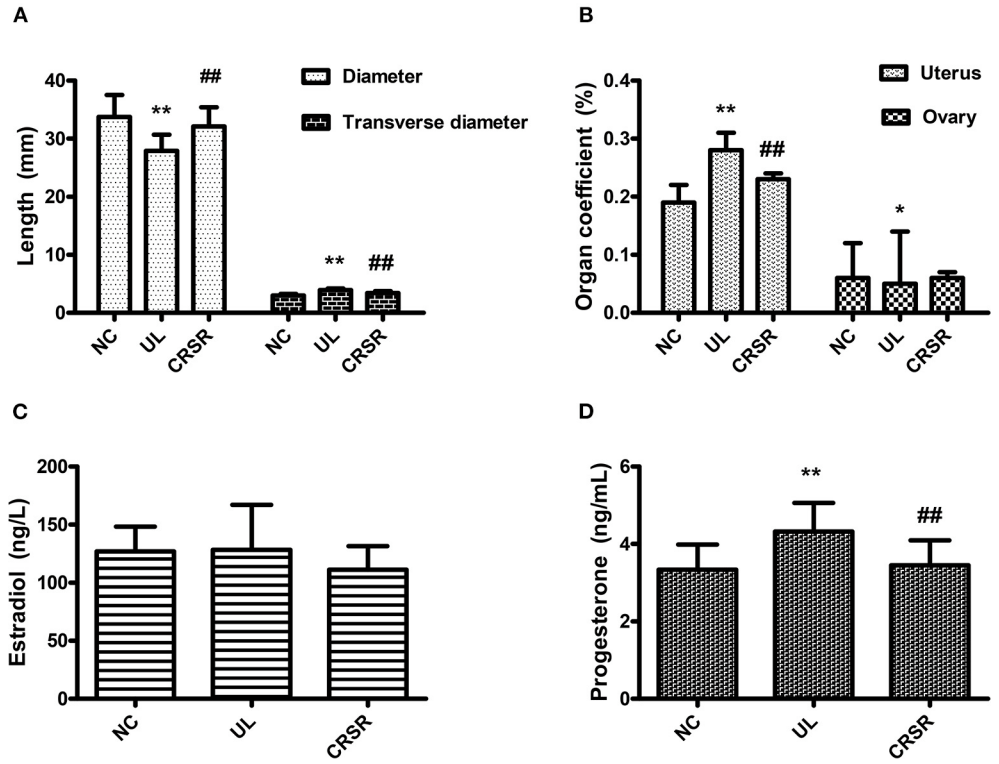


FIGURE 3 | (A) Effects of CRSR on the transverse diameter and diameter of the uterus. **(B)** Effects on the uterine and ovarian coefficients. **(C,D)** Changes of E_2 and P in the serum. Data are reported as mean ± SD. NC, normal control group; UL, uterine leiomyoma model group; CRSR, *Curcumae Rhizoma* and *Sparganii Rhizoma* treatment group; E_2, estradiol; P, progesterone. $^{*}p < 0.05$, $^{**}p < 0.01$ UL vs. NC; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ CRSR vs. UL (one-way ANOVA and LSD test).

RESULTS

Observation of the Rats' General Behavior

Before the establishment of the models, all rats ate and drank normally, had white and glossy fur, and were in good physical and mental health. After we established the UL model, the rats developed mental atrophy, and their fur became yellow and had severe depilation. In the later stage of modeling, the rats were easily irritated and fought.

CRSR Reduced Uterine Swelling in the UL Rats

The uteruses of the rats in the NC group were bilaterally symmetrical and y shaped, with uniform texture; bright color; and no cysts, nodules, or swelling (**Figure 1A**). The length and thickness of the uteruses in the UC group were uneven, with faded color and obvious swelling, nodules, and cysts (**Figure 1B**). The shape of the uteruses in the CRSR group were symmetrical, their volume was greatly reduced, and their color became pale (**Figure 1C**), we observed no swelling, cysts, or nodules. The UL modeling method resulted in swelling, nodules, and cysts. After CRSR treatment, uterine morphology was significantly improved and tended to be normal (**Figure 1A**).

Histology Analysis

In the NC group (**Figure 2A**), the endometrium was intact, with no signs of pathological changes such as hyperplasia, atrophy, hyperemia, edema, denaturation, necrosis, or inflammatory cell infiltration. The epithelial cells were aligned, with no thickening or shedding degeneration. The volume of the smooth muscle cells and serosal layer were normal. In the UL group (**Figure 2B**), the uterine smooth muscle cells showed hyaline degeneration and focal hyperplasia, and the mucosal epithelial cells were vacuolated. The uterine smooth muscles were slightly hypertrophic. After CRSR treatment (**Figure 2C**), the endometrium was largely intact, with only a small amount of lymphocyte infiltration in the lamina propria. These histological changes further demonstrated the preventive and therapeutic effects of CRSR on UL.

CRSR Improved the *r* and *R* of the Uterus

The uterine *r* in the UL group was significantly wider than that in the NC group, and the uterine *R* was significantly shorter than that in the NC group ($p < 0.01$). The *r* of the uteruses in the CRSR group was significantly shorter than that in the UL group, and the *R* was significantly increased, with a value close to that in NC group ($p < 0.01$) (**Figure 3A**).

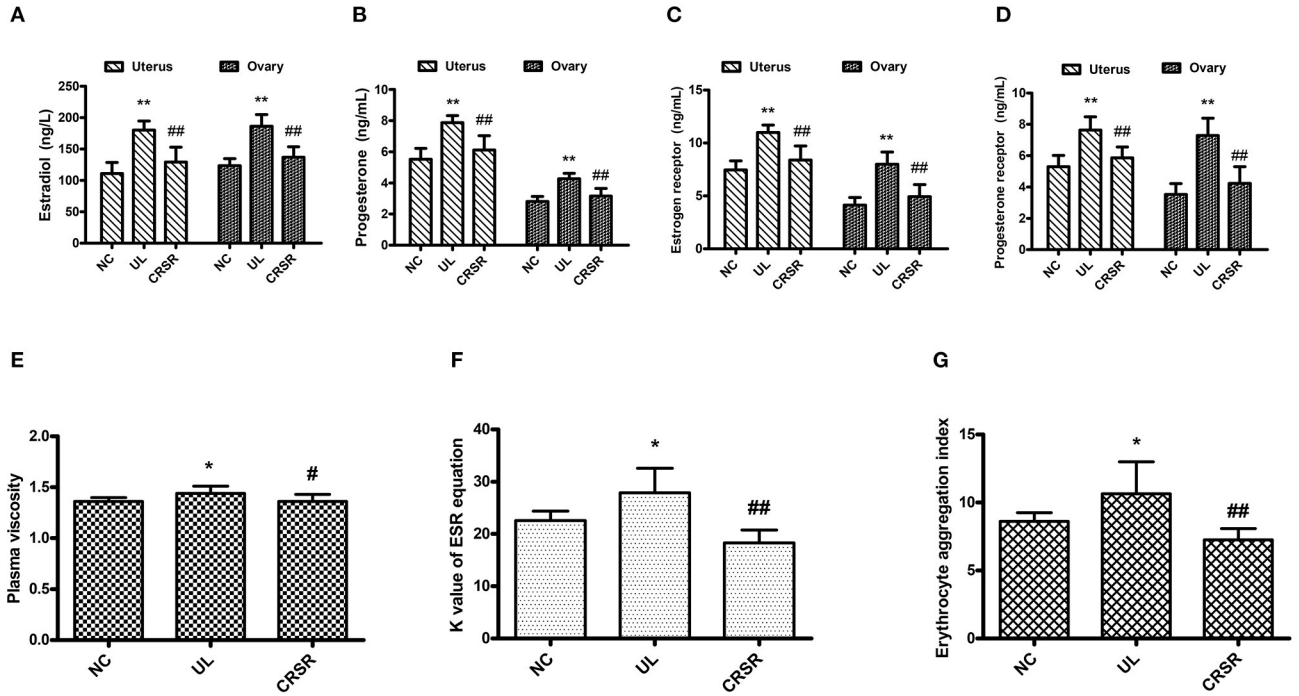


FIGURE 4 | CRSR reduced the levels of key hormones and receptors of UL. **(A)**, estradiol (E_2); **(B)**, progesterone (P); **(C)**, estrogen receptor (ER); **(D)**, progesterone receptor (PR). **(E–G)** Effects of CRSR on hemorheology. **(E)**, PV; **(F)**, K value of ESR equation; **(G)**, EAI. Data are reported as mean ± SD. NC, normal control group; UL, uterine leiomyoma model group; CRSR, *Curcumae Rhizoma* and *Sparganii Rhizoma* treatment group. $^{*}p < 0.05$, $^{**}p < 0.01$ UL vs. NC; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ CRSR vs. UL (Kruskal–Wallis H test).

Effects of CRSR on the Uterus and Ovary Coefficients in the UL Rats

The uterine coefficient increased significantly in the UL group as compared with the NC group ($p < 0.01$). In contrast, the uterine coefficient decreased significantly in the CRSR group as compared with the UL group ($p < 0.01$). As compared with the NC group, the ovarian organ coefficient of the UL group significantly decreased ($p < 0.05$). The ovarian organ coefficient of the CRSR group showed a slight increase as compared with the UL group, but the difference was not statistically significant ($p > 0.05$) (**Figure 3B**).

CRSR Reduced Serum E_2 and P Concentrations in the UL Rats

We observed no significant differences in the concentrations of E_2 among the three groups ($p > 0.05$) (**Figure 3C**). The concentrations of P in the UL group's serum was significantly higher than that in the NC group ($p < 0.01$). The concentrations of P in the CRSR group's serum as significantly reduced as compared with that in the UL group ($p < 0.01$) (**Figure 3D**).

CRSR Significantly Reduced the Levels of E_2, P, ER, and PR in Uterine and Ovarian Tissues

As compared with the NC group, the levels of E_2, P, ER, and PR in the uteruses and ovaries in the UL group were significantly increased ($p < 0.01$). The concentrations of E_2, P, ER, and PR in the uteruses and ovaries of the CRSR group were significantly decreased as compared with the UL group ($p < 0.01$) (**Figures 4A–D**).

CRSR Restored Abnormal Hemorheology

We assayed the PV, *K* value of ESR equation and EAI in the blood samples of all groups. Data collected from each group were not homogeneous by test of variance. Therefore, the Kruskal–Wallis H test was adopted.

The PV, *K* value of ESR equation, and EAI in the UL group increased significantly as compared with those in the NC group ($p < 0.05$). As compared with the UL group, the PV of the CRSR group was significantly lower ($p < 0.05$), and the *K* value of ESR equation and EAI were significantly reduced ($p < 0.01$) (**Figures 4E–G**).

DISCUSSION

UL is a distressing disease for women around the world (1, 2, 18), not only because it seriously affects their physical health but also because it affects their mental health. Women with UL usually feel more depressed, irritable, and uneasy than do women without UL and can have a higher risk of depression (19, 20). Effective prevention and treatment of UL can reduce women's health burden and improve their quality of life. In

clinical practice, TCM treatment of UL has a better overall effect and fewer side effects and other advantages (8, 10, 15).

In our study, the uteruses of the UL group showed obvious swelling and nodules, and the uteruses morphology of the CRSR group tended to be more normally. With the intervention of CRSR, the volume of the uteruses was greatly reduced. The uterine *r* and *R,* as well as the uterus and ovary coefficients, were improved. In addition, the decrease of pathological changes in the uterine tissues showed that CRSR can inhibit the growth of UL.

E_2 and P are the key factors in tumor development, stimulating the mature leiomyoma cells in UL to produce mitogenic substances to promote the proliferation of immature cells (5). UL pathology is also related to some abnormalities of ER and PR and the signaling pathways that they mediate (4, 21). In clinical trials, selective ER and PR modulators can effectively inhibit the growth of UL (5). Therefore, controlling the expression of estrogen and P and their receptors is the primary way to prevent and treat UL.

Through the detection of E_2, P, ER and PR, we found that CRSR can reduce the high expression of E_2, P, ER, and PR in the UL rats. Reduced the concentration of P and E_2 in the serum, especially the concentration of P. The concentration of E_2, P, and their receptors in ovarian and uterine tissues were significantly reduced and tended to be at the levels of the NC group, indicating the pharmacological effects of CRSR (14, 17). The significant changes in the serum, uteruses, and ovaries suggest that CRSR not only targets one location but also has multiple targets.

From the perspective of TCM, blood stasis is an important reason for the formation of UL. The pathogenesis of blood stasis is related to abnormal hemorheology, mainly involving whole blood viscosity, PV, ESR equation, and erythrocyte aggregation (22–25). PV is one of the important factors affecting the viscosity of whole blood. Increased PV will inevitably increase whole blood viscosity. Red blood cells (RBCs) account for nearly 50% of blood volume and are the main component of the cell content in the blood. Both ESR and EAI can reflect the changes of RBCs.

To explore whether the prevention and treatment of UL by CRSR is related to the improvement of congestion, we compared the PV, *K* value of ESR equation, and EAI of the rats from each group. As compared with the NC group, the PV, *K* value of ESR equation, and EAI of the UL group were significantly increased, indicating that blood viscosity increased, erythrocyte aggregation increased, blood flow decreased, microcirculation deteriorated, and blood stasis syndrome existed. These results are consistent with the understanding of UL pathogenesis in TCM theory. TCM can remove blood stasis by activating blood circulation (23–25). The antitumor and antithrombotic effects of *Curcumae Rhizoma* are related to activating blood circulation to dissipate blood stasis (16). The significant decrease of PV, *K* value of ESR equation, and EAI in the CRSR group suggests that CRSR can reduce plasma viscosity, inhibit erythrocyte aggregation, and restore abnormal hemorheology, proving the efficacy of CRSR in promoting blood circulation and removing blood stasis (15, 16, 23, 24). CRSR inhibition of UL growth is related to the improvement of hemorheology.

Our study has proved that CRSR has positive prevention and treatment effects on UL, which is achieved by reducing uterine volume, changing uterine structure, regulating hormone levels, and restoring abnormal blood circulation disorders. Our work provides a new basis for the prevention and treatment of UL for CRSR.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by the Animal Ethics Committee of Chengdu University of Traditional Chinese Medicine.

AUTHOR CONTRIBUTIONS

FP and CY conceived and designed the experiment. QX, YL, and HZ carried out the experiment and analyzed the experimental data. LZ retrieved the relevant literature and wrote the manuscript. XS provided helpful comments and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Cost-Effectiveness Analysis of Abemaciclib Plus Fulvestrant in the Second-Line Treatment of Women With HR+/HER2– Advanced or Metastatic Breast Cancer: A US Payer Perspective

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Introduction: This study evaluated the cost-effectiveness of abemaciclib plus fulvestrant (ABE + FUL) vs. palbociclib plus fulvestrant (PAL + FUL), ribociclib plus fulvestrant (RIB + FUL) and fulvestrant monotherapy (FUL) as second-line treatment for hormone receptor-positive and human epidermal growth factor receptor 2- negative advanced or metastatic breast cancer in the US.

Methods: The 3 health states partitioned survival (PS) model was used over the lifetime. Effectiveness and safety data were derived from the MONARCH 2 trial, MONALEESA-3 trial, and PALOMA-3 trial. Parametric survival models were used for four treatments to explore the long-term effect. Costs were derived from the pricing files of Medicare and Medicaid Services, and utility values were derived from published studies. Sensitivity analyses including one-way sensitivity analysis, probabilistic sensitivity analysis and scenario analysis were performed to observe model stability.

Results: In the PS model, compared with PAL + FUL, ABE + FUL yielded 0.44 additional QALYs at an additional cost of $100,696 for an incremental cost-utility ratio (ICUR) of $229,039/QALY. Compared with RIB + FUL, ABE + FUL yielded 0.03 additional QALYs at an additional cost of $518 for an ICUR of $19,314/QALY. Compared with FUL, ABE + FUL yielded 0.68 additional QALYs at an additional cost of $260,584 for ICUR of $381,450/QALY. From the PS model, the ICUR was $270,576 /QALY (ABE + FUL vs. PAL + FUL), dominated (ABE + FUL vs. RIB + FUL) and $404,493/QALY (ABE + FUL vs. FUL) in scenario analysis. In the probabilistic sensitivity analysis, the probabilities that ABE + FUL was cost-effective vs. PAL + FUL, RIB + FUL and FUL at thresholds of $50,000, $100,000, and $200,000 per QALY gained were 0% and the probabilities that ABE + FUL was cost-effective vs. PAL + FUL and RIB + FUL at thresholds of $50,000, $100,000, and $200,000 per QALY gained were 0.2, 0.6, and 7.3%.

Conclusions: The findings from the present analysis suggest that ABE + FUL might be cost-effective compared with RIB + FUL and not cost-effective compared with PAL + FUL and FUL for second-line treatment of patients with HR+/HER2– advanced or metastatic breast cancer in the US.

Keywords: cost-effectiveness, abemaciclib, CDK4/6 inhibitors, partitioned survival model, breast cancer

INTRODUCTION

Breast cancer is the most common cancer among US women and the second major cause of cancer-related death (1). The global incidence and mortality rates for breast cancer were around 2.1 million (11.6%) and 627,000 (6.6%) in 2018, respectively (2). An estimated 250,000 new cases of breast cancer are diagnosed in the United States annually (3). The incidence of breast cancer in the US has reached 124 per 100,000 in 2015 (4). Nearly, 6% of patients are diagnosed with metastatic disease and approximately half of the patients with primary breast cancer will progress to the metastatic stage (5). A study reported the economic burden on breast cancer care for all women to be $16.5 billion in 2010 dollars. The substantial economic burden imposed by breast cancer in the United States is projected to increase to $20.5 billion by 2020 (6). According to Surveillance, Epidemiology, and End Results (SEER) registries, among patients with known hormone receptor (HR)/human epidermal growth factor receptor 2 (HER2) status in 2010, 36,810 (72.7%) were found to be HR+/HER2–, which is the most frequently diagnosed molecular subtype among all breast cancer types (7).

For hormone receptor-positive and human epidermal growth factor receptor 2- negative advanced or metastatic breast cancer (HR+/HER2-ABC/MBC), the mainstay of treatment is endocrine treatment (8). However, clinical resistance to endocrine therapy can be acquired by most patients, leading to disease progression (9). Therefore, cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) in the setting of endocrine resistance have gained recent interest for improving the efficacy of existing therapies (5). CDK4/6i (palbociclib, ribociclib, and abemaciclib) in combination with fulvestrant have shown clinically meaningful efficacy and a good tolerability profile as second-line treatment in patients with HR+/HER2-ABC/MBC that progressed during prior endocrine therapy, within the PALOMA, MONALEESA, and MONARCH trials, respectively (10–15). Besides, fulvestrant+ CDK4/6 inhibitor is recommended as a preferred regimen for the second-line and subsequent therapy of HER2-negative ER- and/or PR-positive recurrent or stage IV breast cancer by NCCN guideline 2020. Additionally, some published meta-analyses confirmed the superiority of CDK4/6-inhibitor plus endocrine treatment over endocrine monotherapy based on progression-free survival and overall survival (16, 17). If this therapy is adopted in clinical, it will inevitably lead to an increase in the cost of medication.

Abemaciclib is a small-molecule inhibitor of CDK 4 and 6 that are involved in the cell cycle and promotion of cancer cell growth in case of unregulated activity, which was orally administered on a twice-daily continuous schedule (18). It is either given alone in patients who have undergone endocrine therapy and chemotherapy after the metastasis of cancer, or in combination with fulvestrant. Abemaciclib would induce G1 arrest and abrogate cell growth by preventing CDK 4 and 6 phosphorylation of the retinoblastoma tumor suppressor protein. Unlike other CDK inhibitors such as palbociclib and ribociclib, abemaciclib exhibits greater selectivity for CDK4 compared to CDK6 (19). On September 28, 2017, abemaciclib was approved in combination with fulvestrant for women with HR+/HER2-ABC/MBC with disease progression following endocrine therapy based on the MONARCH 2 trial, which was a randomized, multicenter, double-blind, placebo-controlled phase III trial (https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-abemaciclib-hr-positive-her2-negative-breast-cancer).

MONARCH 2 trial assessed the efficacy of abemaciclib plus fulvestrant vs. placebo plus fulvestrant in patients with HR+/HER2-ABC that progressed during prior endocrine therapy. Abemaciclib plus fulvestrant significantly extended progression-free survival (PFS) median time when compared with placebo plus fulvestrant [16.4 vs. 9.3 months; hazard ratio (HR) 0.553; 95% CI, 0.449–0.681; $P < 0.001$] (14). A median overall survival (OS) was 46.7 months for abemaciclib plus fulvestrant and 37.3 months for placebo plus fulvestrant (HR 0.757; 95% CI, 0.606–0.945; $P = 0.01$) (15). Three published studies have assessed the cost-effectiveness of CDK4/6i plus fulvestrant as second-line therapy for HR+/HER2–ABC/MBC in the US, but no one focused on the cost-effectiveness of abemaciclib plus fulvestrant as second-line therapy. Therefore, the purpose of this article is to evaluate the cost-effectiveness of abemaciclib plus fulvestrant for the treatment of patients with HR+/HER2-ABC/MBC in the United States.

METHODS

Model Overview

A partitioned survival model with three mutually exclusive health states (progression-free, post-progression, and death) was developed to estimate the costs and outcomes of patients with HR+/HER2-ABC/MBC that progressed during prior endocrine therapy in Microsoft Excel (**Figure 1**) from the perspective of US payer. For the partitioned survival (PS) model, progression-free survival (PFS) and overall survival (OS) curves were used to directly estimate the proportion of patients in each health state over time. The proportion of patients remaining in the PF state was directly provided by the PFS curve over time and the number of patients was derived by calculating the difference between the

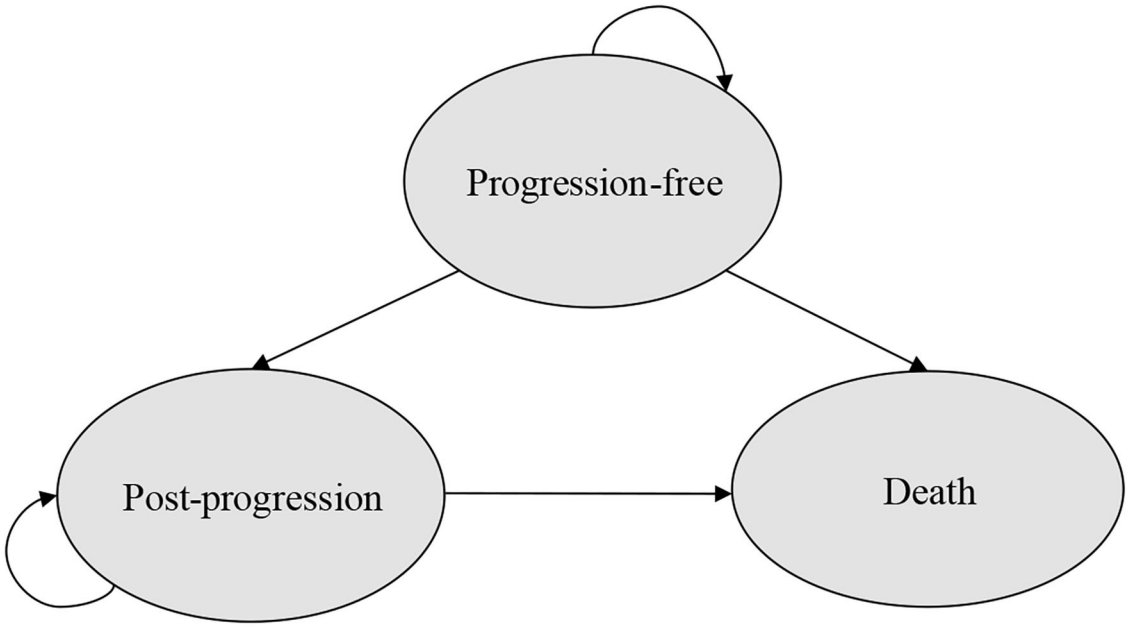


FIGURE 1 | Structure of the PS model.

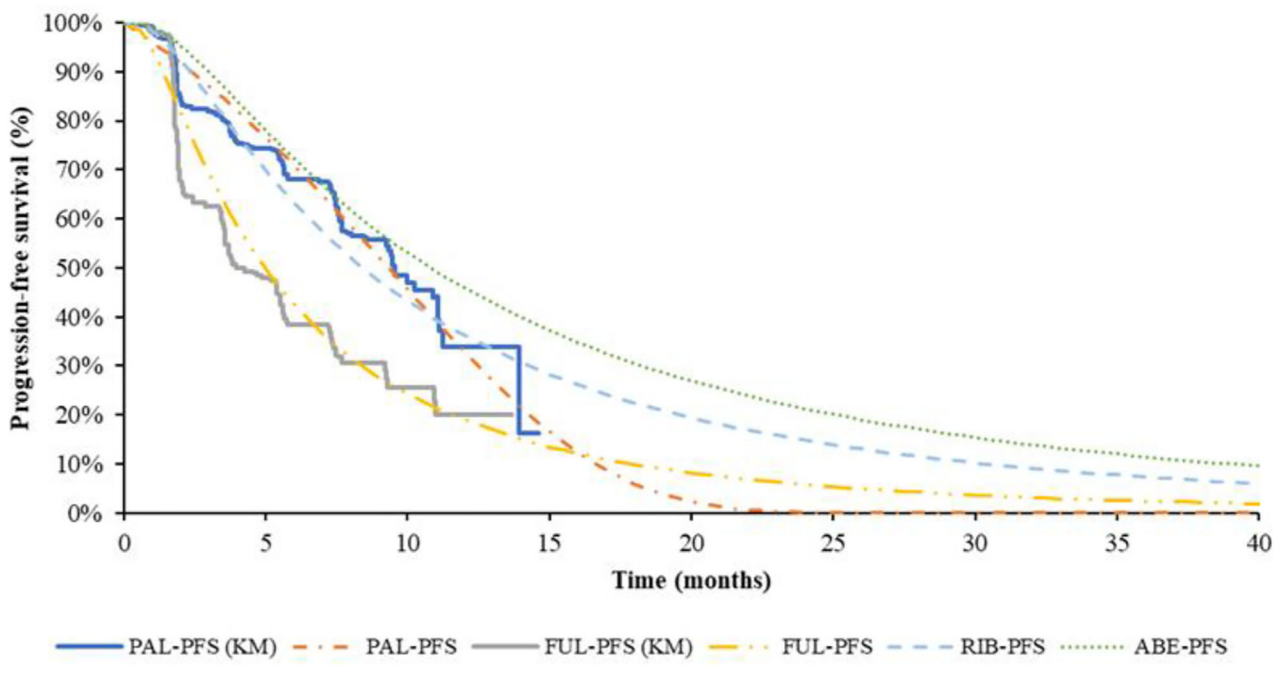


FIGURE 2 | K-M curve and parametric survival distributions for PFS. PFS, progression-free survival; ABE, abemaciclib; RIB, ribociclib; PAL, palbociclib; FUL, fulvestrant.

OS and the PFS curve at each time point in the post-progression (PP) state as this provided the proportion of patients who were alive but not progression-free (PF). Concerning the death state, the number of patients in the death state was calculated as 1 minus the OS curve at each time point (23).

The model assumed that all patients were in the PF health state at the beginning. Each cycle lasted 4 weeks, which was consistent with the dose schedule in MONARCH 2 trial (14, 15), MONALEESA-3 trial (12, 13) and PALOMA-3 trial (10, 11). A lifetime horizon was chosen, and modeled until ≥95% of patients in all groups died. The following outcomes were examined: quality-adjusted life-years (QALYs), life-years gained (LYGs), costs, and all of them were discounted by 3%.

Cohort Patients

The target population in the model is those women with HR+/HER2-ABC/MBC who had progressed while receiving previous endocrine therapy. The intervention group receives abemaciclib 150 mg twice daily during each 28-days cycle combined with 500 mg fulvestrant by intramuscular injection on days 1 and 15 of the first cycle, and day 1 of subsequent cycles. Three control groups were set up to compare the cost-effectiveness between abemaciclib combined with fulvestrant treatment (ABE + FUL) and other CDK4/6 inhibitors (palbociclib and ribociclib) combined with fulvestrant treatment and fulvestrant monotherapy.

Control group 1 (PAL + FUL): In group 1, patients received 125 mg palbociclib once daily for 3 weeks, followed by a week off in one cycle, and 500 mg fulvestrant by intramuscular injection on days 1 and 15 of the first cycle, and day 1 of subsequent cycles.

Control group 2 (RIB + FUL): In group 2, patients received 600 mg ribociclib per day for 3 weeks followed by a week off and 500 mg fulvestrant by intramuscular injection on days 1 and 15 of the first cycle, and day 1 of subsequent cycles.

Control group 3 (FUL): Patients only received 500 mg fulvestrant by intramuscular injection on days 1 and 15 of the first cycle, and day 1 of subsequent cycles.

All patients received the treatment until the disease progressed. After progression, patients would receive subsequent treatments, which were composed of anthracyclines, taxanes, anti-metabolites, vinca alkaloids, hormones, HER2-targeted therapies and non-HER2-targeted therapies. The proportions of these therapies were derived from the study of Sorensen et al. (24).

Clinical Efficacy

The clinical efficacy parameters in the model were mainly derived from three clinical trials (MONARCH 2, PALOMA-3, and MONALEESA-3). PALOMA-3 trial and MONALEESA-3 trial, respectively, compared the effects and safety of palbociclib and ribociclib combined with fulvestrant and fulvestrant monotherapy in patients with HR+/HER2-ABC. They both showed significant advantages compared with fulvestrant monotherapy. The detailed information of three clinical trials has been listed in the **Supplementary Materials**.

The effects of these four treatment options were indirectly compared with the fulvestrant monotherapy group as control.

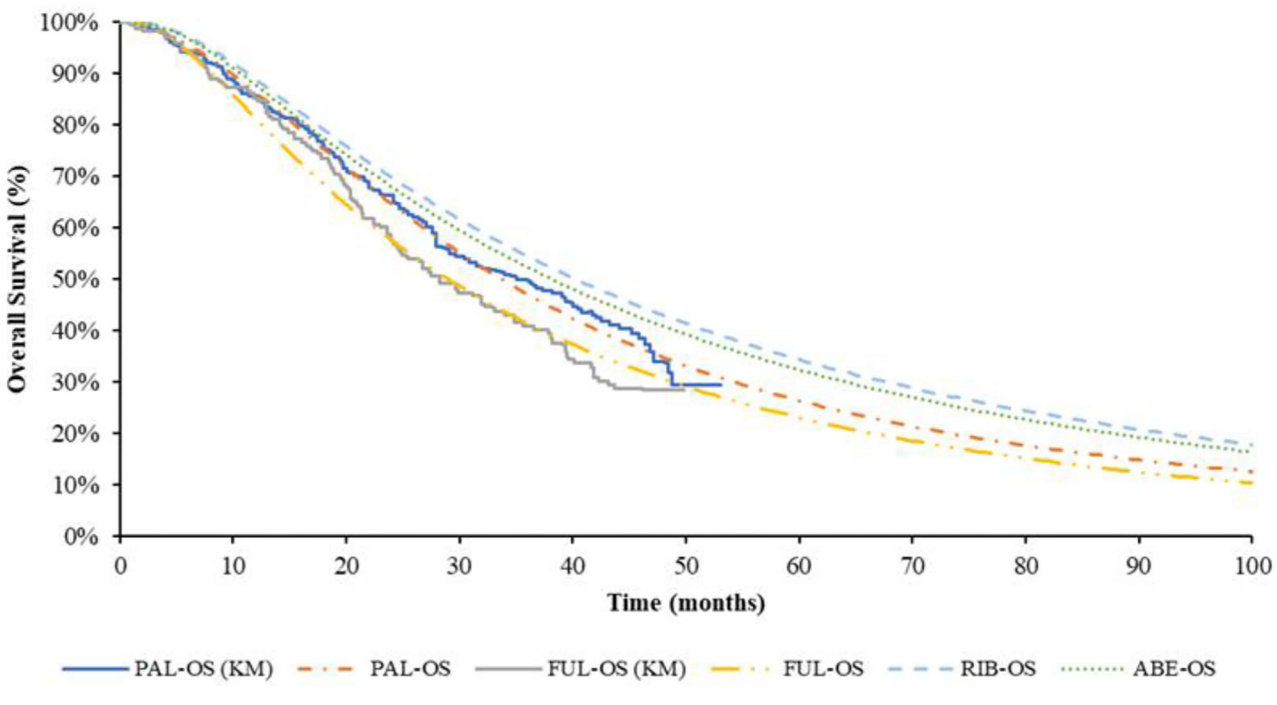


FIGURE 3 | K-M curve and parametric survival distributions for OS. OS, overall survival; ABE, abemaciclib; RIB, ribociclib; PAL, palbociclib; FUL, fulvestrant.

TABLE 1 | Overview of all model parameters.

Model inputs	Value	Distribution	Low	High	Source
HR PFS of ribociclib	0.59	CONSTANT	/	/	(12)
HR PFS of abemaciclib	0.46	CONSTANT	/	/	(14)
HR OS of ribociclib	0.72	CONSTANT	/	/	(13)
HR OS of abemaciclib	0.76	CONSTANT	/	/	(15)
Direct costs per cycle					
Palbociclib	$11,938	CONSTANT	$9,550	$11,938	Medicare Part D
Ribociclib	$13,110	CONSTANT	$10,488	$13,110	Medicare Part D
Abemaciclib	$11,815	CONSTANT	$9,452	$11,815	Medicare Part D
Fulvestrant	$1,808	CONSTANT	$1,446	$1,808	Medicare Part B
Medical follow-up	$2,959	GAMMA	$2,367	$3,551	(24)
Drug administration	$702	GAMMA	$561	$842	(27)
After progression	$6,549	GAMMA	$5,240	$7,859	(24)
Subsequent treatment	$9,061	GAMMA	$7,248	$10,873	(24)
End of life care	$2,601	GAMMA	$2,081	$3,121	(24)
Costs of MAEs per event					
Neutropenia	$16,256	GAMMA	$14,871	$17,642	(28)
Leucopenia*	$16,256	GAMMA	$14,871	$17,642	(28)
Diarrhea	$11,545	GAMMA	$9,170	$13,920	(28)
Anemia	$14,532	GAMMA	$13,262	$15,804	(28)
Infections	$14,595	GAMMA	$11,248	$18,425	(28)
Hepatobiliary toxicity	$7,516	GAMMA	$6,013	$9,019	(27)
Proportion of patients received subsequent treatment					
Palbociclib	71%	BETA	64%	96%	(11)
Ribociclib	61%	BETA	57%	85%	(13)
Abemaciclib	63%	BETA	49%	73%	(15)
Fulvestrant	80%	BETA	50%	76%	(11)
Risk of AEs in palbociclib					
Neutropenia	0.696	BETA	0.557	0.835	(11)
Leucopenia	0.383	BETA	0.306	0.460	(11)
Infections	0.052	BETA	0.042	0.062	(11)
Anemia	0.043	BETA	0.034	0.052	(11)
Risk of AEs in ribociclib					
Neutropenia	0.571	BETA	0.457	0.685	(13)
Leucopenia	0.155	BETA	0.124	0.186	(13)
Hepatobiliary toxicity	0.137	BETA	0.110	0.164	(13)
Infections	0.077	BETA	0.062	0.092	(13)
Anemia	0.039	BETA	0.031	0.047	(13)
Risk of AEs in abemaciclib					
Neutropenia	0.297	BETA	0.238	0.356	(15)
Leucopenia	0.111	BETA	0.089	0.133	(15)
Diarrhea	0.145	BETA	0.116	0.174	(15)
Anemia	0.090	BETA	0.072	0.108	(15)
Risk of AEs in fulvestrant					
Neutropenia	0.006	BETA	0.005	0.007	(11)
Leucopenia	0.035	BETA	0.028	0.042	(11)
Anemia	0.023	BETA	0.018	0.028	(11)

(Continued)

TABLE 1 | Continued

Model inputs	Value	Distribution	Low	High	Source
QoL utility (per year)					
PF	0.837	BETA	0.753	0.921	(29)
PP	0.443	BETA	0.399	0.487	(30)
Disutilities of AEs (per year)					
Neutropenia	−0.2466	CONSTANT	−0.2713	−0.2220	(31)
Leucopenia*	−0.2466	CONSTANT	−0.2713	−0.2220	(31)
Diarrhea	−0.1198	CONSTANT	−0.1318	−0.1078	(31)
Anemia	−0.1914	CONSTANT	−0.2105	−0.1722	(31)
Infections	−0.2303	CONSTANT	−0.2534	−0.2073	(31)
Hepatobiliary toxicity	−0.3080	CONSTANT	−0.3696	−0.2464	(32)
AEs duration (days)					
Neutropenia	2	CONSTANT	/	/	(33)
Leucopenia*	2	CONSTANT	/	/	(33)
Diarrhea	2	Normal	/	/	(34)
Anemia	21	Normal	/	/	(33)
Infections	4.2	Normal	/	/	(35)
Hepatobiliary toxicity	4.3	Normal	/	/	(35)
Duration of subsequent treatment (cycles)	4.66	Normal	3.73	5.59	(36)
Discount rate	3%	CONSTANT	0%	5%	(29)

PFS, progression-free survival; OS, overall survival; HR, hazard ratio; MAE, main adverse event.
**The parameters of leucopenia were assumed to be the same as those of neutropenia.*
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Extrapolation was required in the cost-effectiveness analysis for the limited follow-up time of the K-M curves in clinical trials. The standard parametric models were fitted using Exponential, Weibull, Gompertz, Log-logistic, Log-normal distributions, which determined by Akaike information criterion (AIC) and the Bayesian information criterion (BIC) goodness-of-fit statistics and visual inspection. For PAL + FUL and FUL, the standard parametric models were separately used to extrapolate the PFS and OS curves derived from PALOMA-3 trial, because they did not meet the proportional hazard (PH) assumption. For RIB + FUL and ABE + FUL, the HR of PFS and OS from the MONARCH-2 trial and MONALEESA-3 trial were used since they almost met the proportional hazard assumption.

The pseudo-individual patient data (IPD) was extracted with Engauge Digitizer software from the PALOMA-3 trial, reconstructed through R 3.6.0 (25) and fitted by the standard parametric models through R 3.6.0. For PFS of fulvestrant monotherapy group, the preferred distribution for the base case was Log-normal, which demonstrated the best fit to survival based on AIC and BIC. The Log-logistic model was the preferred distribution for OS of fulvestrant monotherapy group, but for the median value of suboptimal Lognormal distribution was closer to real value. Log-normal distribution was selected in the base-case model finally. For PFS of PAL + FUL, the preferred distribution for the base case was Gompertz distribution. According to the results of AIC and BIC, the Weibull distribution was the best fitting distribution of the OS curve of PAL + FUL. Considering Weibull distribution would lead to logic errors after extrapolation, the suboptimal distribution Log-logistic was selected finally. The reconstructed K-M curve of PFS and OS, as well as the fitted curve, were shown in **Figures 2**, **3**, respectively. The values of AIC and BIC could also be found in the **Supplementary Materials**.

The study of Tevaarwerk et al. (26) showing the 15-year survival probability of advanced breast cancer patients was ∼5%. In this study, when 95% of the patients died, the time for every group was ABE + FUL: 15.67 years; RIB + FUL: 16.5 years, PAL + FUL: 14.75 years and FUL: 11.9 years, which is consistent with the long-term survival in the above study.

Cost

All costs were in 2019 US dollars inflated using the Consumer Price Index (https://fred.stlouisfed.org/series/CPIMEDSL). Only the direct medical care costs were included as the US payer perspective was taken. These included drug acquisition, administration, and medical costs associated with each state, end of life care costs, and AE costs. All costs were derived from database data (such as Centers for Medicare and Medicaid Services) or published literature. The drug unit costs were derived from Centers for Medicare and Medicaid Services (such as Medicare Part B and Medicare Part D), and the costs in each cycle were calculated. The drug costs for subsequent treatment came from published literature. Since fulvestrant monotherapy was administrated in injection, the drug administration costs were included.

When patients were in the PF state, they needed to be followed up and monitored until the disease progressed,

which mainly included lab scans and tests as well as bone metastases management. Costs of patients in PP state included the cost of subsequent treatment drugs and best supportive care costs. The proportion of patients who received subsequent treatments was obtained from the results of related clinical trials (11, 13, 15), and the costs of subsequent treatments were calculated by multiplying the cost in each cycle by the number of cycles. The impact of grade 3 or 4 AEs (≥5%) was considered in the model, and related costs were derived from the published literature. **Table 1** provides an overview of all costs and AE probabilities.

TABLE 2 | Base-case results.

Outcomes	ABE + FUL	RIB + FUL	PAL + FUL	FUL
LYs	4.09	4.29	3.65	3.20
QALYs	2.36	2.33	1.92	1.68
Cost, $	$541,890	$541,372	$441,194	$281,306
Incremental cost	/	$518	$100,696	$260,584
Incremental QALYs	/	0.03	0.44	0.68
Incremental cost per LY, $	/	Dominated	$229,689	$291,323
Incremental cost per QALY, $	/	$19,314	$229,039	$381,450

LYs, life years; QALYs, quality-adjusted life years; ABE, abemaciclib; RIB, ribociclib; PAL, palbociclib; FUL, fulvestrant.

Utility

Utility values for PF were derived from the study of Mistry et al. (29). This utility was calculated using the latest UK value set and data was from EuroQol 5-dimension 5-level (EQ-5D-5L) data collected in the MONALEESA-2 trial. Utility value for PD was derived from the study reported by Lloyd et al. (30), which reported estimated health-state utility values by using the standard gamble technique. Disutilities for adverse events (AEs) whose values were taken from published sources were included. The duration of AEs was derived from the published clinical expert opinion. **Table 1** showed the utility values applied to the PF and PP health states, the disutility values associated with AEs and mean AE duration.

Sensitivity Analyses

One-way sensitivity analysis was performed to identify the parameters to which the model was most sensitive. The upper and lower limits of the inputs were defined by 95% confidence intervals where possible and derived from the original literature or with plausible variation around the base-case values by 10% in utilities and 20% in other parameters. Probabilistic sensitivity analysis (PSA) was conducted using 1,000 iterations to examine parameter uncertainty over the entire model, and cost-effectiveness acceptability curves were then calculated. Distributions of the parameters in the model were mainly referred to the model book (37) and the published cost-effectiveness analysis paper (33). Additionally, all parameters

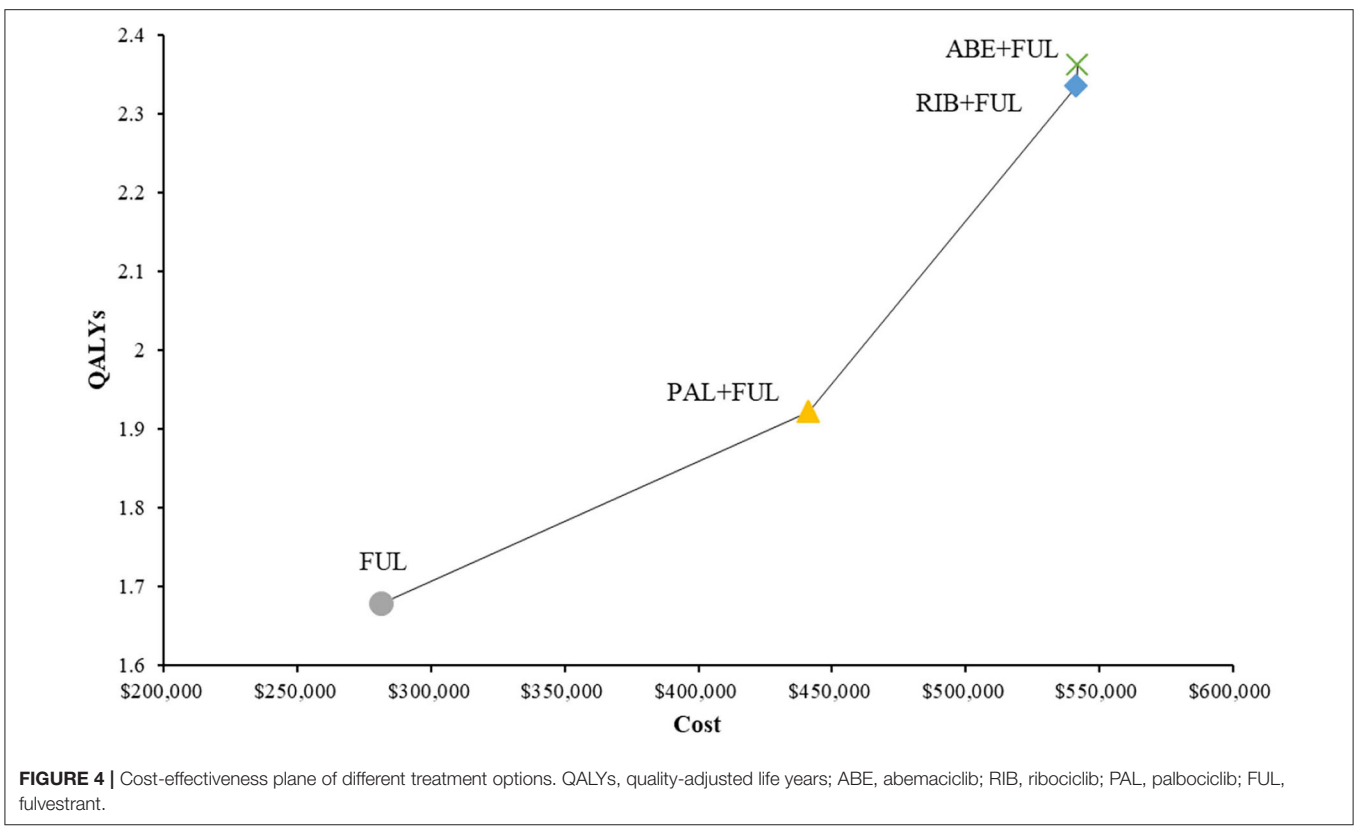


FIGURE 4 | Cost-effectiveness plane of different treatment options. QALYs, quality-adjusted life years; ABE, abemaciclib; RIB, ribociclib; PAL, palbociclib; FUL, fulvestrant.

in the parametric survival model were assessed through Cholesky decomposition.

For the inconsistent source of the utilities used in the base-case analysis, the utilities reported by Beauchemin et al. (31) which were obtained from an exhaustive review of the literature were selected for the scenario analysis (PF utility = 0.76, PP utility = 0.55).

Ethics

The data of the PFS/OS curves were based on previously published trials, not from the database or the medical records. We used the Engauge Digitizer software to get the survival information from the figures in the paper and reconstructed data by ourselves, which was explained in the section Clinical Efficacy. Besides, the utilities and costs were derived from the published literature, so ethics approval or specific consent procedures were not required for this study.

RESULTS

Base-case Results

ABE + FUL had a total cost of $541,890 vs. 441,194 for PAL + FUL, $541,372 for RIB + FUL and $281,306 for FUL (**Table 2**). Total LYs for each treatment option were 4.09 for ABE + FUL, 3.65 for PAL + FUL, 4.29 for RIB + FUL and 3.20 for FUL. Total QALYs for each treatment were 2.36 for ABE + FUL, 1.92 for PAL + FUL, 2.33 for RIB + FUL and 1.68 for FUL. In order to compare four treatments directly, all results were shown in the cost-effectiveness plane (**Figure 4**).

In terms of incremental costs and QALYs, ABE + FUL was associated with the additional cost of $100,696 and a gain of 0.44 QALYs compared with PAL + FUL, giving an ICUR of $229,039 per QALY gained (**Table 2**). Compared with RIB + FUL, ABE + FUL was associated with an incremental cost of $518 and an incremental QALY gain of 0.03, giving an ICUR of $19,314 per QALY gained. Compared with FUL, ABE + FUL was associated with an incremental cost of $260,584 and an incremental QALY gain of 0.68, giving an ICUR of $381,450 per QALY gained. **Table 2** shows the base-case results in the model.

Sensitivity Analyses

According to the DSA, for ABE + FUL vs. PAL + FUL, the key model drivers were cost of abemaciclib, utility (PF) and cost of palbociclib (**Figure 5**). Compared with RIB + FUL, the key model drivers were cost of abemaciclib, cost of ribociclib and cost of post-progression (**Figure 6**). Compared with FUL, the key model drivers were cost of abemaciclib, discount rate and proportion of fulvestrant group received subsequent treatment (**Figure 7**).

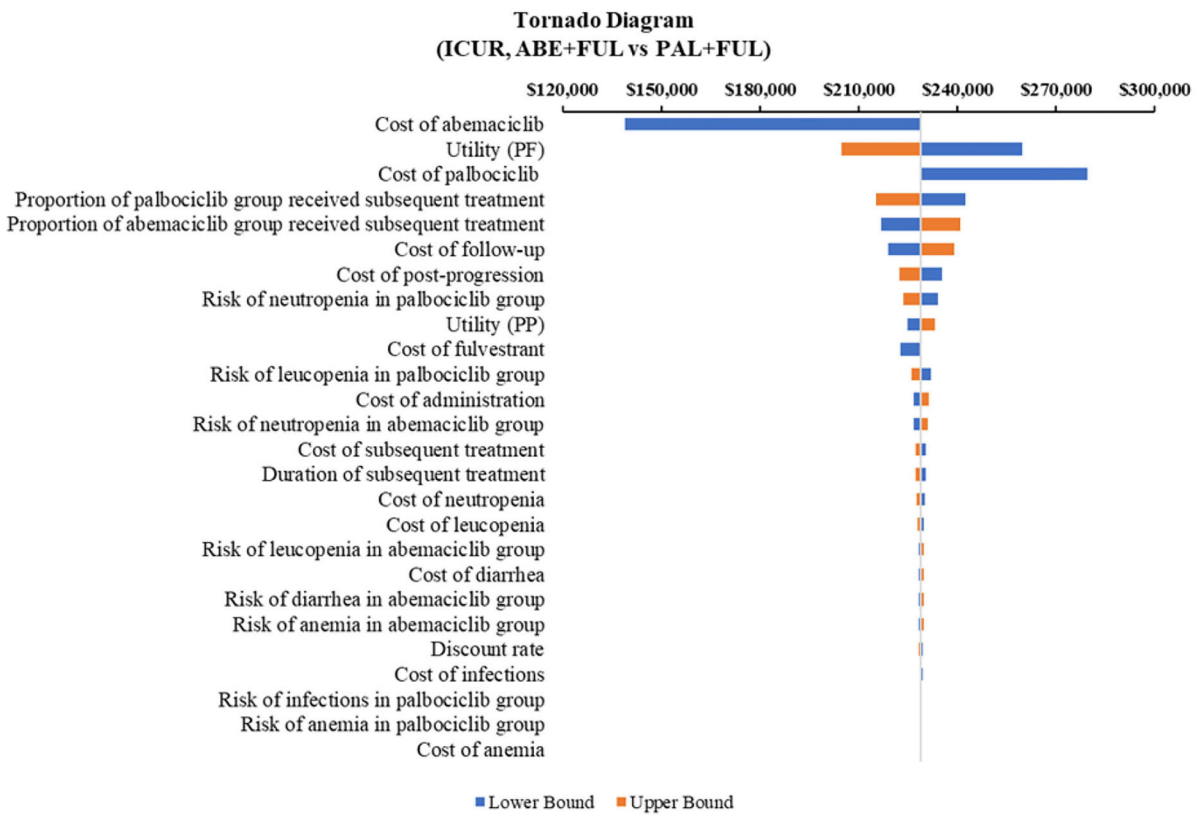


FIGURE 5 | Tornado diagram of the abemaciclib plus fulvestrant vs. palbociclib plus fulvestrant. ICUR, incremental cost-utility ratio; ABE, abemaciclib; PAL, palbociclib; FUL, fulvestrant.

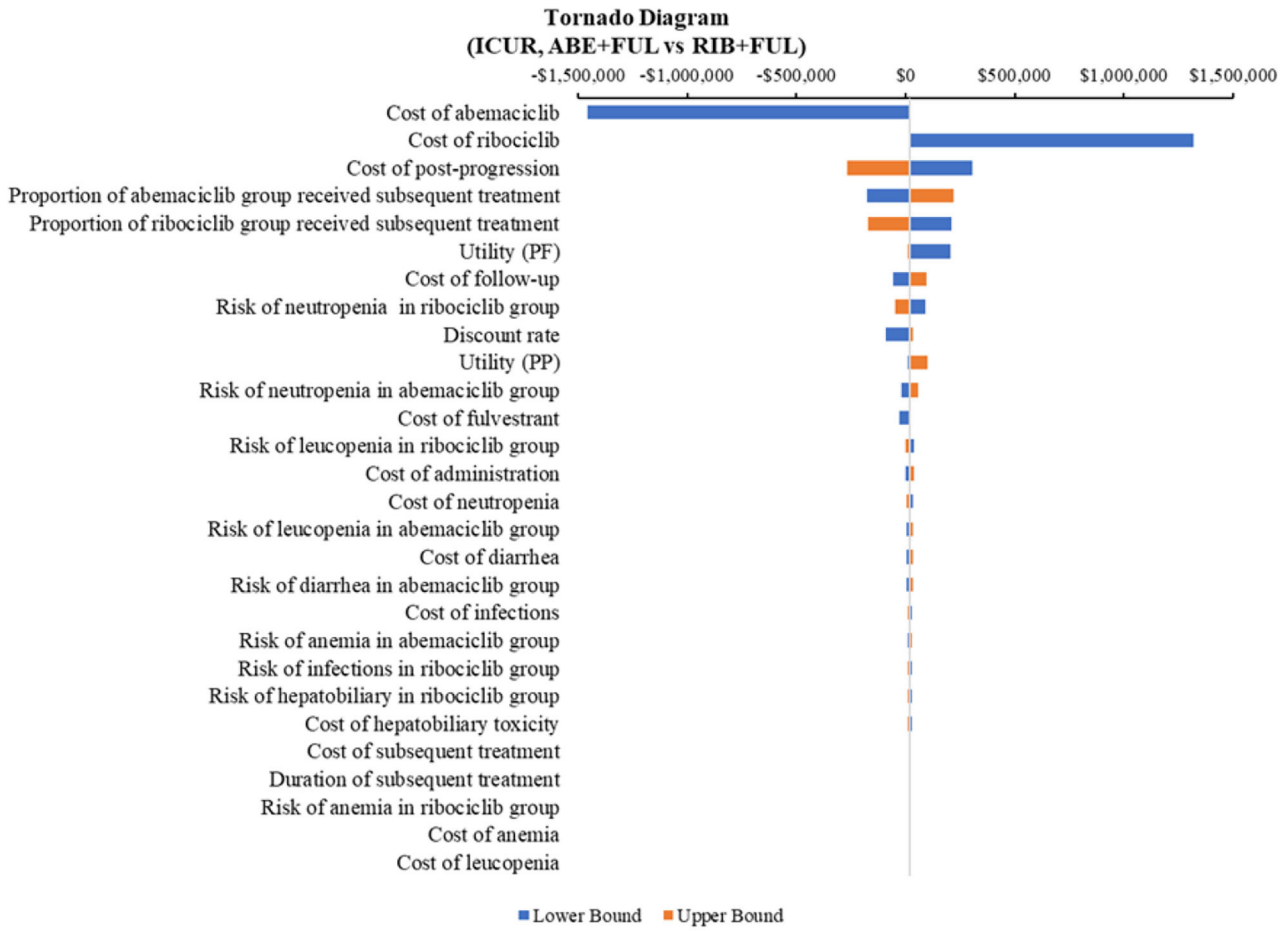


FIGURE 6 | Tornado diagram of the abemaciclib plus fulvestrant vs. ribociclib plus fulvestrant. ICUR, incremental cost-utility ratio; ABE, abemaciclib; RIB, ribociclib; FUL, fulvestrant.

According to the PSA, ABE + FUL was associated with a mean incremental cost increase of $102,001, 899, and 261,175 and a main increase of 0.45, 0.03, and 0.69 QALYs compared with PAL + FUL, RIB + FUL and FUL, giving an ICUR of $ 227,471, 19,314, and 379,754 per QALY gained. The probabilities that ABE + FUL was cost-effective vs. PAL + FUL, RIB + FUL and FUL at thresholds of $50,000, 100,000, and 200,000 per QALY gained were 0%, and the cost-effectiveness acceptability curves among the four treatments options were presented in **Figure 8**. The probabilities that ABE + FUL was cost-effective vs. PAL + FUL and RIB + FUL at thresholds of $50,000, 100,000, and 200,000 per QALY gained were 0.2, 0.6, and 7.3%. The cost-effectiveness acceptability curves for them were presented in **Figure 9**.

According to the scenario analysis where the PF utility of 0.76 and the PP utility of 0.55 were used, the result showed that the ICUR was $270,576/QALY (ABE + FUL vs. PAL + FUL), dominated (ABE + FUL vs. RIB + FUL) and $404,493/QALY (ABE + FUL vs. FUL).

DISCUSSION

For patients with HR+/HER2-ABC who had developed endocrine resistance, CDK4/6 inhibitors added to/combined with endocrine therapy provide a new treatment option instead of cytotoxic chemotherapy. In this study, the cost-effectiveness of abemacicilb was estimated in combination with fulvestrant in the second-line treatment of women with HR+/HER2– ABC/MBC. To the best knowledge, this is the first study to explore the cost-effectiveness of abemaciclib, and also the first study to compare the cost-effectiveness of three approved CDK4/6 inhibitors in the US The results of this study revealed the difference between the long-term clinical effects and costs of four treatment options, suggesting fulvestrant monotherapy would be the most cost-effective treatment among these four choices under the US willingness to pay. If only three CDK4/6 inhibitors were compared, PAL + FUL has the highest probability to be cost-effective.

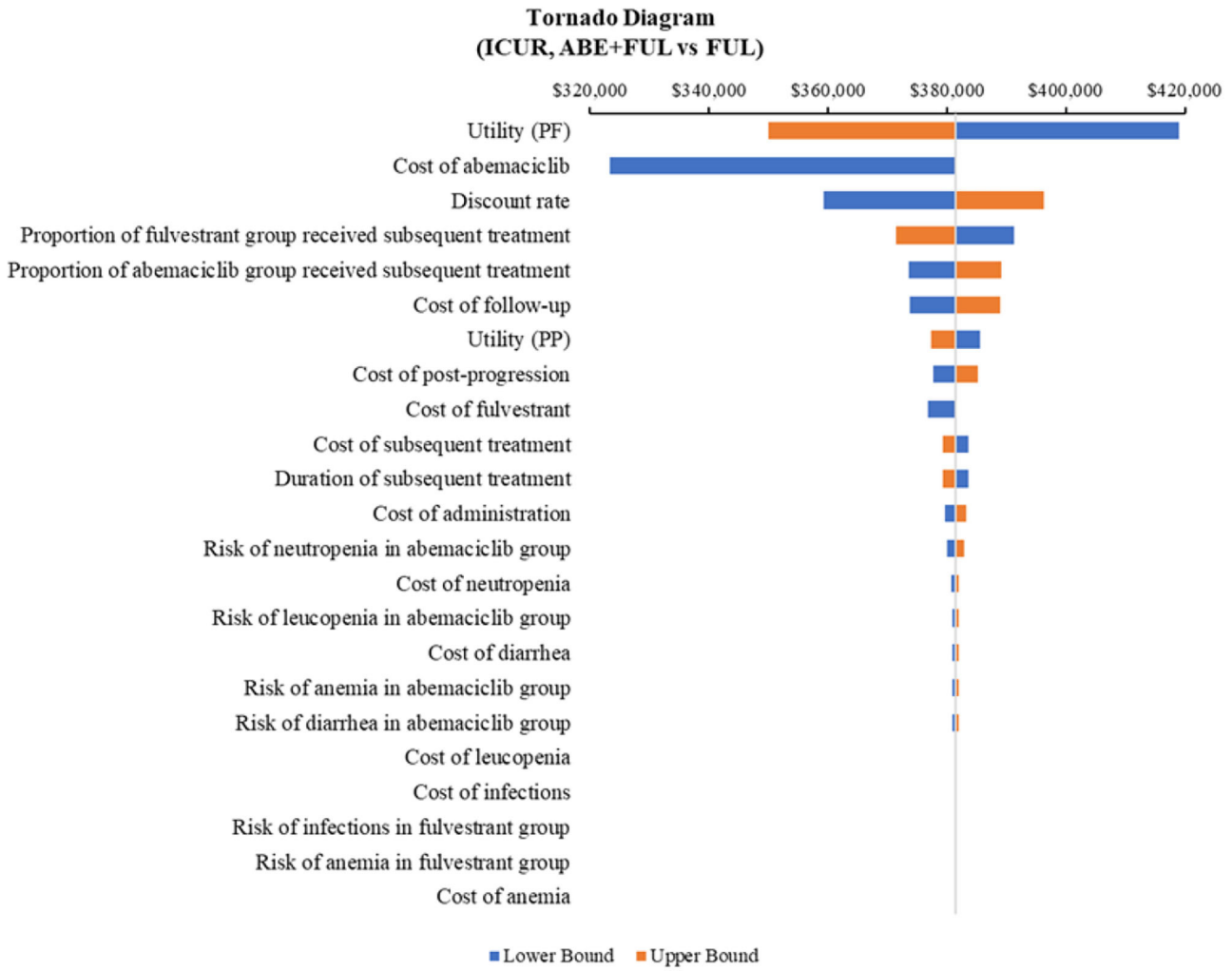


FIGURE 7 | Tornado diagram of the abemaciclib plus fulvestrant vs. fulvestrant monotherapy. ICUR, incremental cost-utility ratio; ABE, abemaciclib; FUL, fulvestrant.

In the United States, traditionally accepted thresholds for cost-effectiveness ratio are $50,000 per QALY. Since some evidence suggests that this was too low, the study used the recommended thresholds of $50,000, 100,000, and 200,000 per QALY (38). In the base case analysis, the ABE + FUL was cost-effective only when compared to RIB + FUL, resulting in an ICUR of $19,314/QALYs. The outcomes between them were close. For ABE + FUL, it gained additional 0.03 QALYs, while RIB + FUL brought more LYs, and the incremental cost was only $518. This result was caused by the longer PFS of ABE + FUL group but the similar OS between them. Thus, ABE + FUL spent more on drug costs and led to the higher quality of life. However, a recent network meta-analysis found no significant differences among the three CDK4/6 inhibitors in combination with fulvestrant in terms of PFS (17). Based on this clinical efficacy, the cost-minimization analysis (CMA) might be more suitable to access the cost-effectiveness between these three treatment options. The result was also sensitive to changes in utility value, as shown in the scenario analysis. RIB + FUL dominated ABE + FUL when using utility values from another source. Since the gap between these two treatments is small, a little change in model inputs can cause extremely different results. Therefore, the cost-effectiveness result between these two options was not robust, which needed more reliable data sources. Different from the other two CDK4/6 inhibitors, abemaciclib has also been approved by FDA as monotherapy for the treatment of adult patients with HR+/HER2- ABC/MBC with disease progression following endocrine therapy and prior chemotherapy (https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-abemaciclib-hr-positive-her2-negative-breast-cancer). Although the cost-effectiveness analysis of abemaciclib monotherapy was not evaluated in this study, it may have potential advantages in cost-effectiveness.

When compared to the PAL + FUL, ABE + FUL resulted in high costs and also improved LYs as well as QALYs, giving an ICER of $229,689/LYs and an ICUR of $229,039/QALYs. The

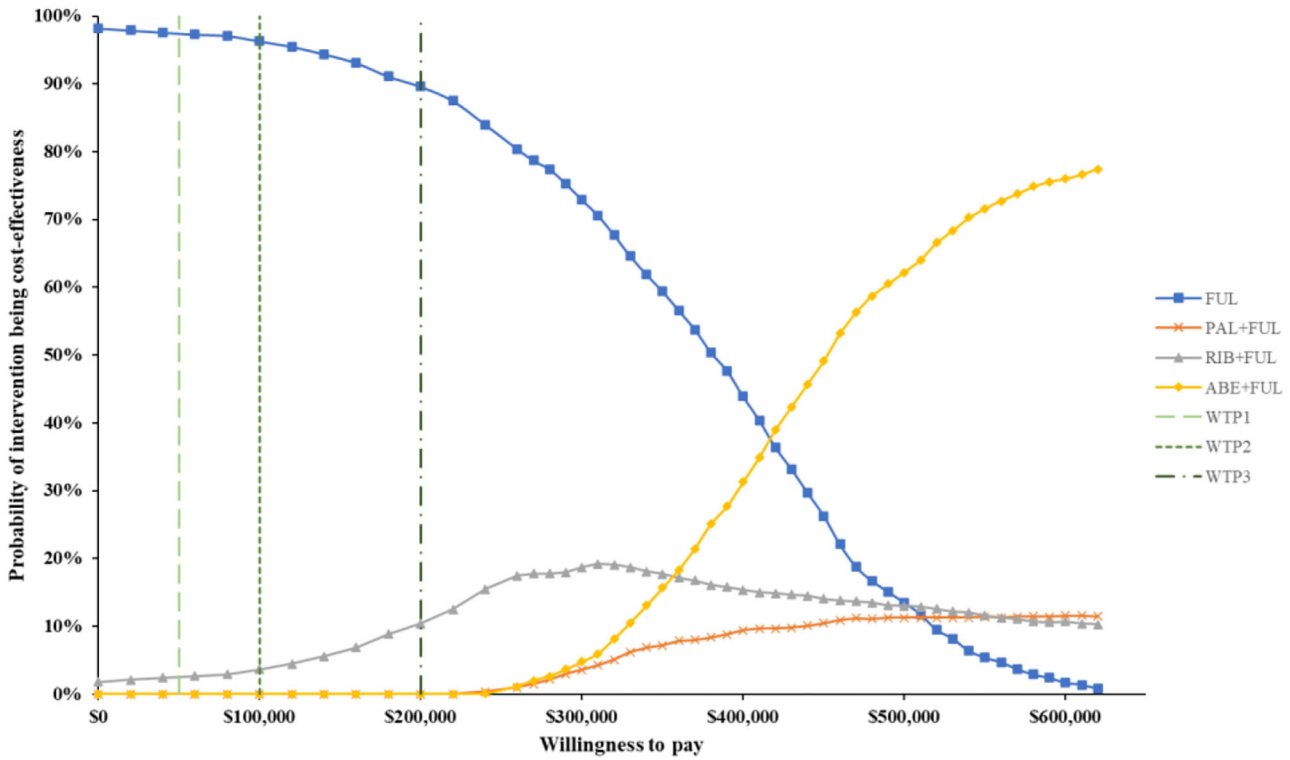


FIGURE 8 | Cost-effectiveness acceptability curves for abemaciclib plus fulvestrant vs. palbociclib plus fulvestrant, ribociclib plus fulvestrant and fulvestrant monotherapy. ABE, abemaciclib; RIB, ribociclib; PAL, palbociclib; FUL, fulvestrant; WTP1, $50,000; WTP2, $100,000; WTP3, $200,000.

results were robust in sensitivity analyses, while only the cost of abemaciclib and palbociclib play an important role. ABE + FUL has better clinical efficacy and fewer adverse events than PAL + FUL, but the probability of being cost-effective than PAL + FUL was still relatively low even under the WTP of $200,000.

When compared to fulvestrant monotherapy, ABE + FUL generated an ICUR of $381,450/QALYs which exceeded the US threshold. Some published studies have already evaluated the cost-effectiveness of PAL + FUL and RIB + FUL with fulvestrant monotherapy in the US (20–22). These studies had reached a common conclusion that when CDK4/6 inhibitors were added to endocrine therapy, it was not a cost-effective choice at current drug prices in the United States. In summary, existing evidence showed the base case result was unstable, and if their effects were assumed to be the same, the CMA might be more suitable. It is recommended to combine the results of PSA and scenario analyses as references for decision-making.

This analysis also had several limitations. First, for no head-to-head clinical trials were available and the lack of IPD, only the indirect comparison was applied into the model to compare the cost-effectiveness of ABE + FUL with the other three treatment options, so there might exist certain deviations in the indirect comparison. The comparable baseline population characteristics in three clinical trials (MONARCH 2, PALOMA-3, and MONALEESA-3) have been listed and compared, and they seemed similar. Galve-Calvo et al. used matching-adjusted indirect comparison (MAIC) to match the individual data of the MONALEESA-2 study with PALOMA-1 and PALOMA-2 studies to obtain the adjusted HR of ribociclib plus letrozole vs. letrozole monotherapy in order to evaluate the cost-effectiveness between ribociclib plus letrozole and palbociclib plus letrozole in the first-line treatment of HR+/HER2- ABC patients in Spain. According to the results from the study, there was little difference between the adjusted HR and non-adjusted HR if the baseline population characteristics were similar in trials (39). Second, appropriate utility of target patients based on the American population was not available, so the utility input in this model was not from the same source and the same situation also occurred in the study of Mistry et al. (29). Therefore, scenario analysis was conducted to explore the uncertainty of health state utility from different sources and the result had been discussed. Third, long-term survival data of HR+/HER2- ABC patients using CDK4/6 inhibitors had not been found to validate the reliability of the extrapolated results of PFS and OS. Though compared with the study of Tevaarwerk et al. which only given the survival probability for the HR+ MBC patients (26), the specific extrapolated PFS or OS of each treatment option still cannot be validated precisely. However, although survival probability was different between treatment options, the overall results were similar and close in the above study.

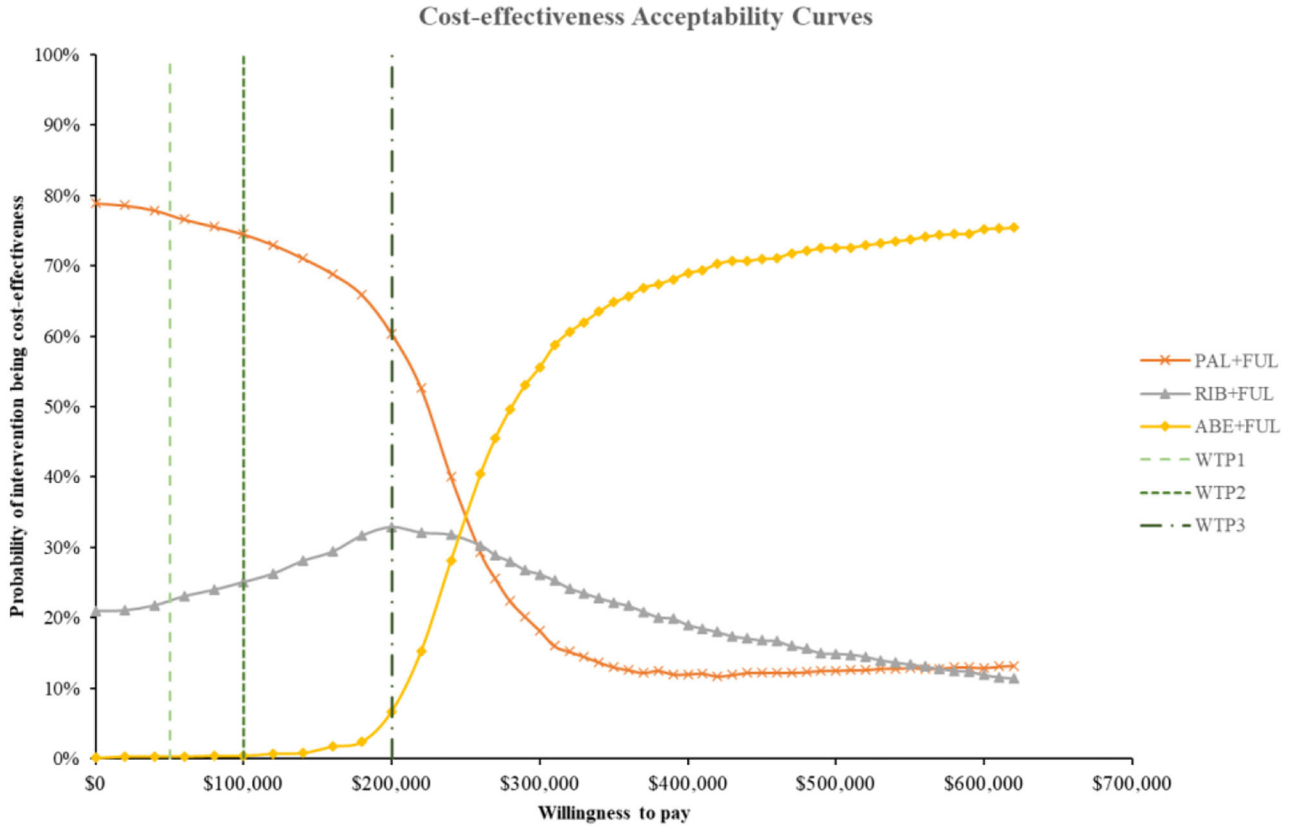


FIGURE 9 | Cost-effectiveness acceptability curves for abemaciclib plus fulvestrant vs. palbociclib plus fulvestrant, ribociclib plus fulvestrant. ABE, abemaciclib; RIB, ribociclib; PAL, palbociclib; FUL, fulvestrant; WTP1, $50,000; WTP2, $100,000; WTP3, $200,000.

CONCLUSION

Based on the results of this cost-effectiveness analysis and sensitivity analyses, second-line treatment of women with HR+/HER2-ABC/MBC with abemaciclib plus fulvestrant may generate QALY gains and cost increase compared with ribociclib plus fulvestrant therapy and be cost-effective at current willingness-to-pay thresholds in the United State. Besides, abemaciclib plus fulvestrant was not cost-effective compared with palbociclib plus fulvestrant and fulvestrant monotherapy for second-line treatment of patients with HR+/HER2- ABC/MBC in the US.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The data of the PFS/OS curve was based on previously published trial, not from the database or the medical records. We used the Engauge Digitizer software to get the survival information from the figures in the paper and reconstructed data by ourselves, which was explained in the section Clinical Efficacy. Besides, the utilities and costs were derived from the published literatures, so ethics approval or specific consent procedures were not required for this study.

AUTHOR CONTRIBUTIONS

YW, MR, XG, and PC developed the economic model and performed the analyses. YW, MR, and YC interpreted the results and wrote the draft manuscript. MR, YW, YC, and PC reviewed, analyzed, and interpreted the data. XG and YW contributed to the design of the primary model and the interpretation of the results. All authors reviewed and approved the final version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.658747/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Knowledge and Determinants of Behavioral Responses to the Pandemic of COVID-19

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Background: Understanding knowledge and behavioral responses to the pandemic of coronavirus disease 2019 (COVID-19) is important for appropriate public health interventions.

Objectives: To assess knowledge of COVID-19 and to examine determinants associated with the adoption of preventive health behaviors among future health care providers.

Methods: An anonymous online survey was sent out to pharmacy students in high and low-endemic areas of COVID-19 in China. Based on recommendations from the Chinese Center for Disease Control and Prevention, preventive health behaviors examined in this study included washing hands, wearing a face mask, and maintaining social distancing. The Health Belief Model (HBM) was used and measured by a seven-point Likert scale (one as extremely unlikely; seven as extremely likely). Multivariate linear regression models were used to examine predictors of preventive health behaviors.

Results: Among 203 respondents who finished the survey, a medium level of knowledge (4.41 ± 0.95) of COVID-19 was reported. Respondents were extremely likely to wear a face mask (6.85 ± 0.60), but only moderately likely to engage in washing hands (5.95 ± 1.38) and maintaining social distancing (6.19 ± 1.60). Determinants of washing hands were cue to action, self-efficacy, knowledge, and gender; wearing a face mask were cue to action, self-efficacy, knowledge, and ethnicity; and maintaining social distancing were cue to action and self-efficacy.

Conclusions: Public health interventions should consider incorporating cue to action, self-efficacy, and knowledge as factors to potentially improve the adoption of face mask-wearing, hand washing, and social distancing as appropriate individual preventive measures, especially if local and regional authorities are considering reopening schools sometime in future.

Keywords: COVID-19, knowledge, determinants of health, preventive health behaviors, pharmacist, student

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) is a new, rapidly spreading infectious disease caused by the "SARS-CoV-2" virus. World Health Organization (WHO) has declared COVID-19 as a pandemic (1). The first case of COVID-19 was reported in Wuhan, China in December 2019 (1). Since then, it has spread globally at an alarming rate. National and regional authorities have implemented different prevention and control measures to contain the quick spread of COVID-19. Individuals also have different behavioral responses to the pandemic of COVID-19.

Government responses to COVID-19 have included implementing lockdowns, canceling public gatherings, imposing travel restrictions, and closing schools. The effectiveness of these measures has been debated in the literature. The implementation of lockdown and travel restrictions was found to be effective in reducing new infections (2, 3). School closures might lead to a reduction in mortality (4). Restricting travels from areas with active outbreaks could reduce disease transmission if combined with public health interventions and individual behavior changes (5).

To encourage individual behavior changes during the pandemic of COVID-19, both local and global health organizations have released recommendations on individual preventive measures to reduce disease transmissibility. World Health Organization recommends frequent hand washing, social distancing, avoidance of face touching, practicing respiratory hygiene, staying home, and seeking medical care early if there are suspected symptoms (6). The Centers for Disease Control and Prevention (CDC) in different countries have similar recommendations on hand washing and social distancing, but have different opinions on face mask-wearing (7, 8). However, little is known about whether individuals have changed their behaviors based on recommendations from health organizations.

This study used the Health Belief Model (HBM) as the conceptual framework. The HBM is one of the most widely used psychosocial models to examine factors associated with individual behavior (9). Key components of the HBM included perceived susceptibility (the risk of getting a disease), perceived severity (the seriousness of a disease), perceived benefits (the gains to perform a behavior), perceived barriers (the obstacles to perform a behavior), and cue to action (the stimulus to perform a behavior) (9). Recent modifications of the HBM have added other components of self-efficacy (the level of confidence to perform a behavior) and knowledge (the level of expertise in an area) (10, 11).

The HBM has been used to assess predictors of adopting preventive health behaviors in previous infectious disease outbreaks. Perceived susceptibility significantly influenced the adoption of preventive health behaviors during the severe acute respiratory syndrome (SARS) and H1N1 outbreaks (12–15). Perceived severity significantly influenced the adoption of preventive health behaviors during the H1N1 outbreak (16, 17). Perceived benefits significantly influenced the adoption of preventive health behaviors during the SARS and H1N1 outbreaks (12, 14–17). Perceived barriers significantly influenced the adoption of preventive health behaviors during the H1N1 outbreak (15–17). Cues to action significantly influenced the adoption of preventive health behaviors during the SARS, H1N1, and Zika virus outbreaks (12–15, 18). Self-efficacy was not associated with the adoption of preventive health behaviors during the SARS and H1N1 outbreaks (13, 15). Knowledge did not influence the adoption of preventive health behaviors during the H1N1 and SARS outbreak (13, 16).

Understanding individuals' knowledge and behavioral responses to the pandemic of COVID-19 is important to contain the outbreak. However, there is a paucity of studies available on the knowledge and preventive health behaviors of COVID-19. Therefore, to address these literature gaps, this study aimed to (1) to assess individuals' knowledge of COVID-19 and (2) to examine determinants associated with the potential adoption of preventive health behaviors, including washing hands, wearing a face mask, and maintaining social distancing, among future pharmacists.

METHODS

Study Participants

This study was conducted in March 2020 in China. During that time, China had slowed the spread of COVID-19 and saw continuous decreases in the newly confirmed cases. In low-endemic areas, most prevention and control measures implemented by local authorities were discontinued (e.g., lockdowns and travel restrictions). However, school closures were still in effect in most parts of China. Specifically, all colleges and universities were still closed and classes were offered online. A significant challenge for schools to reopen is that students might not have enough knowledge and motivation to engage in preventive health behaviors to prevent contracting and spreading COVID-19 in the community.

A pilot study was conducted on eight respondents to test the clarity of survey questions and confusing questions were revised. An anonymous online survey was sent to pharmacy students who lived in high and low-endemic areas in China. We sent surveys to 800 pharmacy students who were 18 years and older from four different colleges/universities, including both comprehensive and professional colleges/universities. High-endemic areas included Hubei, Guangdong, Henan, Zhejiang, and Hunan, where the total number of COVID-19 cases were 1,000 and higher; low-endemic areas included provinces with the total number of COVID-19 cases lower than 1,000. This study was approved by the University institutional review board.

Measurement

The survey collected information on knowledge of COVID-19, preventive health behaviors, and demographics. Respondents' knowledge was assessed by when and how they first heard of COVID-19. This study also tested if respondents knew how COVID-19 was transmitted and of the availability of test kit, medication, and vaccine for COVID-19. Demographics collected in the survey included age, gender, ethnicity, and residence area (high vs. low-endemic areas).

Preventive health behaviors examined in this study included washing hands, wearing a face mask, and maintaining social

distancing as recommended by the China CDC (8). Respondents were asked to indicate their likelihood of performing these preventive health behaviors and measured by a seven-point Likert scale (one as extremely unlikely; seven as extremely likely). Components of the HBM were also measured by a seven-point Likert scale (one as strongly disagree; seven as strongly agree). Perceived susceptibility was assessed by whether respondents believe that they are at risk of getting COVID-19. Perceived severity was assessed by their thoughts of COVID-19 as a serious illness. Perceived benefits were assessed by whether respondents believe each preventive health behavior can prevent COVID-19. Perceived barriers were assessed by whether they believe it is inconvenient to perform each preventive health behavior. Cue to action was assessed by whether respondents would perform each preventive health behavior if recommended. Self-efficacy was assessed by whether they are able to perform each preventive health behavior. Knowledge was assessed by whether respondents have enough knowledge about COVID-19 and defined as low (score 1–2), medium (score 3–5), and high (score 6–7) levels.

Data Analysis

We excluded study participants in the data analysis if they reported extreme answers, defined as having the same response to all survey questions. Preventive health behaviors and components of the HBM were analyzed as means and compared between different demographic groups using independent sample *t*-tests. Pearson correlation coefficients were calculated to examine associations between different preventive health behaviors. To predict preventive health behaviors, three multivariate linear regression models were used. In each model, the dependent variable was the preventive health behavior and independent variables included components of the HBM and demographic variables. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Among 203 respondents who finished the survey (response rate of 25.38%), the majority of them were aged 18–22 years (54.68%), female (69.95%), of Han ethnicity (91.13%), and lived in low-endemic areas (70.44%) (**Table 1**). For the knowledge of COVID-19, most of respondents first heard of COVID-19 in January 2020 (59.61%). The two most common sources of this information were websites (84.73%) and social media (59.11%). Almost all respondents knew that COVID-19 was transmitted through droplets (98.52%) and two-thirds of them also knew that close contact (66.50%) could transmit the virus. For the availability of different medical products, the majority of respondents thought that we have test kits to detect (79.31%) but do not have a vaccine to prevent COVID-19 (78.82%). Approximately half of respondents thought that there is no medication to treat COVID-19 (52.22%).

For preventive health behaviors, respondents reported being extremely likely to wear a face mask (6.85 $\pm$ 0.60), but only moderately likely to engage in hand washing (5.95 $\pm$ 1.38) and social distancing (6.19 $\pm$ 1.60) (**Table 2**). For Pearson correlation coefficients, three preventive health behaviors were positively correlated with each other (washing hands vs. wearing a face mask: $r = 0.24$, $p < 0.01$; washing hands vs. maintaining social distancing: $r = 0.24$, $p < 0.01$; wearing a face mask vs. maintaining social distancing: $r = 0.31$, $p < 0.01$). Different demographic groups had a similar likelihood of performing preventive health behaviors.

For components of the HBM, respondents reported a slightly low perceived susceptibility (2.92 $\pm$ 1.70) of COVID-19 and males reported a lower level of susceptibility (**Table 2**).

TABLE 1 | Characteristics and knowledge of study respondents ($N = 203$).

	N	%
Demographics		
Age		
18–22	111	54.68
23+	92	45.32
Gender		
Female	142	69.95
Male	61	30.05
Ethnicity		
Han	185	91.13
Minority	18	8.87
Area		
Low-endemic area	143	70.44
High-endemic area	60	29.56
First Time Heard of COVID-19		
2019	75	36.95
January 2020	121	59.61
February 2020 and later	7	3.45
Source of Information		
TV	49	24.14
Website	172	84.73
Social media	120	59.11
Radio	9	4.43
In print	7	3.45
Family/friend	54	26.60
Method of Transmission		
Close contact	135	66.50
Droplets	200	98.52
Bodily fluids	90	44.33
Sex	79	38.92
Availability of Test Kit		
Yes	161	79.31
No	23	11.33
Unsure	19	9.36
Availability of Medication		
Yes	56	27.59
No	106	52.22
Unsure	41	20.20
Availability of Vaccine		
Yes	15	7.39
No	160	78.82
Unsure	28	13.79

TABLE 2 | Preventive health behaviors of study respondents by age, gender, ethnicity, and residence area.

	Overall	Age			Gender			Ethnicity			Residence area		
		18–22	23+	*P*	Female	Male	*P*	Han	Minority	*P*	Low-endemic	High-endemic	*P*
	Mean ± SD[†]	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Preventive health behavior of													
Washing hands	5.95 ± 1.38	6.02 ± 1.29	5.87 ± 1.48		6.02 ± 1.34	5.79 ± 1.45		5.91 ± 1.40	6.33 ± 1.03		5.94 ± 1.37	5.97 ± 1.41	
Wearing a face mask	6.85 ± 0.60	6.88 ± 0.51	6.82 ± 0.69		6.82 ± 0.64	6.90 ± 0.47		6.86 ± 0.57	6.72 ± 0.83		6.85 ± 0.54	6.83 ± 0.71	
Maintaining social distancing	6.19 ± 1.60	6.39 ± 1.36	5.96 ± 1.84	*	6.23 ± 1.57	6.11 ± 1.68		6.23 ± 1.56	5.83 ± 2.04		6.14 ± 1.63	6.32 ± 1.56	
Perceived susceptibility of COVID-19	2.92 ± 1.70	3.05 ± 1.72	2.75 ± 1.67		3.08 ± 1.65	2.52 ± 1.77	**	2.91 ± 1.70	3.00 ± 1.78		2.88 ± 1.68	3.00 ± 1.76	
Perceived severity of COVID-19	5.08 ± 1.51	5.00 ± 1.50	5.17 ± 1.53		4.96 ± 1.46	5.36 ± 1.60	*	5.11 ± 1.53	4.72 ± 1.27		5.17 ± 1.46	4.85 ± 1.61	
Perceived benefits of													
Washing hands	5.50 ± 1.27	5.47 ± 1.23	5.54 ± 1.32		5.44 ± 1.29	5.64 ± 1.24		5.50 ± 1.22	5.50 ± 1.76		5.51 ± 1.19	5.48 ± 1.47	
Wearing a face mask	5.87 ± 1.23	5.97 ± 1.15	5.74 ± 1.32		5.83 ± 1.24	5.95 ± 1.22		5.82 ± 1.26	6.33 ± 0.77	**	5.86 ± 1.19	5.88 ± 1.33	
Maintaining social distancing	6.19 ± 0.93	6.25 ± 0.86	6.11 ± 1.01		6.18 ± 0.95	6.20 ± 0.89		6.18 ± 0.91	6.22 ± 1.12		6.18 ± 0.95	6.20 ± 0.88	
Perceived barriers to													
Washing hands	2.65 ± 1.69	2.47 ± 1.63	2.87 ± 1.76	*	2.68 ± 1.63	2.59 ± 1.86		2.73 ± 1.72	1.78 ± 1.06	***	2.62 ± 1.71	2.72 ± 1.67	
Wearing a face mask	5.17 ± 1.66	5.17 ± 1.68	5.17 ± 1.64		5.23 ± 1.57	5.03 ± 1.86		5.26 ± 1.60	4.22 ± 2.02	**	5.13 ± 1.70	5.28 ± 1.56	
Maintaining social distancing	2.58 ± 1.76	2.33 ± 1.68	2.87 ± 1.83	**	2.63 ± 1.75	2.46 ± 1.79		2.59 ± 1.75	2.39 ± 1.88		2.57 ± 1.76	2.60 ± 1.78	
Cue to action of													
Washing hands	6.27 ± 1.03	6.38 ± 1.01	6.13 ± 1.04	*	6.27 ± 1.03	6.26 ± 1.03		6.23 ± 1.06	6.61 ± 0.61	**	6.24 ± 0.99	6.32 ± 1.13	
Wearing a face mask	6.59 ± 0.72	6.69 ± 0.55	6.47 ± 0.87	**	6.57 ± 0.69	6.64 ± 0.80		6.57 ± 0.73	6.78 ± 0.55		6.56 ± 0.75	6.67 ± 0.65	
Maintaining social distancing	6.28 ± 1.18	6.29 ± 1.27	6.26 ± 1.07		6.17 ± 1.29	6.52 ± 0.83	**	6.28 ± 1.15	6.22 ± 1.52		6.28 ± 1.13	6.27 ± 1.29	
Self-efficacy of													
Washing hands	5.84 ± 1.30	5.95 ± 1.26	5.71 ± 1.34		5.84 ± 1.33	5.84 ± 1.24		5.79 ± 1.32	6.33 ± 0.91	*	5.80 ± 1.23	5.93 ± 1.50	
Wearing a face mask	6.60 ± 0.70	6.70 ± 0.53	6.47 ± 0.84	**	6.59 ± 0.73	6.61 ± 0.64		6.58 ± 0.72	6.78 ± 0.43	*	6.61 ± 0.65	6.57 ± 0.81	
Maintaining social distancing	6.07 ± 1.13	6.17 ± 1.04	5.95 ± 1.23		6.08 ± 1.16	6.03 ± 1.06		6.05 ± 1.11	6.28 ± 1.32		6.06 ± 1.15	6.08 ± 1.09	
Knowledge of COVID-19	4.41 ± 0.95	4.32 ± 0.94	4.52 ± 0.95		4.30 ± 0.86	4.69 ± 1.09	**	4.38 ± 0.94	4.72 ± 0.96		4.44 ± 0.98	4.35 ± 0.88	

[†] *1 as extremely unlikely and 7 as extremely likely. *Significant at 0.1, **Significant at 0.05, ***Significant at 0.01.*

Respondents reported a slightly high perceived severity (5.08 ± 1.51) of COVID-19. Perceived benefits were moderately high for all preventive health behaviors (washing hands: 5.50 ± 1.27; wearing a face mask: 5.87 ± 1.23; and maintaining social distancing: 6.19 ± 0.93) and ethnic minorities reported a higher level of benefit of wearing a face mask. Perceived barriers were slightly low to wash hands (2.65 ± 1.69) and maintain social distancing (2.58 ± 1.76). Ethnic minorities reported a lower level of barrier to wash hands and those aged 23 years and older reported a higher level of barrier to maintain social distancing. Perceived barriers to wear a face mask were slightly high (5.17 ± 1.66) and ethnic minorities reported a lower level of barrier. Cue to action was moderately high for washing hands (6.27 ± 1.03) and maintaining social distancing (6.28 ± 1.18). Ethnic minorities reported a higher level of cue to action of washing hands and males reported a higher level of cue to action of maintaining social distancing. Cue to action of wearing a face mask was extremely high (6.59 ± 0.72) and those aged 23 years and older reported a lower level of cue to action. Self-efficacy was moderately high for washing hands (5.84 ± 1.30) and maintaining social distancing (6.07 ± 1.13). Self-efficacy of wearing a face mask was extremely high (6.60 ± 0.70) and those aged 23 years and older reported a lower level of self-efficacy. Respondents reported a medium level of knowledge (4.41 ± 0.95) of COVID-19 and males reported a higher level of knowledge.

In the multivariate regression models, determinants of washing hands included cue to action (β: 0.27; 95% CI: 0.05 to 0.48), self-efficacy (β: 0.56; 95% CI: 0.39 to 0.73), and knowledge (β: 0.15; 95% CI: 0.01 to 0.31) and being a male was negatively associated with washing hands (β: −0.35; 95% CI: −0.68 to −0.03) (**Table 3**). Determinants of wearing a face mask included cue to action (β: 0.20; 95% CI: 0.06 to 0.34), self-efficacy (β: 0.21; 95% CI: 0.06 to 0.35), and knowledge (β: 0.09; 95% CI: 0.01 to 0.18) and being an ethnic minority was negatively associated with wearing a face mask (β: −0.32; 95% CI: −0.60 to −0.03). Determinants of maintaining social distancing included cue to action (β: 0.19; 95% CI: 0.01 to 0.38) and self-efficacy (β: 0.43; 95% CI: 0.19 to 0.66).

DISCUSSION

This study found that respondents had a medium level of knowledge of COVID-19 and the majority of them had heard of the disease through websites and social media. In comparison, a previous study evaluating parents' knowledge of the H1N1 vaccine found that 66% perceived their knowledge of the H1N1 vaccine to be insufficient at best (16). The difference in the level of knowledge might be due to the increasing amount of information being disseminated online and therefore, its accessibility to young adults in this digital era as evidenced by the main sources of information. Despite having prompt awareness of the disease through the internet, we found that not all of respondents' knowledge of COVID-19 was correct. At the time of this study, the majority of our respondents accurately identified droplets and close contact as the main modes of viral transmission, that we have a test kit to test for the disease, that approved medications to treat the disease are not available, and that a vaccine to prevent the disease is not available. However, some respondents held incorrect beliefs about the disease. The WHO identifies that the virus is mainly transmitted by close contact and respiratory droplets produced through the cough or sneeze of an infected person (6). During the study period laboratory tests exist to screen for the disease, however, no approved pharmacological therapy was available (19). Off-label use of some investigational therapies, such as lopinavir with ritonavir-boost, remdesivir, and herb medicine, have been reported with variable efficacy in the literature (20–24). Additionally, few respondents have also incorrectly identified that a vaccine is available for the disease, although robust research effort in vaccine development is underway (25). Our respondents' knowledge of COVID-19 indicated that although the internet can be an effective way of promoting information, the accuracy of medical information is variable. Only 39% of online medical information is found to be accurate (26). Our findings highlight the importance of increasing education to young adults on the correct modes of transmission and the rapid dissemination of reliable information on the availability of screening and treatment strategies for this disease.

The HBM was used in this study to identify determinants of preventive health behaviors, including washing hands, wearing a face mask, and maintaining social distancing, recommended by China CDC. For wearing a face mask, this study identified cue to action, self-efficacy, and knowledge as significant predictors. Our finding that cue to action was a significant predictor of face mask-wearing was similar to previous studies during the SARS and H1N1 outbreaks (12, 13, 15). Cue to action which significantly predicted face mask-wearing in previous studies included recommendations from local government and family members, being in crowded places and places of vulnerability (e.g., hospitals), situational cues (e.g., seeing people coughing or sneezing, seeing others wearing face masks), and availability of face masks (e.g., availability of face masks provided at no cost) (12, 13, 15). Self-efficacy and knowledge were not always assessed in previous studies. However, when included, they were not significantly correlated with face mask-wearing during the SARS and H1N1 outbreaks (13, 15). This study did not find perceived susceptibility as a significant predictor of face mask-wearing, whereas this was consistently identified as a predictor during the SARS and H1N1 outbreaks (12, 13, 15). This discrepancy could be explained by our respondents' perception that they were at low risk of contracting COVID-19. Since previous studies linking perceived susceptibility to face mask-wearing have found that individuals who feel that they were more vulnerable to the disease were more likely to wear a face mask compared to those who perceived a lower susceptibility to the disease (12, 15). In terms of hand washing, we found cue to action, self-efficacy, and knowledge to be significant predictors, and in terms of social distancing, we found cue to action and self-efficacy to be significant predictors. Previous studies have only assessed preventive health behaviors as a whole and have not studied

TABLE 3 | Multivariate linear regressions on preventive health behaviors.

	Washing hands			Wearing a face mask			Maintaining social distancing		
	β	95% CI		β	95% CI		β	95% CI	
Health Belief Model									
Perceived susceptibility	0.03	−0.06	0.11	0.00	−0.05	0.04	0.08	−0.05	0.21
Perceived severity	0.01	−0.08	0.11	0.00	−0.05	0.05	0.04	−0.10	0.18
Perceived benefits	0.02	−0.10	0.13	0.04	−0.02	0.10	0.10	−0.15	0.34
Perceived barriers	−0.01	−0.10	0.07	−0.01	−0.06	0.03	−0.02	−0.15	0.12
Cue to action	0.27	0.05	0.48	0.20	0.06	0.34	0.19	0.01	0.38
Self-efficacy	0.56	0.39	0.73	0.21	0.06	0.35	0.43	0.19	0.66
Knowledge	0.15	0.01	0.31	0.09	0.01	0.18	0.01	−0.22	0.23
Demographics									
Age									
18–22	Ref			Ref			Ref		
23+	0.09	−0.20	0.38	0.00	−0.16	0.16	−0.33	−0.76	0.11
Gender									
Female	Ref			Ref			Ref		
Male	−0.35	−0.68	−0.03	−0.04	−0.21	0.14	−0.12	−0.61	0.38
Ethnicity									
Han	Ref			Ref			Ref		
Minority	−0.18	−0.71	0.34	−0.32	−0.60	−0.03	−0.60	−1.37	0.18
Residence area									
Low-endemic area	Ref			Ref			Ref		
High-endemic area	−0.14	−0.46	0.18	−0.07	−0.24	0.10	0.09	−0.38	0.56

predictors of individual health behaviors of hand washing and social distancing separately. By identifying predictors of these specific preventive health behaviors, our results could facilitate more targeted educational efforts to enhance the potential adoption of these health behaviors.

Respondents reported that they were moderately or extremely likely to adopt preventive health behaviors. The likelihood to adopt these health behaviors was strongest with face mask-wearing (rated extremely likely), followed by social distancing and hand washing (both rated moderately likely). This might be because respondents perceive face mask-wearing as a social norm and a form of civic responsibility, as illustrated in a previous study conducted in Hong Kong during the SARS outbreak (27). Not wearing face masks during the SARS outbreak reportedly led to stigmatization, social seclusion, and discrimination (27). The adverse social consequences of not wearing a face mask, particularly with its visibility, likely serve as a stronger motivator for its use compared to less visible health behaviors such as hand washing. Based on our identified predictors of these behaviors, improving social distancing and hand washing could be achieved by having local governments and/or public health officials exercise cues to action by recommending young adults adopt these measures through websites or social media. These messages should also aim to increase their confidence in adopting these measures in order to improve self-efficacy. Knowledge also significantly predicted washing hands, but not to practice social distancing. Therefore, to further improve hand hygiene among young adults, public health officials can consider creating online videos and/or infographics illustrating the importance of and the methods to proper hand washing.

Pharmacy students were still staying at home and learning online as all colleges and universities were closed during the study period. This study found that respondents were moderately or extremely likely to adopt preventive health behaviors. The high likelihood of engaging individual preventive measures could support the reopening of colleges and universities in China. Special attention should be paid to washing hands as this is not as visible compared to wearing a face mask. In addition, maintaining social distancing might be challenging in the classroom and cafeteria when college students are back to school. Given the medium level of knowledge of COVID-19 in pharmacy students, continued education through the internet is important. Local and school authorities should make clear guidance to support individuals to adopt preventive health behaviors to reduce the risk of community transmission of COVID-19 in colleges and universities.

This study has some limitations worth mentioning. First, this study only included pharmacy students, therefore the results cannot be generalizable to the general public. Second, due to the use of a questionnaire for data collection, the actual level of knowledge and preventive health behaviors might be different from what has been reported. Third, because only components

of the HBM were evaluated, there might be other factors that could motivate health behaviors that were not accounted for in this study. However, the HBM is one of the most widely used belief-based psychosocial theories and has been extensively used to assess preventive health behaviors in previous virus outbreaks.

CONCLUSIONS

This study found that future pharmacists in high and low-endemic areas in China had a medium level of knowledge of COVID-19. Further efforts to improve their knowledge can be focused on providing timely, reliable, and accurate information on the internet. In the HBM, cue to action, self-efficacy, and knowledge were significant predictors of preventive health behaviors of washing hands and wearing a face mask, whereas only cue to action and self-efficacy were significant predictors of maintaining social distancing. To potentially improve the adoption of face mask-wearing, hand washing, and social distancing as appropriate individual preventive measures, targeted educational efforts should be implemented to enhance cue to action, self-efficacy, and knowledge. To prepare for reopening schools, continued monitoring of individuals' knowledge and behavioral responses to COVID-19 is warranted.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Tennessee Health Science Center. The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

GL and JY: conceptualization, methodology, and writing, SH: methodology and writing, RS: methodology and analysis, ML: conceptualization, methodology, analysis, writing, and supervision. All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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Culture-Related Health Disparities in Quality of Life: Assessment of Instrument Dimensions Among Chinese

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Background: Health-related quality of life (HRQoL) is one of the major focuses of primary care. However, HRQoL instruments used in China are mainly developed from Western countries. Such instruments may not cover all important health concepts valued by the Chinese as health is a culture-specific concept.

Objectives: The objectives of this study are to identify culture-specific health dimensions and culture-related health disparities in primary care that are considered important by Chinese living in China.

Methods: A purposive sample of 164 adult Chinese (67 healthy persons and 97 patients) were interviewed face to face. In-depth open-ended questions were asked to elicit culture-specific dimensions of quality of life in primary care settings in China.

Results: Twelve health dimensions were identified. Five most frequently mentioned dimensions were: mood ($N = 52$, 31.71%), physical activities ($N = 48$, 29.27%), work ($N = 40$, 24.39%), diet ($N = 32$, 19.51%), and vitality ($N = 28$, 17.07%). Significantly more healthy persons reported mood (49.25 vs. 19.59%, $P < 0.001$), mindset (16.42 vs. 0.00%, $P < 0.001$), and self-care (11.94 vs. 2.06%, $P = 0.016$) characterizing good HRQoL, while more patients emphasized on work (4.48 vs. 38.14%, $P < 0.001$). Diet and vitality appeared to be culture-specific dimensions related to health among Chinese.

Conclusions: To better adapt or develop HRQoL instruments for Chinese, dimensions or items regarding diet might be included and disparities in the meaning of vitality between Chinese and Western cultures should be considered.

Keywords: health-related quality of life, culture, health disparities, primary care, Chinese

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INTRODUCTION

Health-related quality of life (HRQoL) is one of the major focuses of primary care. However, generic and disease-specific HRQoL instruments used in China are mainly developed from North America and Europe. Such instruments, after careful translation and cultural adaptation, usually work well in Chinese in terms of respondents' acceptability and psychometric properties.

However, as the concept of health or HRQoL may not be the same across different cultures, these instruments might not be adequate for Chinese people (1–5). The working definitions of health or HRQoL used by Western-originated instruments may not be optimal to Chinese. If this is the case, optimal measurements cannot be achieved with such instruments among Chinese. To the best of our knowledge, no empirical research has been done to assess the adequacy of Western-originated instruments for measuring the Chinese population in primary care settings.

This study aimed to elicit the dimensions that Chinese people think should be used to define health in primary care settings. By knowing such information, we can then assess how valid current instruments are for measuring the HRQoL of the Chinese population and will have a better idea about how to improve HRQoL measurements in the setting of Chinese culture.

METHODS

Data used in the qualitative study were obtained from a survey of healthy persons and patients in China. Both healthy and ill subjects were included for a more comprehensive investigation. Healthy persons were recruited using a quota sampling method and patients were recruited using a convenience sampling method from primary care settings. In the survey, the interviewer asked each subject the following two open-ended questions: "what is your best imaginable health state like?" and "what are the characteristics of good quality of life in your own opinion?" Answers to these questions were summarized as individual themes and recorded by the interviewers.

The themes derived from the two surveys were collated and reviewed independently by two HRQoL researchers. In the review, similar or closely related themes were grouped to form dimensions of health. Only those health dimensions mentioned by more than two participants were reported. The two reviewers then met to reconcile the dimensions they identified and the components for each dimension. After complete consensus was reached, dimensions alluded by each respondent were enumerated and the frequency of each health dimension was compared between the two groups of respondents (i.e., healthy and ill) using Chi-square or Fisher's exact test. Within each group, the association between dimensions and demographics including age ($\leq$50 vs. $>$50 years), gender, and education level (high school or lower vs. college or higher) was examined for the most frequently nominated five health dimensions using Chi-square or Fisher's exact test.

RESULTS

A total of 67 healthy persons and 97 patients were successfully interviewed. Females accounted for 52.2 and 40.2% of healthy and ill participants, respectively. Age groups were evenly distributed among healthy persons; while more patients were older than 50 years (40.2%). The distribution of education level was even among patients; while 50.8% of healthy persons had a bachelor's or higher degree. Most of the participants were full-time employees (47.8% of healthy person and 57.7% of patients).

Twelve health dimensions were identified, including physical activities, leisure activities, work, self-care, diet, sleep, pain, mindset, mood, vitality, cognition, and relationship (**Table 1**). These health dimensions covered physical, mental, and social health.

Healthy persons and patients nominated almost the same dimensions, except for mindset (**Table 2**). The most frequently mentioned five dimensions by all participants were: mood (N = 52, 31.71%), physical activities (N = 48, 29.27%), work (N = 40, 24.39%), diet (N = 32, 19.51%), and vitality (N = 28, 17.07%). Significantly more healthy persons than patients reported mood (49.25 vs. 19.59%, $P < 0.001$), mindset (16.42 vs. 0.00%, $P < 0.001$), and self-care (11.94 vs. 2.06%, $P = 0.016$) characterizing good HRQoL, while more patients emphasized on work (4.48 vs. 38.14%, $P < 0.001$). When the five most important health dimensions were considered, there is generally no significant difference between subgroups defined by gender, age, or education in both healthy persons and patients (**Table 3**).

DISCUSSION

Health dimensions identified in this study were similar to those found in previous studies of Chinese people through focus group discussion (6–12). However, some of those health dimensions identified from focus group discussion were not surfaced in the present study. For example, focus discussion revealed that freedom is a dimension of good HRQoL. Instead of reporting any mentioned dimensions of good HRQoL, this study focused on dimensions that were independently alluded to by at least two participants. The use of both qualitative and quantitative evidence minimized the risk of taking idiosyncratic views as commonality, making the findings more useful for informing culture-specific questionnaire adaptation and development.

Similar to the Western population, Chinese people considered mood, physical activities, work, and vitality as important dimensions of good HRQoL. However, vitality, or "jing shen" in Chinese, has different meanings between Chinese and Western cultures (13, 14). In Chinese culture, vitality mainly relates to mental health. On the contrary, in Western culture, vitality is related to both physical and mental health. Indeed, studies on the vitality scale of the SF-36 showed that the relationship between vitality and physical and mental health differed significantly between the Chinese and US populations (15–18). Since vitality is an important health dimension among Chinese but has different meanings from Western culture, attention should be paid to this dimension when adapting or developing HRQoL instruments for use among Chinese.

Different from Western people, Chinese people consider the ability to eat and drink as an important dimension of good HRQoL. Its importance in Chinese culture is evident by the customs that many Chinese acquaintances greet each other with "Have you had your meal?" when they bump into each other at noon or in the evening. In Chinese culture, eating and drinking ability is considered an indicator of good productivity

TABLE 1 | Identified health dimensions from healthy persons and patients.

Component	Dimension	Meaning	Example component terms
Physical health	Physical activities	Ability to perform physical activities	Walk, Usual activities, Physical exercise (e.g., run, climb, and play basketball)
	Leisure activities	Ability to perform leisure activities	Play (e.g., dance, travel, and sing Karaoke)
	Work	Ability to work	Work, farm work, housework
	Self-care	Ability to take care of myself	Take care of myself, do not need help from others
	Diet	Ability to eat or drink well	Eat, drink, good appetite, alcohol consumption
	Sleep	Ability to have a sound sleep	Sleep, sound sleep, high-quality sleep
	Pain	Free from pain	No pain, no discomfort
Mental health	Mindset	Positive attitude	Positive attitude, healthy attitude, optimistic attitude, forgiving attitude
	Mood	Good mood	Good mood, happy mood, no worry, no pressure
	Vitality	High vitality	High spirit, no fatigue, have strength
	Cognition	Good cognition	Sharp mind, clear mind
Social health	Relationship	Good relationship with others	Happy family, good relationship with friends, good relationship with others

TABLE 2 | Importance of each dimension by healthy persons and patients.

Dimensions	Total ($N = 164$)		Healthy person ($N = 67$)		Patient ($N = 97$)		*P*-value
	No	%	No	%	No	%	
Mood	52	31.71	33	49.25	19	19.59	<0.001
Physical activities	48	29.27	20	29.85	28	28.87	0.892
Work	40	24.39	3	4.48	37	38.14	<0.001
Diet	32	19.51	14	20.90	18	18.56	0.710
Vitality	28	17.07	14	20.90	14	14.43	0.280
Pain	25	15.24	13	19.40	12	12.37	0.218
Sleep	17	10.37	5	7.46	12	12.37	0.311
Mindset	11	6.71	11	16.42	0	0.00	<0.001
Relationship	11	6.71	5	7.46	6	6.19	0.760
Self-care	10	6.10	8	11.94	2	2.06	0.016
Leisure activities	7	4.27	3	4.48	4	4.12	1.000
Cognition	4	2.44	3	4.48	1	1.03	0.306

and longevity. Therefore, when adapting HRQoL instruments developed in Western culture, the limitation of not having the diet dimension should be deliberated. When developing Chinese culture-specific HRQoL instruments, diet should be included as an important health dimension.

Significantly more patients emphasized work as a characteristic of good HRQoL. It is not surprising because the loss of working ability is an important concern to patients. The importance of mood and mindset was also different significantly between healthy and ill people. It is understandable that patients may have lowered their expectations and focus more on imminent concerns about their physical health and functions. In order to prevent ceiling or floor effect in measurement, health dimensions in HRQoL instruments for general and patient populations are better to be customized among Chinese. For the general population, dimensions representing mental health should be emphasized; for patient populations, dimensions concerning working ability are important.

The limitation of the study is that some potentially important health dimensions, such as sexuality, could not be identified from face to face interviews due to social desirability. Since talking about sex is taboo in Chinese culture, it is possible that respondents are unwilling to indicate it as a characteristic of good HRQoL in front of interviewers. In addition, the results should be interpreted with caution because study participants might not be representative of the general population.

CONCLUSIONS

Through face to face interviews, this study not only identified 12 health dimensions representing good HRQoL by Chinese but measured their relative importance in Chinese culture. It appears that Chinese people have their culture-specific perception of dimensions characterizing good HRQoL. Diet and vitality are culture-specific dimensions related to health among Chinese. To better adapt or develop HRQoL instruments for Chinese, dimensions or items regarding diet are recommended to be included and disparities in the meaning of vitality between Chinese and Western cultures should be taken into account. In addition, mental health dimensions are important to Chinese

TABLE 3 | Difference in the importance of five most frequently mentioned dimensions among healthy persons and patients.

	Mood (%)	Physical activities (%)	Diet (%)	Vitality (%)	Pain (%)
Healthy persons					
Gender			**		
Male	53.13	21.88	31.25	21.88	21.88
Female	45.71	37.14	11.43	20.00	17.14
Age	***				
18–50	60.87	26.09	19.57	21.74	19.57
51+	23.81	38.10	23.81	19.05	19.05
Education					
High school or lower	48.78	34.15	19.51	24.39	21.95
College or higher	50.00	23.08	23.08	15.38	15.38
Patients					
Gender					
Male	39.66	27.59	20.69	22.41	15.52
Female	35.90	30.77	17.95	12.82	12.82
Age	**	*			
18–50	22.86	40.00	14.29	20.00	20.00
51+	46.77	22.58	22.58	17.74	11.29
Education					
High school or lower	28.57	28.57	21.43	28.57	14.29
College or higher	42.03	28.99	18.84	14.49	14.49

****Significant at 0.01 level; **Significant at 0.05 level; *Significant at 0.1 level.*

generic HRQoL instruments and working ability dimensions are important to Chinese disease-specific HRQoL instruments. More research is needed to elucidate the health concepts held by the Chinese so that better HRQoL instruments can be developed for this population.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by China Pharmaceutical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ML, ZB, JZ, and NL contributed to conception and design of the study. ML and NL organized the database and wrote the first draft of the manuscript. ML, GL, PC, and NL performed the statistical analysis and wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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SYSTEMATIC REVIEW
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Clinical Efficacy of Infantile Massage in the Treatment of Infant Functional Constipation: A Meta-Analysis

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Background: Functional constipation in children is a common disease that causes a psychological burden on infants and young children across the world. It will greatly affect infant quality of life in early childhood and even affect their psychological and physical health. At present, infant functional constipation is treated with western drugs alone, but this can produce drug dependency. In recent years, Traditional Chinese Medicine (TCM) infant massage has been used as a complementary and alternative therapy, and its effectiveness and safety have been proven, attracting the attention of numerous researchers.

Objective: Our study aimed to compare the influence of infant massage intervention on defecation frequency and consistency, determine the effectiveness, and safety of infant massage in the treatment of infant functional constipation, and obtain high-quality clinical evidence.

Methods: Based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Statement, inclusion, and exclusion criteria were formulated. Randomized controlled trials (RCTs) on TCM infant massage for the treatment of infant functional constipation were found following a search of four mainstream medical databases. RCTs found to meet the study's requirement were included; data information was then extracted, and the quality was assessed using the Cochrane bias risk assessment tool. Through RevMan software, a meta-analysis was carried out for overall effective rate, stool form, defecation frequency, defecation difficulty, and constipation symptom scoring index. The relative risk (RR) and 95% confidence interval (95% CI) were calculated, heterogeneity was tested and its source was found, and publication bias was assessed through the Egger's and Begg's tests and by means of funnel plots.

Results: A total of 23 RCTs and 2,005 patients were included. The results of the meta-analysis showed that compared to drug therapy alone, TCM infant massage had a superior effect on the treatment of infant functional constipation. This difference was statistically significant ($p < 0.05$) and evaluated according to the overall effective rate (RR = 1.25; 95% CI = 1.17, 1.33), defecation frequency [mean difference (MD) = −0.72; 95% CI = −0.80, −0.65], and constipation symptom score (MD = −0.81; 95% CI = −1.20, −0.43), showing that TCM infant massage is indeed superior to drug therapy alone in the treatment of infant functional constipation. TCM infant massage was found

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to be equivalent to drug therapy alone in terms of the stool form score [−0.30 (−0.38, −0.22)] and the defecation difficulty score [−0.73 (−0.81, −0.65)], since the difference was not statistically significant ($p > 0.05$). The source of heterogeneity might be related to the state of patient, manipulation of the massages, efficacy of drugs in the control group, and difference in judgment criteria for efficacy. The Egger's test and Begg's test showed that publication bias did not occur in our study.

Conclusion: TCM infant massage can increase defecation frequency and reduce the symptoms of constipation in children suffering from functional constipation; in addition, the clinical trial showed beneficial effects. Since some of the RCTs featured a very small sample size, the reliability and validity of our study's conclusion may have been affected as well; therefore, the explanation should be treated with some caution. In the future, a large number of higher-quality RCTs are still needed to confirm the results of our study.

Keywords: children's constipation, children's functional constipation, randomized controlled trials, Traditional Chinese Medicine, infant massage, meta-analysis

INTRODUCTION

Infant functional constipation is a common disease in childhood; it has an incidence rate of 0.3–8%, accounting for 3–5% of pediatric outpatients (1). Its prevalence rate is 0.7–29.6% in the field of pediatric health care across the world, including both developed and developing countries (2). In China, there are relatively few epidemiological studies on this disease. The condition has adverse effects on infant sleep and appetite and even endangers their growth and development (3). It affects children's quality of life. Compared to healthy children, those with constipation were found to have a lower score of quality of life, far lower than even the impact score mentioned in studies related to gastroesophageal reflux disease (GERD) and inflammatory bowel disease (IBD) (4). In addition, a heavy economic burden is brought by this disease (5); the average annual expenditure for treating children with constipation are three times higher than those without this disease (6). Moreover, some diseases such as headache, depression, anxiety, influenza, otitis media, and asthma are more common in children with constipation, which will further increase their medical expenses (7).

According to the recommendations of the North American Society for Pediatric Gastroenterology, Hepatology & Nutrition, therapies for constipation in children usually include family education, diet changes, potty training, use of laxatives and other drugs, and behavioral changes (8). Among the existing treatment options, drug therapy is still the first choice. The most commonly used laxatives for children with functional constipation are lubricants and penetrants (9). Osmotic laxatives are the most popular drugs, and polyethylene glycol (PEG) has become a successful choice for laxative treatment (10). Drugs for infant functional constipation have a certain effect on alleviating the symptoms of constipation, but they take a long time, usually 3–6 months; in addition, the overall curative effect is not satisfactory, with a high recurrence rate (11). It has been proven that only 60% of children have no symptoms 6–12 months after treatment (12). In longer follow-ups, one of four of children still have symptoms, and in some cases, the symptoms continue into adulthood (11). Therefore, both study and assessment are urgently required to identify more effective treatment regimens for infantile constipation.

Due to the limitations of current standard care, investigators are searching other methods from complementary and alternative medicine (CAM) therapies. About 24.1% of children with functional constipation received CAM therapies; 93% of parents believed that clinical studies were necessary for CAM, and only 51% agreed for their children to participate in such studies (13). Aside from parents' views, it is realistic, and even urgent, to evaluate the effectiveness and safety of CAM therapies in children. Massage therapy has a long history of use as a traditional diagnosis/treatment method within CAM therapy and is an important component of Traditional Chinese Medicine (TCM). Infantile massage is a subset of TCM massage and is the result of historic advances for patients in certain states of development; it emerged as a result of traditional practices. The first records of infantile massage can be found in "Folk Recipes for Infantile Disease and Proven Recipes for Infants in the Prescriptions for Fifty-Two Diseases" (a medical book copied on silk that was unearthed from the Mawangdui Tomb, dated to the Western Han Dynasty). TCM is based on the following concepts: by exerting a certain stimulation on the surface of an infant's body, the technique is used to dredge channels, collaterals, qi, and blood and thereby to prevent and treat diseases. Moreover, since the viscera of infants are traditionally viewed as "clear and bright" in terms of physiological characteristics and show a near-instantaneous response to pinching, a high efficacy can be achieved for infants *via* massage. Infantile massage is a common method of physical therapy, partly as it is highly environmentally friendly, free of toxic chemicals or side effects, and therefore likely to be accepted by the infants' parents or family (14).

In this systematic review and meta-analysis, TCM infant massage was selected as a representative CAM therapy to treat

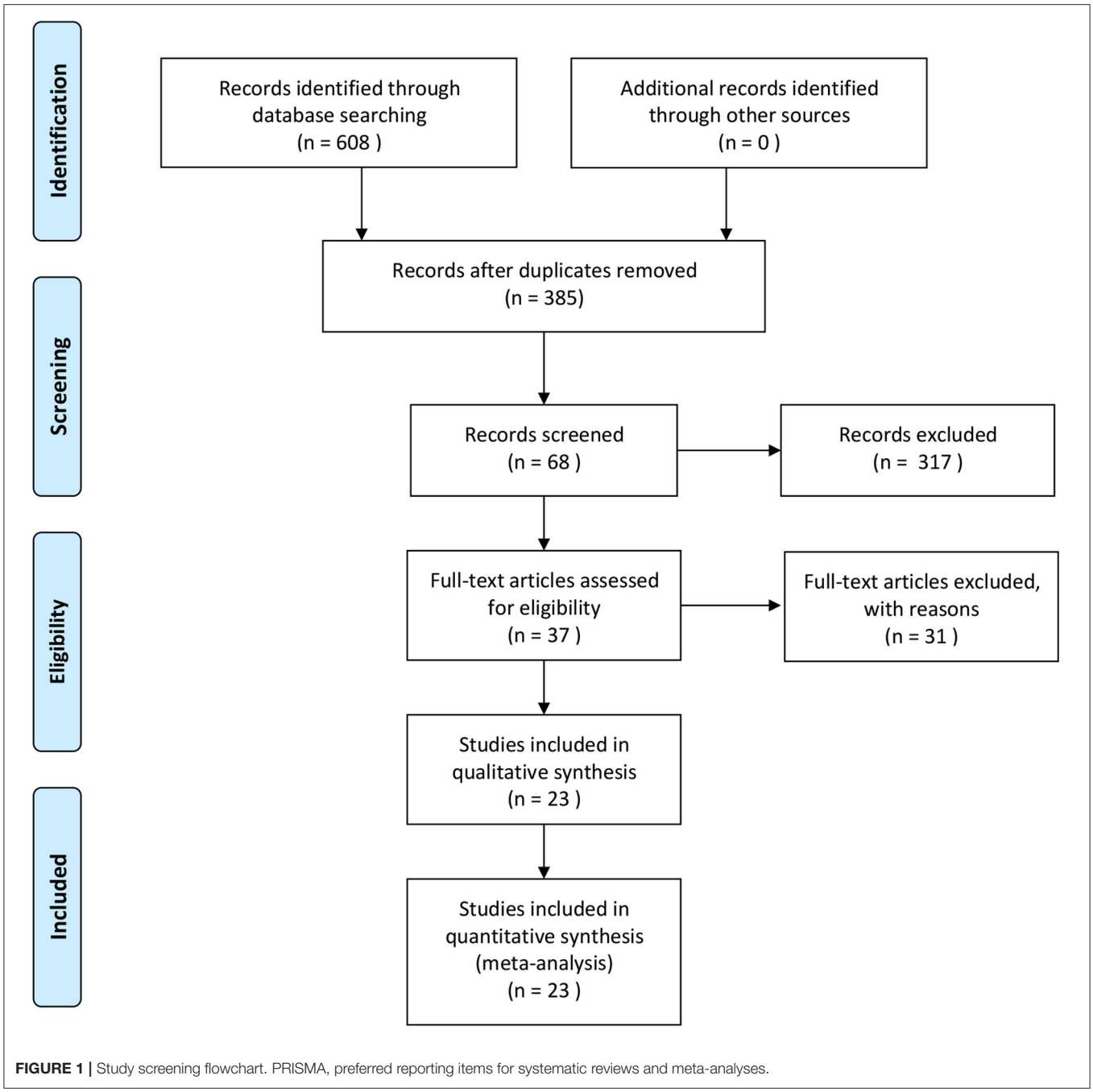


FIGURE 1 | Study screening flowchart. PRISMA, preferred reporting items for systematic reviews and meta-analyses.

infant functional constipation and evaluate its efficacy and safety in the treatment of constipation in children.

METHODS

Searches

Four mainstream medical databases were searched, including PubMed, China Network Knowledge Infrastructure (CNKI), WanFang, and China Science and Technology Journal Database (CSTJ). The time frame used for database queries was from the earliest indexed studies to March 19, 2020. Search words included "Tuina" (Chinese for "massage"), massage, manipulation, chiropractic, spinal manipulation, children, infantile, and child constipation. In order to ensure the completeness of the search, the language of the database was not restricted; a search was carried out through a combination of MeSH keyword and free words; the retrieval strategy could thus be finalized (the concrete retrieval formula of the database is shown in **Appendix**). Gray literature was manually retrieved for supplementation

at the library of the Tianjin University of Traditional Chinese Medicine; if the full texts were not available, a mail was sent to its author in an attempt to obtain the full document.

Inclusion Criteria

Type of Studies

Randomized controlled trials (RCTs), with no language restrictions.

Subjects

Children diagnosed with functional constipation according to the diagnostic criteria were not restricted in terms of gender, source of cases, and age. The diagnostic criteria for functional constipation included Rome III Criteria (15), Interim Standards for Diagnosis and Treatment of Constipation formulated by the editorial board of the Chinese Medical Journal (16), Pediatrics of Chinese Medicine (17), Diagnostic Efficacy Standard of TCM Diseases and Symptoms (18) and Guiding Principles for Clinical Research of New Chinese Medicines (19) formulated by the NATCM, and Constipation Symptoms and Efficacy Evaluation (20) formulated by the Anorectal Surgery Group of the Chinese Medical Association Surgery Branch.

Intervention Measures

In the treatment group, massage therapy combined with basic treatment, or combined with other therapies (without limitation on the techniques and positions of massage), was adopted; in the control group, basic treatment or other therapies were adopted, with no massage therapy (the basic treatment or other therapies were the same in the two groups).

Evaluation Indices

Evaluation indices included overall effective rate, stool form score, defecation difficulty score, defecation frequency, and constipation symptom score. Overall effective rate was evaluated based on the assessment criteria for efficacy of infant functional constipation in the following documents: Guideline for Clinical Trial on New Drugs of Chinese Medicines, Tentative Criteria for Diagnosis and Treatment of Constipation (Group of Anus & Intestine Surgery, Society of Surgery, Chinese Medical Association), or Assessment of Symptoms and Efficacy of Constipation (Group of Anus & Intestine Surgery, Society of Surgery, Chinese Medical Association), or Criteria for Diagnosis and Efficacy of Syndromes of Chinese Medicine. Stool form score was assessed through stool form assessment table (Bristol); defecation difficulty score was evaluated through constipation assessment scale (CAS); defecation frequency was assessed through complete spontaneous bowel movements (CSBMs); constipation symptom score was evaluated through patient assessment of their constipation symptoms (PAC-SYM).

Exclusion Criteria

(1) Studies without random grouping; (2) studies that provided incomplete information, no correct data could be obtained even after contacting the authors and through data calculations, etc.; (3) studies without control groups; (4) studies with obvious data errors; (5) duplicated studies; (6) papers of non-RCTs, such as review, clinical experience introduction, summary analysis, clinical case reports, literature involving massage genre, animal experiments; (7) studies with control group treatment of infant massage; (8) studies that did not use constipation as a research object; (9) literature on nursing.

Data Selection and Data Extraction

First, all literature was screened using End-Note 9.0 software according to the preset inclusion/exclusion criteria, and any duplicated literature from different databases was removed. Then, any obviously irrelevant literature was excluded based on the title and abstract. Finally, the full text of all remaining literature was read intensively, and those papers conforming to the requirements were included (see **Figure 1**: Study flowchart). The data were extracted independently by two investigators; a cross-check was made. Any disagreement was settled through discussion or the arbitration of a third investigator. The extracted data included the name of the first author, year of publication, sample size, average age and gender of participants, interventions of treatment group and control group, duration of treatment, prognostic indicators, and a literature quality evaluation. Adverse events were tabulated to record the occurrence in the test group and control group. Adverse events included intestinal reactions, allergic reactions, mental fatigue, and poor sleep.

Quality Evaluation

The quality of studies included was evaluated with reference to the quality evaluation criteria recommended by the Cochrane System Evaluator Manual Version 4.2.2. The contents of this evaluation included generation of random sequence allocation concealment, investigator/subject blinding, blind-method evaluation of study outcome, integrity of outcome data, selective reporting of study results, and source of other biases. Two evaluators would conduct independent evaluations based on uniform quality standards, and if they found any discrepancy, they would resolve them through discussion; if it still could not be solved, a third investigator would be asked to reach a consensus. Using the RevMan software, the bias risk assessment chart and bias risk assessment table were exported to show evaluation results for all included literature.

Statistical Analysis

Excel tables were made for the data extraction. The differences in outcome measures before and after treatment in the treatment group and the control group were calculated, and two evaluators would input the data for the differences between the treatment group and the control group, and their standard deviations into RevMan5.3 software independently, to perform the meta-analysis. The count data were expressed as a relative risk (RR), measurement data were expressed as a mean difference (MD), and the interval estimation used a 95% confidence interval (95% CI). $p < 0.05$ indicates that the difference was statistically significant. Q test and I^2 value were used to analyze the heterogeneity among the included studies. $p > 0.1$ and $I^2 < 50\%$ indicated a good consistency or lower heterogeneity among included studies, and a fixed-effects model was adopted; otherwise, a random-effects model was used. $I^2 \leq 25\%$ indicated a smaller heterogeneity; $25\% < I^2 \leq 50\%$ indicated a moderate

TABLE 1 | Basic characteristics of the included literature.

References	Sample size	Number of cases (M/F)		Age (years)		Interventions		Course of treatment (days)	Evaluation indexes
		T	C	T	C	T	C		
Sun (21)	64	16/16	14/18	2.68 ± 1.90	2.64 ± 1.83	Infant massage	Wangshi Baochi Pills, Oral	12	①
Li (22)	76	12/26	16/22	2.10 ± 1.21	1.95 ± 1.14	Infant massage	Live Combined *Bifidobacterium*, *Lactobacillus*, and *Enterococcus* Capsules, Oral	14	①②④⑤
Chen and Wang (23)	60	14/16	12/18	2.27 ± 1.48	2.10 ± 1.44	Infant massage	Medilac-Vita, Oral	14	① ②③④
Huang (24)	80	22/18	21/19	1.80 ± 0.24	1.98 ± 1.17	Infant massage	Conventional medication	60	①
Chen et al. (25)	120	33/27	35/25	2.8 ± 1.2	2.9 ± 1.5	Infant massage	Medilac-Vita, Oral	14	①②④
Jia (26)	72	19/17	20/16	5.88 ± 1.62	5.91 ± 1.59	Infant massage + Simotang oral liquid and Medilac-Vita	Simotang oral liquid and oral Medilac-Vita	14	①
Hao et al. (27)	72	19/17	20/16			Infant massage	Medilac-Vita, Oral	10∼20	①
Xu (28)	122	30/31	32/29	7.24 ± 2.51	7.41 ± 2.46	infant massage+ oral Chinese medicines	Oral Chinese medicines alone	14	①
Xu (29)	40	10/10	9/11	5.35 ± 4.17	5.58 ± 4.39	Infant massage	Chinese medicine prescription	5∼10	①
Shen et al. (30)	106	32/21	28/25			Infant massage + Oral Zengye Decoction	TCM Decoction-Oral Zengye Decoction	20	①
Wang (31)	90	21/24	23/22	3.3 ± 0.8	3.1 ± 0.6	Infant massage	Medilac-Vita, oral	10	①
Wang et al. (32)	105					Infant massage + Probiotic treatment	Live Combined *Bifidobacterium*, *Lactobacillus*, and *Enterococcus* Capsules, oral	未提及	②
Wang (33)	120	25/35	22/38	5.53 ± 0.78	5.84 ± 0.62	Infant massage + Baohe Pills	Baohe Pills, Oral	7	①
Mao (34)	94	25/22	24/23	7.51 ± 3.16	7.43 ± 3.08	Infant massage + standard care	Qidaozhi Tongfu Recipe+standard care	14	②
Kang (35)	78	21/18	16/23	1.18 ± 1.15	1.37 ± 1.62	Infant massage + standard care	Live Combined *Bifidobacterium*, *Lactobacillus*, and *Enterococcus* Capsules +standard care	7∼35	③
Zhang (36)	84	23/19	25/17	1.54 ± 0.39	1.48 ± 0.37	Infant massage + Medilac-Vita	Medilac-Vita	14	①
Cao (37)	70	16/19	18/17	1.40 ± 0.13	1.43 ± 0.10	Infant massage	Siliankang	14	①
Zhu and Huang (38)	116	32/28	30/26			Infant massage + Siliankang and standard care	Siliankang and standard care	30	①
Li and Lin (39)	80	23/17	22/18	6.69 ± 3.74	6.58 ± 3.88	Infant massage + Medilac-Vita and routine care	Medilac-Vita and routine care	5	①
Li et al. (40)	90	22/23	23/22	3.6 ± 0.5	3.5 ± 0.7	Infant massage	Xiaoer Kaiwei Zengshi Mixture, Oral	21	①
Li et al. (41)	86	24/22	22/18			Infant massage	Medilac-Vita, Oral	5∼10	①
Yu et al. (42)	80	21/19	18/22			Infant massage	Retention enema with kaiselu	3∼6	①
Liu and Yang (43)	100	31/19	29/21	3.02 ± 0.82	2.92 ± 0.85	Infant massage	Medilac-Vita, Oral	10	①

Evaluation indicators: ① Efficacy; ② Stool form; ③ Defecation frequency; ④ Defecation difficulty; ⑤ Score of constipation symptoms.

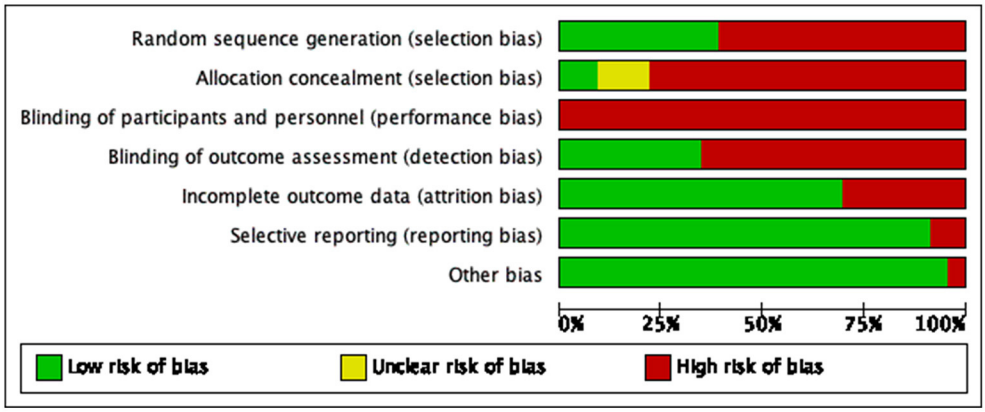


FIGURE 2 | Bias risk diagram: judgment of risk of bias expressed as a percentage of all included studies.

heterogeneity, both of which could be acceptable. $I^2 > 50\%$ indicated high heterogeneity between the results of the study. For higher heterogeneity, a subgroup analysis was made to explore the source of this heterogeneity; when necessary, a sensitivity analysis was made to assess the stability of the study. Through the Egger's test and the Begg's test carried out in the Stata software and the funnel chart, publication bias was tested. As required by the index, more than 10 pieces of literature should be included, since it would be difficult to find the reason for asymmetry if there were too few studies.

RESULTS

Results of Literature Retrieval

A total of 608 pieces of literature were obtained through database retrieval, though no other routes, such as manual retrieval, were taken. There were 480 Chinese papers and 128 English papers. After the elimination of duplicate literature, 385 papers were obtained. After the reading of title and abstract, 317 pieces of literature not conforming to the requirement were removed; the remaining 37 papers entered the stage of full-text reading. Finally, a total of 23 articles on RCTs were included in our study (21–43).

Basic Characteristics of the Studies Included

As shown in **Table 1**, 23 studies involving 2,005 patients (including 1,006 subjects in the test group and 999 subjects in the control group) were analyzed. In our study, the sample size ranged from 40 to 122. The time span for literature publication was from 2010 to 2020. All studies were carried out in China. Only five studies (22, 24, 35, 36, 38) reported adverse events, and no subsequent studies were mentioned. General information on the subjects was lacking in six articles (26, 29, 31, 37, 39, 40), and there was no statistically significant difference in baseline in 21 articles (20–30, 32–40, 42). The basic characteristics of these articles are shown in **Table 1**.

Quality Evaluation of Included Studies

Generation of random sequences: Random number tables were used for random grouping in eight studies (20–22, 24, 29, 32, 34, 35), random envelopes were used for random allocation in one study (28); visiting time was used for randomization in one study (27), visiting sequence was used for random allocation in one study (31), and other studies only mentioned the word "randomization." Allocation concealment: A total of two studies (21, 28) used allocation concealment. Investigator/subject blinding: None of the studies used the blinding method. Selective reporting of study results: Follow-up was reported in three studies (21, 23, 38). Integrity of outcome data: No criteria for termination, rejection, or withdrawal were established in any of the included studies, and no dropouts were reported. Detailed results of bias risk assessment are summarized in **Figures 2**, **3**.

Results of Meta-Analysis

Analysis of Effective Rate

A total of 21 papers covering 1,822 patients were included. Analytical results are shown in **Figure 4**; the included studies were of significant heterogeneity ($p < 0.05$, $I^2 = 59\%$); using the random-effects model, where statistics were combined. As compared with traditional drug therapy alone, the combination with infantile massage had a higher effective rate for infant functional constipation (RR = 1.25; 95% CI = 1.17, 1.33), where the difference was statistically significant ($p < 0.05$). Since heterogeneity was higher, which might be related to the type of drug used in the control group, a subgroup analysis was carried out based on classification into Chinese medicine and western medicine. In the control group, the degree of heterogeneity was still higher for Chinese medicine ($p < 0.05$, $I^2 = 56\%$) and western medicine ($p < 0.05$, $I^2 = 68\%$), which did not change significantly; therefore, different types of drug in the control group was not the source of heterogeneity. In our view, higher heterogeneity might be related to multiple factors, such as different illnesses of subjects included in each study, different manipulation of massage in the treatment group, and different judgment criteria for efficacy.

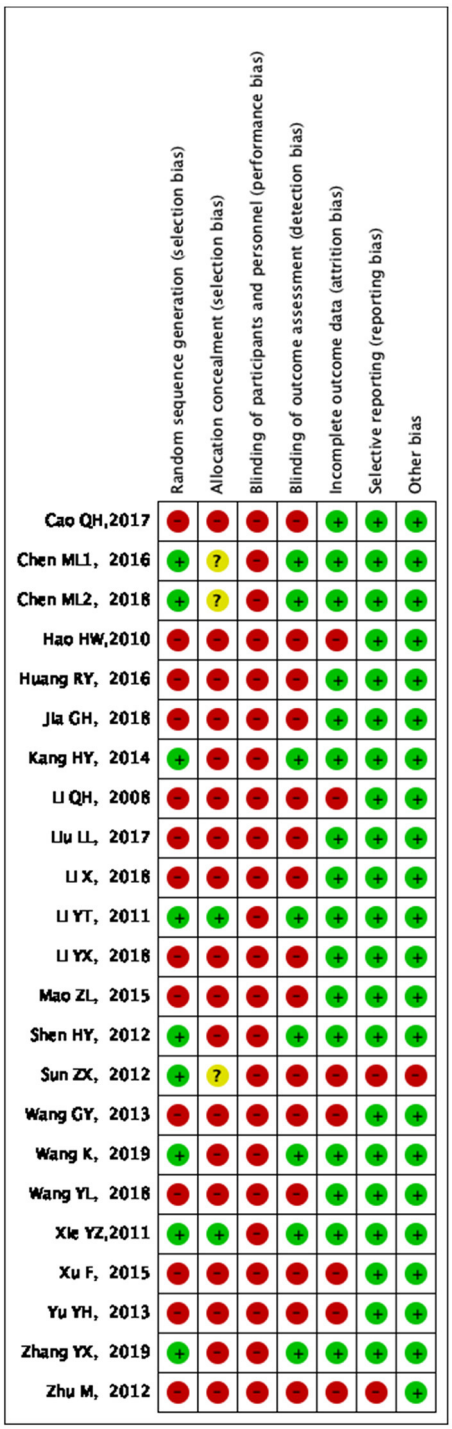


FIGURE 3 | Bias risk summary: judgment of risk of bias and items with bias included in the studies; "+" = low risk, "−" = high risk, "?" = unclear.

Scoring of Stool Form

A total of four papers (21, 22, 24, 31) covering 361 patients were included. Results are shown in **Figure 5**. The included studies were of significant heterogeneity ($p < 0.05$, $I^2 = 95\%$); through the random-effects model, the statistics were combined. As compared with traditional drug therapy alone, the combination with infantile massage had an equivalent efficacy in stool form score (MD = −0.26; 95% CI = −0.72, 0.20), where the difference was not statistically significant ($p > 0.05$). Since the heterogeneity was higher, the results of the sensitivity analysis showed that the outcome of the disease was influenced by intervention measures, which were not consistent with overall results (see the **Appendix**). Therefore, the included studies were of larger overall influence and displayed unstable results.

Defecation Frequency

A total of four papers (22, 31, 34, 36) covering 313 patients were included. Results are shown in **Figure 6**. The included studies were of significant heterogeneity ($p < 0.05$, $I^2 = 97\%$); through the random-effects model, statistics were combined. Compared with traditional drug therapy alone, the combination with infantile massage showed an equivalent efficacy in the increase of defecation frequency (MD = −0.74; 95% CI = −0.35, 1.83), where the difference was not statistically significant ($p > 0.05$). Since the heterogeneity was higher, the results of the sensitivity analysis showed that the outcome of the disease was not influenced by intervention measures, which was not consistent with overall results. The reason for heterogeneity increase could not be screened out. In our view, the higher heterogeneity might be related to multiple factors, such as sample size, different illnesses of subjects included in each study, different manipulation methods for massage in the treatment group, and different judgment criteria for efficacy.

Defecation Difficulty Score

A total of four papers (20–22, 24) covering 320 patients were included. Results are shown in **Figure 7**. The included studies were not of significant heterogeneity ($p > 0.05$, $I^2 = 17\%$); using the fixed-effects model, the statistics were combined. As compared with traditional drug therapy alone, the combination with infantile massage had a higher score for improving defecation difficulty (MD = −0.72; 95% CI = −0.80, −0.65), where the difference was statistically significant ($p < 0.05$). Since the heterogeneity of the included studies was better, a subgroup analysis was not required to explore the source of this heterogeneity.

Constipation Symptom Score

A total of four papers (21, 30, 38, 39) covering 336 patients were included. Results are shown in **Figure 8**. The included studies showed significant heterogeneity ($p < 0.05$, $I^2 = 98\%$); through the random-effects model, the statistics were combined. Compared with traditional drug therapy alone, the combination with infantile massage was more superior in reducing constipation symptom scores (MD = −0.81; 95% CI = −1.20, −0.43), where the difference was statistically significant ($p < 0.05$). Since the heterogeneity was higher, the results of the sensitivity analysis showed that the outcome of the disease was influenced by intervention measures, which was consistent with overall results (see the **Appendix**). The reason for heterogeneity increase could not be screened out.

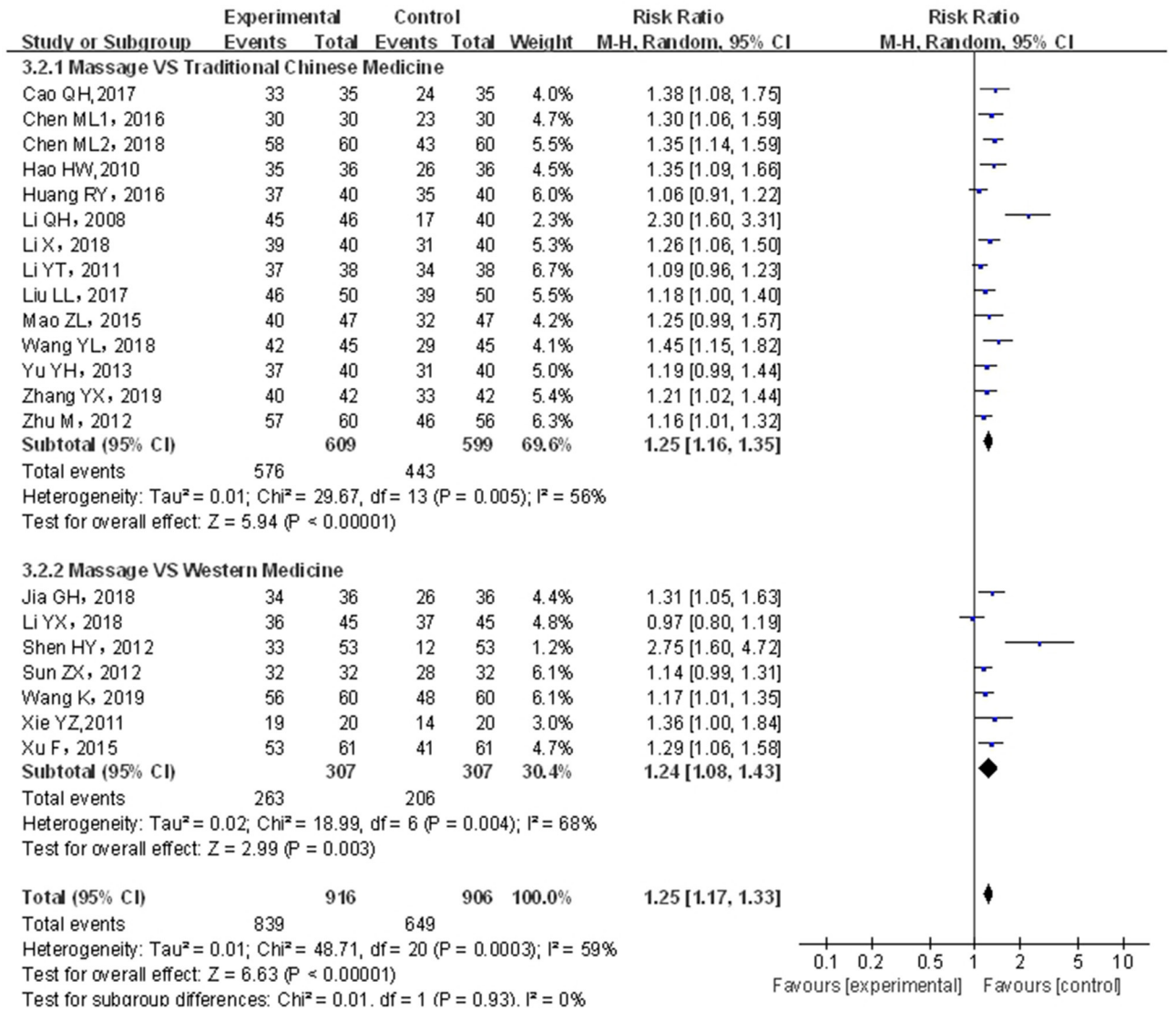


FIGURE 4 | Meta-analysis of infant massage and drug therapy in the treatment of children with functional constipation.

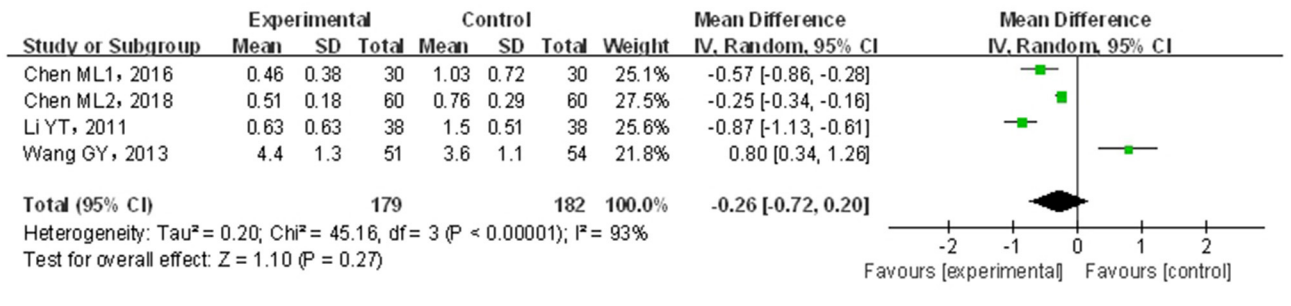


FIGURE 5 | Meta-analysis of infant massage and drug therapy in the treatment of children with functional constipation to reduce stool form scores.

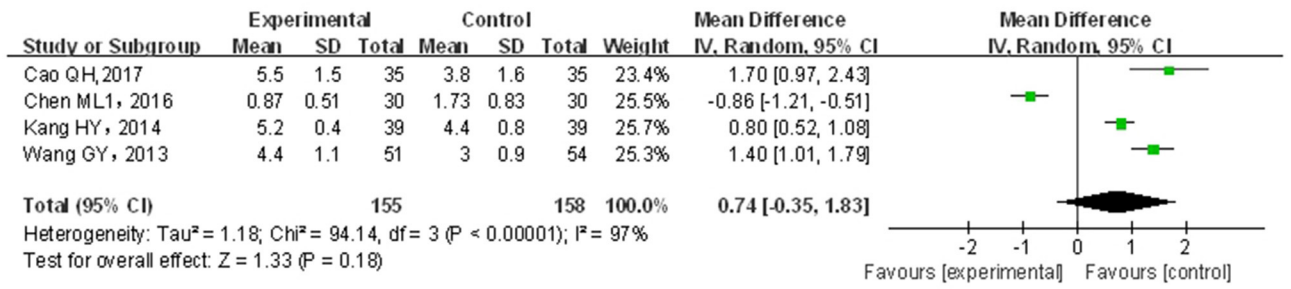


FIGURE 6 | Meta-analysis of infant massage and drug therapy in the treatment of children with functional constipation on change in defecation frequency.

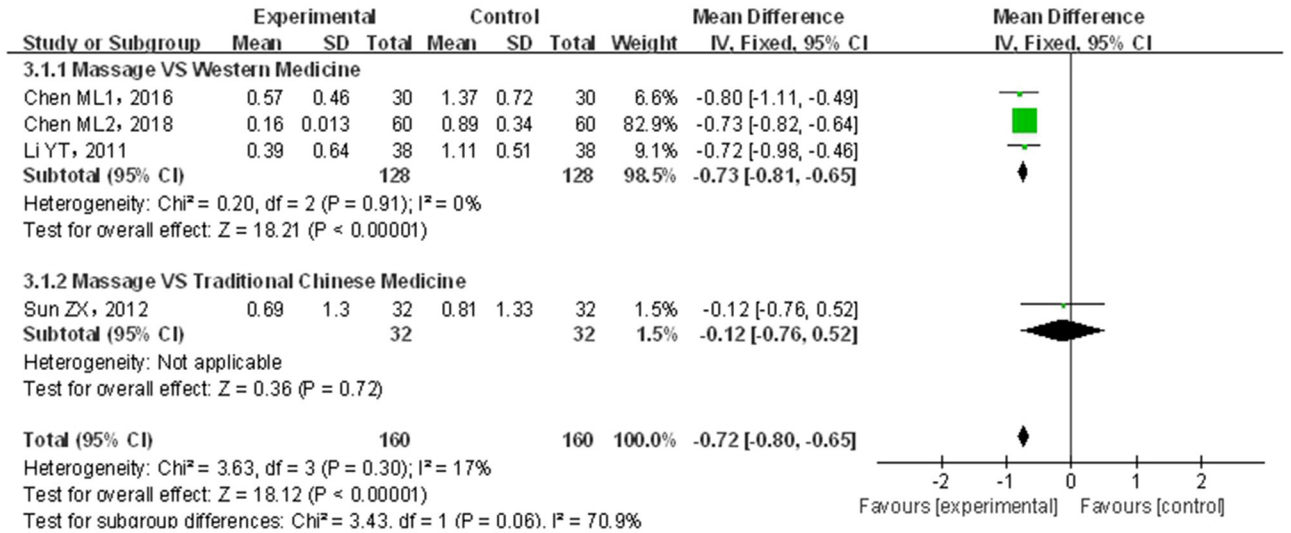


FIGURE 7 | Meta-analysis of infant massage and drug therapy in the treatment of children with functional constipation to reduce defecation difficulty score.

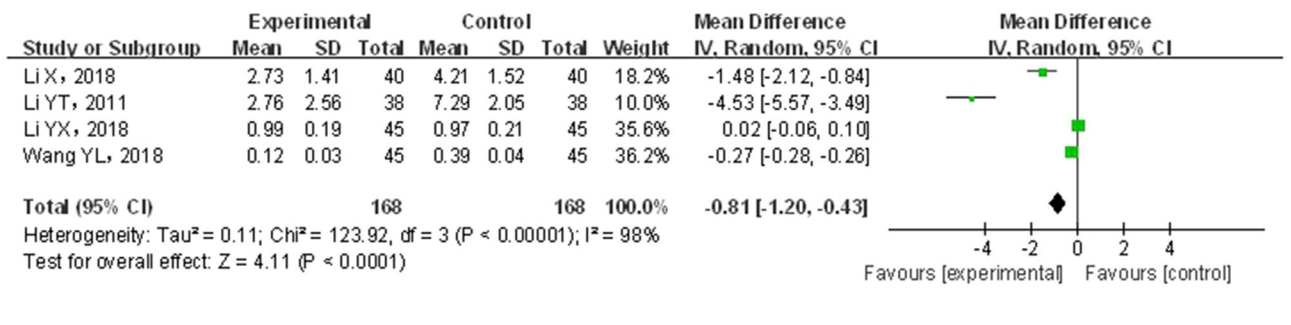


FIGURE 8 | Meta-analysis of infant massage and drug therapy in the treatment of children with functional constipation to reduce constipation symptom score.

In our view, higher heterogeneity might be related to multiple factors, such as sample size, different illnesses of subjects included in each study, different manipulation techniques in the massage treatment group, and different judgment criteria for efficacy.

Adverse Events

Among the included literatures, five papers (22, 24, 35, 36, 38) mentioned adverse events. Four of these five saw no adverse event reported in either of their research groups, while in the remaining article (38), 22 cases of adverse events were reported, including

three cases in the test group and 19 cases in the control group. The number of cases with adverse events in the test group was less than that in the control group.

Analysis of Publication Bias

Publication bias was analyzed by means of a funnel chart. After combination with infantile massage, the included studies showed no symmetric distribution in terms of overall effective rate, indicating that there was a publication bias. As shown by the results of the statistical analysis, $Pr>|z|$ index was 0.401 in the Egger's test and $p > t$ index was 0.420 in the Begg's test, indicating that there was no publication bias based on the statistical tests.

DISCUSSION

As found by clinical trials on infant constipation, infantile functional constipation refers to constipation that is not caused by organic factors. Defecation frequency in healthy babies and children decreases with age. Breastfeeding children may defecate as much as 12 times a day, or in very rare cases, only once every 3–4 weeks. After infants are fed with milk powder, their stools are generally formed at Week 1. Infants can frequently experience pain during defecation and develop functional constipation. As an *in vitro* method of physical diagnosis/treatment, massage is not only effective but also more able to ensure the safety of children with functional constipation; it alleviates or eliminates the dependence of such children on drug therapy alone and eliminates the risk of side effects from drugs. It thus better promotes their growth and should be strongly recommended in future guidelines for clinical practical methods.

At present, clinical trial methods for various massages (including TCM infantile spinal pinching) are not of high quality, and clinical evidence is weak. On this basis, a meta-analysis was carried out in our study. Compared with conventional drug therapy, a combination with infantile massage was definitely superior for the treatment of children with functional constipation in terms of effective rate, defecation difficulty score, and constipation symptom score, where the difference was statistically significant. However, since the included studies were of lower quality and higher heterogeneity, these results should be treated with a certain amount of caution. In recent years, numerous studies on CAM therapy for infantile constipation have been published. For example, in a study of meta-analysis of acupuncture combined with Chinese medicine for functional constipation (44), this combined therapy was effective and safe for functional constipation and could improve the constipation symptom score. Compared with this study, our study possessed two features. (1) Since the age of the children studied was younger, massage combined with drug therapy was of higher clinical safety and more suitable for clinical popularization than acupuncture combined with drug therapy. (2) Our study involved more literature review (203 vs. 608). However, publication bias was the main reason for influencing the validity of results of the meta-analysis because it was the main basis for making a conclusion to obtain the published studies. Moreover, positive results were overemphasized by some editors or in some magazines, so that some negative results were concealed. Meanwhile, a loss of literature could be caused by an insufficient retrieval method and various other reasons. In our study, the analysis of the effective rate showed no publication bias; however, since four other indices were limited by too small a sample size, the corresponding analysis was not made.

This systematic evaluation and meta-analysis were performed strictly according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Statement: it first evaluated the clinical efficacy and safety of infantile massage for infant functional constipation; it evaluated how standard the clinical trial was from a methodological point of view and also offered a direction for further study. However, it is important to note that our study still had certain limitations. (1) The included literature was of low quality; the generation of random allocation sequences and the concealment of randomization protocols were not reported in some studies; the conditions of dropout and withdrawal from the study were not described in detail; certain problems occurred (such as missing study data), which influenced the evidence level and popularization degree. (2) Cases were not fully included according to generally recognized international diagnostic criteria; standard uniform outcome measurement indices were not observed; a subjective composite outcome scoring index was adopted, and the evaluation criteria for efficacy were formulated by ourselves. (3) Treatment courses were shorter; there were no important clinical indices for long-time observation, and the superiority of infantile massage in terms of overall efficacy could not be fully displayed.

CONCLUSION

At present, infantile massage is a safer, more effective method of CAM therapy for infant functional constipation. It has various advantages, such as high clinical effectiveness, improvement of constipation symptoms, and alleviation of defecation difficulty. It is worthy of clinical popularization and application. Since the original studies were of too low quality, a strict standard clinical trial should be made for verification in the future under the premise that the TCM characteristics of infantile massage are ensured.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/**Supplementary Material**.

AUTHOR CONTRIBUTIONS

ZL and LG took part in the design of the study, performed the literature survey, and drafted the manuscript. MY took part in data management implementation of the study. ZL was responsible for the statistical analysis and methodological

design of the study. All the authors read and approved the final manuscript and have made substantive contributions to this study in regard to design and implementation.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.663581/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Effect of Cost-Related Medication Non-adherence Among Older Adults With Medication Therapy Management

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Background: Medication therapy management (MTM) was established by the Center for Medicare and Medicaid Services (CMS) with the aim to improve medication adherence. However, the national prevalence of cost-related medication non-adherence (CRN) is still unknown and there is a literature gap in the association between MTM services and CRN.

Methods: A cross-sectional study was conducted. A nationally representative study sample from Medicare Current Beneficiary Surveys (MCBS) was used. Survey sampling weights were applied for national estimates of CRN. Weighted multivariable logistic regressions controlling for covariates were conducted to investigate the effect of the MTM on the CRN.

Results: The study identified 1,549 MTM-eligible beneficiaries. The prevalence of CRN was higher in MTM-eligible individuals than in non-MTM eligible individuals (24.14 vs. 13.44%; $P < 0.001$). According to the results of multivariable logistic regressions, we found that MTM eligibility was significantly associated with a higher prevalence of CRN (OR: 1.59; 95% CI: 1.28–1.96). Additionally, some other variables such as health status, with or without low-income subsidy are also associated with CRN.

Conclusions: Our findings suggest that the prevalence of CRN in MTM-eligible beneficiaries was higher than in non-MTM eligible beneficiaries. Further studies with the longitudinal design are warranted to clarify the relationship between MTM and CRN. Alternative strategies to improve CRN should be considered in future Medicare Part D Enhanced MTM Models.

Keywords: medication therapy management, pharmacist, cost-related medication non-adherence, Medicare beneficiaries, Medicare part D

INTRODUCTION

Since 2006, the Centers for Medicare and Medicaid Services (CMS) in the U.S. have required health plans for Medicare prescription drug benefit (Part D) to provide medication therapy management (MTM) service for Medicare eligible beneficiaries under the Medicare Modernization Act of 2003 (1). MTM services include providing education, improving adherence, and detecting adverse drug events and medication misuse (2). By providing these services, pharmacists can help eligible enrollees avoid drug-related problems and achieve desired clinical benefits of medications (3). There are five core elements in the MTM service module, including medication therapy review (MTR), personal medication record (PMR), medication-related action plan (MAP), intervention and/or referral, and documentation and follow-up (4, 5). Several studies have demonstrated that pharmacist-provided MTM services improve health outcomes and medication adherence (6–8). A recent systematic review reported that MTM programs might be able to reduce medication non-adherence and lower health care costs, but the evidence was insufficient due to inconsistency and imprecision that stem in part from underlying heterogeneity in populations and interventions (9). In addition, several studies have shown that some MTM programs were not able to improve medication non-adherence (10, 11). The association between MTM and medication non-adherence has not been fully confirmed.

An important type of medication non-adherence is cost-related medication non-adherence (CRN), which is specifically defined as behavior when patients take medication less than as prescribed due to costs (12). CRN is associated with serious health consequences, including decrements in self-reported health status, increased hospital admissions and death (13, 14). It has become a focus on policy research in understanding if an increase in insurance coverage through health policy can lead to the reduction of access barriers (15, 16). Early evaluations of Part D indicated modest nationwide reduction in CRN in 2006 and 2007 (15, 17). As an essential strategy to optimize medication use for Medicare Part D beneficiaries, MTM was assumed to reduce CRN among these beneficiaries. However, little is known about the prevalence of CRN among Medicare beneficiaries of the U.S. In addition, there is a literature gap in the association between MTM services and CRN among Medicare beneficiaries. We, therefore, conduct a study to provide national estimates of the prevalence of CRN among Medicare beneficiaries and identify the association between MTM services and CRN. We hypothesized that MTM-eligible beneficiaries will show lower CRN compared with non MTM-eligible beneficiaries.

MATERIALS AND METHODS

Data and Study Design

This research was a cross-sectional study. Data from Medicare Current Beneficiary Surveys (MCBS) 2012 was used for this study. MCBS is a nationally representative sample of the Medicare population administrated by the Centers for Medicare and Medicaid Services (CMS). MCBS aim to determine spending and source of payment for services used by Medicare beneficiaries, relate coverage to sources of payment, and trace outcomes related to eligibility and impacts of the Medicare program. The MCBS sample is selected from Medicare Administrative Registration (MAE) data. A panel design is used for selection and each beneficiary selected is interviewed 12 times up to 4 years. The survey of the MCBS collects information on beneficiaries' demographic characteristics, insurance, health status, and the healthcare utilization and costs, and the information is merged with Medicare claims. The data in the MCBS are cleaned and structured. For participants who are not able to conduct in-person interviews because of unconsciousness, respondents can answer the survey questions on their behalf.

Measurement

Medicare beneficiaries eligible for MTM in this study are Part D enrollees with at least two chronic diseases, taking at least three Part D drugs, and those who are likely to exceed a predetermined cost threshold of $3,100 according the MTM eligibility criteria (18, 19).

The outcome for this study was the CRN. Because there is no survey question specific to the CRN in the MCBS, we constructed a summary indicator of CRN for analysis based on references (15, 17, 20). Specifically, participants were identified as having the CRN if they answered "yes" to any of the following MCBS prompts: "decide not to fill or refill a prescription because it was too expensive," "skipped doses to make the medicine last longer," "taken smaller doses of a medicine to make the medicine last longer" and "spent less money on food, heat or other basic needs so that you would have money for medicine." These questions were not specific to a particular class of medications.

To investigate the independent effect of MTM eligibility on CRN in the multivariate logistic regression models, we summarized potential confounders based on the literature (21–24). Potential confounders included demographic characteristics: age (18–64, 65–74, 75–84, 85+), gender (male, female), race (non-Hispanic white, non-Hispanic black, Hispanic, other), education (less than high school, high school graduate, some college, college graduate), marital status (married, widowed, single), residence (non-metropolitan, metropolitan), census region (Northeast, Midwest, South West); socio-economic factors: annual income (<$10,000, $10,001–20,000, $20,001–40,000, $\geq$ $40,000), low-income subsidy (LIS) (yes, no); and health behavior and physical health factors: smoking (no, former, current), health status (excellent, very good or good, fair or poor), body mass index (BMI) (underweight, normal, overweight, obese), and activities of daily living (ADL) (0, 1–2, 3+). They can be measured in the MCBS.

Analysis

Survey sampling weights were applied to obtain national estimates of CRN. The analyses correct variance estimates for the complex survey design of the MCBS. Descriptive statistics were used to characterize the overall sample subjects. Chi-square or Fisher's exact test, whenever appropriate, was used in the study for categorical variables. Initial analyses focused on differences between the MTM-eligible beneficiaries and the non-MTM-eligible beneficiaries in responders' demographic characteristics

TABLE 1 | Respondent characteristics of the study population.

Characteristics	MTM-eligible Weighted (%)	Non-MTM-eligible Weighted (%)	*P*-value
CRN			<0.001
Yes	24.14	13.44	
No	75.86	86.56	
Age			<0.001
18–64	26.44	15.18	
65–74	34.50	43.46	
75–84	28.62	29.48	
85+	10.44	11.88	
Gender			0.015
Male	38.46	42.71	
Female	61.54	57.29	
Race			0.383
Non-hispanic white	70.99	73.34	
Non-hispanic black	10.27	10.24	
Hispanic	12.56	11.40	
Other	6.19	5.02	
Education			0.044
Less than high school	28.08	24.55	
High school graduate	26.85	28.23	
Some college	24.26	23.19	
College graduate	20.82	24.04	
Marital status			<0.001
Married	39.00	48.64	
Widowed	27.61	25.41	
Single	33.39	25.95	
Annual income			<0.001
<$10,000	20.33	12.66	
$10,001–20,000	33.93	28.42	
$20,001–40,000	25.76	31.74	
≥ $40,000	19.98	27.17	
Residence			0.241
Non-metropolitan	24.85	22.74	
Metropolitan	75.15	77.26	
Census region			0.028
Northeast	20.00	18.79	
Midwest	21.24	22.92	
South	39.66	35.48	
West	19.10	22.81	
Health status			<0.001
Excellent, very good, or good	57.92	78.59	
Fair or poor	42.08	21.41	
BMI			<0.001
Underweight	1.77	2.51	
Normal	25.46	33.38	
Overweight	33.16	36.68	
Obese	39.61	27.43	
Smoking			<0.001
No	36.65	42.56	
Former	45.76	43.38	
Current	17.58	14.06	
ADL			<0.001
0	47.57	66.65	
1–2	32.12	22.52	
3+	20.31	10.82	
LIS			<0.001
Yes	47.87	25.94	
No	52.13	74.06	

MTM, medication therapy management; CRN, cost-related non-adherence; BMI, body mass index; ADL, activities of daily living; LIS, low-income subsidy.

and CRN behaviors. Multivariate logistic regression models were fit within each group to determine the independent effect of MTM eligibility on CRN, controlling for participants' age, gender, race, income, education, comorbidities, health status, low-income subsidy, and insurance coverage. In the logistic regression, when defining a reference group, we sorted the variables from lowest to highest of the original data and defined the lowest group as the reference group. However, we used the age group "65–74" as the reference group because Medicare beneficiaries mainly consist of older adults aged 65 years or older. We used normal as the reference group other than underweight for BMI. Institutional Review Board approval was obtained for this study. all the statistical analyses were performed using SAS (version 9.4; SAS Institute, Inc., Cary, NC).

RESULTS

This study identified 1,549 MTM-eligible beneficiaries in the MCBS. **Table 1** shows weighted percentages of respondents with CRN by individual characteristics. Overall, the prevalence of CRN among MTM-eligible beneficiaries was 24.14%, with the following predominant characteristics: female (61.54%), non-Hispanic whites (70.99%), metropolitan (75.15%), excellent, very good, or good health status (57.92%), and without LIS (52.13%). The prevalence of CRN was much lower among respondents of non-MTM-eligible beneficiaries than those MTM-eligible beneficiaries (13.44%), with the following predominant characteristics: non-Hispanic white (73.34%), metropolitan (77.26%), excellent, very good, or good health status (78.59%), low ADL score (66.65%) and without LIS (74.06%).

Figure 1 shows that MTM eligibility was significantly associated with a higher prevalence of CRN [odds ratio (OR): 1.59; 95% confidence interval (CI): 1.28–1.96]. In addition to the MTM, we also found that the CRN was significantly associated with some demographic, socio-economic, health behavior, and physical health factors. Specifically, compared to Medicare beneficiaries aged between 65 and 74 years, those aged between 75 and 84 years (OR: 0.54; 95% CI: 0.44–0.68) and aged 85 years or older (OR: 0.29; 95% CI: 0.21–0.42) had a lower prevalence of the CRN. Females had a higher CRN prevalence than males (OR:

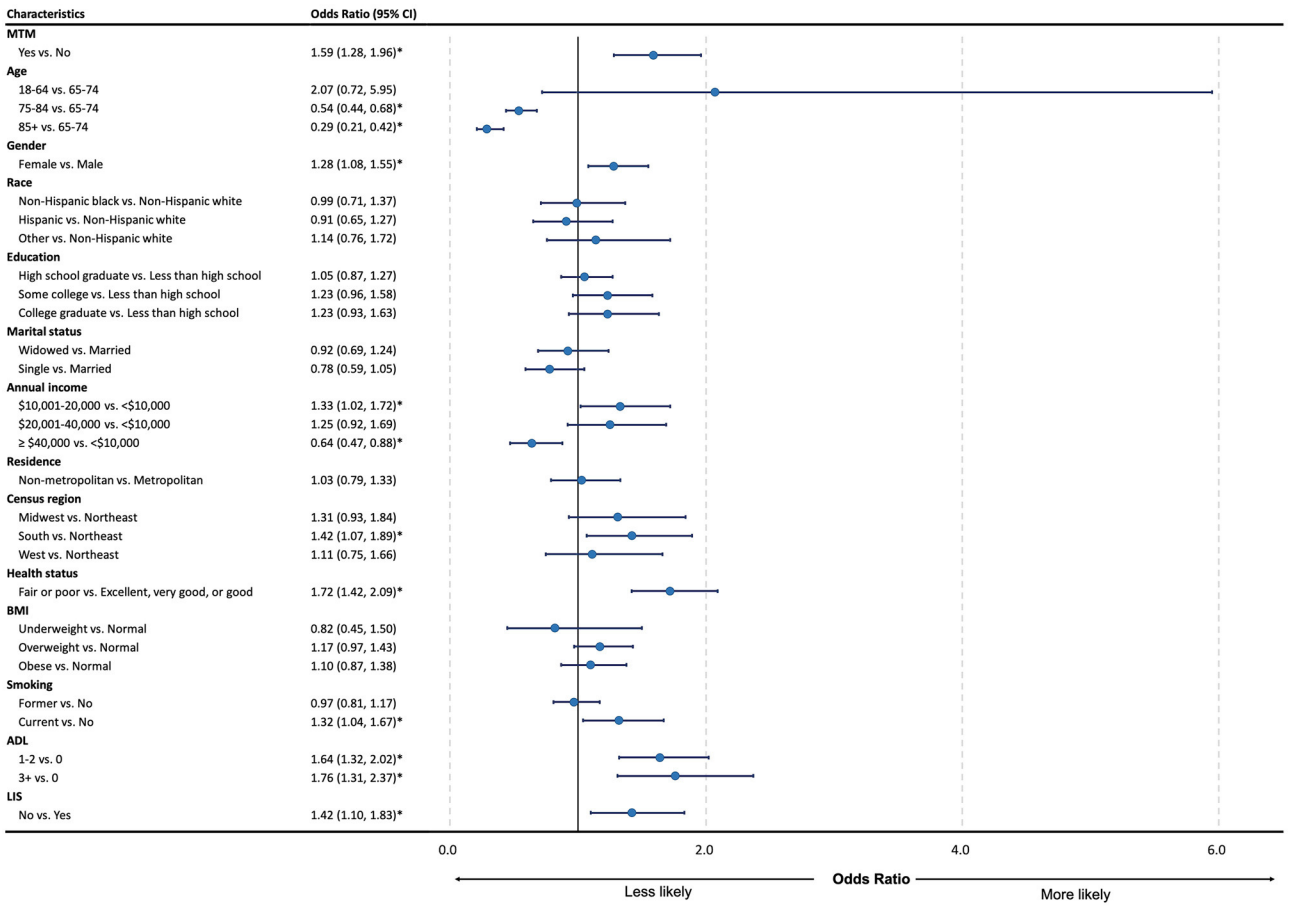


FIGURE 1 | Forest plot for odds ratio and 95% CI of regression for cost-related medication non-adherence among the study group. MTM, medication therapy management; CRN, cost-related non-adherence; BMI, body mass index; ADL, activities of daily living; LIS, low-income subsidy; CI, confidence interval; LL, lower limit; UL, upper limit. $^{*}P < 0.05$.

1.28; 95% CI: 1.08–0.55). Also, Medicare beneficiaries living in the South had a higher CRN prevalence compared to those living in the Northeast (OR: 1.42; 95% CI: 1.07–1.89). Compared with Medicare beneficiaries with an annual income of <10,000 those with an annual income between 10,001 and 20,000 had a higher CRN (OR: 1.33; 95% CI: 1.02–1.72), while those with an annual income of more than 40,000 had a lower CRN (OR: 0.64; 95% CI: 0.47–0.88). Meanwhile, people without the LIS had a higher prevalence of the CRN than those with (OR: 1.42; 95% CI:1.10–1.83). In terms of health behaviors, current smokers had a higher prevalence of the CRN compared to non-smoker (OR: 1.32; 95% CI:1.04–1.67). Medicare beneficiaries with excellent, very good, or good status had a lower prevalence of the CRN compared to those with fair or poor status (OR: 1.72; 95% CI:1.42–2.09), and Medicare beneficiaries with ADL had a higher prevalence of the CRN compared to those without ADL ($1 \leq$ ADL ≤ 2 vs. ADL $= 0$: OR: 1.64; 95% CI:1.32–2.02; ADL ≥ 3 vs. ADL $= 0$: OR: 1.76; 95% CI:1.31–2.37).

DISCUSSION

MTM aims to enhance patient understanding of appropriate drug use, increase patient adherence with prescribed drug therapies, reduce the risk of adverse events associated with drugs, and cut down on the need for other costly medical services (25). Previous studies demonstrated that MTM was optimal in saving cost, decreasing medication adverse events, and especially in improving adherence (6–8). In this study, we found that MTM eligibility was significantly associated with a higher prevalence of CRN.

The MTM-eligible beneficiaries were individuals with a higher estimated annual medical cost, many underlying disease state(s), and medications that are restricted by Medicare Part D prescription drug plans (26). These individuals with multiple medications tended to incur higher out-of-pocket medication costs and were reluctant to take medications and preferred to minimize medication intake (13, 27). That might be the main reason that contributed to higher CRN in the MTM-eligible beneficiaries. Though some previous studies showed the effect of MTM in improving medication non-adherence, the target populations in these studies were those with some specific diseases, such as diabetics (28, 29), osteoporosis (30), HIV/AIDS (31), hypertension (11), and other diseases. In our study, the MTM-eligible beneficiaries were from a general population, had many kinds of diseases, and received different

MTM programs. Additionally, there was some evidence that showed no significant improvement in medication adherence in some MTM programs (10, 11).

The literature indicated that the relationship between patients' out-of-pocket medication costs and medication adherence was complex and may be affected by multiple contextual factors. In this population-based study, we also analyzed the independent association between CRN and other covariates such as sociodemographic characteristics, comorbidities, health status, and insurance coverage. We found some variables were also significantly related to CRN. Older people had a lower prevalence of CRN, which may be because they have better care or more care about health issues with age. In terms of gender, women had a higher prevalence of CRN, indicating that there are gender disparities in CRN. Policymakers should issue policies to eliminate the difference between men and women in order to promote healthcare equality. Disparities also reflect geographically, the Medicare beneficiaries living in the South had a higher prevalence rate than the beneficiaries in the Northeast, which may be due to the level of development in different regions and the uneven healthcare supply situation. In terms of socio-economic, compared to low-income beneficiaries (annual income <10,000), those with high income (annual income >40,000) had a significantly lower prevalence of the CRN, while those with middle-income (annual income between 10,001 to 20,000) had a higher prevalence. Meanwhile, beneficiaries without low-income subsidy had a higher prevalence of the CRN, which was consistent with previous study (23, 27). As such, the economic level will affect the CRN, and financial subsidies may reduce the prevalence of the CRN. In any case, a small amount of financial assistance may have unexpected consequences and increase the prevalence. More research is needed in the future to find out what level of financial assistance can most effectively help patients reduce CRN. Because smokers had a higher prevalence of the CRN, it is possible to consider holding educational sessions about quitting smoking to reduce the prevalence of the CRN. In terms of physical health, the worse the health is, the higher the prevalence of CRN. This may be because patients with worse health can not take good care of themselves and non-adherence will partly further result in bad health. However, the causal relationship between the two needs further studies.

This study has a broad implication for health and social policy. It reported the prevalence of CRN among MTM-eligible beneficiaries in a nationally representative sample for the first time. The higher CRN rate in MTM-eligible beneficiaries suggested that these MTM-eligible beneficiaries with a higher estimated annual medical cost, multiple diseases, and medications, may still have problems in affording their medical or medication cost, which may, in turn, lead to bad therapeutic outcomes.

In this study, we also illustrated that MTM eligibility was associated with CRN. That means some strategies should be developed to evaluate the MTM from a comprehensive perspective. To address this issue, CMS is initiating and testing a Medicare Part D Enhanced MTM Model with a five-year performance period that began January 1, 2017. The goals of this model are to learn the best "right-size" for MTM services, to optimize medication use, to improve care coordination, and to strengthen health care system linkages (32). Our study suggests that the identification of alternative strategies to improve CRN should be considered in future Medicare Part D Enhanced MTM Models for better medication management.

There are several limitations in this study. Firstly, we were not able to identify MTM-eligible beneficiaries who used MTM services, which might bias the prevalence of CRN in the MTM users to a certain extent. Secondly, this study used a cross-sectional study design with 1 year of data, which was not able to demonstrate a long-term effect of MTM on CRN, and the causal reference between MTM-eligible beneficiaries and CRN could not be identified. Finally, in this study, because there were no specific identifiers of MTM, we used MTM-eligibility to determine if Medicare beneficiaries participated in MTM programs, which might bring biases to the results. However, according to CMS documentation, patients with MTM-eligibility are identified by Medicare sponsors using claims data and are enrolled in the MTM programs. Therefore, MTM-eligible patients in this study were expected to have already participated in the MTM program and the biases were minimal.

CONCLUSION

We found that the prevalence of CRN among MTM-eligible individuals was higher in the MTM group than in the non-MTM-eligible group. MTM was associated with CRN and the odds of CRN increased with participating MTM programs. Understanding the effect of MTM on CRN is essential for comprehensively evaluating and optimizing MTM service. Further studies with the longitudinal design are warranted to clarify the relationship between MTM and CRN. Alternative strategies to improve CRN should be considered in future Medicare Part D Enhanced MTM Models.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The data will not be made readily available for the privacy of the participants. Requests to access these datasets should be directed to https://www.cms.gov/Research-Statistics-Data-and-Systems/Research/MCBS.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of the University of South Carolina. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

WZ and GL took part in the study design, literature review, and critical draft writing. XX and ML performed data analysis. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Pandemic Worry and Preventive Health Behaviors During the COVID-19 Outbreak

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Objective: As schools are preparing for onsite learning, it is urgently needed to characterize the extent of pandemic worry and to examine predictors of adopting preventive health behaviors of hand washing, face mask wearing, and maintaining social distance among student pharmacists.

Methods: An online survey was sent to 326 student pharmacists in the United States. Pandemic worry was measured using a seven-point Likert scale ranging from extremely not afraid of, to extremely afraid of getting COVID-19. The health belief model (HBM) was the theoretical framework of this study. Preventive health behaviors and components of the HBM were also measured using seven-point Likert scales (one indicated extremely unlikely; seven indicated extremely likely). Multivariable linear regression models were used to identify predictors of each behavior.

Results: A medium level of pandemic worry ($M = 4.2$, $SD = 1.92$) was identified and females reported a higher pandemic worry. Respondents reported that they were extremely likely to wash their hands ($M = 6.8$, $SD = 0.48$) and maintain social distance ($M = 6.6$, $SD = 0.92$), but were moderately unlikely to wear face masks ($M = 2.2$, $SD = 1.51$). Determinants of face mask wearing included pandemic worry, perceived benefits, cue to action, self-efficacy, and being of an Asian American. Perceived barriers were negatively associated with face mask wearing.

Conclusion: Strategies should be implemented to reduce the psychological impact of COVID-19 pandemic among student pharmacists. Predictors identified in this study should be incorporated in efforts to improve face mask wearing. Continued monitoring of pandemic worry and preventive health behaviors is of great significance when universities and colleges are for onsite learning.

Keywords: COVID-19, pandemic worry, hand washing, face mask wearing, maintaining social distance

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a new respiratory illness caused by SARS-CoV-2 coronavirus. It was first detected in Wuhan, China in December 2019 and has rapidly spread worldwide (1). COVID-19 was declared as a pandemic by the World Health Organization (WHO) in March 2020 (2). The first US case of COVID-19 was reported in Washington State on January 19, 2020 (3). From the initial clusters identified in the states of Washington, California, and New York, confirmed cases of COVID-19 quickly expanded to all 50 states (4). The federal government implemented Coronavirus Guidelines and put forth certain preventative measures to slow the spread of COVID-19, such as maintaining good hand hygiene, avoiding social gatherings, closing schools, and non-essential businesses in areas with evidence of community transmission. Subsequently, multiple state and local officials implemented stay-at-home orders. Despite these containment efforts, the number of confirmed cases of COVID-19 continued to rise nationally (5). The United States has now the highest number of COVID-19 infections and has become the new epicenter of the pandemic (1).

The COVID-19 outbreak has generated significant pandemic worry. Pandemic worry refers to the constant, uncontrollable, and unwanted negative thoughts about the future outcomes of disease (6). These thoughts might impede individuals' problem-solving skills, prevent engagement in protective health behaviors, and contribute to the development of anxiety and depression. College students might be particularly vulnerable to the psychological impacts as they face pressure in many aspects of life, such as in academics and employment, especially given their immaturely developed psychological system. With the current COVID-19 outbreak, significant pandemic worry has been reported among college students in China (7, 8). This psychological impact might be due to the consequences of national and local measures taken during the outbreak, including school closures and rising unemployment rates secondary to lockdowns. Colleges and universities in the United States have implemented certain preventive measures, such as closures of campuses, cancellation of experiential rotations, changes in the delivery of didactic courses and exams, which might adversely affect the psychological well-being of college students (9). Negative psychological consequences due to the abruptness and timing of these implementations near the end of the academic school year include graduation delays, jeopardization of campus housing, and meal programs security, poor adaptation to the new learning style and exam delivery, and inability to continue with lectures for those with resource constraints.

Individuals' preventive health behaviors are important to contain the spread of COVID-19. The health belief model (HBM) is a theoretical framework that has been widely used in previous infectious disease outbreaks to evaluate individuals' motivations to adopt preventive health behaviors (10–14). Key components of the HBM include perceived susceptibility (how likely the individual perceives they will get the disease), perceived severity (individuals' perception of the severity of the illness), perceived benefits (individuals' belief about the effectiveness of the health behavior), perceived barriers (individuals' belief of the obstacles that prevent them from adopting the health behavior), cue to action (an external stimulus that triggers an individual to adopt the behavior), and self-efficacy (individuals' confidence of their ability to engage in the behavior) (15). In the 2002 to 2003 Severe Acute Respiratory Syndrome (SARS) epidemic, perceived susceptibility, perceived benefits, and cue to action significantly predicted face mask wearing and hand washing in Hong Kong (10, 11). In the 2009 H1N1 pandemic, perceived susceptibility, perceived severity, perceived benefits, and cue to action determined the adoption of maintaining social distance and hand washing in South Korea (12). For face mask wearing during the H1N1 pandemic, perceived susceptibility, perceived benefits, perceived barriers, and cue to action were significant predictors in Hong Kong (14).

To slow the spread of COVID-19, the Center for Disease Control and Prevention (CDC) has recommended that individuals adopt certain preventive health behaviors. These recommendations include hand washing with soap and water or hand sanitizer, keeping a six-feet social distance from other people, and covering the mouth and nose with a cloth face mask when around others (16). The guidance on face mask wearing was modified in April 2020 in light of recent evidence suggesting that transmission of the SARS-CoV-2 coronavirus might still occur among asymptomatic and pre-symptomatic individuals (17). Because these individuals comprise of a significant proportion of people infected with COVID-19, the CDC revised previous recommendation that face masks should only be worn by sick or caregivers of sick individuals, to the new recommendation that everyone should wear a cloth face mask in public settings when social distancing is hard to maintain.

To the best of our knowledge, no studies have evaluated the impact of pandemic worry on the adoption of preventive health behaviors during the pandemic of COVID-19 among student pharmacists. Health professional students are facing a high risk of COVID-19 infections through their interning, practicing, and working environments. To fill the gap in the literature, the objectives of this study were: (1) to characterize the extent of pandemic worry and (2) to examine predictors of adopting CDC-endorsed preventive health behaviors, including hand washing, face mask wearing, and maintaining social distance, among student pharmacists.

METHODS

An online survey was sent to 326 student pharmacists enrolled in a PharmD program in the south of the United States. Both those attended didactic course and engaged in experiential learning were surveyed in this study. A pilot study of five respondents was conducted before the formal study to make sure the clarity of survey questions. The survey was distributed in March 2020 and finished in 2 weeks. During that time, the number of COVID-19 cases continued to grow in the United States. Following the federal Coronavirus Guidelines and state and local stay-at-home orders, most colleges, and universities were closed and didactic courses were adjusted to virtual learning. In addition, preceptors at some clinical sites were unable to take student pharmacists who

are considered non-essential. Thus, most clinical rotations were rescheduled or canceled.

Information collected in this study included demographics, academic setting, pandemic worry, knowledge, and preventive health behaviors. Demographic information collected included age, gender, and race. Didactic course and experiential learning were two academic settings studied. Pandemic worry was measured by frequency (seven-point Likert scale, from never to always worried about getting COVID-19) and severity (seven-point Likert scale, from extremely not afraid of to extremely afraid of getting COVID-19). Knowledge of COVID-19 was measured by the source of information, availability of test kit, medication, and vaccine, and perceived knowledge (seven-point Likert scale, from extremely low to extremely high).

CDC-endorsed preventive health behaviors, including hand washing, face mask wearing, and maintaining social distance, were examined in this study (16). The likelihood of performing these preventive health behaviors was reported using seven-point Likert scales, where one indicated extremely unlikely and seven indicated extremely likely. Key components of the HBM, including perceived susceptibility, perceived severity, perceived benefits, perceived barrier, cue to action, and self-efficacy, were also measured using seven-point Likert scales.

The distributions of demographics, academic setting, pandemic worry, and knowledge were reported by frequency and percentage. Means of pandemic worry, knowledge, and preventive health behaviors were analyzed and compared by different age, gender, race, and academic setting groups using *t*-tests or analysis of variance (ANOVA) tests. The correlations between different preventive health behaviors were measured using Pearson correlation coefficients. Multivariable linear regression models were used to identify predictors of hand washing, face mask wearing, and maintaining social distance. In each regression model, the preventive health behavior was the dependent variable and pandemic worry, knowledge, components of the HBM, demographics, and academic setting were independent variables. SAS version 9.4 (SAS Institute, Cary, NC) was used to perform all statistical analyses.

RESULTS

Among 326 respondents who completed the survey, the majority of them were aged 18–26 years (79%), female (74%), and Caucasian (68%). The distribution between different academic settings at the time of survey completion was approximately equal, including 53% attending didactic course and 47% engaged in experiential learning (**Table 1**). Most respondents reported hearing about COVID-19 through digital channels such as social media (73%), TV (43%), and websites (40%). Respondents reported a medium level of pandemic worry severity (M = 4.2, SD = 1.92). The availability of a test kit (92%), lack of availability of approved medications (74%), and lack of availability of a vaccine (93%) for COVID-19 were correctly identified by the majority of respondents (**Table 1**). Respondents reported a slightly high perceived knowledge of COVID-19 (M = 4.8, SD = 1.03). Females reported a significantly lower knowledge compared to males (4.7 vs. 5.2, $p < 0.001$), and those attended didactic course reported a significantly lower knowledge compared to those engaged in experiential learning (4.7 vs. 4.9, $p = 0.03$; **Table 2**).

Respondents reported a medium level of pandemic worry severity (M = 4.2, SD = 1.92). Females reported a significantly higher worry severity compared to males (4.4 vs. 3.7, p = 0.004). No differences between worry severity were found among students of different ages, races, and academic settings (**Table 2**). For the pandemic worry frequency in the past week, 51% of respondents reported that they worried about getting COVID-19 less than half the time and 37% of respondents reported more than half the time. Specifically, 7% of respondents reported always worried about getting COVID-19 in the past week (**Table 1**).

Hand washing was positively correlated with face mask wearing (r = 0.14, p = 0.01) and maintaining social distance (r = 0.26, $p < 0.001$). However, face mask wearing was not correlated with maintaining social distance ($r = 0.10$, $p = 0.07$). Respondents reported that they were extremely likely to wash their hands (M = 6.8, SD = 0.48) and maintain social distance ($M = 6.6$, $SD = 0.92$), but were moderately unlikely to wear a face mask in public (M = 2.2, SD = 1.51). Females were significantly more likely to wash hands compared to males (6.9 vs. 6.7, p = 0.006). Asian Americans were significantly more likely to wear a face mask compared to other racial groups (Caucasian: 2.1, African American: 2.0, Asian American: 3.0, Other: 2.1, p = 0.004; **Table 2**).

Respondents reported a slightly high perceived susceptibility to COVID-19 ($M = 4.7$, $SD = 1.79$). The perceived susceptibility was different among different racial groups (Caucasian: 4.8, African American: 4.6, Asian American: 4.0, Other: 5.5, p = 0.006) and those attended didactic course perceived a significantly lower susceptibility compared to those engaged in experiential learning (4.4 vs. 5.1, $p < 0.001$). Respondents reported a moderately high perceived severity of COVID-19 (M = 5.8, SD = 1.13). Perceived benefits were moderately high for hand washing (M = 6.1, SD = 1.01) and maintaining social distance ($M = 6.2$, $SD = 0.97$), but were medium for face mask wearing (M = 3.5, SD = 1.71). Perceived barriers were slightly high for face mask wearing (M = 4.9, SD = 1.88), slightly low for hand washing (M = 3.4, SD = 2.04), and moderately low for maintaining social distance (M = 2.4, SD = 1.47). Cue to action was extremely high for hand washing (M = 6.7, SD = 0.57), moderately high for maintaining social distance (M = 6.4, SD = 0.97), and slightly high for face mask wearing (M = 5.3, SD = 1.75). Females reported a significantly higher cue to action of hand washing (6.8 vs. 6.5, $p = 0.003$) and a significantly higher cue to action of maintaining social distance (6.5 vs. 6.2, p = 0.03) compared to males. Self-efficacy was extremely high for hand washing (M = 6.5, SD = 0.87), moderately high for maintaining social distance (M = 6.2, SD = 1.15), and slightly low for face mask wearing ($M = 3.4$, $SD = 1.98$). Those attended didactic course reported a significantly higher self-efficacy of hand washing (6.6 vs. 6.4, p = 0.01) and a significantly higher self-efficacy of maintaining social distance (6.3 vs. 6.0, $p = 0.02$) compared to those engaged in experiential learning (**Table 2**).

TABLE 1 | Demographics, academic setting, pandemic worry, and knowledge of study participants ($N = 326$).

	N	%
Demographics		
Age		
18–26	258	79.1
27+	68	20.9
Gender		
Female	242	74.2
Male	84	25.8
Race		
Caucasian	222	68.1
African American	40	12.3
Asian American	45	13.8
Other	19	5.8
Academic setting		
Didactic course	172	52.8
Experiential learning	154	47.2
Pandemic worry		
Frequency		
Never	30	9.2
Occasionally	74	22.7
Sometimes	63	19.3
About half the time	37	11.3
Often	59	18.1
Most of the time	41	12.6
Always	22	6.7
Knowledge		
Source		
TV	140	42.9
Website	129	39.6
Social media	239	73.3
Radio	22	6.7
In print	23	7.1
Family/friend	136	41.7
Availability of test kit		
Yes	299	91.7
No	17	5.2
Unsure	10	3.1
Availability of medication		
Yes	33	10.1
No	242	74.2
Unsure	51	15.6
Availability of vaccine		
Yes	5	1.5
No	303	92.9
Unsure	18	5.5

Perceived severity (β: 0.08; 95% CI: 0.04–0.13) and cue to action (β: 0.21; 95% CI: 0.11–0.30) were predictors for hand washing. Being a male was negatively associated with hand washing (β: −0.13; 95% CI: −0.24 to −0.01). Determinants of face mask wearing included pandemic worry (β: 0.18; 95% CI: 0.10–0.26), perceived benefits (β: 0.29; 95% CI: 0.21–0.38), cue to action (β: 0.10; 95% CI: 0.01–0.18), self-efficacy (β: 0.18; 95% CI: 0.11–0.25), and being of an Asian American (β: 0.57; 95% CI: 0.17–0.97). Perceived barriers were negatively associated with face mask wearing (β: −0.12; 95% CI: −0.20 to −0.05). Cue to action (β: 0.38; 95% CI: 0.28–0.49) and self-efficacy (β: 0.13; 95% CI: 0.04–0.23) were predictors for maintaining social distance (**Table 3**).

DISCUSSION

This study found that student pharmacists had a medium level of pandemic worry severity and females had a higher worry severity than males. Pandemic worry might be associated with adverse psychological outcomes and students are more vulnerable. Cao et al. (7) found that 25% of college students reported experiencing anxiety amidst the COVID-19 outbreak in China. Wang et al. (8) reported that moderate or severe psychological impact was experienced by 54% of the general population in China. Females and students were significant predictors of experiencing greater psychological impact amidst the COVID-19 outbreak (8). Student pharmacists might be more psychologically vulnerable due to their younger age, the challenges they face with the transition into adulthood and to the profession (e.g., managing finances, adapting to new learning regimes, making new friends, and creating a new identity as a pharmacist). The abrupt change in their daily lives associated with strict government measures to contain the outbreak (e.g., school and non-essential business closures), the consequences of these measures (e.g., financial pressure to pay tuition expenses amidst uncertain employment prospect and social isolation from friends), and the rapid changes in the social and economic climate during the COVID-19 outbreak, might further compound their pandemic worry.

Additional psychosocial and economic factors that disproportionately affect females, such as low social status, income inequality, gender-based violence, and caregiving responsibility, might explain the higher level of pandemic worry observed (18). Potential protective factors of pandemic worry during the COVID-19 outbreak include social support and living with parents (7). Therefore, strategies such as creating virtual peer support groups, organizing virtual activities, and encouraging students to maintain contact with their family and friends virtually, might help to mitigate the psychological impact of COVID-19. If appropriate and feasible, student pharmacists might also consider moving back with their parents during the COVID-19 outbreak.

Student pharmacists reported their knowledge of COVID-19 to be slightly high. Improvement of knowledge, dissemination of additional health information, provision of regular updates on the latest information, and accessibility of information *via* reliable sources, have been identified as protective factors against adverse psychological outcomes during the COVID-19 outbreak (8). Websites and social media proved to be effective strategies for getting knowledge to student pharmacists based on our results. Therefore, increasing education and providing regular updates through government websites or social media accounts

TABLE 2 | Pandemic worry, knowledge, and preventive health behaviors of study participants by age, gender, race, and academic setting.

	Total	Age			Gender			Race					Academic setting		
		18–26	27+	*p* value	Female	Male	*p* value	Caucasian	African American	Asian American	Other	*p* value	Didactic Course	Experiential Learning	*p* value
	M (*SD*)[†]	*M* (*SD*)	*M* (*SD*)		*M* (*SD*)	*M* (*SD*)		*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)		*M* (*SD*)	*M* (*SD*)	
Pandemic worry	4.2 (1.92)	4.2 (1.93)	4.3 (1.90)	0.50	4.4 (1.87)	3.7 (1.96)	0.004*	4.1 (1.92)	4.1 (2.00)	4.8 (1.83)	4.5 (1.81)	0.13	4.2 (1.88)	4.2 (1.97)	0.85
Knowledge	4.8 (1.03)	4.8 (1.00)	4.7 (1.16)	0.33	4.7 (1.02)	5.2 (0.99)	<0.001*	4.9 (0.96)	4.7 (1.09)	4.5 (1.18)	4.6 (1.34)	0.14	4.7 (1.04)	4.9 (1.02)	0.03*
Preventive health behavior															
Hand washing	6.8 (0.48)	6.8 (0.43)	6.8 (0.62)	0.53	6.9 (0.44)	6.7 (0.56)	0.006*	6.8 (0.50)	6.9 (0.35)	6.8 (0.53)	6.9 (0.32)	0.34	6.8 (0.48)	6.8 (0.48)	0.51
Face mask wearing	2.2 (1.51)	2.1 (1.45)	2.3 (1.74)	0.37	2.2 (1.49)	2.2 (1.59)	0.89	2.1 (1.46)	2.0 (1.27)	2.9 (1.91)	2.1 (0.97)	0.004*	2.2 (1.51)	2.1 (1.52)	0.72
Maintaining social distance	6.6 (0.92)	6.6 (0.94)	6.6 (0.85)	0.86	6.6 (0.91)	6.5 (0.96)	0.20	6.6 (0.98)	6.5 (1.06)	6.8 (0.47)	6.5 (0.70)	0.46	6.6 (0.79)	6.5 (1.05)	0.16
Perceived susceptibility	4.7 (1.79)	4.7 (1.81)	4.8 (1.75)	0.64	4.7 (1.80)	4.8 (1.77)	0.59	4.8 (1.73)	4.6 (1.84)	4.0 (1.94)	5.5 (1.54)	0.006*	4.4 (1.87)	5.1 (1.62)	<0.001*
Perceived severity	5.8 (1.13)	5.8 (1.08)	5.9 (1.29)	0.80	5.9 (1.07)	5.7 (1.27)	0.17	5.8 (1.12)	5.9 (1.03)	6.0 (0.95)	5.4 (1.64)	0.27	5.8 (1.19)	5.9 (1.05)	0.17
Perceived benefits															
Hand washing	6.0 (1.01)	6.1 (1.01)	5.9 (1.00)	0.27	6.1 (1.00)	5.9 (1.02)	0.11	6.0 (0.99)	6.2 (1.08)	6.0 (1.00)	6.1 (1.18)	0.85	6.0 (1.04)	6.1 (0.98)	0.83
Face mask wearing	3.5 (1.71)	3.5 (1.68)	3.8 (1.81)	0.24	3.6 (1.70)	3.3 (1.73)	0.09	3.5 (1.72)	3.6 (1.75)	3.9 (1.76)	3.3 (1.33)	0.43	3.4 (1.67)	3.6 (1.75)	0.29
Maintaining social distance	6.2 (0.97)	6.3 (0.94)	6.1 (1.06)	0.13	6.3 (0.96)	6.1 (0.98)	0.12	6.2 (0.99)	6.2 (1.11)	6.5 (0.73)	6.5 (0.77)	0.19	6.3 (0.95)	6.2 (0.98)	0.20
Perceived barrier															
Hand washing	3.4 (2.04)	3.4 (2.05)	3.3 (2.04)	0.56	3.4 (2.03)	3.5 (2.09)	0.72	3.5 (2.01)	3.0 (2.17)	3.7 (2.10)	2.7 (1.89)	0.18	3.3 (1.97)	3.6 (2.12)	0.23
Face mask wearing	4.9 (1.88)	4.9 (1.87)	4.8 (1.93)	0.91	4.8 (1.90)	5.1 (1.82)	0.26	4.9 (1.83)	4.5 (2.09)	5.0 (2.09)	4.6 (1.50)	0.54	4.8 (1.80)	5.0 (1.96)	0.31
Maintaining social distance	2.4 (1.47)	2.4 (1.47)	2.1 (1.49)	0.17	2.3 (1.51)	2.4 (1.37)	0.84	2.3 (1.43)	2.4 (1.56)	2.4 (1.63)	2.4 (1.54)	>0.99	2.4 (1.49)	2.3 (1.46)	0.58
Cue to action															
Hand washing	6.7 (0.57)	6.7 (0.58)	6.7 (0.55)	0.93	6.8 (0.48)	6.5 (0.75)	0.003*	6.7 (0.52)	6.8 (0.42)	6.6 (0.83)	6.5 (0.70)	0.20	6.7 (0.60)	6.7 (0.55)	0.88
Face mask wearing	5.3 (1.75)	5.3 (1.73)	5.3 (1.83)	0.91	5.4 (1.64)	5.1 (2.00)	0.13	5.3 (1.76)	5.5 (1.60)	5.7 (1.53)	4.6 (2.19)	0.12	5.3 (1.79)	5.3 (1.71)	0.85
Maintaining social distance	6.4 (0.97)	6.4 (0.97)	6.4 (0.95)	0.93	6.5 (0.87)	6.2 (1.18)	0.03*	6.4 (0.87)	6.5 (0.91)	6.6 (0.89)	5.9 (1.85)	0.07	6.5 (1.03)	6.4 (0.90)	0.49
Self-efficacy															
Hand washing	6.5 (0.87)	6.5 (0.74)	6.3 (1.25)	0.19	6.5 (0.89)	6.4 (0.83)	0.54	6.5 (0.79)	6.5 (1.09)	6.4 (1.16)	6.7 (0.45)	0.61	6.6 (0.68)	6.4 (1.03)	0.01*
Face mask wearing	3.4 (1.98)	3.4 (1.96)	3.5 (2.04)	0.86	3.3 (1.95)	3.8 (2.04)	0.06	3.5 (1.93)	3.2 (1.99)	3.7 (2.17)	2.8 (2.01)	0.39	3.6 (1.97)	3.2 (1.97)	0.13
Maintaining social distance	6.2 (1.15)	6.2 (1.07)	6.0 (1.39)	0.17	6.2 (1.16)	6.1 (1.12)	0.37	6.1 (1.18)	6.3 (1.01)	6.4 (0.87)	5.9 (1.56)	0.26	6.3 (0.95)	6.0 (1.32)	0.02*

[†] *1 as extremely low; 7 as extremely high.*

*$p < 0.05$.

TABLE 3 | Factors associated with preventive health behaviors.

	Hand washing			Face mask wearing			Maintaining social distance		
	β	95% CI		β	95% CI		β	95% CI	
Pandemic worry	−0.01	−0.03	0.02	0.18	0.10	0.26	0.04	−0.01	0.09
Knowledge	0.02	−0.03	0.06	−0.03	−0.16	0.11	−0.02	−0.10	0.07
Health belief model									
Perceived susceptibility	0.03	0.00	0.06	−0.01	−0.09	0.07	0.03	−0.03	0.08
Perceived severity	0.08	0.04	0.13	−0.04	−0.18	0.09	0.07	−0.01	0.16
Perceived benefits	0.03	−0.02	0.08	0.29	0.21	0.38	−0.03	−0.13	0.06
Perceived barriers	0.00	−0.03	0.02	−0.12	−0.20	0.05	−0.06	−0.13	0.00
Cue to action	0.21	0.11	0.30	0.10	0.01	0.18	0.38	0.28	0.49
Self-efficacy	0.06	0.00	0.12	0.18	0.11	0.25	0.13	0.04	0.23
Demographics									
Age									
18–26	Ref			Ref			Ref		
27+	−0.05	−0.17	0.08	−0.01	−0.35	0.34	−0.02	−0.24	0.20
Gender									
Female	Ref			Ref			Ref		
Male	−0.13	−0.24	−0.01	0.21	−0.11	0.53	0.02	−0.18	0.23
Ethnicity									
Caucasian	Ref			Ref			Ref		
African American	0.10	−0.05	0.25	−0.09	−0.50	0.32	−0.11	−0.37	0.16
Asian American	0.01	−0.14	0.15	0.57	0.17	0.97	0.13	−0.13	0.39
Other	0.18	−0.03	0.39	0.03	−0.56	0.61	0.21	−0.16	0.59
Academic setting									
Didactic course	Ref			Ref			Ref		
Experiential learning	0.02	−0.08	0.12	0.00	−0.28	0.28	−0.10	−0.28	0.08

could be used to mitigate the psychological impact associated with COVID-19.

Student pharmacists reported that they were extremely likely to wash their hands and maintain social distance, but were moderately unlikely to wear a face mask. Given the low willingness to wear a face mask, predictors identified in our study should be considered to encourage face mask wearing. Components of the HBM that predicted face mask wearing were perceived benefits, perceived barriers, cue to action, and self-efficacy. Perceived benefits and cue to action as predictors of face mask wearing were consistent with previous studies conducted in Asia (10–12). Barriers to face mask wearing identified in previous studies included discomfort (e.g., difficulty with breathing), inconvenience (e.g., need to remove masks during meal times), forgetfulness, and social acceptance (19). Strategies should be taken to improve face mask wearing following the recent CDC guidelines revision. For example, government, public health officials, and healthcare professionals can actively promote face mask wearing, as well as improve the public's knowledge on the effectiveness of face masks in reducing COVID-19 transmission. By widely promoting face mask wearing, this can increase social acceptance and reduce stigmatization and discrimination against people who wear them (20). Messaging should also make clear of the recommendations for the use of cloth masks and to not use medical masks reserved for medical professionals (17). Videos on how to make cloth masks can be created by public health officials or organizations and be uploaded on official government websites and YouTube, in order to improve self-efficacy of face mask use. YouTube, due to its considerable reach, has recently been identified as an under-tapped platform for promoting preventive health behaviors amidst the COVID-19 pandemic (21). As this study also identified cue to action as a predictor of hand washing and maintaining social distance, public messaging should continue to emphasize the importance of hand washing and maintaining social distancing, along with face mask wearing, in containing the spread of COVID-19.

There are several strengths of this study. First, this is the first study evaluating pandemic worry among student pharmacists. The results of this study highlighted the vulnerability of student pharmacists to the psychological impact of the pandemic and emphasize the need to implement strategies to mitigate this effect. Second, predictors of face mask wearing could be used to improve face mask use among the public in light of recent expansion in CDC guidelines. Third, this study applied the theoretical framework of the health belief model to systematically assess the determinants of preventive health behaviors. This could inform public health initiatives to contain the COVID-19 outbreak when universities and colleges reopen for onsite learning. This study has some limitations worth noting. First, the survey was conducted prior to CDC modifying recommendations on face

mask wearing. Respondents' perception of face mask wearing reported might change in light of the new recommendations. Second, the survey collected information at a single point in time. Thus, it cannot capture changes in the students' pandemic worry and preventive health behaviors as the COVID-19 pandemic evolves. Third, this study relied on students' self-reports using a survey. It might not reflect their actual level of pandemic worry and preventive health behaviors due to social desirability. Fourth, this study only included student pharmacists in the study population. The results might not be generalizable to other health professional students.

CONCLUSION

The COVID-19 pandemic has generated a medium-level of pandemic worry among student pharmacists in the United States. Females reported a higher level of pandemic worry than males. Strategies should be implemented to reduce the psychological impact of COVID-19 pandemic. For preventive health behaviors, student pharmacists reported that they were moderately unlikely to use a face mask and were extremely likely to engage in hand washing and social distancing. The health belief model components that predicted face mask wearing (i.e., perceived benefits, perceived barriers, cue to action, and self-efficacy) should be incorporated in efforts to improve face mask wearing following CDC's recent expansion of face mask recommendations. Continued monitoring of pandemic worry and preventive health behaviors among student pharmacists are of great significance when universities and colleges are preparing for onsite learning.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Tennessee Health Science Center. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ML and GL: conceptualization, methodology, and writing. SH: methodology and writing. RS: methodology and analysis. JY: conceptualization, methodology, analysis, writing, and supervision. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The Effects of Aspirin With Combined Compound Danshen Dropping Pills on Hemorheology and Blood Lipids in Middle-Aged and Elderly Patients With CHD: A Systematic Review and Meta-Analysis

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Background: Coronary heart disease (CHD) is one of the most common diseases in clinical cardiovascular practice, mainly afflicting the middle-aged and elderly. It will greatly affect elderly quality of life, and even affect their psychological and physical health. At present, CHD is treated with western drugs alone, but this can produce drug dependency. In recent years, Traditional Chinese Medicine (TCM) combine western drugs has been used as a complementary and alternative therapy, and its effectiveness and safety have been proven, attracting the attention of numerous researchers.

Objective: Our study aimed to compare the efficacy of Aspirin with Combined Compound Danshen Dropping Pills had a superior effect on the treatment of Hemorheology and Blood Lipids in Middle-aged and Elderly Patients with CHD. Determine the effectiveness and safety of Aspirin with Combined Compound Danshen Dropping Pills in the treatment of CHD, and obtain high quality clinical evidence.

Methods: Based on the PRISMA Statement, inclusion and exclusion criteria were formulated. Randomized controlled trials (RCTs) on the Effects of Aspirin with Combined Compound Danshen Dropping Pills on Hemorheology and Blood Lipids in Middle-aged and Elderly Patients with CHD were found following a search of 4 mainstream medical databases. RCTs found to meet the study's requirement were included; data information was then extracted, and the quality assessed using the Cochrane bias risk assessment tool. Through RevMan software, Meta analysis was carried out for overall TC, TG, HDL-C, LDL-C hematocrit, high shear viscosity, low shear viscosity, plasma viscosity, PAGM, and TXB_2 effective rate. The relative risk (RR) and 95% confidence interval (95% *CI*) were calculated; heterogeneity was tested and its source found; publication bias was assessed through the Egger and Begg tests, and by means of funnel plots.

Result: 22 RCTs were found, involving 1,987 cases. The results of the Meta analysis showed that, compared to drug therapy alone, Aspirin with Combined Compound Danshen Dropping Pills had a superior effect on the treatment of Hemorheology and

Blood Lipids in Middle-aged and Elderly Patients with CHD. The meta analysis results show the effects on TC [MD = −0.91, 95% CI (−1.09, −0.73)], on TG [MD = −0.94, 95% CI (−1.22, −0.66)], on HDL-C [MD = 0.40, 95% CI (0.27, 0.53)], on LDL-C [MD = −0.99, 95% CI (−1.24, −0.74)], on hematocrit [MD = −2.69, 95% CI (−3.73, −1.65)], on high shear blood viscosity [MD = −1.11, 95% CI (−2.18, −0.05)], on low shear viscosity [MD = −0.79, 95% CI (−0.89, −0.68)], on plasma viscosity [MD = −0.26, 95% CI (−0.52, 0.01)], on PAMG [MD = −10.75, 95% CI (−16.84, −4.67)], and on TXB_2 [MD = −11.84, 95% CI (−14.75, −8.92)]. The source of heterogeneity might be related to the state of patient, efficacy of drugs in the control group and difference in judgment criteria for efficacy. The Egger test and Begg test showed that publication bias did not occur in our study.

Conclusions: The combination of compound dropping pill DSP with aspirin has some therapeutic effect on blood lipids and hemorheology in patients with CHD, ince some of the RCTs featured a very small sample size, the reliability and validity of our study's conclusion may have been affected as well; therefore, the explanation should be treated with some caution. In the future, a large number of higher-quality RCTs are still needed to confirm the results of our study.

Keywords: compound Danshen dropping pills, aspirin, coronary heart disease, blood lipids, hemorheology, meta-analysis

INTRODUCTION

Coronary heart disease (CHD) is one of the most common diseases in clinical cardiovascular practice, mainly afflicting the middle-aged, and elderly. Characterized by acuteness, repeated relapse, and severe clinical manifestations, if not timely treated, it may induce myocardial infarction and sudden cardiac death. It is a life-threatening disease whose pathogenesis is related to hemadostenosis and coronary atherosclerosis (1, 2) reducing patients' quality of life (3). The key to its clinical treatment is improving myocardial blood supply, usually using antiplatelet agents. The efficacy of aspirin as an anticoagulant has been fully affirmed in clinical practice, and its price is relatively low, so it has become a first-line drug for treatment of CHD. However, it has been often reported in recent years that long-term use of antiplatelet agents can cause adverse reactions. Most patients become resistant to aspirin, weakening its efficacy (4). Therefore, it is imperative to enhance its anticoagulant effect through combination with other drugs. In elderly patients, the decline of physical function and aging progression further exacerbates various cardiovascular risk factors, making them more susceptible to CHD and other acute cardiovascular events than other age groups. Meanwhile, elderly patients are also more likely to have other systemic complications and to receive multi-drug treatment, further increasing their risk of hemorrhage during treatment with antiplatelet agents. Thus, their risk and benefits should be comprehensively evaluated prior to application to select the best therapeutic schedule to prevent the incidence of bleeding, while achieving the best curative effect (5).

According to Traditional Chinese Medicine (TCM), CHD is a symptom of "thoracic obstruction," closely related to *qi* deficiency, blood stasis, and choroidal obstruction, so it can be treated on the principles of promoting circulation and relaxing the muscles and joints. The compound Danshen dropping pill (DSP), mainly composed of Salvia miltiorrhiza Bunge (danshen); Panax notoginseng; F.H.Chen(sanqi)and Borneol, is effective in promoting circulation, removing stasis, regulating vital energy, and easing pain, with high value for the clinical treatment of cardiovascular diseases (6). Previous studies have shown that DSP significantly improves vascular endothelial function, alleviating angina pectoris and preventing restenosis after coronary stenting, but there are relatively few reports on its influence on coronary artery lesions. Moreover, salvia miltiorrhiza, its major ingredient, can effectively control platelet activity to reduce blood viscosity, and clear out free radicals to enhance oxygen supply, so that cells and tissues can maintain normal myocardial function (7).

This paper carries out a meta-analysis on RCTs from China and elsewhere to investigate the clinical effect of DSP in combination with aspirin on CHD, aiming to provide more reliable clinical evidence for TCM.

MATERIALS AND METHODS

Searches

Four mainstream medical databases were searched, including PubMed, CNKI, WANFANG and VIP. The timeframe used for database queries was from the earliest indexed studies to FEB 1, 2020. Search words included "Compound Danshen Dropping Pills" DSP, Danshen Dropping Pills, fufang danshen, salvia miltiorrhiza, compound red-rooted salvia, acetylsalicylic acid, Coronary Heart Disease, CHD, Blood Lipids, Hemorheology, Middle-aged, Elderly. In order to ensure the completeness of the search, the language of

the database was not restricted; a search was carried out through a combination of MeSH keyword and free words; the retrieval strategy could thus be finalized (the concrete retrieval formula of the database is shown in Attachment 2). Gray literatures were manually retrieved for supplementation at the library of the Tianjin University of Traditional Chinese Medicine; if the full texts were not available, a mail was sent to its author in an attempt to obtain the full document.

Inclusion Criteria

Study Types

Randomized controlled trials (RCTs) were selected, whether or not they were blinded. with no language restrictions.

Subjects

Patients with CHD were used, according to the CHD diagnosis criteria of the clinical diagnosis standards set by the WHO (8, 9), with average age above 50, regardless of nationality and gender, with normal hepatic and renal functions, who had not recently taken anticoagulants or antiplatelet agents.

TCM diagnosis standards: the diagnosis standards for "heart impediments" in the New Guidelines for TCM Clinical Studies (Tentative).

Intervention

The experimental group was treated with DSP combined with aspirin for more than 4 weeks, regardless of dosage, while the control group was treated with aspirin alone; however the use of non-anticoagulants and non-lipid-lowing drugs was allowed.

Primary Outcomes

Blood lipid indices: Triglyceride and total cholesterol (TC).

Secondary Outcomes

Blood lipid indexes: high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C); hemarheology indexes: hematocrit, high shear blood viscosity, low shear blood viscosity, plasma viscosity; platelet aggregation functions: thromboxane B_2 level (TXB_2), and maximal platelet aggregation (PAGM).

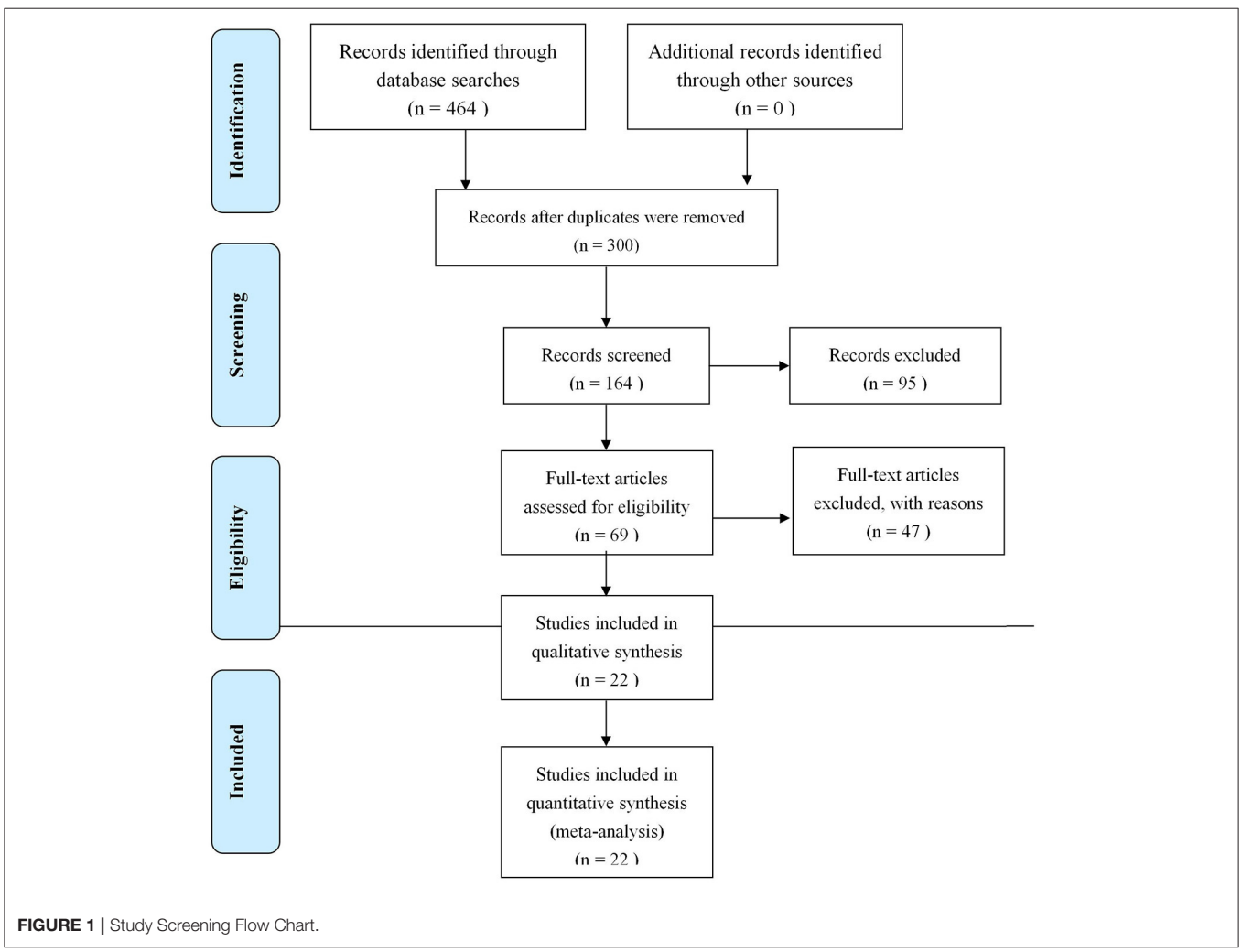


FIGURE 1 | Study Screening Flow Chart.

Exclusion Criteria

The following studies were excluded from the meta-study: (1) Non-randomized trials; (2) studies lacking a control group; (3) studies reporting obviously incorrect data; and (4) duplicate studies.

Data Selection and Data Extraction

Two researchers selected the papers independently.

First, Notexpress-2 was used for screening according to preset criteria, with repeated literature in the databases excluded. Then the researchers read the titles and abstracts to exclude clearly irrelevant literature.

TABLE 1 | Characteristics of the included studies.

Study ID	Sample size (M/F)		Age (median or mean or range), y		Intervention		Course of treatment, m	Outcome
	T	C	T	C	T	C		
Zhang (10)	28/17	33/12	67.4 ± 2.1	66.9 ± 2.1	Compound Danshen Dropping Pills+Asprin	Asprin	2	①②③⑤⑥⑦
Liang et al. (11)	36/23	19/11	/	/	Compound Danshen Dropping Pills+Asprin	Asprin	24	①②③④
Li (12)	29/21	28/22	/	/	Compound Danshen Dropping Pills+Asprin	Asprin	/	③④
Huang et al. (13)	30/15	27/18	59.2 ± 0.5	56.7 ± 0.3	Compound Danshen Dropping Pills+Asprin+RT	Asprin+RT	1	①②③④
Hu and Wang (14)	25/18	24/19	61.56 ± 19.25	60.25 ± 19.86	Compound Danshen Dropping Pills+Asprin	Asprin	1	①②③④
Tong (15)	14/11	14/11	/	/	Compound Danshen Dropping Pills+Asprin+RT	Asprin+RT	3	①③④
Lü et al. (16)	45/19	45/19	68.54 ± 10.58	65.98 ± 8.85	Compound Danshen Dropping Pills+Asprin	Asprin100 Mg/d	2	①②③④⑨⑩
Lin et al. (17)	20/20	22/18	50.16 ± 3.02	53.06 ± 3.10	Compound Danshen Dropping Pills+Asprin	Asprin	2	①②③④
Zhou (18)	25/21	22/24	62.4 ± 5.6	61.7 ± 4.7	Compound Danshen Dropping Pills+Asprin+RT	Asprin+RT	2	①②③④
Wang (19)	19/9	18/10	59.4 ± 6.5	59.2 ± 6.7	Compound Danshen Dropping Pills+Asprin+RT	Asprin+RT	3	①②③④
Tang et al. (20)	/	/	/	/	Compound Danshen Dropping Pills+Asprin+RT	Asprin+RT	3	①②③④⑨⑩
Wang (21)	18/13	17/14	54.7 ± 1.2	56.9 ± 1.5	Compound Danshen Dropping Pills+Asprin	Asprin+RT	/	①②③④
Wang (22)	/	/	/	/	Compound Danshen Dropping Pills+Asprin+RT	Asprin	2	①②③④
Yang (23)	20/10	18/12	55.8 ± 8.9	54.6 ± 8.2	Compound Danshen Dropping Pills+Asprin+RT	Asprin+RT	1	①②③④⑤⑥⑦⑧
Xu (24)	/	/	/	/	Compound Danshen Dropping Pills+Asprin	Asprin	2	①②③④⑤⑥⑦
Xiong (25)	/	/	/	/	Compound Danshen Dropping Pills+Asprin	Asprin	6	③④
Sun (26)	21/18	19/20	/	/	Compound Danshen Dropping Pills+Asprin	Asprin	2	①②③④
Chen (27)	34/26	35/25	/	/	Compound Danshen Dropping Pills+Asprin+RT	Asprin+RT	3	③④⑧⑨
Lin and Zhao (28)	/	/	/	/	Compound Danshen Dropping Pills+Asprin	Asprin	2	③④
Hong (29)	28/36	28/36	58.9 ± 3.1	59.1 ± 3.0	Compound Danshen Dropping Pills+Asprin	Asprin	2	⑥⑦⑧
Guo et al. (30)	25/5	23/7	61.4 ± 10.5	56.8 ± 13.4	Compound Danshen Dropping Pills+Asprin+RT	Asprin+RT	1	⑨⑩
Liang et al. (31)	39/21	33/27	51.29 ± 3.38	50.19 ± 4.02	Compound Danshen Dropping Pills+Asprin+RT	Asprin+RT	6	⑨⑩

①TG(Triglycerides) ②TC(Total serum cholesterol) ③HDL-C(High-density lipoprotein cholesterol) ④LDL-C(Low-density lipoprotein cholesterol) ⑤Hematocrit ⑥Whole Blood Viscosity at High Shear ⑦Low Shear Blood Viscosity ⑧Plasma Viscosity ⑨PAGM(Maximum platelet aggregation rate) ⑩TXB_2(Thromboxane B2).

Finally, the remaining studies were read in full, finalizing the literature selection based on the inclusion and exclusion criteria. After selection, the two researchers independently extracted the data from the included studies using Excel, including the first author's name, publication date, sample size, participants' mean age and gender, interventions in the experimental and control groups, duration of treatment, prognostic indexes, and GRADE assessment.

Adverse events were tabulated independently, and occurrences in the experimental and control groups were recorded, respectively. The adverse events collected were intestinal reactions, allergic reactions, headaches, myocardial infarctions, heart failures, cerebral hemorrhaging, cerebral infarctions, and hypertension. The two researchers cross-checked their results and discussed any issues in dispute during tabulation, resolving any outstanding issues with help from a third party.

Quality Evaluation

The quality of the included studies was assessed in accordance with the quality assessment standards recommended in Cochrane Handbook for Systematic Reviews of Interventions 4.2.2. The assessment items included random allocation (i.e., selection bias), allocation concealment (i.e., selection bias), and blinding (i.e., performance bias). The two researchers worked independently, and resolved any issues in dispute through discussion, with outstanding issues resolved with the help of a third party.

Using the RevMan software, the bias risk assessment chart and bias risk assessment table were exported to show evaluation results for all included literature.

Statistical Analysis

Data were extracted from the studies and entered into Excel to calculate the difference in clinical outcome between the experimental and control groups. Then, the two assessors independently entered the difference in clinical outcomes into RevMan5.3 for meta-analysis. Q test and I^2 value were used to analyze the heterogeneity among the included studies. $P > 0.1$ and $I^2 < 50\%$ indicated a good consistency or lower heterogeneity among included studies, and a fixed effect model was adopted; otherwise, a random effect model was used. $I^2 \leq 25\%$ indicated a smaller heterogeneity; $25\% < I^2 \leq 50\%$ indicated a moderate heterogeneity, both of which could be acceptable. $I^2 > 50\%$ indicated high heterogeneity between the results of the study. For higher heterogeneity, a subgroup analysis was made to explore the source of this heterogeneity; when necessary, a sensitivity analysis was made to assess the stability of the study. Through the Egger test and the Begg test carried out in the Stata software and the funnel chart, publication bias was tested. As required by the index, more than 10 pieces of literature should be included, since it would be difficult to find the reason for asymmetry if there were too few studies.

RESULTS

Search Results

In the end, 22 research papers on RCTs were selected, involving 1,987 cases.

Basic Characteristics Assessment of the Studies

As shown in **Figure 1**, 22 studies (10–31) involving 1,987 patients (1,008 experimental and 979 control) were included in the present meta-study, with sample sizes ranging from 50 to 188. All the studies were carried out in China from 2008 to 2017. The adverse events reported in five studies have no follow-up information, and all of the papers explain basic information, with no statistically significant differences regarding the patients. See **Table 1** for the basic characteristics of these papers.

Summary of Test Quality and Bias Risks

Two independent researchers evaluated the methodology, quality and all the methods in the included studies in accordance with the Cochrane handbook; any disputed issue was solved through discussion. Twenty two of the papers were low-quality. All papers had separate groups; ten reported the specific grouping method (correct grouping methods were used in five papers, while an improper method was used in another five papers); the other

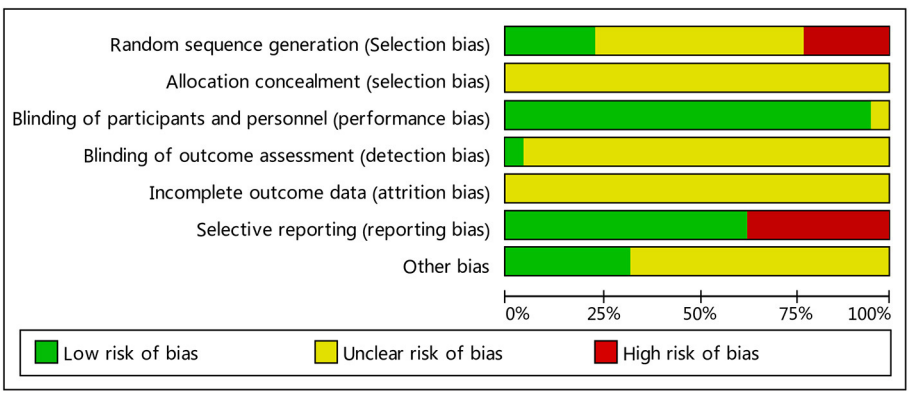


FIGURE 2 | Bias risk map: the reviewers' judgment of each type of bias risk, expressed as a percentage of all included studies.

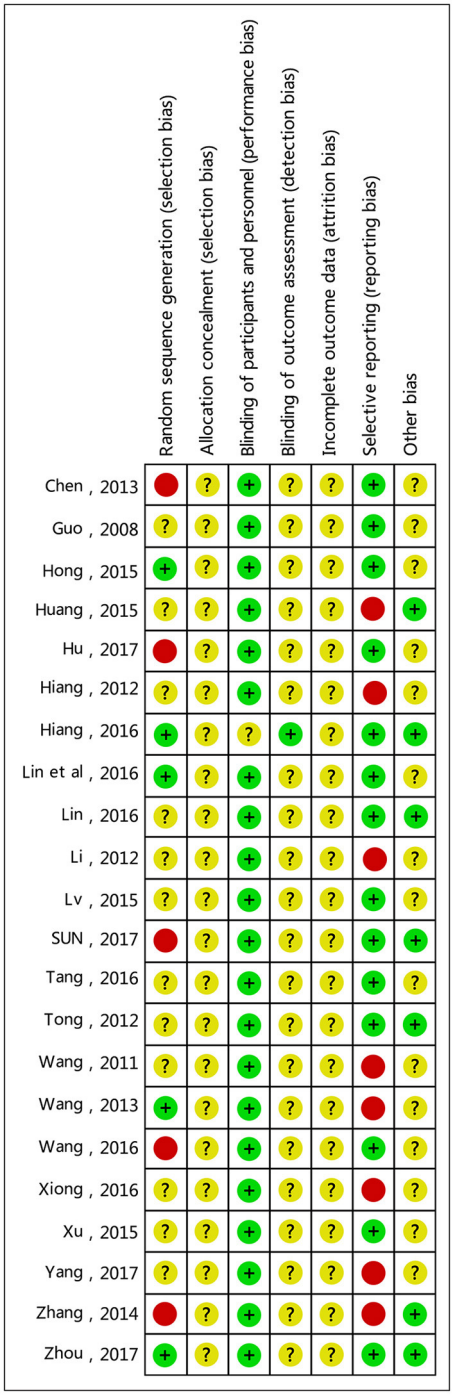


FIGURE 3 | Summary of bias risks: the reviewers' judgment of risk for each bias item in each included study.

12 only analyzed grouping, but did not describe the grouping method in detail. They included no information about loss to follow-up or withdrawal. All studies failed to note the blinding of participants and researchers. See **Figures 2**, **3** for summaries of the quality and bias risks of the included studies.

Total Cholesterol (TC)

Figure 4 shows that 14 of the included studies report the effect of DSP combined with aspirin on TC in patients with CHD. These studies included 1,273 cases – 651 in the experimental group, and 622 in the control. The heterogeneity test showed statistical significance ($P < 0.00001$, $I^2 = 83\%$), so the random effect model was used for meta-analysis. The results showed high heterogeneity between the studies, so we conducted a sensitivity analysis (see **Annex 1**), finding relatively high heterogeneity in one paper (18). On the premise of not removing this paper, we conducted subgroup analysis (see **Annex 2**), still finding high heterogeneity. We determined that this might be related to the quality of the included papers. The results showed statistical differences between the two groups [MD = −0.91, 95% CI (−1.09, −0.73)] (see **Figure 4**). The statistical results show that the combination of DSP with aspirin was effective in reducing TC in the patients with CHD. The quality of this part was very low according to the GRADE standard (see **Table 2**).

Triglycerosis (TG)

Figure 5 shows that 15 of the included papers reported the effect of DSP combined with aspirin on TG in patients with CHD. These papers included 1,323 cases: 676 in the experimental group, and 647 in the control. The heterogeneity test showed statistical significance ($P < 0.00001$, $I^2 = 94$), so the random effect model was used. The meta-analysis found high heterogeneity between the studies. A sensitivity analysis (see **Annex 3**) found relatively high heterogeneity in two papers (14, 17). On the premise of not removing these papers, we conducted subgroup analysis (see **Annex 4**), still finding high heterogeneity, which we determined may be related to the quality of the papers. The results showed statistical differences between the two groups [MD = −0.94, 95% CI (−1.22, −0.66)] (see **Figure 5**). The statistical results show that the combination of DSP with aspirin was effective in reducing TG in patients with CHD. The quality of this part was very low according to the GRADE standard (see **Table 2**).

HDL-C

Figure 6 shows that 19 of the included papers reported on the effect of DSP combined with aspirin on HDL-C in patients with CHD. Thousand six hundred and seventy nine cases were included: 854 in the experimental group, and 825 in the control. The heterogeneity test between the studies was statistically significant ($P < 0.00001$, $I^2 = 93\%$), so the random effect model was used. The analysis results showed high heterogeneity between the studies. After a sensitivity analysis (see **Annex 5**) and subgroup analysis (see **Annex 6**), there was still relatively high heterogeneity, which we ascribed to the quality of the included papers. The results showed statistically significant differences between the groups [MD = 0.40, 95% CI (0.27, 0.53)] (see **Figure 6**). The results showed that that the combination of DSP with aspirin was not effective in raising HDL-C in patients with CHD. The quality of this part was very low according to the GRADE standard (see **Table 2**).

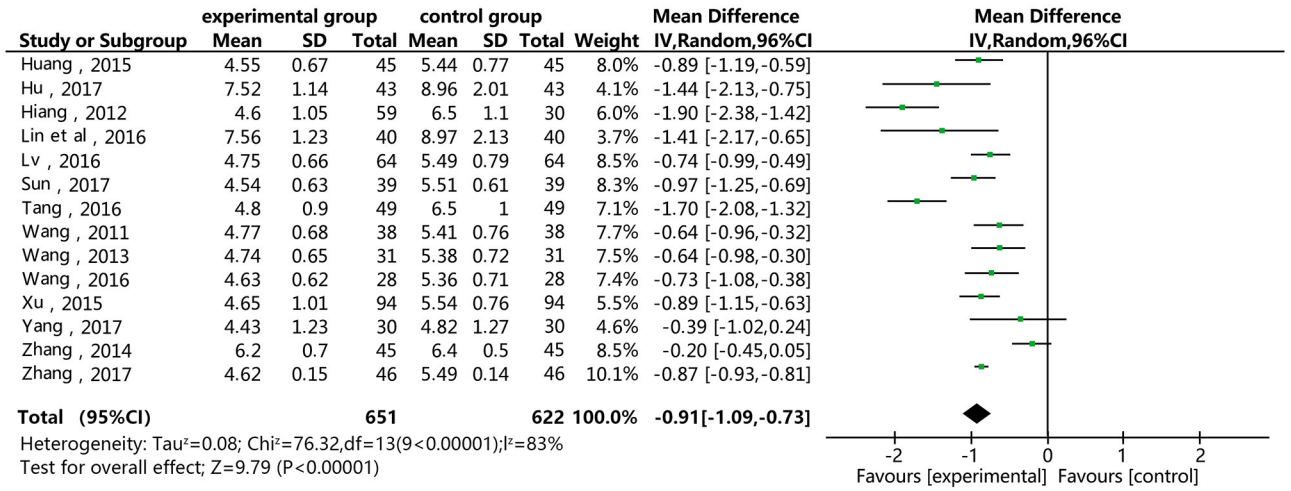


FIGURE 4 | Meta-analysis forest map for the of the effect of DSP combined with aspirin on TC in patients with CHD.

LDL-C

Figure 7 shows that 18 of the papers reported the effect of DSP combined with aspirin on LDL-C in patients with CHD. The studies included 1,589, with 809 in the experimental group and 780 in the control. The heterogeneity test showed statistical significance ($P < 0.00001$, $I^2 = 93\%$), so the random effect model was used for meta-analysis. The results found high heterogeneity between the studies. After a sensitivity analysis (see **Annex 7**) and subgroup analysis (**Annex 8**), there was still relatively high heterogeneity, which we ascribed to the quality of the papers. The results showed statistical differences between the groups [MD = −0.99, 95% CI (−1.24, −0.74)] (see **Figure 7**). The results of the meta-analysis show that that the combination of DSP with aspirin was effective in reducing LDL-C in patients with CHD. The quality of this part was very low according to the GRADE standard (see **Table 2**).

Hematocrit

As shown in **Figure 8**, three of the papers reported the effect of DSP combined with aspirin on hematocrit in patients with CHD. The studies included 337 cases: 183 in the experimental group and 154 in the control. There was no heterogeneity between the studies ($P = 0.40$, $I^2 = 0\%$), thus, the random effect model was used for meta-analysis. The results showed statistical differences between the groups [MD = −2.69, 95% CI (−3.73, −1.65)] (see **Figure 8**). The results of the meta-analysis showed that that the combination of DSP with aspirin was effective in reducing hematocrit in patients with CHD. The quality of this part was very low according to the GRADE standard (see **Table 2**).

High Shear Blood Viscosity

Figure 9 shows that four of the papers report the effect of DSP combined with aspirin on high shear blood viscosity at in patients with CHD. The studies include 465 cases: 247 in the experimental group and 218 in the control. There was heterogeneity between the studies ($P < 0.00001$, $I^2 = 98\%$), so the random effect model was used for meta-analysis. After a subgroup analysis (see **Annex 9**), there was still relatively high heterogeneity, which we ascribed to the quality of the included papers. The results showed statistical differences between the groups [MD = −1.11, 95% CI (−2.18, −0.05)] (see **Figure 9**). The meta-analysis results showed that that the combination of DSP with aspirin was effective in reducing high shear blood viscosity in patients with CHD. The quality of this part was very low according to the GRADE standard (see **Table 2**).

Low Shear Blood Viscosity

Figure 10 shows that four of the papers reported the effect of DSP combined with aspirin on low shear blood viscosity in the patients with CHD. The studies included 465 cases: 247 in the experimental group and 218 in the control group. There was no heterogeneity between the studies ($P = 0.93$, $I^2 = 0\%$), thus a random effect model was used for meta-analysis. The result showed statistical differences between the groups [MD = −2.69, 95% CI (−3.73, −1.65)] (see **Figure 10**). The meta-analysis results showed that that the combination of DSP with aspirin was effective in reducing low shear blood viscosity in the patients with CHD. The quality of this part was very low according to the GRADE standard (see **Table 2**).

Plasma Viscosity

Figure 11 shows that three of the papers reported the effect of DSP combined with aspirin on plasma viscosity in patients with CHD. They included 308 cases: 154 in the experimental group and 154 in the control. The heterogeneity test between the studies showed statistical significance ($P < 0.00001$, $I^2 = 97\%$), so the random effect model was used for meta-analysis. The result showed statistical differences between the groups [MD = −0.26, 95% CI (−0.52, 0.01)] (see **Figure 11**). The meta-analysis showed that that the combination of DSP with aspirin was effective in reducing plasma viscosity in patients with CHD. The quality of

TABLE 2 | GRADE quality of evidence summary table for the comparisons of Fufangdanshen Dripping combined with Aspirin vs. Aspirin for CHD.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Asprin	**Corresponding risk** Asprin comparisons Compound Danshen Dropping Pills				
TC	The mean TC in the intervention groups was 0.91 lower (1.09–0.73 lower)			1,273 (14 studies)	⊕⊖⊖⊖ **very low**[1,2,3,4]	
TG	The mean tg in the intervention groups was 0.94 lower (1.22–0.66 lower)			1,323 (15 studies)	⊕⊖⊖⊖ **very low**[1,4,5]	
HDL-C	The mean hdl-c in the intervention groups was 0.4 higher (0.27–0.53 higher)			1,679 (19 studies)	⊕⊖⊖⊖ **very low**[1,4]	
LDL-C	The mean ldl-c in the intervention groups was 0.99 lower (1.24–0.74 lower)			1,589 (18 studies)	⊕⊖⊖⊖ **very low**[1,4]	
Hematocrit	The mean Hematocrit in the intervention groups was 2.71 lower (3.77–1.66 lower)			337 (3 studies)	⊕⊕⊕⊖ **moderate**[5]	
Whole Blood Viscosity at High Shear	The mean Whole Blood Viscosity at High Shear in the intervention groups was 1.11 lower (2.18–0.05 lower)			465 (4 studies)	⊕⊖⊖⊖ **very low**[1,4,5]	
Low Shear Blood Viscosity	The mean Low Shear Blood Viscosity in the intervention groups was 0.79 lower (0.89–0.68 lower)			465 (4 studies)	⊕⊖⊖⊖ **very low**[1,2,3]	
Plasma Viscosity	The mean Plasma Viscosity in the intervention groups was 0.26 lower (0.52 lower to 0.01 higher)			308 (3 studies)	⊕⊖⊖⊖ **very low**[1,2]	
PAGM	The mean PAGM in the intervention groups was 7.69 lower (8.87–6.5 lower)			406 (4 studies)	⊕⊖⊖⊖ **very low**[1,2,3]	
TXB_2	The mean TBX_2 in the intervention groups was 11.84 lower (14.75–8.92 lower)			406 (4 studies)	⊕⊕⊕⊖ **moderate**[2]	

**the basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*
CI, Confidence interval.
GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
1. High heterogeneity value.
2. Lack of blinding.
3. Lack of allocation hiding.
4. Lack of allocation hiding and blinding.
5. Wide confidence interval leads to a decline in the quality of the evidence.
⊖TG(Triglycerides) ⊜TC(Total serum cholesterol) ⊛HDL-C(High-density lipoprotein cholesterol) ④LDL-C(Low-density lipoprotein cholesterol) ⑤Hematocrit ⑥Whole Blood Viscosity at High Shear ⑦Low Shear Blood Viscosity ⑧Plasma Viscosity ⑨PAGM ⑩TXB_2.

this part was very low according to the GRADE standard (see **Table 2**).

Maximal Platelet Aggregation (PAMG)

Figure 12 shows that five of the papers reported the effect of DSP combined with aspirin on PAMG in the CHD patients. They included 526 cases: 263 in the experimental group and 263 in the control. The heterogeneity test was statistically significant ($P < 0.00001$, $I^2 = 97\%$), so the random effect model was used for meta-analysis. We conducted a sensitivity analysis, finding relatively high heterogeneity in one paper (27), and then conducted subgroup analysis (see **Annex 10**). We removed this paper, finding that heterogeneity $I^2 = 0\%$, which might be related to its quality. The results showed statistical differences between the groups [MD = −10.75, 95% CI (−16.84, −4.67)] (see **Figure 12**). The meta-analysis showed that that the combination of DSP with aspirin was effective in reducing PAMG in patients with CHD. The quality of this part was very low according to the GRADE standard (see **Table 2**).

Thromboxane B_2 (TXB_2)

Figure 13 shows that 4 of the papers reported the effect of DSP combined with aspirin on TXB_2 in patients with CHD. The studies included 406 cases: 203 in the experimental group, and 203 controls. The heterogeneity test showed statistical significance ($P = 1.00$, $I^2 = 0\%$), thus the random effect

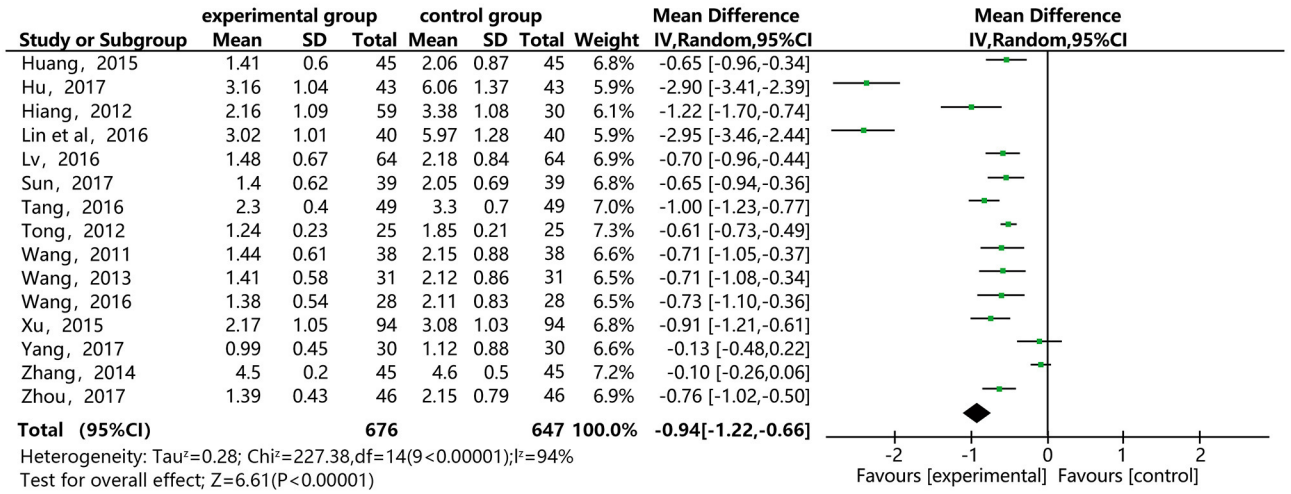


FIGURE 5 | Meta-analysis forest map for the effect of DSP combined with aspirin on TG in patients with CHD.

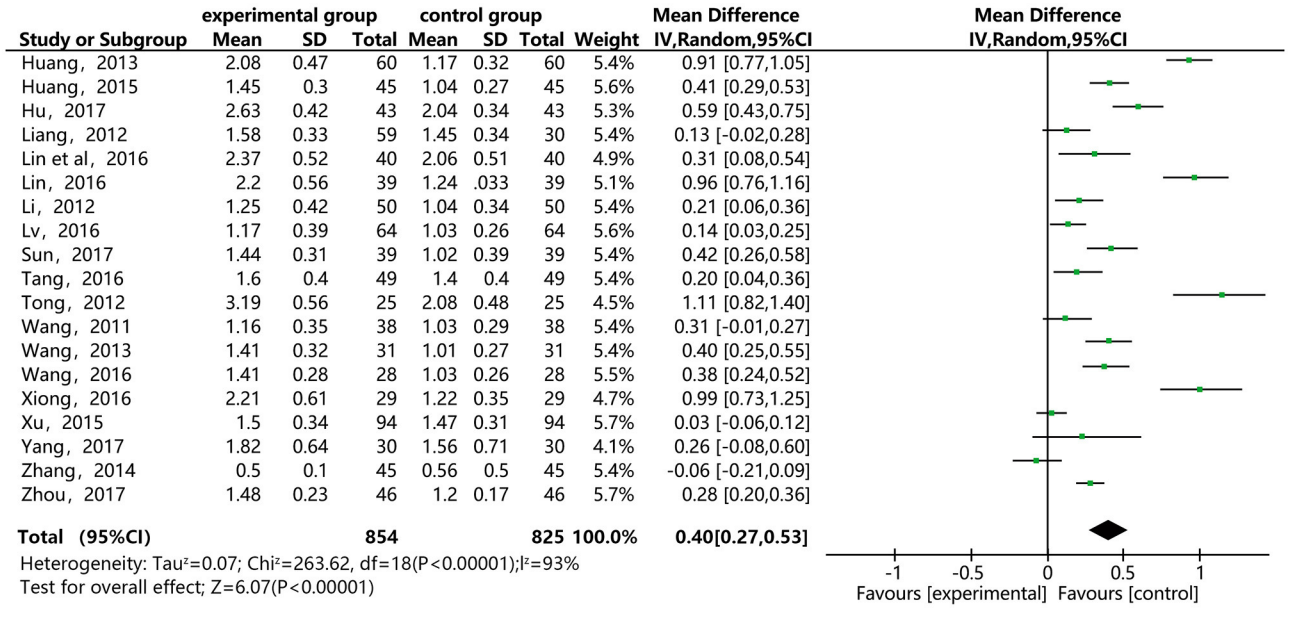


FIGURE 6 | Meta-analysis forest map for of the effect of DSP combined with aspirin on HDL-C in patients with CHD.

model was used for meta-analysis. The results showed statistical differences between the groups [MD = −11.84, 95% CI (−14.75, −8.92)] (see **Figure 13**). The meta-analysis showed that that the combination of DSP with aspirin was effective in reducing TXB_2 in patients with CHD. The quality of this part was very low according to the GRADE standard (see **Table 2**).

DISCUSSION

CHD is frequently encountered in clinical practice, primarily in middle-aged and elderly patients, with angina pectoris as a common clinical symptom (32). It also has great impact on cardiovascular and other tissues. Its aggravation can induce significant complications, such as myocardial infarction and thrombosis, posing a serious threat to life. Thus, great attention should be paid to CHD. Conservative therapy is usually used to treat CHD in current clinical practice, using Western antiplatelet agents as major therapeutic drugs. Aspirin is an effective antithrombotic drug used to treat the secondary complications of primary atherosclerotic and atherosclerosis thrombotic diseases (32, 33). Studies have shown that regular use of aspirin can effectively reduce the occurrence of myocardial infarction, ischemic stroke, and lethal coronary artery diseases (34), but in recent years there have been reports of resistance to antiplatelet agents, including aspirin, and increased dosage causing severe

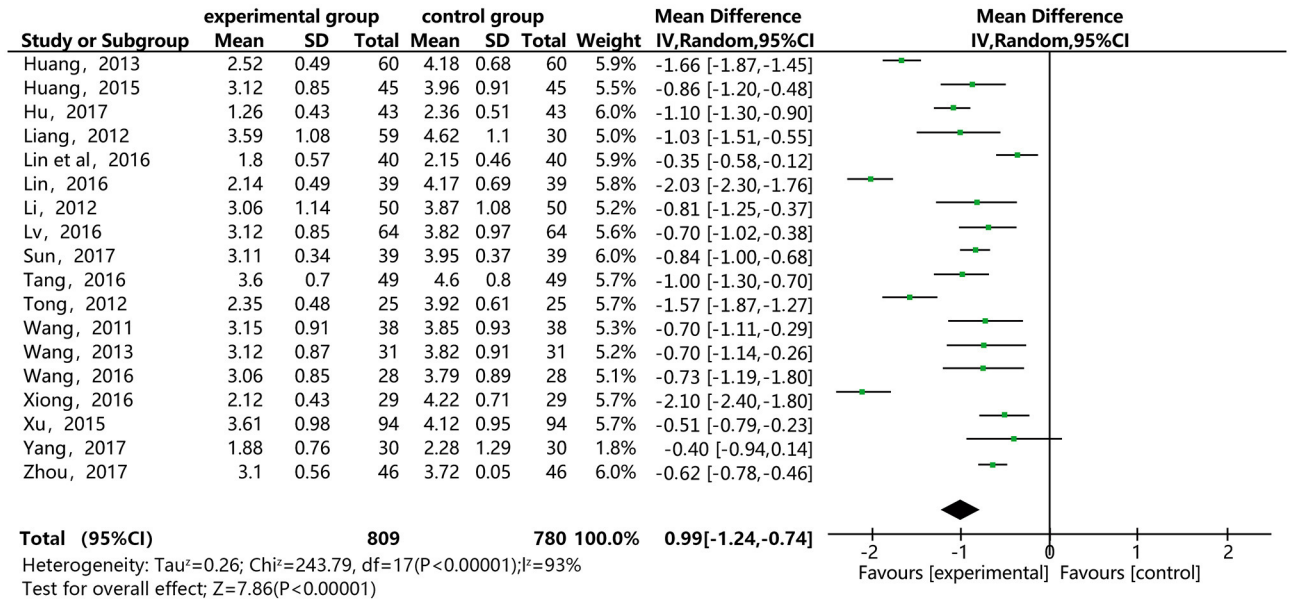


FIGURE 7 | Meta-analysis forest map for the effect of DSP combined with aspirin on LDL-C in patients with CHD.

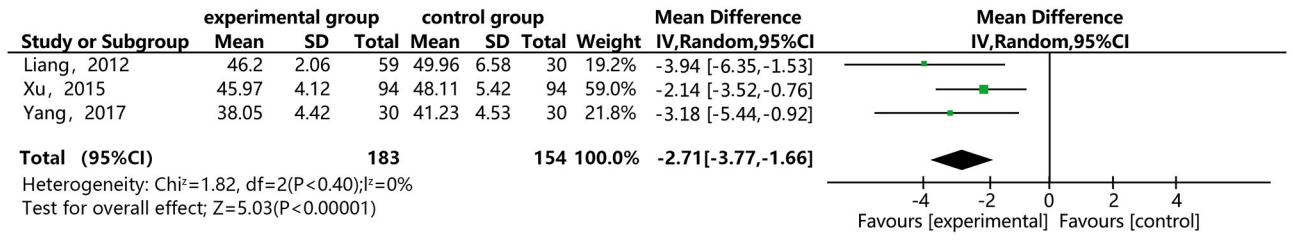


FIGURE 8 | Meta-analysis forest map for the effect of DSP combined with aspirin on hematocrit in patients with CHD.

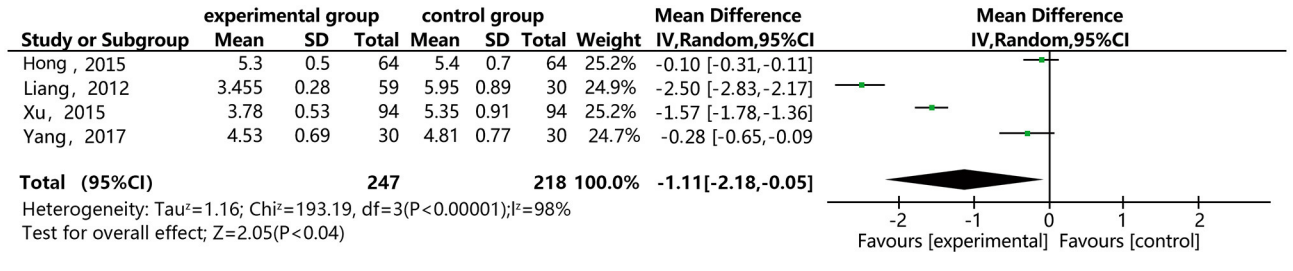


FIGURE 9 | Meta-analysis forest map of the effect of DSP combined with aspirin on high shear blood viscosity in patients with CHD.

gastrointestinal reactions. Thus, its efficacy has been questioned. The main ingredients of DSP include salvia miltiorrhiza, pseudo-ginseng, and borneol (35). Salvia miltiorrhiza is effective in promoting blood circulation and dispersing stasis, and has been proved by modern pharmacological research to inhibit platelet adhesion and aggregation, reduce blood viscosity, accelerate red blood cell flow, regulate internal and external blood coagulation, and promote fiber dissolution. Pseudo-ginseng is effective in tonifying *qi* and blood, easing pain, eliminating blood stasis, reducing blood sugar and lipids, and improving immunity. Borneol is effective against inflammation and bacteria, improving coronary flow and reducing myocardial consumption of oxygen (36).

At present, clinical trial methods for various clinical treatments of CHD (including: TCM treatment) are not of high quality, and clinical evidence is weak. On this basis, a Meta

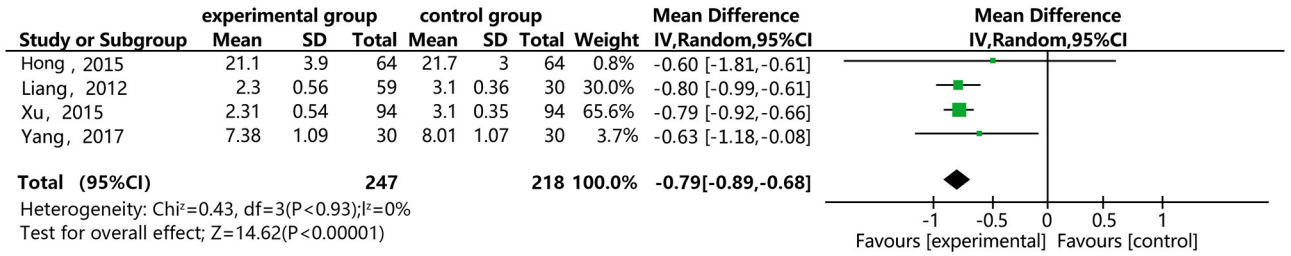


FIGURE 10 | Meta-analysis forest map for the effect of DSP combined with aspirin on low shear blood viscosity in patients with CHD.

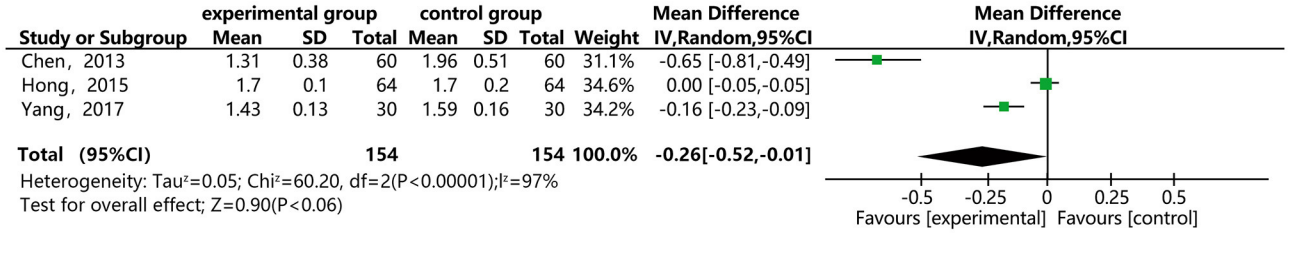


FIGURE 11 | Meta-analysis forest map for the effect of DSP combined with aspirin on plasma viscosity in patients.

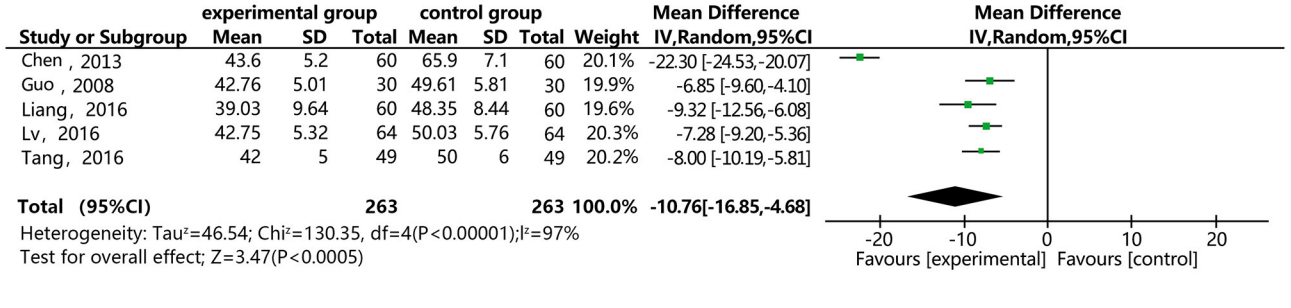


FIGURE 12 | Meta-analysis forest map of the effect of DSP combined with aspirin on PAMG in patients with CHD.

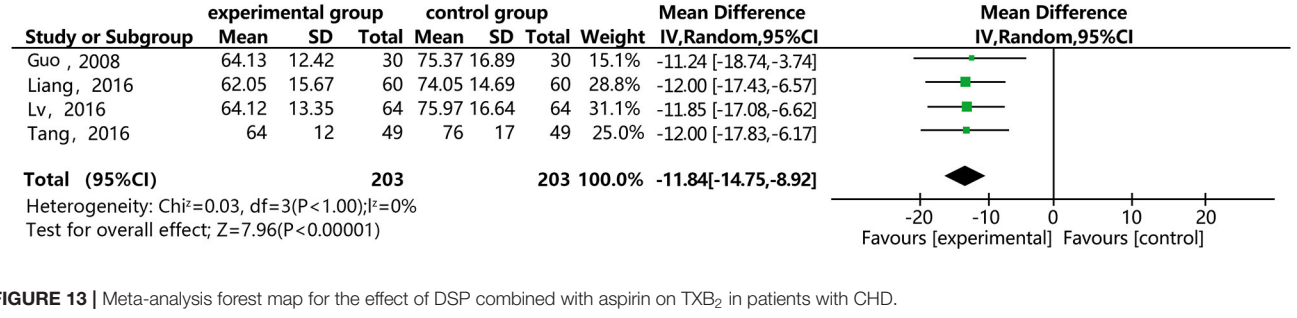


FIGURE 13 | Meta-analysis forest map for the effect of DSP combined with aspirin on TXB_2 in patients with CHD.

analysis was carried out in our study. Studies have shown that the combination of DSP with aspirin can effectively treat CHD and reduce adverse reactions in patients, improving to their prognosis (37). In this study, in patients treated with DSP combined with aspirin, HDL-C rose to a normal level, and LDL-C decreased to a normal level, achieving a better effect than treatment with aspirin alone. Previous research has shown that DSP, which has high stability and is not easily decomposed, can act for a long time to effectively regulate blood lipids in patients. In this study, TC, TG and LDL-C decreased more significantly in the patients treated with DSP combined with aspirin, than in those treated by aspirin alone (38). Where difference was statistically

significant. However, since the included studies were of lower quality and higher heterogeneity, these results should be treated with a certain amount of caution. In recent years, numerous studies on combine therapy in Middle-aged and Elderly Patients with CHD have been published. For example: in a study of Meta analysis of Meta Analysis Based on Efficacy and Safety of Aspirin and Clopidogrel in the Treatment of Elderly Patients with Coronary Heart Disease, this combined therapy was effective and safe for CHD (39). Compared with this study, our study possessed two features: (1)Because clopidogrel and aspirin are prone to dependence after long-term service, Chinese patent medicine combined with western medicine has higher clinical safety than two kinds of western medicine, which is more suitable for clinical promotion. (2) Our study involved more literature review (18 vs. 22). However, publication bias was the main reason for influencing the validity of results of the Meta analysis, because it was the main basis for making a conclusion to obtain the published studies. Moreover, positive results were over-emphasized by some editors or in some magazines, so that some negative results were concealed. Meanwhile, a loss of literature could be caused by an insufficient retrieval method and various other reasons. In our study, the analysis of the effective rate showed no publication bias; however, since four other indices were limited by too small a sample size, the corresponding analysis was not made.

This systematic evaluation and Meta analysis were performed strictly according to the PRISMA Statement: it first evaluated the clinical efficacy and safety of Aspirin with Combined Compound Danshen Dropping Pills on the treatment in Middle-aged and Elderly Patients with CHD. it evaluated how standard the clinical trial was from a methodological point of view, and also offered a direction for further study. However, it is important to note that our study still had certain limitations: (1) The included literature was of low quality; the generation of random allocation sequences and the concealment of randomization protocols were not reported in some studies; the conditions of dropout and withdrawal from the study were not described in detail; certain problems occurred (such as missing study data), which influenced the evidence level and popularization degree. (2) Cases were not fully included according to generally recognized international diagnostic criteria; standard uniform outcome measurement indices were not observed; a subjective composite outcome scoring index was adopted and the evaluation criteria for efficacy was formulated by ourselves. (3) Treatment courses were shorter; there were no important clinical indices for long-time observation, and the superiority of TCM combine drugs in terms of overall efficacy could not be fully displayed. (4) The study have registered Prospero, but the registration is not approved yet. It is a concern as it introduces potential bias to the review and does not align with Cochrane guidance.

CONCLUSION

At present, Aspirin with Combined Compound Danshen Dropping Pills in the treatment of CHD is a safer, more effective method of therapy for CHD. It has various advantages, such as high clinical effectiveness, TC, TG, and LDL-C decreased more significantly in the patients treated with DSP combined with aspirin, than in those treated by aspirin alone. It is worthy of clinical popularization and application. Since the original studies were of too low quality, a strict standard clinical trial should be made for verification in the future under the premise that the TCM characteristics is ensured.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

ZL and GL took part in the design of the study, performed the literature survey, and drafted the manuscript. YWM took part data management implementation of the study. LL was responsible for statistical analysis and the methodological design of study. All authors have made substantive contributions to this study in regard to design and implementation. All the authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.664841/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Chinese Medicine Combined With EGFR-TKIs Prolongs Progression-Free Survival and Overall Survival of Non-small Cell Lung Cancer (NSCLC) Patients Harboring EGFR Mutations, Compared With the Use of TKIs Alone

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Objective: To explore the efficacy comparison between epidermal growth factor receptor–tyrosine kinase inhibitors (EGFR-TKIs) combined with traditional Chinese medicine (TCM) and single EGFR-TKIs for advanced non-small cell lung cancer (NSCLC).

Methods: A total of 91 NSCLC patients with EGFR mutation were divided into an experimental group and a control group (in a ratio of 2:1) to receive TCM and EGFR-TKIs (61 cases) or single EGFR-TKIs (30 cases). Patients in the control group took EGFR-TKIs and those in the experimental group took EGFR-TKIs plus TCM. We analyzed the progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and treatment-related adverse events of two groups.

Results: The mPFS of the experimental group and the control group was 12.3 and 8.9 months ($P = 0.02$), respectively, and the mOS of the experimental group and the control group was 28.2 and 24.2 months ($P = 0.02$), respectively. Subgroup analysis showed that for the patients with exon 19 deletion mutation (19DEL), mPFS between experimental group and control group was 12.7 and 10.1 months, respectively ($P = 0.12$). For exon 21 deletion mutation (L858R), the PFS of two groups was 10.8 vs. 8.2 months, respectively ($P = 0.03$). The subgroup analysis also showed that, for the patients with exon 19 deletion mutation, mOS between the experimental group and the control group was 30.3 and 28.7 months, respectively ($P = 0.19$). For exon 21 deletion mutation, the mOS of two groups was 25.5 vs. 21.3 months, respectively ($P = 0.01$). The DCR of the experimental group and the control group was 93.3% and 80.1%, respectively ($P = 0.77$). Grade 3–4 treatment-related adverse events were less common with the experimental group (11.48%) than the control group (26.67%).

Conclusion: For NSCLC patients with EGFR mutation, EGFR-TKIs combined with TCM had a certain effect to prolong mPFS and mOS, compared with the use of EGFR-TKIs alone, especially for the patients with L858R. This conclusion has a significant effect on improving the survival of NSCLC patients after EGFR-TKIs resistance. It deserves further study.

Keywords: traditional Chinese medicine, non-small cell lung cancer, progression-free survival, overall survival, cohort study, disease control rate

BACKGROUND

Lung cancer ranks first in the incidence and mortality of malignant tumors in China, accounting for 18% of newly diagnosed cases in 2018, and more than 690,000 people died as a result (1). Lung cancer also has a high morbidity and mortality among all malignancies in the world today (2). According to histological type, it can be divided into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), the latter accounting for about 80–85% (3). Surgical treatment is the radical cure for patients with early- and middle-stage NSCLC in the National Comprehensive Cancer Network (NCCN) guidelines. However, due to the lack of typical clinical manifestations, early screening of lung cancer is difficult. Most of them have diagnosed at advanced stage and have lost the opportunity for surgery. Patients generally have a poor prognosis.

At present, the choice of first-line treatment for advanced NSCLC is based on the presence or absence of specific gene mutations, and epidermal growth factor receptor (EGFR) mutations are the most common gene mutations in Asian NSCLC patients (about 50%) (4). For NSCLC patients with EGFR mutations, the first-line treatment is epidermal growth factor receptor–tyrosine kinase inhibitors (EGFR-TKIs). Compared with chemotherapy, many studies have shown that EGFR-TKIs can significantly improve the progression-free survival (PFS), objective response rate (ORR), and quality of life of patients with advanced NSCLC (5).

However, while patients obtain considerable clinical benefits, the inevitable drug resistance after 9–12 months of medication has greatly limited the clinical application of EGFR-TKIs (6). Therefore, how to enhance the efficacy of EGFR-TKIs and delay drug resistance is a current research focus of advanced NSCLC. In addition to combined chemotherapy, targeted therapy or timely replacement of new-generation TKI preparations (7–9), a number of studies have shown that traditional Chinese medicine (TCM) combined with EGFR-TKIs can improve the quality of life of patients, further prolong patient survival, reduce side effects, and increase curative effect. It also has a definite effect on reversing EGFR-TKIs obtained resistance (10). Therefore, this study aimed to use a cohort study method to analyze the efficacy of TCM combined with EGFR-TKIs in the first-line treatment of advanced NSCLC.

MATERIALS AND METHODS

Diagnostic, Inclusion, and Exclusion Criteria

The diagnostic criteria for advanced lung cancer refer to the Diagnosis and Treatment Specifications for Primary Lung Cancer (2018 edition) (11) and the staging criteria refer to the 8th Edition of the International Lung Cancer TNM Phase formulated by the International Society for Lung Cancer Research (IASLC) in 2015 (12).

Inclusion criteria: (1) Patients older than 18 years. (2) Clinical or pathological diagnosis of stage III B-IV, tissue, body fluid, or cytological genetic test showing exon 19 deletion mutation or exon 21 point deletion mutation (also known as 19DEL and L858R, respectively). (3) Eastern Cooperative Oncology Group Performance Status (ECOG-PS) 0–3 points. (4) Patients expected survival time is >3 months. (5) All enrolled patients signed an informed consent form.

Exclusion criteria: (1) Patients with clinically significant cardiac dysfunction, renal dysfunction, hepatic dysfunction, active infection, or neurologic or psychiatric disorders. (2) Patients administered Chinese medicine for <3 months or if the interval is prolonged to 1 week. (3) The patients were also participating in any other pharmaceutical research. (4) Patients lost to follow-up.

Study Design

This is a cohort study that included a total of 91 patients with NSCLC. Eligible patients were recruited from First Hospital Affiliated Hospital of Chongqing Medical University and Hospital of Chengdu University of Traditional Chinese Medicine. Patients were divided into an experimental group and a control group (in a ratio of two to one), to receive TCM and EGFR-TKIs (61 cases) or single EGFR-TKIs (30 cases). Patients in the control group were administered EGFR-TKIs and the experimental group were administered EGFR-TKIs plus TCM. Patients in both groups were followed up in outpatient clinics or by telephone every month, and CT (Computed Tomography) or MRI (Magnetic Resonance Imaging) was checked every 3 months to evaluate the curative effect. The patients were followed up until death or the end of clinical trial.

Drug Administration

Patients in the control group were administered EGFR-TKIs (gefitinib 250 mg/days, erlotinib 150 mg/days, or icotinib 125 mg

tid). Patients in the experimental group were given TCM orally on the basis of the same dosage of EGFR-TKIs, one prescription was decocted in water and administered three times a day, 30–50 ml each time.

The basic composition of TCM includes the following: *Huangqi (Astragalus)* (60 g), *Ginseng* (20 g), and *Rhizoma atractylodis macrocephalae* (15 g). For cough symptoms, add *apricot kernel* (10 g) and *Platycodon grandiflorus* (10 g). For symptoms of excessive phlegm, add *Rhizoma pinellinae praeparata* (15 g) and *Dried tangerine peel* (10 g). For symptoms of dizziness and shortness of breath, add *Schisandra seed* (10 g) and *white hyacinth bean* (20 g). For symptoms of diarrhea, add *Rhizoma coptidis* (5 g). For symptoms of night sweats, add *Ophiopogon japonicus* (20 g) and *Radix adenophora* (15 g). For symptoms of rash, add *Honeysuckle* (15 g), *Forsythia* (15 g), and *Cortex Phellodendri* (15 g).

Evaluation Index

The main observation index is PFS, which is defined as the time from the start of treatment to the first tumor progression or death of the patient due to any reason. The secondary endpoints include overall survival (OS), disease control rate (DCR), and adverse drug reactions. OS is from the time the patient was enrolled to death by any cause or the time of last follow-up. DCR is defined as complete response (CR) + partial response (PR) + stable disease (SD), and tumor progression is evaluated according to the evaluation standards of the WHO.

Follow-Up

Follow-up in the outpatient clinic or telephone every 2–4 weeks, and check CT or MRI every 2 months to evaluate the disease control rate until death or the time of the last follow-up. Patients who did not attend the outpatient clinic or could not be contacted by phone more than three times (no answer, shutdown, or refusal to answer) were considered as lost cases. The follow-up period started from the first patient enrolled on January 17, 2016, and the last follow-up time was January 31, 2019. The total follow-up time was 36 months. The median follow-up time was 26.2 months (23.5–28.9 months).

Statistical Analysis

Statistical analysis was performed using SPSS21.1 statistical software: baseline data were analyzed by χ^2 test, curative effect analysis was performed by rank sum test, PFS risk ratio was used for Cox regression model, PFS and OS were tested by Kaplan–Meier and Logrank, and GraphPadPrism6 was used to draw survival curve. $P < 0.05$ was considered statistically significant.

RESULTS

Characteristics of Study Participants

From January 2016 to January 2019, 109 patients with NSCLC-sensitive EGFR mutation were included in the study. Among them, three patients were excluded because they did not meet the criteria, five patients were excluded because they were unwilling to participate in the trial, and three patients were excluded due to personal reasons. Finally, they were randomly divided into experimental group (65 cases) and control group (33 cases) according to the ratio of 2:1. During the follow-up period, five cases were lost in the experimental group, one case was lost, and one case was withdrawn due to severe allergic reaction in the control group. There was no significant difference in age, gender, mutation site, clinical stage, PS score, targeted drugs, and brain metastases between the two groups, as shown in **Table 1** ($P > 0.05$).

TABLE 1 | Characteristics of patients [*n* (%)].

Characteristics	Experimental group ($n = 60$)	Control group ($n = 31$)	χ^2	*P*
Sex				
Male	27 (45.0%)	11 (35.5%)	0.761[a]	0.38
Female	33 (55.0%)	20 (64.5%)		
Age				
<60 years	24 (33.3%)	12 (38.7%)	0.014[a]	0.90
≥60 years	36 (66.7%)	19 (61.3%)		
Gene inspection				
Exon 19 deletion	38 (63.3%)	21 (67.7%)	0.174[a]	0.67
Exon 21 deletion	22 (36.7%)	10 (32.3%)		
Clinical stage				
Stage IIIB	9 (15.0%)	5 (16.1%)	0.020[a]	0.88
Stage IV	51 (85.0%)	26 (83.9%)		
PS Score				
0–2 points	52 (86.7%)	26 (83.9%)	0.130[a]	0.72
3 points	8 (13.3%)	5 (16.1%)		
Targeted therapy				
Gefitinib	53 (88.3%)	25 (80.6%)	1.060[a]	0.60
Erlotinib	4 (6.7%)	3 (9.7%)		
Icotinib	3 (5.0%)	3 (9.7%)		
Brain metastases				
Exist	11 (18.3%)	5 (16.1%)	0.069[a]	0.79
Not exist	49 (81.7%)	26 (83.9%)		

[a] *Represents the χ^2 value for the chi-square test.*

mPFS

The mPFS of the experimental group treated with EGFR-TKIs and TCM was 12.3 months, which was 3.4 months longer than the 8.9 months mPFS of the control group only using EGFR-TKIs [**Figure 1**, hazard ratio (HR) = 0.46, 95% CI = 0.23–0.94, $P = 0.002$].

Subgroup Analysis of mPFS

For 19DEL patients, the mPFS of the experimental group and the control group were 12.7 and 10.1 months, respectively (**Figure 2**, HR = 0.54, 95% CI = 0.23–1.27, $P = 0.11$). For L858R patients, the mPFS of the experimental group was 10.8 months, which was significantly better than the control group at 8.2 months (**Figure 3**, HR = 0.32, 95% CI = 0.08–1.40, $P = 0.003$).

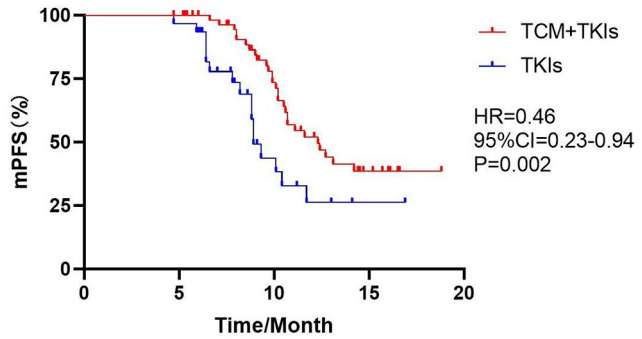


FIGURE 1 | Comparison of mPFS by two groups.

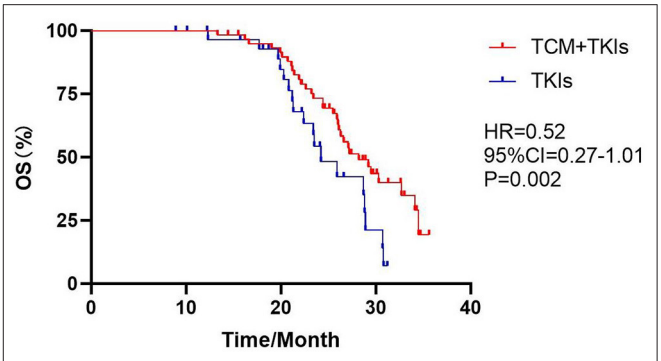


FIGURE 4 | Comparison of mOS by two groups.

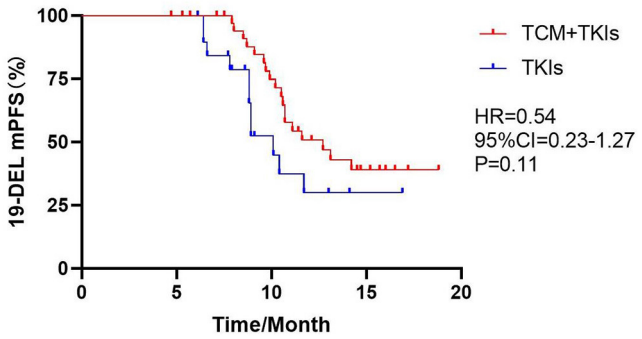


FIGURE 2 | Comparison of 19DEL mPFS by two groups.

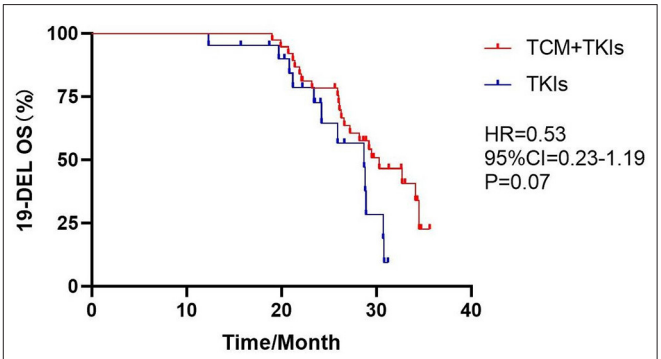


FIGURE 5 | Comparison of 19DEL mOS by two groups.

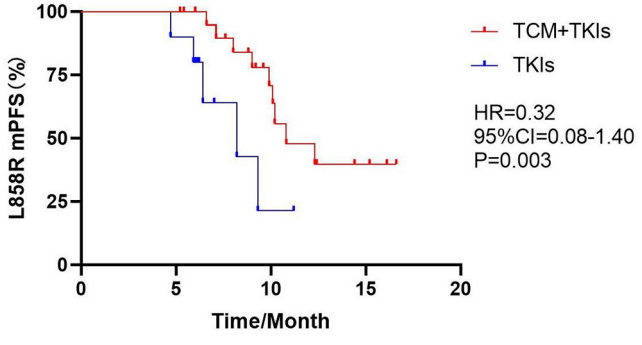


FIGURE 3 | Comparison of L858R mPFS by two groups.

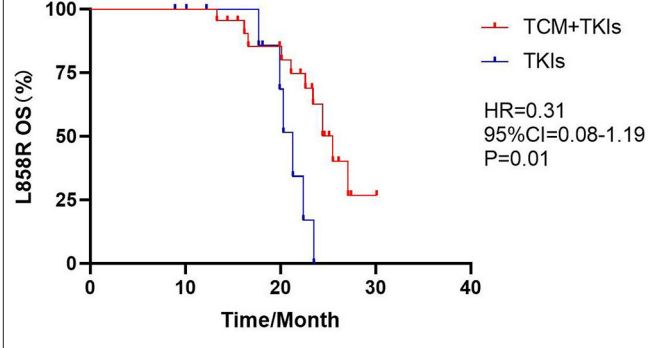


FIGURE 6 | Comparison of L858R mOS by two groups.

mOS

The mOS of the experimental group and the control group were 28.2 and 24.2 months, with statistical differences (**Figure 4**, HR = 0.52, 95% CI = 0.27–1.01, $P = 0.002$).

Subgroup Analysis of mOS

For 19DEL patients, the mOS of the experimental group was 30.3 months and that of the control group was 28.7 months; there was no statistical difference (**Figure 5**, HR = 0.53, 95% CI = 0.23–1.19, $P = 0.07$). For L858R patients, the mOS of the experimental group was 25.5 months, which was clearly better than the control group of 21.3 months (**Figure 6**, HR = 0.31, 95% CI = 0.08–1.19, $P = 0.01$).

DCR

The DCR of the experimental group and the control group was 93.3 and 80.1%, respectively ($P = 0.18$); there was no statistical difference, as shown in **Table 2**.

TABLE 2 | DCR (*n*, %), ($P = 0.18$).

Group	CR	PR	SD	PD	DCR
Experimental group	0 (0%)	38 (63.3%)	18 (30.0%)	4 (6.7%)	56 (93.3%)
Control group	0 (0)	14 (45.1%)	11 (35.5%)	6 (19.4%)	25 (80.1%)

TABLE 3 | Adverse reaction comparison table (*n*, %), ($P = 1$).

	EGFR-TKIs plus TCM (*n* =61)		EGFR-TKIs (*n* =30)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Adverse reaction	48 (78.69%)	7 (11.48%)	36 (120%)	8 (26.67%)
Rashes	27 (44.26%)	3 (4.92%)	21 (58.33%)	4 (13.33%)
Diarrhea	11 (18.03%)	3 (4.92%)	6 (20.00%)	3 (16.67%)
ALT/AST increasing	6 (9.84%)	1 (0%)	4 (13.33%)	1 (3.33%)
Dental ulcer	4 (6.56%)	0 (0%)	3 (10.00%)	0 (0%)
Paronychia	0 (0%)	0 (0%)	2 (6.67%)	0 (0%)

Drug-Related Adverse Reactions

The incidence of grade 3–4 serious side effects such as skin rash, diarrhea, liver damage, oral ulcers, paronychia, etc. between the two groups was as follows: 11.48% in the experimental group and 26.67% in the control group; there was no statistical difference ($P = 1$), as shown in **Table 3**.

DISCUSSION

In China, the number of deaths due to cancer in 2014 was as high as 2.296 million, of which lung cancer accounted for 27.3% (13). Surgical radical treatment is still the first choice for lung cancer, but due to atypical early symptoms, about 70% of patients are diagnosed in the late stage, and the 5-years survival rate tends to be <10% (14). Adjuvant chemotherapy is recommended as a traditional first-line treatment; although its curative effect is objective, it has entered a bottleneck period. With the deepening of the world's tumor molecular biology research, lung cancer targeted therapy has made outstanding achievements, especially the EGFR-TKIs, which has significantly improved the life cycle of lung cancer patients in the past 10 years. According to NCCN Non-small Cell Lung Cancer Clinical Practice Guidelines (Version 1.2021), TKIs are the first-line treatment for patients with EGFR-sensitive mutations. Compared with chemotherapy, TKIs can effectively prolong the PFS of patients, but it cannot be ignored that almost all patients will develop acquired drug resistance after 9–12 months. Therefore, how to enhance the efficacy of EGFR-TKIs and delay drug resistance is an issue to be explored in-depth.

TCM has its unique advantages in the treatment of tumors. It is a unique treatment method with obvious advantages in cancer treatment in China. Chinese medicine has a very early understanding of tumors. As early as 3,500 years ago, there was a record of "tumor" in the oracle bone inscriptions of the Shang Dynasty. With the development of medicine, TCM has changed from the past macro differentiation to the use of modern medical technology to use micro syndrome differentiation to unify prevention and treatment, forming a model of integrated Chinese and Western medicine treatment of tumors with Chinese characteristics. By reviewing many domestic and foreign experimental studies on the treatment of tumors with TCM, we found that TCM can effectively improve the sensitivity of radiotherapy and chemotherapy, minimize the toxic and side effects of radiotherapy and chemotherapy, reduce the recurrence and metastasis of tumor, completely cure the patients with tumors who have received radical treatment, improve the quality of life of patients with advanced tumors, and prolong the survival of patients to achieve "survival with tumors" (15).

In the study of TCM combined with EGFR-TKIs, a number of clinical and basic experiments have confirmed that TCM has the characteristics of multiple pathways, targets, and pharmacological effects, and hard-to-produce drug resistance. It can achieve anti-tumor effects by regulating multiple pathways, effectively reduce the toxic and side effects of TKIs, increase TKIs' sensitivity, and even overcome drug resistance and improve survival benefits (16). Studies have found that many extracts of TCM can reverse the acquired resistance of EGFR: such as astragaloside IV (17), resveratrol (18), curcumin (19), shikonin (20), dihydroartemisinin (21), *Sophora flavescens* (22), *Taxus* (23), Paris saponin (24), etc. Wang et al. through prospective cohort experiments found that the comprehensive treatment program of TCM was not inferior to the maintenance chemotherapy program of modern medicine in prolonging mPFS and mOS in patients with advanced NSCLC. Compared with the control group, the mOS of the treatment group using TCM alone was 75 days longer and showed advantages in terms of low adverse reactions and high quality of life (25). After conducting a cohort study of 60 patients, Zhang et al. found that the PFS of Yiqi Tongluo Jiedu Decoction combined with targeted treatment group was 29.5 months, which was significantly different from that of the single target treatment group, which was 12.4 months (26). Jiang et al. through a cohort study, found that the mPFS of patients in the experimental group treated with Ginsenoside Rg3 combined with Osimertinib was 16 months, which was better than the 13 months of patients in the control group treated with Osimertinib alone (27).

This study collected the clinical data from Chengdu First People's Hospital and Hospital of Chengdu University of Traditional Chinese Medicine to explore the role of TCM on EGFR-TKIs in improving the prognosis of NSCLC patients with EGFR mutations. PFS and OS are important evaluation indicators for the treatment efficacy of advanced lung cancer and also reflect the therapeutic benefit from the aspects of tumor control and OS time. In this study, the mPFS and mOS of patients who used EGFR-TKIs alone were 9.3 and 23.4 months, which were basically consistent with previous studies and related reports (28–30). However, after combined treatment with TCM, the mPFS and mOS of the experimental group were increased to 12.3 and 28.2 months, mPFS has been prolonged by 3.4 months, and mOS has been prolonged by 4 months. Compared with similar studies, with the extension of follow-up time, the mPFS of the study sample did not change much, but the analysis and comparison found that there was a statistical difference in mOS of the two groups of patients, reflecting the efficacy advantage of TCM combined with TKIs. However, it is worth noting that after

the disease progression of the enrolled 44 patients, 13 patients stopped EGRF-TKIs treatment and switched to chemotherapy, 15 patients received chemotherapy on the basis of the original EGRF-TKIs treatment, and 10 patients chose to combine other targeted therapies (seven of them used bevacizumab and three used cetuximab), and six patients chose to use third-generation TKIs after detecting the T790M mutation positive, and they were all included in the mOS observation. This may have an impact on the results. Since there seems to be no obvious difference in the proportion of patients between the two groups after changing the treatment plan, and the number of patients is small, data analysis was not performed. However, this trial has continuity and is still under follow-up. In the future, with the gradual increase of sample size, if there are representative results in the follow-up statistics, we will conduct further data analysis. Although some studies have shown that chemotherapy combined with EGFR-TKIs can prolong mPFS by about 5 months than single EGFR-TKIs (31–33), patients in such studies tended to have lower PS scores (0–1 points) and better physical fitness, while patients with better physical condition benefit more from chemotherapy (34); the PS scores of patients included in this study are relatively poor (mostly 2–3 points). It should not be overlooked that although first-line chemotherapy is effective at the initial stage, most patients will progress in 3–4 months (35), and the proportion of patients who can continue to receive second-line chemotherapy is only 30–40% (36), and the efficiency is only about 10% (37). In addition, using EGFR-TKIs combined with chemotherapy and radiotherapy as the first-line treatment will limit the choice of second-line treatment options after tumor progression, while using EGFR-TKIs alone as the first-line treatment, radiotherapy and chemotherapy can also be used as an effective second-line regimen after tumor progression.

The most common EGFR gene mutations in NSCLC are 19DEL and L858R. There is heterogeneity in the predictive effect of different mutation sites for TKIs treatment, and the prognoses of patients with 19DEL and L858R are different. Several studies have shown that although the initial response of EGFR-TKIs to 19DEL NSCLC patients and L858R is similar, the mPFS and mOS of 19DEL patients are significantly higher than those of L858R patients (38–40), and this difference may be attributed to the resistance mechanism. Compared with 19DEL, L858R lung cancer patients have a weaker response to TKI treatment, a worse prognosis, and less survival benefit (mPFS: 9.0 vs. 7.0 months, mOS: 25 vs. 16 months) (41, 42). Relevant studies suggest that patients with exon 21 deletion mutations benefit more when treated with TCM combined with EGFR-TKIs, and mPFS is prolonged by 5 months (14). However, the sample size of this study is larger, and with the extension of follow-up time, the analysis and comparison found that the mOS of the two groups of patients with different mutation sites also has significant differences. For 19DEL patients, the mOS of the control group was 30.3 months, while that of the experimental group was 28.7 months, and the mOS was only prolonged by 1.6 months, with no statistical difference. The reason may be that the insufficient sample size and the low level of evidence-based effect make the difference between the two groups not obvious. For L858R patients, the mOS treated with EGFR-TKIs alone was only 21.3 months, which is basically consistent with the related literature reports (43–45). In this study, the mOS can be extended to 25.5 months after EGFR-TKIs combined with TCM. This suggests that exon 21 deletion mutation patients have greater benefits for mPFS and mOS after combined treatment with TCM in EGFR-TKIs treatment. The result of this research have not been found on domestic and foreign literature websites, and this study is the first article to discover and report this result.

In addition, in this study, the DCR of the control group was 80.1%, and the drug-related adverse reactions were 26.67%. After the combined treatment of TCM, the DCR of the experimental group increased to 93.3%, and the drug-related adverse reactions decreased to 11.48%. Although there was no statistical difference in the disease control rate and drug-related adverse reactions, it also showed that the combination of the two drugs had a tendency to enhance the therapeutic efficacy and reduce the drug side effects.

CONCLUSION

In conclusion, the choice of EGFR-TKIs combined with TCM as first-line treatment can achieve longer mPFS than EGFR-TKIs treatment alone and has a clear prolongation of patient survival, especially for exon 21 deletion mutations. Compared with other studies, this study supports the idea that EGFR-TKIs combined with TCM treatment can effectively delay the development of disease and prolong the survival of patients, which can provide more survival possibilities and basis for patients with advanced NSCLC, especially for the patients with exon 21 deletion mutation who have poor efficacy in the first generation of EGFR TKIs. However, there are still some shortcomings in this study. First of all, this study was a cohort study with a low level of evidence base, and there may be some bias affecting the results. For example, the ingredients of TCM water decoction are difficult to stabilize, the number of patients is different between the two groups, the optimal administration time is unknown, etc. Secondly, although this study to some extent proves the effectiveness of TCM in the treatment of advanced NSCLC, the comprehensive treatment of TCM is more complex, the quality control is difficult, and the follow-up time of patients collected in the later stage is shorter. All of these may have some impact on the outcome judgment. In the later stage, we will continue to follow up and strive to obtain longer OS data to continue data analysis to provide more rigorous and high-level evidence for the treatment of advanced NSCLC with Chinese medicine combined with TKIs.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethics Committee of the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine. The

patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Comparison of Two Malnutrition Assessment Scales in Predicting Postoperative Complications in Elderly Patients Undergoing Noncardiac Surgery

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Background: The present study was designed to investigate the relationship between two malnutrition assessment scales, perioperative nutrition screen (PONS) and Nutritional Risk Screening 2002 (NRS2002), with postoperative complications in elderly patients after noncardiac surgery.

Methods: This was a secondary analysis of a prospective cohort study. Elderly patients (65–90 years) undergoing noncardiac surgery were enrolled in Peking University First Hospital. Malnutrition was screened by PONS and NRS2002 at the day before surgery. Multivariable analysis was employed to analyze the relationship between PONS and NRS2002 and postoperative 30-day complications. Receiver operating characteristic (ROC) curve was generated to evaluate the predictive value of PONS and NRS2002 in predicting postoperative complications.

Results: A total of 915 patients with mean age of 71.6 ± 5.2 years were consecutively enrolled from September 21, 2017, to April 10, 2019. The incidence of malnutrition was 27.3% (250/915) by PONS $\geq$ 1 and 53.6% (490/915) by NRS2002 $\geq$ 3. The overall incidence of complications within postoperative 30 days was 45.8% (419/915). After confounders were adjusted, malnutrition by PONS $\geq$ 1 (OR 2.308, 95% CI 1.676–3.178, $P < 0.001$), but not NRS2002 $\geq$ 3 (OR 1.313, 95% CI 0.973–1.771, $P = 0.075$), was related with an increased risk of postoperative complications. ROC curve analysis showed that the performances of PONS [area under the ROC curve (AUC) 0.595, 95% CI 0.558–0.633] showed very weak improvement in predicting postoperative complications than NRS2002 score (AUC 0.577, 95% CI 0.540–0.614).

Conclusion: The present study found that malnutrition diagnosed by PONS was related with an increased risk of postoperative complications. The performances of PONS and NRS2002 were poor in predicting overall postoperative complications.

Clinical Trial Registration: www.chictr.org.cn, identifier: ChiCTR-OOC-17012734.

Keywords: malnutrition, Nutritional Risk Screening 2002 (NRS2002), perioperative nutrition screen (PONS), postoperative complications, elderly patient

INTRODUCTION

Malnutrition has been considered as a great challenge to patient's safety in perioperative settings (1, 2). It is estimated that 24–51% of surgical patients are at risk of malnutrition (3, 4). The incidence of malnutrition reaches up to 60–86% in the elderly (4, 5). Malnutrition is associated with increased risk of morbidity (i.e., gastrointestinal fistula, wound dehiscence, and infection) and mortality (1–5). Nutrition support in malnourished patients can reduce the risk of postoperative complications such as surgical site infections and gastrointestinal complications (6–8). Selection of proper assessment tools is the key step for early diagnosis and treatment of malnutrition (9).

Perioperative malnutrition can be mainly attributed to inadequate food intake, decreased physical activity, and catabolic metabolic derangements (1, 2). But manifestations of malnutrition vary greatly among surgical patients such as body weight loss, skeleton muscle mass loss, inflammatory response, low serum albumin, and micronutrient insufficiency (i.e., vitamin D) (1, 2). Several terms, "sarcopenia," "cachexia," and "myostetosis," have been advocated to describe the different characteristics and nutritional syndromes of malnourished patients (10). Although the underlying definition of malnutrition phenotypes is complex and challenging, several assessment instruments have been proposed to facilitate clinical diagnosis of malnutrition based on the following core criteria: body mass index (BMI), body weight loss, serum albumin, and oral food intake (1, 2).

There are dozens of tools to assess nutritional status for metabolic care or clinical nutrition purposes (11). Utility of these instruments should be based on patient population. For example, patient-generated subjective global assessment was generated in cancer patients, and geriatric nutritional risk index was used for patients with heart failure (12, 13). In surgical patients, perioperative nutrition screen (PONS) and Nutritional Risk Screening 2002 (NRS2002) are recommended to screen malnutrition (1, 10). There are insufficient data to elucidate their associations with clinical outcomes in elderly Chinese patients.

PONS is developed and proposed by the American Society for Enhanced Recovery for preoperative screening of malnutrition in 2018 (1). PONS is a modified version of the malnutrition universal screening tool and determines the presence of nutrition risk based on BMI, recent body weight loss, decrement of dietary intake, and preoperative albumin concentration (1, 14). NRS2002 is another assessment tool that has been widely validated in perioperative settings (15). Compared with PONS, NRS2002 includes the severity of disease as supplemental parameter (1, 15). In patients undergoing gastrointestinal surgery and hip fracture surgery, malnutrition (diagnosed by NRS2002 $\geq$ 3) is highly related with increased risk of postoperative complications, prolonged in-hospital stay, and mortality (16, 17). However, up to now, there is lack of evidence to illustrate the relationship between PONS and postoperative complications in the elderly surgical patients and which instrument (PONS or NRS2002) has better performance in predicting the risk of postoperative complications.

The present study was designed to investigate the association between two malnutrition assessment scales, PONS and NRS2002, with postoperative complications in elderly patients after noncardiac surgery.

METHODS

The present study was a secondary analysis of a prospective observational study. The ethical approval for this study was provided by the Clinical Research Ethics Committee of Peking University First Hospital (Chairperson Prof Guo Xiaohui) on August 4, 2017 [2017 (1419), Beijing, China], and registered with Chinese Clinical Trial Registry on September 19, 2017 (ChiCTR-OOC-17012734). Written informed consent was obtained from all participants or their legal representatives.

Participants

Elderly patients (aged 65–90 years) were included if they were scheduled to undergo noncardiac surgery with an expected duration $\geq$2 h under general anesthesia. Patients who met any of the following criteria were excluded: (1) refused to participate in the study; (2) previous history of schizophrenia, epilepsy, Parkinson's disease, or myasthenia gravis; (3) unable to communicate due to severe dementia, being comatosed, or language barrier; (4) traumatic brain injury or neurosurgery; or (5) an American Society of Anesthesiologists (ASA) classification of IV or above.

Anesthesia and Perioperative Management

All patients received standard monitoring on arrival in the operating room including electrocardiogram, noninvasive blood pressure, pulse oxygen saturation, and urine output. During general anesthesia, end-tidal carbon dioxide, expired concentration of inhalational anesthetics, and bispectral index (BIS) were also monitored. Invasive arterial pressure and central venous pressure were used when necessary.

Induction of general anesthesia was completed by propofol and/or etomidate, opioids (sufentanil and/or remifentanil), and muscle relaxants (rocuronium or cisatracurium). Anesthesia was maintained with propofol infusion and/or sevoflurane inhalation. Nitrous oxide could be used as supplementary when necessary. Muscle relaxants were administered when considered necessary. The target depth of general anesthesia was to maintain BIS between 40 and 60.

Muscle relaxants were stopped for at least 30 min before the end of surgery; propofol infusion and sevoflurane inhalation were decreased or stopped according to BIS monitoring; sufentanil was administered when considered necessary. At the end of surgery, residual neuromuscular blockade was reversed with 0.05 mg/kg of neostigmine and 0.02 mg/kg of atropine. Patients were extubated when they met the following criteria: (1) easy to wake up; (2) sufficient reflexes that protect the airway; (3) adequate gas exchange (respiration rate 10–30 breaths per minute and tidal volume > 6 ml/kg); and (4) acceptable hemodynamic status (systolic blood pressure $\geq$ 90 mmHg and heart rate $\leq$ 100 beats per minute).

As a routine practice, patients were transferred to the post-anesthesia care unit (PACU) after extubation. Patients were monitored in PACU for at least 30 min and then transferred to the general ward when the Aldrete score was higher than 9.

Nutrition Assessment by Perioperative Nutrition Screen

The criteria of PONS include the level of preoperative albumin and the following three questions: (1) Does the patient have a low BMI <18.5 kg/m^2 (<20 kg/m^2 for patients $>$ 65 years old)? (2) Has the patient experienced weight loss $>$ 10% in the past 6 months? and (3) Has the patient had a reduced oral intake by $>50\%$ in the past week? (1, 18). Patients who had any positive response to the three questions and/or serum albumin <30 g/L were considered as at high risk of malnutrition.

Nutrition Assessment by Nutritional Risk Screening 2002

NRS2002 contains two components: undernutrition and disease severity, giving a total score of 0–6 (15). Undernutrition was estimated by using BMI, percent of recent weight loss, and change in food intake. Each item of impaired nutritional status was classified into absent, mild, moderate, and severe with relevant score of 0–3, respectively. Disease severity is a reflection of stress metabolism, which is divided into normal to severe status with score of 0–3. For example, patients with chronic diseases (i.e., diabetics) are considered as mild grade with a score of three; patients undergoing abdominal surgery are considered as moderate grade with a score of two; and patients with head injury are considered as severe grade with a score of three. Patients are classified as being at nutritional risk when the total score was three or above.

Postoperative Complications

Postoperative complications are defined as new-onset events that have adverse effect on patient's clinical outcome and need medical treatment (i.e., Clavien-Dindo classification grade II or above) (19). Major complications are listed in **Table 1** and include the following items: central nervous system (delirium and stroke), cardiovascular system (myocardial infarction, new-onset arrhythmia, cardiac failure, and pulmonary embolism), respiratory system (pneumonia and respiratory failure), acute kidney injury, surgery-related complications (intestinal obstruction, anastomotic fistula, and bleeding), infection (sepsis, abdominal abscess, and incision infection), and death.

Data Collection and Postoperative Follow-Up

Data collection was performed after obtaining written informed consent. Baseline data included demographics, surgical diagnosis, comorbidities, preoperative medication, smoking, Charlson Comorbidity Index, laboratory test results, and ASA classification.

Emergence delirium was defined as delirium that occurred during PACU stay and was assessed using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).

TABLE 1 | Frequency and definitions of major postoperative complications.

Variables	Number of all patients ($N = 915$)
Number of patients with complications, *n* (%)	419 (45.8%)
Individual complication, *n* (%)	
Central nervous systems	
Delirium[a]	386 (42.1%)
Stroke[b]	6 (0.7%)
Cardiovascular system	
Myocardial infarction[c]	20 (2.2%)
New-onset arrhythmia[d]	25 (2.7)
Cardiac failure[e]	20 (2.2%)
Pulmonary embolism[f]	1 (0.1%)
Respiratory system	
Pneumonia[g]	13 (1.4%)
Respiratory failure[h]	16 (1.7%)
Acute kidney injury[i]	26 (2.8%)
Surgery-related complications	
Intestinal obstruction[j]	3 (0.3%)
Anastomotic fistula[j]	11 (1.2%)
Unexpected surgical bleeding[j]	3 (0.3%)
Gastrointestinal bleeding[j]	7 (0.8%)
Infection	
Sepsis[k]	9 (1.0%)
Abdominal abscess[j]	7 (0.8%)
Incision infection[l]	16 (1.7%)
Death	13 (1.4%)

[a] *Delirium was established when the patient suffered any episode of delirium after surgery. According to onset time, it is divided into emergence delirium [from anesthesia emergency to discharge of post-anesthesia care unit (PACU)] and postoperative delirium (from discharge of PACU to postoperative 5 days). Emergence delirium happened in 282 (30.8%) patients and postoperative delirium in 47 (5.1%). A total of 57 (6.2%) patients suffered both emergence and postoperative delirium.*

[b] *Confirmed by imaging examination and diagnosed by a neurologist.*

[c] *Cardiac troponin I concentration met the criteria for clinical diagnosis, or ECG showed new emerging Q-waves lasting longer than 0.003 s, or ST-T changes lasting longer than 4 days.*

[d] *Confirmed by ECG and needed medical treatment, i.e., medicine or electrical cardioversion.*

[e] *Requiring the use of inotropic agents and/or vasopressors $\geq$ 24 h to maintain hemostasis.*

[f] *Diagnosed by clinical presentation and/or imaging examination, i.e., CT or angiography.*

[g] *New-onset infiltration on chest radiographs, body temperature $\geq 38^{\circ}$C, and white blood cell (WBC) elevated.*

[h] *Respiratory failure was defined as mechanical ventilation $\geq$ 24 h.*

[i] *Serum creatinine increased 1.5–1.9 times baseline or >0.3 mg/dl.*

[j] *Confirmed by clinical symptoms, imaging examinations, or surgery.*

[k] *Systemic inflammatory response involved two or more than two systems, existed in at least one organ system dysfunction, or required the use of vasopressors to maintain hemostasis.*

[l] *Diagnosed by clinical symptoms or positive bacteria culture.*

Postoperative delirium was defined as delirium that occurred in the general ward during postoperative days 1 to 5 and was assessed using the CAM twice daily (8:00–10:00 a.m., 6:00–8:00 p.m.) (19). Pain severity was assessed with the numerical rating scale (NRS; an 11-score scale, with 0 representing no pain and

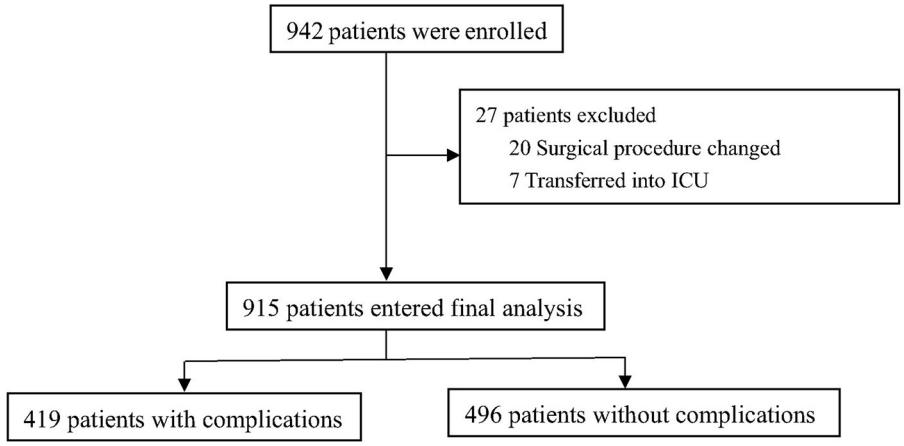


FIGURE 1 | Flowchart of the study.

10 representing severe pain) at the same time interval as that of delirium.

Complications within postoperative 30 days were recorded. From the sixth day after surgery, patients were followed up weekly until postoperative day 30 for the occurrence of postoperative complications. For those who were discharged from the hospital, follow-ups were performed by telephone interview.

Statistical Analysis

Normality of continuous data was tested by the Kolmogorov–Smirnov method in prior. Data with normal distribution were presented as mean ± standard deviations (SDs), and differences between groups were compared by independents sample *t*-test. Data without normal distribution were presented as median [interquartile range (IQR)], and differences between groups were compared by the Mann–Whitney U test. Categorical data were presented by number (percentage), and differences between groups were compared by chi-square test.

The relationship between NRS2002 and PONS and postoperative complications was firstly analyzed by univariate analysis, followed by multivariable logistic regression analysis adjusted for confounding factors including the baseline characteristics and perioperative variables that showed an imbalance between patients with and without postoperative complications (i.e., *P*-value < 0.05).

Receiver operating characteristic (ROC) curves were used to evaluate the predictive ability of PONS and NRS2002 against postoperative complications.

Two-sided $P < 0.05$ was considered as statistically significant. Statistical analysis was performed using SPSS 26 Inc (Chicago, IL, USA).

RESULTS

Patients

From September 21, 2017, to April 10, 2019, 942 patients were enrolled and 915 patients were included with mean age of 71.6 ± 5.2 years (**Figure 1**). The 30-day all-cause mortality was about 1.4% (13/915).

Overall incidence of postoperative complications was about 45.8% (419/ 915), and the incidence of individual complication is listed in **Table 1**.

In comparison with patients without complications, the mean age was higher in patients with complications (72.7 ± 5.7 vs. 70.7 ± 4.6, $P < 0.001$) (**Table 2**). In patients with complications, they had higher incidence of preoperative comorbidities such as coronary heart disease ($P = 0.023$), pulmonary disease ($P = 0.024$), and mild cognitive dysfunction ($P < 0.001$) (**Table 2**). Preoperative albumin was lower in patients with complications than in patients without complications (40.0 ± 4.6, vs. 41.0 ± 4.7, $P = 0.001$) (**Table 2**).

Patients with complications experienced higher volume of blood loss ($P < 0.001$), received more allogeneic blood transfusion ($P < 0.001$), and had prolonged surgery time ($P < 0.001$) (**Table 3**).

Perioperative Confounding Factors of Postoperative Complications

Univariate analysis was firstly used to screen potential risk factors of postoperative complications from baseline and perioperative variables. Variables with $P < 0.05$ were then entered into multivariable analysis (i.e., age, coronary heart disease, pulmonary disease, ASA classification, mild cognitive dysfunction, duration of surgery, and allogeneic blood transfusion) (**Table 4**).

The Relationship Between Perioperative Nutrition Screen and Postoperative Complications

According to PONS ≥ 1, 27.3% (250/915) patients were at risk of malnutrition. PONS ≥ 1 was associated with an increased risk of postoperative complications in both univariate analysis (OR 2.787, 95% CI 2.061–3.768, $P < 0.001$) and multivariable analysis (OR 2.308, 95% CI 1.676–3.178, $P < 0.001$) after adjusting for the above confounding factors.

TABLE 2 | Baseline characteristics.

Variable	All patients ($n = 915$)	Non-complication group ($n = 496$)	Complication group ($n = 419$)	*P*
Age, year, mean ± SD	71.6 ± 5.2	70.7 ± 4.6	72.7 ± 5.7	<0.001
≥75 years old, *n* (%)	264 (28.9%)	109 (22.0%)	155 (37%)	<0.001
Male, *n* (%)	548 (59.9%)	309 (62.3%)	239 (57.0%)	0.106
BMI, kg/m^2, mean ± SD	24.2 ± 3.5	24.2 ± 3.4	24.1 ± 3.6	0.783
Preoperative comorbidity, *n* (%)				
Stroke	52 (5.7%)	28 (5.6%)	24 (5.7%)	0.957
Hypertension	475 (51.9%)	252 (50.8%)	223 (53.2%)	0.466
Coronary heart disease	129 (14.1%)	58 (11.6%)	71 (16.9%)	0.023
Arrhythmia	57 (6.2%)	24 (4.8%)	33 (7.9%)	0.058
Pulmonary disease[a]	66 (7.2%)	27 (5.4%)	39 (9.3%)	0.024
Diabetes	219 (23.9%)	112 (22.6%)	107 (25.5%)	0.296
Hyperlipidemia	95 (10.4%)	48 (9.6%)	47 (11.2%)	0.447
Hepatic dysfunction, *n* (%)[b]	45 (4.9%)	19 (3.8%)	26 (6.2%)	0.098
Malignant tumor, *n* (%)[c]	105 (11.5%)	53 (10.7%)	52 (12.4%)	0.415
Chronic smoking, *n* (%)[d]	223 (24.4%)	128 (25.8%)	95 (22.7%)	0.271
CCI, median (IQR)	2 (2, 3)	2 (2, 3)	2 (2, 3)	0.102
Mild cognitive dysfunction, *n* (%)[e]	597 (65.2%)	286 (57.7%)	311 (74.2%)	<0.001
PONS, median (IQR)	0 (0, 1)	0 (0, 0)	0 (0, 1)	<0.001
PONS ≥ 1, *n* (%)	250 (27.3%)	90 (18.1%)	160 (38.2%)	<0.001
NRS2002, median (IQR)	3 (2, 4)	2 (2, 3)	3 (2, 4)	<0.001
NRS2002 ≥ 3, *n* (%)	490 (53.6%)	235 (47.4%)	255 (60.9%)	<0.001
ASA classification, *n* (%)				
II	678 (74.0%)	395 (79.6%)	283 (67.5%)	
III	237 (26.0%)	101 (20.4%)	136 (32.5%)	
Laboratory tests				
Albumin (g/L)	40.6 ± 4.7	41.0 ± 4.7	40.0 ± 4.6	0.001
<30 g/L, *n* (%)	22 (2.4%)	12 (2.4%)	10 (2.4%)	0.974
Creatinine (μmol/L)	80.2 ± 20.9	79.5 ± 19.9	81.0 ± 22.0	0.300
Glucose, mmol/L, mean ± SD	6.0 ± 1.7	6.0 ± 1.6	6.0 ± 1.9	0.832

SD, standard deviation; BMI, body mass index; CCI, Charlson Comorbidity Index; PONS, perioperative nutrition screen; IQR, interquartile range; NRS2002, Nutritional Risk Screening 2002; ASA, American Society of Anesthesiology.

[a] *Pulmonary disease included chronic obstructive pulmonary disease and asthma.*

[b] *Hepatic dysfunction was defined as alanine transaminase and/or aspartate transaminase higher than five times the upper normal limit.*

[c] *Malignant tumor was defined as carcinoma (carcinoma, squamous cell carcinoma, and adenocarcinoma), sarcoma, and undifferentiated carcinoma.*

[d] *Chronic smoking was defined as half a pack of cigarettes per day for at least 2 years.*

[e] *Mild cognitive dysfunction was defined as Montreal cognitive assessment score <27.*

The Relationship Between Nutritional Risk Screening 2002 and Postoperative Complications

According to NRS2002 ≥ 3, 53.6% (490/915) patients were at risk of malnutrition. NRS2002 ≥ 3 was associated with an increased risk of postoperative complications in univariate analysis (OR 1.727, 95% CI 1.327–2.248, $P < 0.001$), but not in multivariable analysis (OR 1.313, 95% CI 0.973–1.771, $P = 0.075$) after adjusting the above confounders (**Table 4**).

Predictive Performance of Perioperative Nutrition Screen and Nutritional Risk Screening 2002 Against Postoperative Complications

ROC curve analysis showed that the performances of PONS [area under the ROC curve (AUC) 0.595, 95% CI 0.558–0.633] and NRS2002 (AUC 0.577, 95% CI 0.540–0.614) were poor in predicting overall postoperative complications (**Figure 2**).

DISCUSSION

The present study found that malnutrition diagnosed by PONS was related with an increased risk of postoperative complications. However, use of PONS in predicting postoperative complications requires more attention because its performance may be affected by the type of complications.

Perioperative malnutrition has raised up more and more attention because it is highly related with poor patient outcome (1, 2, 10). Its clinical manifestation varies greatly in surgical patients and mainly includes lower BMI, body weight loss, hypoalbuminemia, decrement of oral intake, and microelement insufficiency (1, 2, 10). There are emerging studies to support that preoperative lower BMI is an independent predictor of

TABLE 3 | Perioperative variables.

Variable	All patients (n = 915)	Non-complication group (n = 496)	Complication group (n = 419)	P
Type of anesthesia, *n* (%)				0.262
General anesthesia	420 (45.9%)	229 (46.2%)	191 (45.6%)	
General-PNB anesthesia[a]	469 (51.3%)	257 (51.8%)	212 (50.6%)	
Epidural-general	26 (2.8%)	10 (2.0%)	16 (3.8%)	
Intraoperative medication				
Use of nitrous oxide, *n* (%)	553 (60.4%)	299 (60.3%)	254 (60.6%)	0.917
Use of sevoflurane, *n* (%)	287 (31.4%)	150 (30.2%)	137 (32.7%)	0.425
Use of dexmedetomidine, *n* (%)	430 (47.0%)	232 (46.8%)	198 (47.3%)	0.884
Use of midazolam, *n* (%)	189 (20.7%)	105 (21.2%)	84 (20.0%)	0.676
Use of etomidate, *n* (%)	699 (76.4%)	367 (74.0%)	332 (79.2%)	0.063
Propofol (mg) median (IQR)	840 (642, 1,075)	800 (620, 1,040)	875 (680, 1,132)	<0.001
Sufentanil equivalent (μg)[b] median (IQR)	110 (77, 160)	109 (75, 158)	80 (112, 165)	0.162
Surgery time (h), mead ± SD	3.4 ± 1.2	3.3 ± 1.1	3.5 ± 1.2	0.001
Location of surgery, *n* (%)				0.296
Intra-thoracic	198 (21.6%)	114 (23.0%)	84 (20.0%)	
Intra-abdominal	530 (57.9%)	289 (58.3%)	241 (57.5%)	
Spinal/extremities/others	187 (20.4%)	93 (18.8%)	94 (22.4%)	
Estimated blood loss, ml, median (IQR)	100 (10, 250)	50 (10, 200)	100 (10, 300)	<0.001
Allogeneic blood transfusion, *n* (%)	79 (8.6%)	27 (5.4%)	52 (12.4%)	<0.001
Total fluid infusion (ml), median (IQR)	2,200 (1,600, 2,850)	2,100 (1,600, 2,600)	2,350 (1,750, 3,100)	<0.001
Urine output (ml), median (IQR)	400 (250, 600)	250 (400, 600)	350 (200, 600)	0.632
Use of parenteral nutrition, *n* (%)	343 (37.5%)	168 (33.9%)	175 (41.8%)	0.016
Postoperative LOS, days, median (IQR)	8 (6, 11)	7 (5, 9)	9 (6, 12)	<0.001

PNB, peripheral nerve block; SD, standard deviation; IQR, interquartile range; LOS, length of in-hospital stay.

[a]Combined general-PNB anesthesia indicated that patients received both general anesthesia and peripheral nerve block (including epidural anesthesia).

[b]Intraoperative opioids included remifentanil and sufentanil. The dosage of remifentanil was converted into equivalent of sufentanil according to the following formula: dosage of sufentanil (μg) = the dosage of remifentanil (μg)/10.

TABLE 4 | The relationship between PONS and postoperative complications.

Variables	Univariate analysis			Multivariate analysis PONS score ≥ 1[a]			Multivariate analysis NRS2002 score ≥ 3[a]		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Age (per year increase)	1.076	1.048–1.104	< 0.001	1.059	1.029–1.089	<0.001	1.055	1.024–1.087	<0.001
Coronary heart disease (yes)	1.541	1.060–2.240	0.024	—	—	—	1.149	0.754–1.752	0.519
Pulmonary disease (yes)[b]	2.043	1.220–3.422	0.007	2.088	1.205–3.619	0.009	—	—	—
Mild cognitive dysfunction[c]	2.114	1.595–2.804	< 0.001	2.100	1.557–2.833	<0.001	2.083	1.553–2.794	<0.001
ASA classification (per grade increase)	1.879	1.393–2.535	< 0.001	1.399	1.009–1.939	0.044	1.523	1.108–2.092	0.009
NRS2002 score ≥ 3	1.727	1.327–2.248	< 0.001	NA	NA	NA	1.313	0.973–1.771	0.075
PONS score ≥ 1	2.787	2.061–3.768	< 0.001	2.308	1.676–3.178	<0.001	NA	NA	NA
Duration of surgery (per hour increase)	1.203	1.074–1.348	0.001	1.149	1.014–1.302	0.029	1.212	1.073–1.369	0.002
Allogeneic blood transfusion (yes)	2.461	1.516–3.996	< 0.001	2.119	1.259–3.567	0.005	2.091	1.250–3.497	0.005

ASA, American Society of Anesthesiologists; NRS2002, Nutritional Risk Screening 2002; PONS, perioperative nutrition screen; OR, odds ratio; CI, confidence interval; NA, not available.

[a]PONS ≥ 1 and NRS2002 ≥ 3 were put into the multivariate analysis separately.

[b]Pulmonary disease was defined as chronic obstructive pulmonary disease and asthma.

[c]Mild cognitive impairment was defined as Mini-Mental State Examination (MMSE) score <27.

postoperative complications such as in patients with gastric cancer resection and hip surgery (20, 21). A prospective study including 331 cardiac surgery patients shows that preoperative unintended weight loss more than 10% baseline is related with increased risk of postoperative infections and prolonged stay in the intensive care unit (22). In patients undergoing spinal surgery, hypoalbuminemia is associated with increased risk (about two to five times) of postoperative 30-day mortality and

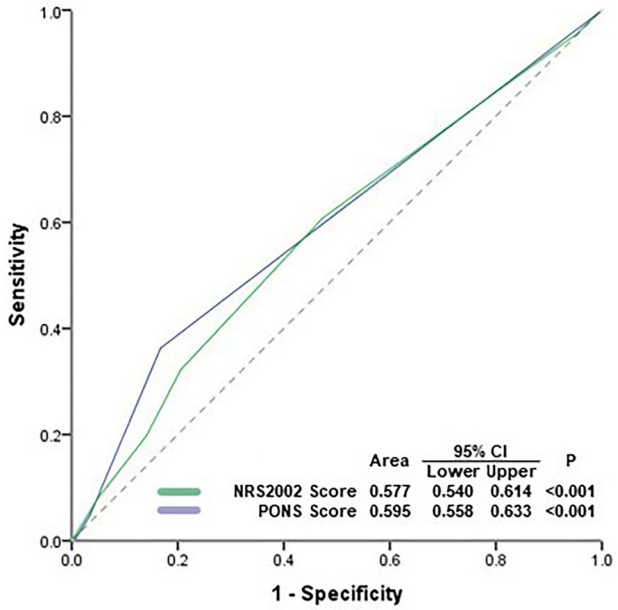


FIGURE 2 | Receiver operating characteristic (ROC) analysis. ROC curve analysis showed that the performances of PONS and NRS2002 were poor in predicting postoperative complications. PONS, perioperative nutrition screen; NRS2002, Nutritional Risk Screening 2002; AUC, area under curve; CI, confidence interval.

complications with a dose-dependent effect (23). Microelement (i.e., magnesium and vitamin D) insufficiency is common in surgical patients and highly related with increased mortality and complications (such as delirium, postoperative cognitive dysfunction, and infection) (24, 25).

Beyond the miscellaneous symptoms listed above, definition and diagnosis of malnutrition are still a major concern in clinical practice (1, 2, 10). The inconsistency in malnutrition criteria may lead to vast differences in its incidence and incomparability between clinical trials. For example, the incidence of malnutrition was 27.3% by PONS and 53.6% by NRS2002 in the present study. Compared with PONS, NRS2002 includes more items for diagnosis criteria, which may increase the incidence of malnutrition (1, 15). First, NRS2002 takes severity of disease as an important predictor if the patient will experience impaired food intake and increased stress metabolism during the forthcoming clinical treatment. Second, the criteria of abnormal body weight loss and oral intake are easier to achieve in NRS2002 than in PONS. For example, oral intake of 50–75% normal requirement is considered as mild deficit in NRS2002, whereas oral intake $<$50% baseline was considered as abnormal in PONS. Third, NRS2002 considers age $\geq$70 years as additional score.

Although PONS has been recommended by American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement, there are no sufficient data to elucidate its relationship with postoperative complications (1). In a validation study of 273 patients, the incidence of malnutrition based on PONS criteria among surgical patients was about 27%, which was consistent with the present study (18). But it did not examine the relationship between malnutrition and postoperative complications. The present study found that PONS was associated with increased risk of complications within postoperative 30 days in elderly surgical patients.

In the present study, we found that both PONS score and NRS2002 score performed poorly in predicting postoperative complications by ROC analysis. First, it seems that malnutrition may have different impact on the occurrence of complications in different systems. In the present study, the AUC of PONS score in predicting surgery-related complications and infection was 0.803 (95% CI 0.715–0.891) and 0.754 (95% CI 0.656–0.852), respectively, but the AUC in predicting cardiovascular complications was only 0.611 (95% CI 0.517–0.704). However, we did not present the *post-hoc* analysis in the present report because the individual incidences of these complications were merely about 1–5% and the sample size could not provide sufficient statistical power.

Multivariable analysis showed that age, pulmonary disease, mild cognitive dysfunction, ASA classification, duration of surgery, and allogeneic blood transfusion were related with postoperative complications. These findings were in accordance with previous studie (26–31). It indicated that the underlying disease of patients and intrinsic risk of surgical procedures also played important roles in the development of postoperative complications.

This study has two limitations. First, our result was generated from a single-center study, which might limit its generality. Second, the 30-day mortality was about 1.4% in the present study, and the sample size was insufficient to analyze the relationship between malnutrition and mortality.

CONCLUSION

The present study found that malnutrition diagnosed by PONS was related with an increased risk of postoperative complications. However, use of PONS in predicting postoperative complications requires more attention because its performance may be affected by the type of complications.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical approval for this study was provided by the Clinical Research Ethics Committee of Peking University First Hospital (Chairperson Prof Guo Xiaohui) on August 4, 2017 [2017 (1419), Beijing, China], and registered with Chinese Clinical Trial Registry on September 19, 2017 (ChiCTR-OOC-17012734). Written informed consent was obtained from all participants or their legal representatives.

AUTHOR CONTRIBUTIONS

FZ helped in data acquisition, data analysis, and manuscript drafting. S-TH helped in data acquisition and data analysis.

YZ helped in data acquisition and data analysis. D-LM helped in concept and design, data analysis, data interpretation, manuscript drafting, and final approval of submission. D-XW helped in concept and design, administrative or material support, and critical revision of the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SYSTEMATIC REVIEW
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Efficacy of Qigong Exercise for Treatment of Fatigue: A Systematic Review and Meta-Analysis

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Objective: Several studies suggested that Qigong exercise (QE) can relieve fatigue in patients diagnosed with various diseases. Our review aimed to evaluate the efficacy of QE for alleviating fatigue.

Methods: A related literature search was performed in the PubMed, Web of Science, Embase, Cochrane Library, China Biology Medicine disc (CBM), China National Knowledge Infrastructure (CNKI), Wanfang, and VIP data bases from inception to November 2020. Information on fatigue, malaise, tiredness, and Qigong research data was collected.

Results: Sixteen randomized controlled trials (RCTs) were reported in patients with cancer ($n = 4$), chronic fatigue syndrome ($n = 2$), and other diseases ($n = 10$). The QE groups showed significant improvements in total fatigue intensity [15 RCTs, $p < 0.00001$; standard mean difference (SMD) −0.69 (−0.95 to −0.44)]. The QE groups did not show significant improvement in quality of life [4 RCTs, $p = 0.08$; SMD 0.53 (−0.07 to 1.14)]. The statistically significant difference of the subgroup analyses (different primary diseases, QE types, and study quality) also remained unchanged.

Conclusion: The findings of this meta-analysis indicate that QE may be beneficial for improving fatigue in patients diagnosed with various diseases. Considering the limitations of the study, we draw a very cautious conclusion regarding the resulting estimate of the effect. Further studies are warranted to better understand the benefits of QE in primary medical care.

Keywords: qigong exercise, fatigue, quality of life, systematic review, meta-analysis

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INTRODUCTION

Fatigue, a subjective symptom, is the embodiment of complex physiological, psychological, and pathological phenomena, wherein the body's physical strength or energy is weakened or lost (1). With the rapid industrialization of society, chronic fatigue is prevalent in 15–20% of the general population (2, 3). In some occupations or specific environments, the incidence rate of fatigue symptoms is even >70% (4, 5). Fatigue is also one of the most common symptoms in primary medical care. Approximately 10–20% of patients complain of fatigue (6, 7), and 10–30% of patients consider fatigue an important accompanying symptom (8, 9). Several drugs, such as anti-neoplastic agents (10) and antidepressants (11), may be associated with secondary fatigue, which is produced by the adverse effects of the administered treatment. For the general population, fatigue is an

alarm signal given by the body when it attains its physical limits. Without effective treatment, the symptoms of physical illness and common psychological disorders may lead patients into a vicious cycle associated strongly with fatigue, depression, anxiety, chronic pain, and sleep disturbances (12). However, clinically, patients describe fatigue in varying ways, such as sleepiness, weakness, lethargy, pain, and heaviness, and physicians may overlook or underestimate its severity (13).

The treatment options for fatigue should address the etiology and mechanism of the primary diseases, if possible. However, the multidimensionality and subjective nature of fatigue, and the lack of consensus on its pathophysiology make effective treatment difficult (14). As a result, a standardized and specific treatment that may improve or prevent fatigue in population groups that are considered "patients at risk" has not been established (15, 16). Methods for improving fatigue in patients are divided into pharmacological and non-pharmacological categories. However, some drugs used for treating fatigue possess insufficient evidence of efficacy and should be further investigated (17, 18); the adverse effects of other medications could cause more complications in patients (19, 20). Aerobic exercise has been recommended as a non-pharmacological alternative for treating fatigue (21, 22). It is a practical option and can easily be adhered to by patients in the long-term. Unfortunately, the efficacy of aerobic exercise in improving fatigue has also been questioned in some systematic reviews (23, 24).

Qigong exercise (QE), a distinctive traditional technique that has amassed a large following in China, is a form of low-intensity exercise (25, 26). Numerous clinical guidelines related to the use of QE for the rehabilitation of fatigue in patients with cardiopulmonary diseases and Parkinson's disease are available, with positive recommendations (27, 28). Other systematic reviews either evaluated QE as a component of aerobic exercise or aimed to summarize the potential of QE to address the multifaceted needs of cancer survivors (21, 22). In this study, we aimed to comprehensively evaluate the therapeutic benefits of QE on fatigue. We investigated a broader scope of primary diseases and patient clinical outcomes by summarizing and analyzing the existing literature.

METHODS

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (**Supplementary Appendix 1**). The study had been registered on INPLASY (https://inplasy.com) and the registration number is INPLASY2020110133. There was no direct patient or public involvement in this review.

Data Sources and Searches

We searched the related studies from PubMed, Web of Science, Embase, Cochrane Library, China Biology Medicine disc, China National Knowledge Infrastructure, Wanfang, and VIP Data Knowledge Service Platform published from inception until November 2020.

Exhaustive search strategies for each electronic database were developed by the review team members. The English-language search strategy containing relevant terms was based on the concepts: (1) "Fatigue" or "Malaise" or "Tiredness," (2) "Qigong," and (3) "Randomized Clinical Trial." In the Chinese databases, we used equivalent search terms. Search tactics for PubMed are shown in **Supplementary Appendix 2**.

Inclusion and Exclusion Criteria

Studies considered in this meta-analysis were required to meet the following inclusion criteria. First, studies published in English or Chinese up to November 30, 2020 with a randomized controlled trial (RCT) design investigating the use of QE interventions for fatigue symptoms were considered for inclusion. Studies were included if appropriate data were available for the calculation of effect sizes in each treatment arm. Second, studies involving patients with primary disease-related symptoms of fatigue were included, regardless of the underlying disease, age, sex, education, ethnicity, and occupation of the studied patients. If the patients experienced serious complications, such as cognitive communication disorders, the study was excluded. Third, studies were included if QE alone (any form of Qigong category, including Baduanjin, Yijinjing, and Wuqinxi) or QE combined with other treatments was the main intervention in the observation group. No limit was set on the duration and frequency of treatment. Moreover, in the control group, the patients were treated with any type of intervention, including exercise, stretching, or sham Qigong; studies with observation groups were also included. Finally, the primary outcome defined to be compared was the severity, duration, frequency, or improvement of fatigue, evaluated through the following scales: Functional Assessment Chronic Illness Therapy–Fatigue, Chalder's Fatigue Scale, Multidimensional Fatigue Inventory-20, Fatigue Scale-14, Visual Analog Scales for fatigue, Fatigue Severity Scale, or Revised Piper fatigue Scale, and medical scales for some specific diseases including Functional Assessment of Cancer Therapy-General, 16-item Parkinson Fatigue Scale, or Fatigue scale in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30. Other secondary outcomes were quality of life (QOL), assessed through the MOS item short-form health survey-36 and Medical Outcomes Study 12-Item Short-Form Health Survey.

Study Selection and Data Extraction

When the results of one study were presented in several publications, only the most recent publication and complete data were considered. The eligibility of trials was assessed by two authors independently (WR and W-YQ). The following information was extracted by two authors (WR and H-XY) based on a fixed protocol: geographical location, primary disease, number of QE group and control participants, interventions of QE type, duration, and outcomes results. Discrepancies were settled by agreement, and a third author (SD) was consulted if necessary.

Risk of Bias Assessment

Two researchers (WR and H-XY) independently assessed the quality of the selected studies according to the Cochrane Collaboration's tool for randomized controlled trials (29). Items

were evaluated in three categories: low risk of bias, unclear bias, and high risk of bias. The following characteristics were evaluated: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases resulting from these questions were graphed and assessed using Review Manager 5.4. Any disagreements were resolved by discussion or with the help of a third author (SD).

Data Synthesis and Statistical Analysis

The traditional pair-wise efficacy data in populations were synthesized and statistically analyzed using Review Manager 5.4 by random effects modeling (weighted by the inverse of the variance). For continuous data including the total fatigue intensity and QOL scale score, which were measured using different tools, the standard mean difference (SMD) and 95% confidence intervals were used for effective evaluation. To ensure uniformity of the included data, all of them were used in the intention-to-treat analysis. *P*-values < 0.05 were considered statistically significant unless otherwise specified.

Between-study heterogeneity was assessed using the χ^2 and I^2 tests. According to the Cochrane handbook, an I^2 value $>$ 60% was considered substantial, 30 −60% moderate, and $<$ 30% non-important heterogeneity (30). An I^2 statistics of 50% or higher indicated the presence of heterogeneity. To further assess the influence of heterogeneity on the meta-analyses' conclusions, meta-regression and subgroup analysis were performed to assess the primary outcome data according to the primary diseases, QE type, sample size, year of publication, intervention length,

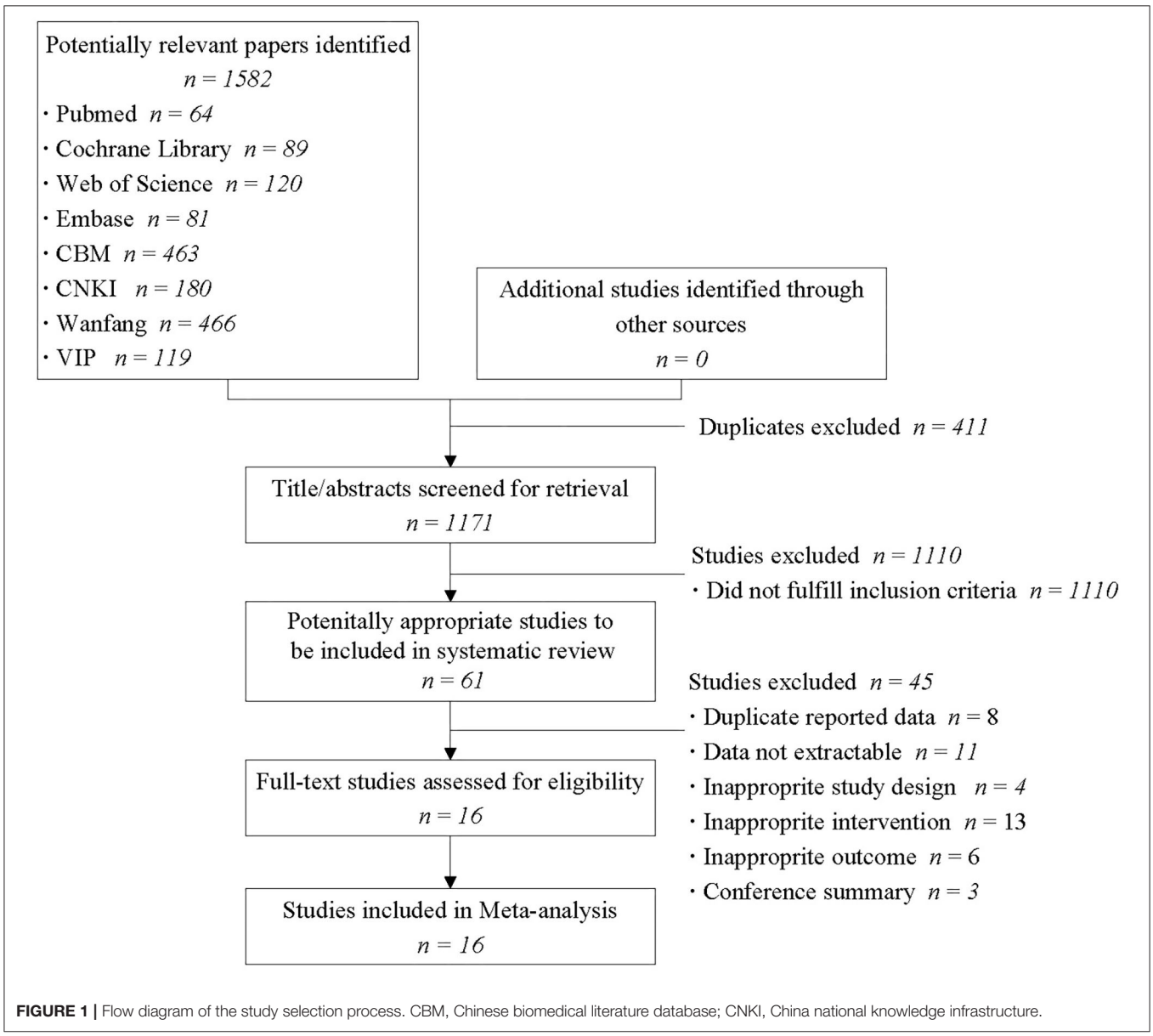


FIGURE 1 | Flow diagram of the study selection process. CBM, Chinese biomedical literature database; CNKI, China national knowledge infrastructure.

TABLE 1 | Characteristics of the included studies.

References	Location	Primary disease	QE group N	Control group N	QE type	Duration (weeks)	Primary outcomes
Campo et al., (45)	The United States	Cancer	20	20	Self-improving QE	12	Functional assessment chronic illness therapy–fatigue.
Chan et al., (32)	China	Chronic fatigue syndrome	72	65	Wu Xing Ping Heng Gong	17	Chalder's fatigue scale.
Chan et al., (33)	China	Chronic fatigue syndrome	75	75	Baduanjin	9	Chalder's fatigue scale1.
Duan (31)	China	Chronic fatigue syndrome	27	30	Shaolin QE	12	Multidimensional fatigue inventory-20, the MOS item short from health survey-36.
Lee, (34)	China	Cancer	16	29	Self-improving QE	12	Functional assessment of cancer therapy-general.
Lee, 2018b (34)			15	30			
Liu et al., (35)	The United States	Fibromyalgia	8	6	"Six healing sound" Qigong	6	Multidimensional fatigue inventory-20..
Moon et al., (36)	The United States	PD	8	9	"Six healing sound" Qigong	12	16-item parkinson fatigue scale.
Na et al., (37)	China	Chronic fatigue syndrome	15	30	Wuqinxi	4	Fatigue scale-14.
Na et al., (37)			15	15			
Na et al., (37)			30	15			
Oh et al., (38)	Australia	Cancer	79	83	Self-improving QE	10	Functional assessment of cancer therapy-general.
Rainbow, (44)	China	Chronic fatigue syndrome	33	31	Wu Xing Ping Heng Gong	17	Chalder's fatigue scale, medical outcomes study 12-item short-form health survey.
Sarmento et al., (39)	The United States	Fibromyalgia	10	10	"Six healing sound" Qigong	10	Visual analog scales for fatigue.
Tang et al., (40)	China	Inflammatory bowel disease	31	31	Baduanjin	12	Multidimensional fatigue inventory-20.
Wang, (41)	China	Post-stroke	30	30	Baduanjin	4	Fatigue severity scale.
Xu, (42)	China	Cancer	46	46	Baduanjin	26	Fatigue scale in the European organization for research and treatment of cancer quality of life questionnaire- core 30.
Yu et al., (43)	China	Chronic fatigue syndrome	21	21	Yijinjing	6	Fatigue scale-14.
Yu et al., (43)			21	42			
Yu et al., (43)			42	21			
Zhang, (44)	China	COPD	30	30	Baduanjin	26	Revised piper fatigue scale.

and study quality (depending on whether random sequence generation and allocation concealment are used to determine the high or low quality of the studies). Visual inspection of asymmetry in funnel plots was conducted. Egger-weighted regression method using STATA 15.0 (Stata-Corp) was also used to statistically assess the publication bias.

RESULTS

Studies Included in the Meta-Analysis

Figure 1 presents a flow chart of the study selection process. Following the initial literature review, a total of 1,836 studies were found. Of these, 1,820 were excluded as only 16 studies met the inclusion criteria (**Table 1**) (31–46). The total number of participants included was 1,313, and the concise summary characteristics of each study are presented in **Table 1**. Of the 16 published studies, 11 were conducted in China, 4 in the United States, and 1 in Australia. Among these studies, the primary disease was cancer in 4 studies, chronic fatigue syndrome in 6, fibromyalgia in 2, post-stroke in 1, chronic obstructive lung disease in the stable phase in 1, inflammatory bowel disease in 1, and Parkinson's disease in 1. Sample sizes ranged from 14 to 162, and drop-out rates ranged from 0 to 33.33%.

Quality of Studies

The quality of each study was evaluated considering certain methodological aspects by two authors (WR and H-XY) and is summarized in **Figure 2**. The generation of random sequences was adequate in 13 trials and unclear in the remaining trials. Allocation concealment was judged to be sufficient to minimize

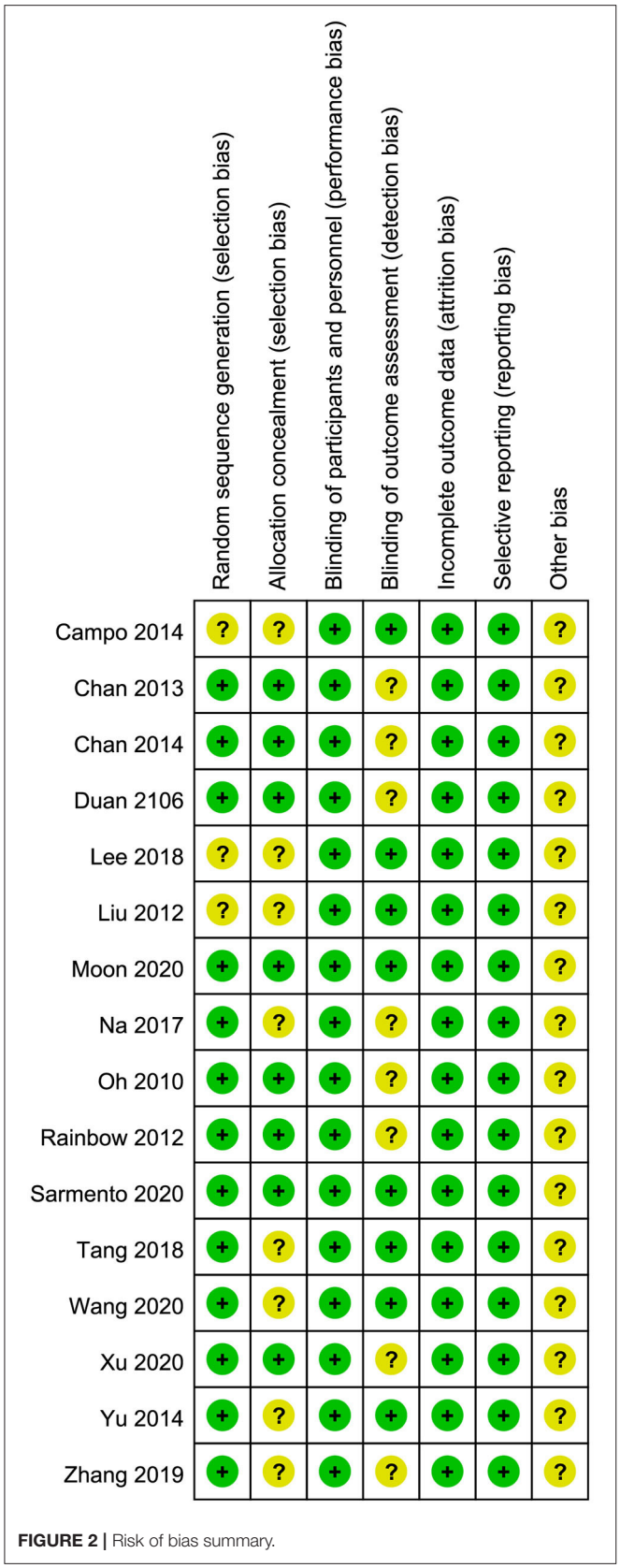


FIGURE 2 | Risk of bias summary.

the selection bias in 8 trials; however, it was unclear in other trials. In particular, as blinding could not be applied to both participants and researchers owing to the nature of QE, blinding was judged adequate to prevent performance bias in all trials. Blinding of the outcome assessment was considered sufficient to prevent detection bias in eight trials and was unclear in eight trials. In all the trials, the quality of incomplete outcome data was adequate. No selective reporting of outcomes was observed, and other biases were classified as unclear.

Evidence From Randomized Trials

Primary Outcomes

Total Fatigue Intensity

Fifteen RCTs involving 1,253 participants reported changes in fatigue intensity. In this cohort, 614 patients performed QE; and 639 patients received other treatments in the control groups. Heterogeneity was evident ($I^2 = 76\%$, $p < 0.00001$). Analysis of data in the random effect method showed that QE could improve the symptoms of fatigue (SMD −0.69, 95% CI −0.95 to −0.44, $p < 0.00001$; **Figure 3A**).

Physical and Mental Fatigue Intensity

Six studies involving 530 patients were included in our meta-analysis on the efficacy of QE in lowering physical and mental fatigue intensity. The intensity in all the studies was significantly lower with an overall SMD of −1.06 for physical fatigue intensity (95% CI −1.32 to −0.80) and −0.76 for mental fatigue intensity (95% CI −1.07 to −0.44; **Figure 3B**).

Decreased Activity and Interest Scales

Two studies involving 122 patients reported the change in activity and interest levels between baseline and endpoint. In these studies, 61 patients performed QE and 61 served as controls. The results showed that QE could improve the decreased activity levels but not the decreased interest levels. The SMDs were −0.92 and −0.49 for the decreased activity levels (95% CI −1.77 to −0.07, $p = 0.03$) and decreased interest levels (95% CI −2.06 to 1.08, $p = 0.54$; **Figure 3C**), respectively.

Secondary outcomes

QOL

Four RCTs reported comparisons of QOL scale scores between patients who performed QE and those who received other treatments. Significant heterogeneity was noted in the enrolled 364 patients (166 in the QE groups and 198 in the control groups) ($I^2 = 84\%$, $p < 0.0001$). QE could not improve the QOL scale scores (SMD 0.53, 95% CI −0.07 to 1.14; **Figure 4A**).

Four RCTs reported data on physical and mental functioning scale scores. Heterogeneity was not significant in studies comparing the physical functioning scale scores ($I^2 = 29\%$, $p = 0.24$) but was significant in those assessing mental functioning ($I^2 = 79\%$, $p < 0.001$). Data analyses showed that QE could not improve the physical functioning scale scores (SMD 0.20, 95% CI −0.05 to 0.44, $p = 0.12$) but improved the mental functioning scale scores (SMD 0.79, 95% CI 0.31 to 1.28, $p = 0.001$; **Figures 4B,C**).

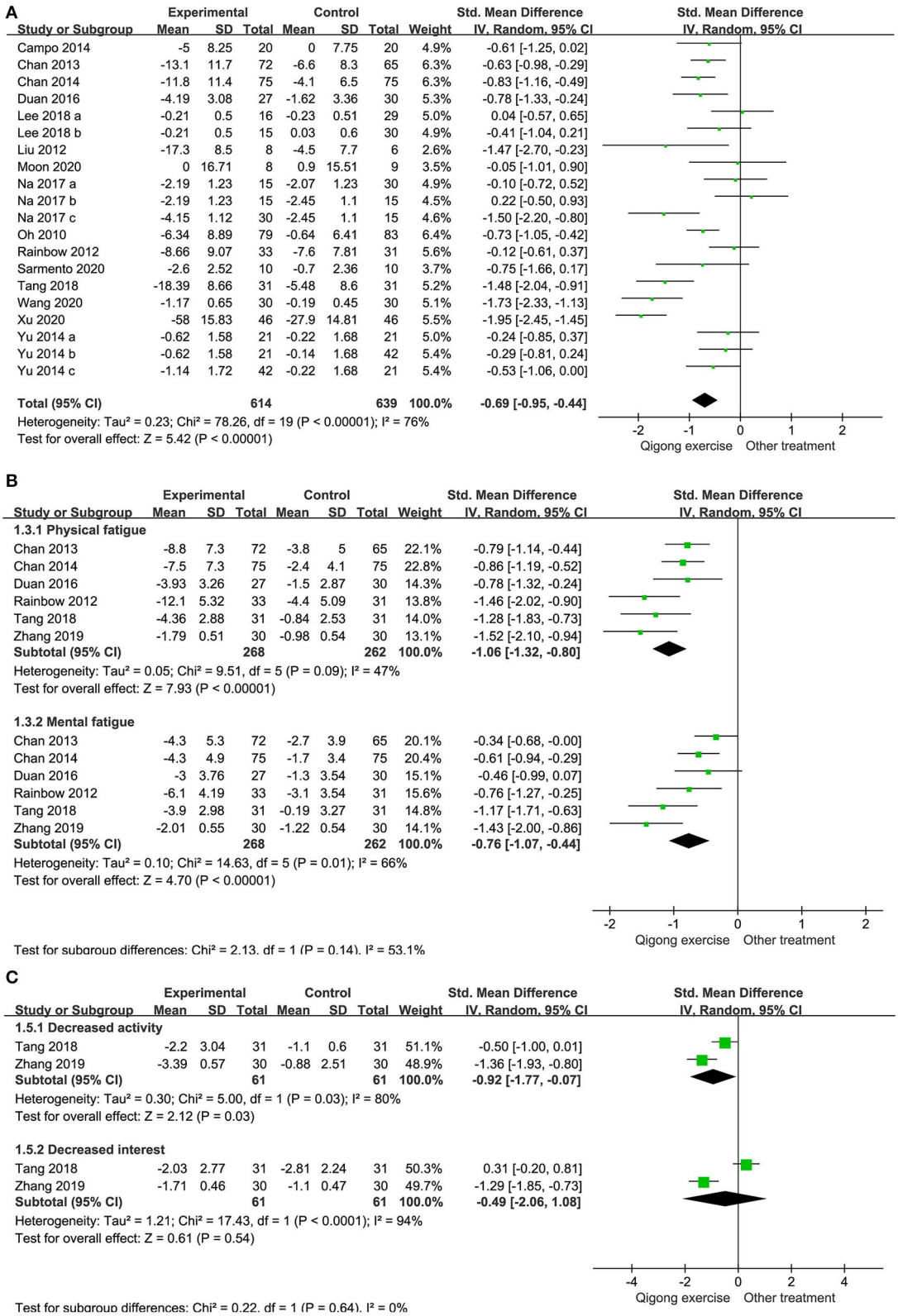


FIGURE 3 | Forest plots illustrating the meta-analysis of outcomes with Qigong exercise (QE) vs. other treatments for fatigue symptoms. The outcomes analyzed were **(A)** total fatigue intensity, **(B)** physical and mental fatigue intensity, and **(C)** decreased activity and interest scale.

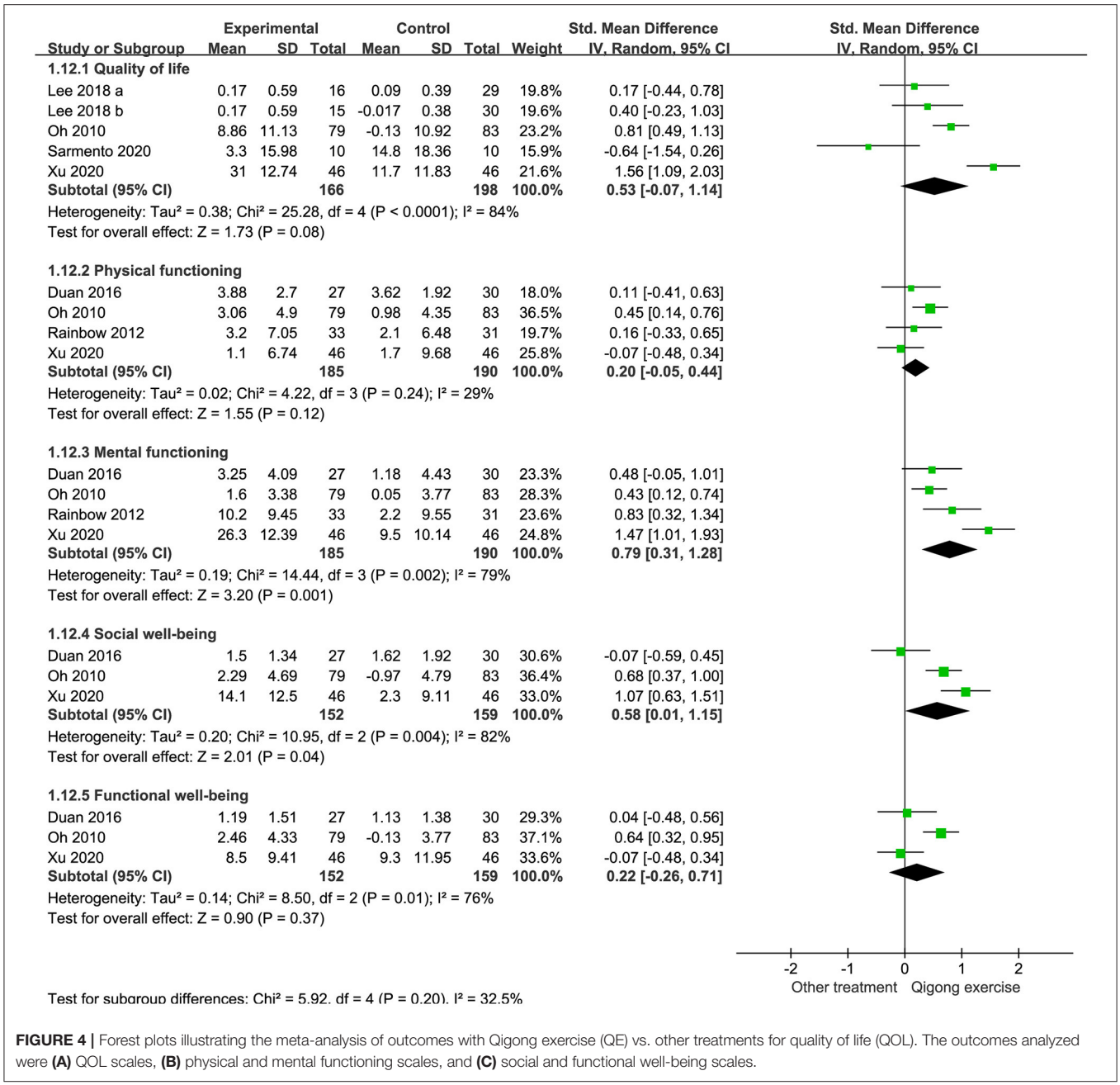


FIGURE 4 | Forest plots illustrating the meta-analysis of outcomes with Qigong exercise (QE) vs. other treatments for quality of life (QOL). The outcomes analyzed were **(A)** QOL scales, **(B)** physical and mental functioning scales, and **(C)** social and functional well-being scales.

Three RCTs compared the social and functional well-being scale scores between the QE and control groups. A combined analysis of 311 patients revealed that QE could improve social well-being (SMD 0.58, 95% CI 0.01 to 1.15, $p = 0.04$) but not functional well-being (SMD 0.22, 95% CI −0.26 to 0.71, $p = 0.37$). Heterogeneities were significant in these two comparisons ($I^2 = 82\%$, $p = 0.04$ and $I^2 = 76\%$, $p = 0.01$, respectively; **Figures 4D,E**).

Meta-Regression

Factors examined individually in the meta-regression model of total fatigue intensity included primary diseases (cancer-related fatigue, chronic fatigue syndrome, or other diseases related fatigue), QE type (Baduanjin, other traditional Chinese QE, Wu Xing Ping Heng Gong, "Six healing sound" Qigong, or other self-improving QE), sample size, year of publication, intervention length, or study quality (high or low quality). No significant associations were found between fatigue intensity and the factors (**Table 2**).

Subgroup Analysis

Although meta-regression did not detect significant factors responsible for heterogeneity, we selected different primary disease, QE type, and study quality for subgroup analysis

based on the clinical characteristics of the included studies. The results suggested that the QE group with other primary disease-related fatigue showed superior total fatigue intensity improvement compared with that seen in patients with chronic fatigue syndrome and cancer-related fatigue. The Baduanjin QE group presented a trend toward better score improvement when compared with the various types of QE groups. We also found that high-quality studies were better than low-quality studies in demonstrating the benefits of QE for fatigue improvement (**Table 3**, **Supplementary Appendix 3**).

Sensitivity Analysis

Sensitivity analysis was performed in each domain of the primary outcomes to assess the stability of the meta-analysis. When any single study was deleted, the corresponding pooled SMD changed only slightly. The statistical results before and after the deletion were similar, indicating that the stability of the performed meta-analysis was good (**Supplementary Appendix 4**).

Publication Bias

Publication bias of the literature was tested using the Egger test. A potential publication bias in the meta-analysis on QE intervention was not detected using the funnel plot on total fatigue intensity. The graphical funnel plots of the 15 studies seemed to be symmetrical (**Figure 5**). We found no evidence of publication bias in the Egger regression test ($t = 0.27$, 95% CI −2.71 to 3.50, $p = 0.79$; **Supplementary Appendix 5**).

TABLE 2 | Meta-regression.

Variables	Coefficient	Standard error	p	95% CI
Primary diseases	−0.166	0.203	0.413	−0.564 to 0.232
QE type	0.149	0.087	0.088	−0.022 to 0.320
Sample size	−0.003	0.003	0.403	−0.009 to 0.004
Year of publication	−0.053	0.047	0.267	−0.145 to 0.040
Intervention length	−0.025	0.025	0.315	−0.075 to 0.024
Study quality	0.103	0.288	0.722	−0.463 to 0.668

DISCUSSION

Whether QE is effective in alleviate fatigue is currently unknown. This meta-analysis demonstrated that QE could result in total fatigue intensity improvement in patients with symptoms of fatigue due to various diseases. Moreover, similar results were shown in both physical and mental fatigue intensity and decreased activity levels; however, the change in decreased interest levels was not significant. Moreover, the mental functioning and social well-being scale scores and the pooled

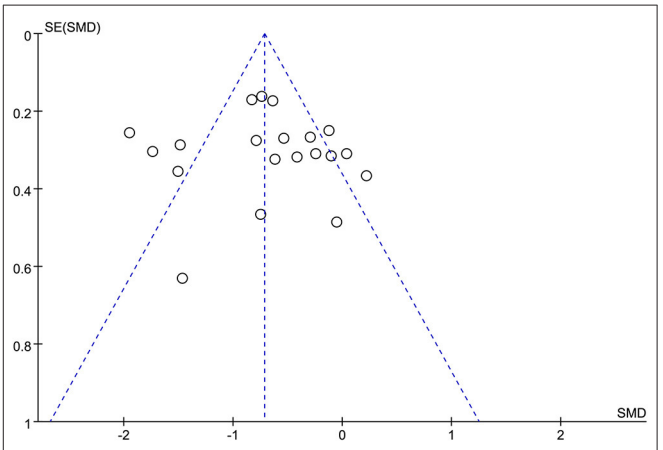


FIGURE 5 | Funnel plot on total fatigue intensity to evaluate the publication bias of the literature. SMD, standardized mean difference.

TABLE 3 | Subgroup analysis.

Variables	Eligible Studies N	Eligiblearms N	Frequency		SMD (95% CI)	*P*	Heterogeneity Test		Effect Model
			QE group N	Control group N			p	I^2, %	
Different primary diseases									Random
Cancer related fatigue	4	5	176	208	−0.75 (−1.37 to −0.13)	0.02	<0.00001	86%	
Chronic fatigue syndrome	6	10	351	345	−0.50 (−0.75 to −0.24)	0.0001	0.009	59%	
Other diseases related fatigue	5	5	87	86	−1.15 (−1.73 to −0.57)	<0.0001	0.03	62%	
Different types of QE									Random
Baduanjin	4	4	182	182	−1.47 (−2.04 to −0.90)	<0.00001	0.0009	82%	
Other traditional Chinese QE	2	6	144	144	−0.40 (−0.82 to 0.01)	0.06	0.02	64%	
Wu Xing Ping Heng Gong	2	2	105	96	−0.41 (−0.90 to 0.09)	0.10	0.10	64%	
"Six healing sound" Qigong	3	3	26	25	−0.68 (−1.43 to 0.07)	0.07	0.20	38%	
Other self-improving QE	4	5	157	192	−0.56 (−0.83 to −0.28)	<0.0001	0.22	30%	
Different quality of studies									Random
High quality	8	8	350	349	−0.77 (−1.12 to −0.41)	<0.0001	<0.0001	77%	
Low quality	7	12	264	290	−0.65 (−1.02 to −0.27)	<0.01	<0.01	76%	

data of QOL scale, physical functioning scale, and functional well-being scale scores suggest that QE was not effective.

The marked heterogeneity is a constraint of the analysis of the RCTs included in this study. An important possible reason for the observed heterogeneity is that fatigue symptoms caused by various primary diseases cannot be standardized in the baseline analysis, and differences exist in the individualized assessment scales. The effect of QE on the total fatigue intensity did not vary with the subgroup analysis of the primary diseases. Different types of QE interventions included in this study may also have led to heterogeneity. However, we found that distinguishing between different QE types had little effect on the results of fatigue improvement. In this study, the possible influence of research quality on heterogeneity was also considered, but the results of the subgroup analysis remained unchanged considering the QE effects.

We found that QE did not lead to an improved QOL in patients with fatigue. We hypothesize that this may be due to the overly complex factors that could affect the changes in indicators of QOL. Notably, QE has been effectively used in the rehabilitation of a wide range of diseases (47); it was found to improve the risk factors associated with metabolic syndrome, enhance the QOL of community-dwelling older adults with chronic disease (48), and maintain the health of patients with stable chronic obstructive lung disease (49). The mechanisms by which QE improves fatigue may include positive modulation of immune function (50), balancing the frequency of α1 and α2 waves in different brain regions (51), and increasing serum nitric oxide levels and superoxide dismutase activity to reduce the harmful effects of free radicals in patients (52). However, the mechanism underlying the therapeutic effects requires further studies. The current study revealed certain new negative findings on QE.

Reports on the effects of low-intensity exercise are conflicting. Gendron et al. considered active mind-body movement therapies as an adjunct to, or in comparison with, pulmonary rehabilitation for people with chronic obstructive pulmonary disease; however, the results remain inconclusive (53). Kelley et al. also expressed that a lack of certainty exists with regard to the benefits of exercise on chronic fatigue syndrome in adults (54). The reasons for this contrast could be attributed to the flawed trial protocol design and the poor quality of evidence, which limits their confidence in the observed effects.

We believe that the fatigue in patients may be caused by an intertwining of various diseases and varies in degree depending on age, sex, marital status, occupation, and education, which complicate the analysis of the fatigue symptoms (12). Many hypotheses regarding the pathogenesis of fatigue have been developed; however, no substantial understanding has been garnered so far, which in turn further complicates the treatment (55, 56).

Aerobic exercise, including but not limited to QE, tai chi, walking, and yoga, has been applied as rehabilitation modalities for people with fatigue in primary care, but the abovementioned recent studies did not support these treatments. However, the results of our meta-analysis were mainly positive and the quality of clinical studies in China is also improving. Previous studies often unconsciously ignored the Chinese literature, which was included in our study, since aerobic exercise itself is very popular in China. When we performed data synthesis, we did not eliminate studies based on primary disease, as a result of which we were able to assess a larger number of studies than that done by previous studies. As we sought for an intervention program with a broad clinical effect, our results differ from studies focusing on aerobic exercise.

This study had several limitations. First, the inclusion of multiple different diseases in our study, despite the statistically significant results, is likely to have produced biological bias and is one of the main reasons for the large heterogeneity. Although we performed a meta-regression analysis, it was not successful in identifying the source of heterogeneity in the correlates. The fact that fatigue, as a common symptom in primary care, occurs in different diseases is the reason for the inevitable heterogeneity of this study. We therefore performed subgroup analysis according to different primary diseases, which still showed positive results. Second, the determination of fatigue is very subjective and this has led to differences in the evaluation criteria across the included literatures. Finally, the lack of uniform QE types and intervention length may have contributed to the bias in the overall results of this study. Moreover, if individual patient data are accurate and detailed, subgroup analyses can be adjusted for age, race, and geographic location. Therefore, the statistical power of the relevant sections was influenced to a certain extent. These limitations can be overcome by conducting larger and higher quality clinical trials so that we can standardize the details of the specific diseases and QE intervention conditions.

CONCLUSION

Our meta-analysis demonstrated that QE was able to improve fatigue symptoms, including total fatigue intensity and physical and mental fatigue intensity. QE for fatigue in patients or the general population has not been well investigated, with only a few publications regarding this common but under-diagnosed clinical problem. Future well-designed, high-quality studies with larger sample sizes are warranted.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

DS: conceptualization, supervision, writing — review, and editing. RW: data curation, funding acquisition, validation, and writing — original draft. RW and XH: methodology. XH and YW: software. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.684058/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Patient Choice and Willingness Toward Gatekeepers as First-Contact Medical Institutions in Chinese Tiered Healthcare Delivery System: A Cross-Sectional Study

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Introduction: Gatekeeping mechanism of primary care institutions (PCIs) is essential in promoting tiered healthcare delivery system in China. However, patients seeking for higher-level institutions instead of gatekeepers as their first contact has persisted in the past decade. This study aims to explain patients' choice and willingness and to provide potential solutions.

Methods: A survey was conducted among residents who had received medical care within the previous 14 days. Patients' choice and willingness of PCIs for first contact together with influencing factors were analyzed using binary logistic regression.

Results: Of 728 sampled patients in Hubei, 55.22% chose PCIs for first contact. Patients who are older, less educated, with lower family income, not living near non-PCIs, with better self-perceived health status, only buying medicines, and living in rural instead of urban area had significantly higher probability of choosing PCIs. As of willingness, over 90% of the patients inclined to have the same choice for their first contact under similar health conditions. Service capability was the primary reason limiting patients' choice of PCIs.

Conclusions: The gatekeeper system did not achieve its goal which was 70% of PCIs among all kinds of institutions for first contact. Future measures should aim to improve gate-keepers' capability.

Keywords: patient choice, patient willingness, gatekeeper, primary care institutions, first contact, tiered health care delivery system, influencing factors

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INTRODUCTION

The healthcare delivery system in China is hospital-centric and fragmented: primary care institutions (PCIs) were not trusted by public for its poor quality of care and hospitals kept expanding to serve more patients (1), and there is little coordination of care among different tiers of healthcare providers (2), instead they even compete for patients and hold onto patients when

they should be referred elsewhere (3). This medical chaos caused an inefficient healthcare delivery system, as well as prohibitive medical costs and widespread public discontent. To solve this chaos, in 2009, China launched a comprehensive health reform. For the first step of the reform (2009–2011), Chinese government emphasized strengthening infrastructure of PCIs, then for the second step (2012 onwards) a reform of healthcare delivery system was prioritized (4), aiming to limit specialty care access from high-level hospitals and help systems reduce overuse of inappropriate care by having PCIs perform gatekeeping functions.

In 2017, the State Council issued guidelines for initiating tiered healthcare delivery system (TDS) to enhance capability of PCIs and vertical integration among healthcare institutions in different tiers to facilitate gatekeeping function of PCIs (5). Measures of TDS include redefining facility roles, especially hospitals, within a vertical integrated network, developing formalized facility networks and establishing provider-to-provider relationships through technical assistance and skill building. One of the major goals of this policy was to promote the percentage of patients who choose PCIs for their first contact to 70% among all available kinds of medical institution.

However, to date the implementation of the system has been unsatisfactory. The share of outpatient visits at PCIs (71% in 2005, 57% in 2018) kept decreasing relative to those treated at hospitals (26% in 2005, 40% in 2018) (6). PCIs did not become more popular under the reform, and the flow of patients remained in chaos and brought about descending efficiency in healthcare delivery system (1).

To analyze the cause of failure of redirecting patients' first contact at PCIs and find feasible solutions, it is essential to understand factors influencing their choice of institutions at the first point of contact. Existing studies on the factors influencing the selection of healthcare institution for first contact have focused on individuals' willingness or attitude to go to PCIs (7–10). Studies on the reported actual behavior of people with medical treatment needs are lacking. Besides, no studies have investigated patients' first-contact willingness for medical institutions after their experience in first-contact medical institutions. Therefore, this study aims to explore the factors affecting the patients' actual choice of a medical institution for first contact, as well as first-contact willingness for medical institutions if experiencing a similar illness in the future. We use the findings of the study to provide feasible suggestions for promoting the normal function of TDS.

MATERIALS AND METHODS

The study was part of the background research designed and implemented by the Research Center for Rural Health Services, Key Research Institute of Humanities and Social Sciences at Huazhong University of Science and Technology, aiming to understand the health service needs of Chinese residents and the factors influencing these needs. The research protocol was approved by the Ethics Committee of Tongji Medical College of Huazhong University of Science and Technology (IRB No. S459, 2018). With the approval of this committee, written informed consent was obtained from respondents.

Abbreviations: PCIs, primary care institutions; TDS, Tiered Healthcare Delivery System.

Research Setting

After comprehensive consideration of economic, medical resources, and medical accessibility, we chose Hubei, a central province as the sample area. In 2018, per capita disposable income (US$3,947), the number of licensed physicians per 1,000 people and hospital beds per 1,000 people (2.1 and 6.65) of Hubei ranked middle-upper level (12, 14, and 8) among 31 provinces in mainland China. On the other hand, like most central provinces in China, the landforms of Hubei consist of mountains (56%), hills (24%), and plain lake areas (20%) (11), and convenient transportation enables both rural and urban residents in Hubei to have access to general or specialist medical services. Following State Council guidelines, Hubei government introduced goals and measures for TDS in June 2017. The main goal was to build up at least one effective vertical network in each city of Hubei by the end of 2017, and measures included defining responsibilities, rights, and duties of network members, integration of resources (medical techniques, medical personnel, information of patients), and establishing dual referral within networks (12). As of 2018, Hubei had already built up 626 networks covering 133 tertiary hospitals, 486 Secondary Hospitals, and 1,598 PCIs. However, no available evidence showed the effects of policy implementation on promoting gate-keeper function of PCIs.

Among 12 cities and one autonomous prefecture in Hubei, we selected Yichang as our study case. Yichang had a permanent resident population of 4,169,200 in 2018 with a moderate level of economic development. In the establishment of TDS, Yichang has put efforts on establishing dual referral system, increasing insurance reimbursement rate for PCIs, promoting family doctor system, and building information platform among institution of different tiers to facilitate first contact at PCIs and integrated clinical pathways (13). More specifically, for example, for referral system, an online referral information platform was established among 774 public healthcare institutions in 2014. As to increase reimbursement for PCIs, insured patients in Yichang diagnosed and treated in PCIs can enjoy lower deductibles and higher reimbursement rates. To promote family doctors, Yichang has implemented measures including government subsidies for health services provided by family doctors, lower prices for services, technical support from higher-level hospitals, and performance reward.

We randomly selected one urban area (X) and one rural area (D) in Yichang. Area X has a total area of 58.97 km^2 and a permanent population of 394,200. Urban residents account for 97.94% of the total population, and per capita disposable income in 2018 is US$5,863. Area D has a total area of 2,159 km^2, 20% of which is arable land. The area's permanent population is 469,300, with the urban population accounting for only 51.16%, and the per capita disposable income in 2018 is US$4,073. In terms of medical resources, area X has eight public hospitals and 20 PCIs (three community health service centers, eight community health service stations, and nine village clinics). Area D has three public

hospitals and 155 PCIs (seven township hospitals, three street hospitals, and 145 village clinics). Area D and area X differ in terms of medical resources, with area D having fewer large public hospitals but more PCIs compared with area X.

Study Participants and Sampling

The study participants were individuals who had received services from a medical institution in 14 days prior to the administration of the questionnaire survey. Five urban/rural communities were randomly selected in both Area X and Area D. A total of 42 households were randomly selected in each of these communities. A total of 210 urban households and 210 rural households were selected for the study sample. The average number of residences per households was 2.52.

Questionnaire Design

The questionnaire was designed by Huazhong University of Science and Technology based on standard National Health Service Survey, published literatures, and opinions from several experts. For questionnaire validation, a presurvey of 30 respondents was conducted to test its external and internal validity. Amendments were made based on the feedback received. The final version of questionnaire contained four parts of questions: basic information of household and individual, health-related quality of life and health behaviors, uses, and demand of health services. The survey was conducted in August 2018. Based on our study design, only part of the survey questions was included as variables.

Variables

The research outcomes were the first-contact selection and willingness of a medical institution in a similar illness. Institutions were categorized as PCIs (community health service centers in urban areas, village clinics and township street hospitals in rural areas) or non-PCIs (county/city/district health institutions, municipal health institutions, and provincial- and higher-level health institutions). We identified eight types of potential influencing factors based on published studies (14–18): (1) demographic factors: gender and age; (2) socioeconomic factors: education level, employment status, marital status, annual family income, and medical insurance; (3) accessibility of medical resources: nearest medical service provider and transportation time to the nearest medical institution; (4) health-related factors: self-perceived severity of illness and concurrence of chronic illness; (5) aims of service use this time: buying medicine, outpatient or inpatient visit; (6) residence: urban or rural area; and (7) other policy factors: registration with a family doctor or not.

Quality Control

Before the survey, community investigators who administered the questionnaire were trained, and unified coding rules for the questionnaire and implementation steps for the survey were explained in detail. Before investigation, the purpose and significance of the investigation were explained to the respondents using a unified instruction. For low educated or illiterate respondents, investigators asked them questions and questionnaire were filled out by investigators on their behalf. Promise was made to keep the information confidential and use it only for research. With the approval of the ethics committee, written informed consent was obtained from respondents. Validity of questionnaire was checked after questionnaire collection. Questionnaires with a response rate of over 85% and no logical errors are considered valid. Questionnaires with the same answer of all items, contradictory answers, and missing or wrong answer were excluded. For data entry, Epidata 3.1 software was used to create a database, and the accuracy of these data was checked to ensure the quality of the data input.

Statistical Analysis

The distribution of sample characteristics was statistically described. The chi-square test was used to assess the statistical significance of differences in the measured characteristics between sample populations, with $p < 0.05$ set as the two-sided significance level. The first-contact choice was analyzed using binomial logistic regression analysis (non-PCI = 0, PCI = 1). A binomial logistic regression analysis was also performed with the dependent variable of first-contact willingness (non-PCI = 0, PCI = 1). Previous studies have showed that the experience or satisfaction of PCIs were significantly associated with willingness to a future contact (15, 19). Therefore, the first-contact choice and independent variables that were significant ($p < 0.05$) in the previous regression model were included as the independent variables in this regression analysis for willingness of first contact. SPSS, version 22.0 was used for all data analyses.

RESULTS

A total of 854 patients were investigated, and 728 effective questionnaires were collected (effective recovery rate: 85.25%). **Table 1** presents the top 10 illnesses for which participants contact PCIs or non-PCIs.

Table 2 presents the baseline characteristics of participants by first-contact choice. Of the 728 participants, 402 (55.22%) had selected PCIs for their first contact. Compared with the

TABLE 1 | Top 10 illnesses for which participants received medical services.

Non-PCIs	Proportion	PCIs	Proportion
Hypertension	11.08%	Hypertension	30.58%
Heart diseases	9.85%	Disc disease	9.02%
Disc disease	8.31%	Common cold	8.02%
Cancer	5.83%	Heart diseases	6.52%
Diabetes mellitus	5.23%	Diabetes mellitus	4.76%
Cerebrovascular disease	4.31%	Endocrine, nutritional, metabolic, and immune diseases	4.51%
Acute and chronic gastroenteritis	3.38%	Motor system disease	4.01%
Urethral calculus	3.38%	Cerebrovascular disease	3.01%
Common cold	3.08%	Acute and chronic gastroenteritis	2.51%

TABLE 2 | Demographic characteristics of participants by first-contact choice.

Variable	PCIs [*n* = 402 (%)]	Non-PCIs [*n* = 326 (%)]
Gender		
Male	179 (44.86)	157 (48.31)
Female	220 (55.14)	168 (51.69)
Age (years)**		
0–45	28 (7.02)	55 (16.92)
46–65	235 (58.90)	162 (49.85)
≥66	136 (34.09)	108 (33.23)
Education**		
Uneducated	66 (16.67)	29 (9.24)
Primary school to Junior high school	289 (72.98)	198 (63.06)
Senior high school to junior college	39 (9.85)	80 (25.48)
Bachelor degree or above	2 (0.51)	7 (2.23)
Employment status**		
Employed	268 (68.37)	166 (53.55)
Retired	66 (16.84)	103 (33.23)
Student	2 (0.51)	3 (0.97)
Unemployed	56 (14.29)	38 (12.26)
Marital status		
Unmarried	12 (3.04)	23 (7.08)
Married	329 (83.29)	266 (81.85)
Divorced	2 (0.51)	2 (0.62)
Widowed	52 (13.16)	34 (10.46)
Annual family income (Chinese yuan)**		
≤30,000	261 (64.93)	134 (41.36)
30,000–100,000	117 (29.10)	145 (44.75)
≥100,000	24 (5.97)	45 (13.89)
Medical insurance		
No medical insurance	6 (1.52)	6 (1.85)
Basic medical insurance	337 (85.32)	272 (83.95)
Basic medical insurance and commercial medical insurance	52 (13.16)	46 (14.20)
Nearest medical service provider**		
Non-PCIs	2 (0.50)	16 (4.91)
PCIs	380 (94.53)	242 (74.23)
Private hospital or private clinic	2 (0.50)	2 (0.61)
Pharmacies and others	18 (4.48)	66 (20.25)
Time to nearest medical institution*		
1–10 min	317 (79.45)	289 (88.65)
11–20 min	58 (14.54)	28 (8.59)
≥21 min	24 (6.02)	9 (2.76)
Self-perceived disease severity*		
Not severe at all or not too severe	66 (16.46)	41 (12.58)
Average	174 (41.73)	111 (32.36)
More severe	164 (40.90)	106 (32.52)
Very severe	17 (4.08)	22 (6.41)
Chronic disease or not		
Yes	314 (78.30)	234 (72.22)
No	87 (21.70)	90 (27.78)
Utilization of health services**		
Buying medicines	248 (61.69)	134 (41.10)
Outpatient	137 (34.08)	101 (30.98)
Inpatient	17 (4.23)	91 (27.91)
Place of residence**		
Urban area	26 (6.47)	99 (30.37)
Rural area	376 (93.53)	227 (69.63)
Register a family doctor or not**		
Yes	172 (43.77)	108 (34.73)
No	145 (36.90)	161 (51.77)
Not know	76 (19.34)	42 (13.50)

*$p < 0.05$, **$p < 0.001$.

patients choosing non-PCIs, the patients choosing PCIs had significantly higher percentages of individuals between 46 and 65 years old (PCIs: 58.90%; non-PCIs: 49.85%), with less than a junior high school education level (PCIs: 89.65%; non-PCIs: 72.30%), employed (PCIs: 68.37%; non-PCIs: 53.55%), with low annual family income (≤30,000 Chinese yuan) (PCIs: 64.93%; non-PCIs: 41.36%), with PCIs as their nearest medical service provider (PCIs: 94.53%; non-PCIs: 74.23%), with not severe or average self-perceived illness (PCIs: 58.19%; non-PCIs: 44.94%), those who used services of buying medicine or outpatient (PCIs:95.77%; non-PCIs: 72.08%), rural residents (PCIs: 93.53%; non-PCIs: 69.63%), and those who were registered with a family doctor (PCIs: 43.77%; non-PCIs: 34.73%). Also, patients with a maximum of 10 min of travel time to the nearest medical institution made up significantly lower percentages of the group choosing PCIs than of the group choosing non-PCIs (PCIs: 79.45%; non-PCIs: 88.65%). However, no significant differences were found between those choosing PCIs and those choosing non-PCIs for the first contact in terms of gender, marital status, medical insurance, or presence of chronic disease.

Table 3 shows the results of the binomial logistic regression analysis for the factors influencing first-contact choice. Patients between 46 and 65 years old (OR = 2.638, 95% CI: 1.350–5.157) or more than 66 years old (OR = 3.412, 95% CI: 1.621–7.183), those who used outpatient service (OR = 1.569, 95% CI: 1.009–2.441), and those living in a rural area (OR = 5.379, 95% CI: 2.148–13.467) had higher odds of choosing PCIs for the first contact. Patients with high school to junior college education (OR = 0.354, 95% CI: 0.169–0.740), those with middle family income (OR = 0.540, 95% CI: 0.365–0.798), those with more severe self-perceived disease status (OR = 0.401, 95% CI: 0.227–0.706), and those who used inpatient services (OR = 0.152, 95% CI: 0.081–0.285) were more likely to choose non-PCIs for the first contact.

Table 4 shows patients' first-contact choice and willingness. The sample size was reduced to 346 as some patients did not answer relative questions. Of the 346 patients, only 41.04% were more willing to go to PCIs at first point of contact. Of the patients who chose PCIs for first contact, 90.91% were more willing to go to PCIs and 9.10% were more willing to go to non-PCIs. Of the

TABLE 3 | Binomial logistic regression analysis of factors influencing first-contact choice.

Variable	OR	95%CI	
Gender vs. male			
Female	0.895	0.626	1.278
Age (years) vs. 0–45			
46–65	2.638*	1.350	5.157
≥66	3.412**	1.621	7.183
Education vs. Uneducated			
Primary school to junior high school	0.829	0.467	1.474
Senior high school to junior college	0.354*	0.169	0.740
Bachelor degree or above	0.860	0.138	5.375
Employment status vs. employed			
Retired	0.807	0.461	1.410
Student	3.522	0.279	44.423
Unemployed	0.938	0.528	1.666
Marital status vs. unmarried			
Married	1.588	0.368	6.853
Divorced	11.344	0.474	271.639
Widowed	1.921	0.396	9.322
Annual family income (Chinese yuan) vs. ≤30,000			
30,000–100,000	0.540*	0.365	0.798
≥100,000	0.881	0.427	1.816
Medical insurance vs. no medical insurance			
Basic Medical Insurance	1.516	0.330	6.979
Basic Medical Insurance and Commercial Medical Insurance	1.114	0.228	5.451
Nearest medical service provider vs. non-PCIs			
PCIs	2.153	0.375	12.352
Private hospital or private clinic	61.069*	2.878	1295.694
Pharmacies and others	1.658	0.306	8.994
Time to nearest institution vs. 1–10 min			
11–20 min	1.300	0.751	2.251
≥21 min	1.642	0.674	3.999
Self-perceived disease severity vs. not severe			
Average	0.646	0.365	1.142
More severe	0.401*	0.227	0.706
Very severe	0.479	0.186	1.232
Chronic disease or not vs. yes			
No	0.812	0.508	1.297
Utilization of health services vs. buying medicines			
Outpatient	1.569*	1.009	2.441
Inpatient	0.152**	0.081	0.285
Place of residence vs. rural area			
Urban area	5.379**	2.148	13.467
Register a family doctor or not vs. yes			
No	0.941	0.622	1.422
Not know	1.041	0.616	1.759

*$p < 0.05$, **$p < 0.001$.

patients who chose non-PCIs for first contact, only 1.04% were more willing to go to PCIs and 98.96% were more willing to go to non-PCIs.

TABLE 4 | First-contact choice and first-contact willingness.

First-contact willingness	First-contact choice	
	PCIs [$n = 154$ (%)]	Non-PCIs [$n = 192$ (%)]
PCIs	140 (90.91)	2 (1.04)
Non-PCIs	14 (9.10)	190 (98.96)

TABLE 5 | Binomial logistic regression analysis of factors influencing first-contact willingness.

Variable	OR	95% CI	
Education vs. uneducated			
Primary school to junior high school	0.266	0.044	1.631
Senior high school to junior college	1.151	0.103	12.818
Bachelor degree or above	1.977	0.007	552.010
Annual family income (Chinese yuan) vs. ≤30,000			
30,000–100,000	1.184	0.316	4.431
≥100,000	8.515	1.081	67.061
Self-perceived disease severity vs. not severe			
Average	1.759	0.332	9.327
More severe	0.773	0.171	3.485
Very severe	0.048*	0.004	0.547
Nearest medical service provider vs. non-PCIs			
PCIs	1.790	0.046	69.514
Private hospital or private clinic	2.782	0.001	9,483.602
Pharmacies and others	1.190	0.037	38.478
Utilization of health services vs. outpatient			
Inpatient	1.733	0.272	11.061
Place of residence vs. urban area			
Rural area	8.939**	2.573	31.059
First-contact institution vs. non-PCIs			
PCIs	979.264**	197.554	4,854.159

*$p < 0.05$, **$p < 0.001$.

Table 5 presents the results of binomial logistic regression analysis for the factors influencing first-contact willingness. The results show that for patients living in a rural area (OR = 8.939, 95% CI: 2.573–31.059), those who previously chose a PCI (OR = 979.264, 95% CI: 197.554–4854.159) are more willing to choose PCIs in similar illness. Patients with very severe self-perceived disease status (OR = 0.048, 95% CI: 0.004–0.547) are more willing to choose non-PCIs.

Figure 1 presents the reasons of why they were willing to go to PCIs or non-PCIs for first contact. Better doctor's techniques/skills (71.0%), more medical equipment (39.30%), lower medical costs (23.4%), better service attitude (21.5%), and wider range of medicines (20.6%) are the top 5 reasons for higher willingness to go to non-PCIs. For PCIs, the top 5 reasons are convenience distance (34.8%), better doctor's techniques/skills (32.0%), convenience of procedures (29.9%), better service attitude (21.8%), and lower medical costs (19.0%).

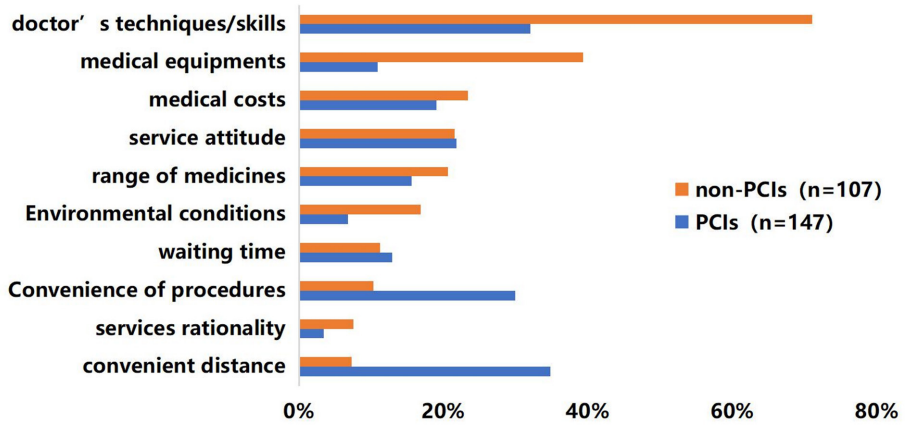


FIGURE 1 | Reasons for first-contact willingness.

DISCUSSION

In this study, the percentage selecting PCIs for the first contact among participants was 55.22%, which is lower than the policy goal (≥70%) proposed by the Chinese government in 2015. We found that patients who are older, less educated, with lower family income, living nearer PCIs, with milder self-perceived disease status, buying medicine or using outpatient services (as compared to inpatient services) for their visit purpose, and living in rural area as compared with urban area are more likely to choose PCIs for their first contact.

Patients who have PCIs as nearest medical service provider were more likely to choose PCIs. Previous studies found similar results. Yong Gan et al. have reported that patients living closer to PCIs were more likely to go to PCIs for first contact (9). Jingjing Liu et al. identified distance to the nearest medical institutions as the most important factor associating with PCI preference (20). Therefore, close proximity is an advantage for PCIs such as community health centers. Given that patients with chronic diseases need dietary, lifestyle, regulatory, and pharmacological interventions (21), nearby PCIs are well-positioned to provide a cost-effective management of risk factors for chronic diseases (22).

The results show that patients who only bought medicines were more likely to choose PCIs. There are several reasons that may explain this finding. Firstly, convenient location of PCIs makes it easier to have access to pharmaceutical services. On the other hand, prices of medicines in PCIs are cheaper due to higher reimbursement in PCIs. Thus, convenience and cheaper medicines may be incentives for buying medicines in PCIs rather than non-PCIs.

Rural residents were more likely to choose PCIs than were urban residents, which is consistent with previous studies (8, 14). Haiyan Song et al. found that the health resources have impact on patients' willingness to make their first visit to PCIs (10). As is reflected in the differences in health resources between the two areas included in this study, it is a common problem in China that health resources in rural areas are lacking, compared with urban areas (23). Therefore, rural residents only passively select PCIs and their medical needs are not being met effectively (24).

Gender, medical insurance enrollment had no significantly different influence between two groups choosing PCIs or non-PCIs, which may be contradictory with existing evidence (25, 26). Besides, we found no significant impact of an individual's chronic disease status on the choice of first contact. However, according to the government guidelines, the diagnosis and treatment of chronic diseases, such as hypertension and diabetes, are considered an opportunity for a breakthrough in realizing gatekeeping function of PCIs. Consistent with this goal, Menghan Shan et al. found an increasing utilization of healthcare in PCIs and a reduction in non-PCIs with no changes in total healthcare utilization in an economically advanced city of China (27). Our finding may indicate that the system in the study areas had not been effectively promoted.

Primary healthcare has been recognized as the cornerstone of the health services system worldwide (28). Family medicine has become the dominant model for primary care in many countries (29). Family doctor system, which has been shown to play an important role in gatekeeping function of PCIs (30, 31), was not an influencing factor in our study. Da Feng et al. found that family doctors may reduce patients' tendency for unnecessary use of medical resources (32). However, according to our finding, family doctors were not playing a role in guiding healthcare seeking behaviors of patients. Well education and training of general practitioners and an effective family doctor system under the national policy are needed throughout China (33, 34).

Our findings in willingness of first-contact institutions show that patients with milder self-perceived disease status, living in rural area as compared with urban area and previously choosing a PCI for first contact as compared with non-PCIs are more willing to choose PCIs in a similar illness, which are also found in previous studies (9, 14). Besides, we also found that although most patients' first-contact willingness was consistent with their actual first-contact choice, the percentage of patients who were more willing to choose PCIs for first contact decreased compared with first-contact choice of PCIs (41.04 vs. 44.51%).

Most patients believe non-PCIs rather than PCIs can better meet their medical needs.

According to the reasons for first-contact willingness, the main reason for choosing non-PCIs was doctor's techniques (71.0%). In contrast, the most important reason for choosing PCIs were convenience distance (34.8%). As to medical costs, which is much lower in PCIs thank to higher reimbursement and cheaper services; however, only 19.0% of patients considered it as their reason for choosing PCIs. To conclude, doctor's techniques and convenience may be decisive in first-contact willingness but lower medical costs in PCIs are not that attractive. Previous studies found similar results and mainly attribute these to the growth of income and the pursuit of better healthcare (35, 36).

Together, it is disappointing for policy makers and implementers to know that there is continuing decreasing choice and willingness of patients choosing PCIs as their first-contact institutions. However, the tendency is not irreversible given the Chinese government have been informed with the elephant in the room that the grassroot capability has been weakening during the past decade (34, 37–39). Similar with China, Korean government also faced up with an inefficient use of healthcare resources that about 15% of outpatient visits eligible for primary care happened in high-level hospitals (40). A cross-sectional study in Taiwan shows that the trends of bypassing primary care for treatment of common diseases decreased from 2,000, but still high for diabetes in 2017 (41). Another study in Austria found that visiting specialists were quite common and the simple presence of a general practitioner as a usual source of care was insufficient (42). In Japan, patients also can access any medical institution without referral. A study in Japan found that introduction of a gatekeeping system was necessary to reduce the incidence of referral to advanced care (43).

On the basis of the above analysis, we propose the following suggestions for potential solution for a better functioning TDS. The government of China should continue to increase financial investment, improve accessibility, and advance service capacity for PCIs (1). To meet the medication needs of patients with chronic diseases, the government should also equip PCIs with sufficient supplies of a variety of common drugs to treat these diseases. For construction of TDS specifically, efforts should be taken for a better vertical integration of urban and rural health resources (39). Potential measures could include developing distance medical services, forming exports teams to contribute to improve medical skills of staff, consultation of patients, health education, and providing smooth two-way referral in rural areas (44, 45). Besides, the number of general practitioners is still insufficient in this country given the largest population in the world and way lags behind the growth in the numbers of specialists (46). Thus, the Chinese government should pay attention to the training and incentive structures available to general practitioners, to increase the number of general practitioners and improve the level of service they offer to meet patients' medical needs.

Our study deeply explored into one factor of the TDS—the patients' choice and willingness of first-contact institution as compared with existing evidences. This study is not without limitations though. First, the sample was small and consisted only of individuals living in one city. Thus, the generalizability of the results is limited. However, from another perspective, compared with the one-fit-all approach, it is reasonable to believe that due to the differences in policies, culture, demography, environment, and so on, tailored studies in different contexts is more valid in terms of exploring behavioral causes for first-contact choice. Second, only patient-level influencing factors were considered; factors from institutional level were not investigated. Institutional characteristics such as capacity, equipment, and drug allocation are also important factors affecting patients' selection of a first-contact medical institution (25). Besides, for policy factors where only family doctor system was considered in this study, other important reform actions for TDS, like referral system, are not analyzed. In addition, even at the patient level, not all factors were included in this study. For example, previous contact history (19) and trust in PCIs (47) were not considered.

CONCLUSIONS

This study compared first-contact choice and willingness of patients, offering a new perspective to understand factors influencing patients' selection of healthcare institution for first contact. We found that the percentage of patients choosing PCIs for the first contact fell short of the expected policy target in China's TDS, and patients who actually selected PCIs for first contact were more willing to choose non-PCIs. PCIs still need to strengthen their capacities to change patients' behavior inertia of going to large hospitals to seek medical care. Further study is still needed to develop helpful evidence on how to redirect patients' first contact to PCIs.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the data that support the findings of this study are available from the Research Center for Rural Health Services, Key Research Institute of Humanities and Social Sciences at Huazhong University of Science and Technology but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Research Center for Rural Health Services, Key Research Institute of Humanities and Social Sciences at Huazhong University of Science and Technology. Requests to access the datasets should be directed to Liang Zhang, zhangliang@tjmu.edu.cn.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Tongji Medical College of Huazhong University of Science and Technology (IRB No. S459,2018). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

WT conceptualized the research idea, developed the research design, and contributed to the manuscript revision. XL performed the data analysis and drafted the manuscript. ZL and LZ helped colleting and cleaning the data. All authors read and approved the final manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Developing a Scale for the Evaluation of People With Post-prandial Distress Syndrome

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Background: Functional dyspepsia (FD) is one of the most critical health problems worldwide. Although there has been an increased intervention to improve FD symptoms, it is difficult to compare the effect of intervention measures with the existing methods of reporting the outcome, and it is a lack of clinical evaluation tools that can be used to evaluate patients' symptoms and treatment. One way of potentially addressing this way is to offer a patient-reported symptom scoring scales, which can be self-reported by patients to highlight interventions' authenticity and reliability. Nevertheless, there is still a lack of validated patient-reported outcome instruments for post-prandial distress syndrome (PDS). This study aims to establish a symptom scoring scale to evaluate the effectiveness of interventions for PDS.

Methods: The study consists of two steps. The first step was to formulate the scale. Through a systematic literature review and group discussion, an item pool and scale framework were formed. Then, through the expert consultation and pre-investigation, the formal version of the scale was formed. The second step is to test the reliability and validity of the scale. The scale is tested in the target population to determine whether the reliability and validity of the scale.

Discussion: The improvement in patients' self-reported symptoms had a significant impact on the researchers' evaluation of the intervention's authenticity. Therefore, we develop a symptom scoring scale for reporting studies evaluating the effectiveness of PDS interventions. The scale will be used for a more significant comparison to evaluate PDS interventions' effectiveness. The scale also improves trial reporting, reducing research waste by prioritizing the collection and reporting of critical results for all relevant stakeholders.

Clinical Trial Registration: ChiCTR, ChiCTR2100044489. Registered on March 22, 2021.

Keywords: scale, post-prandial distress syndrome, curative effect evaluation, scale development, scale evaluation

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INTRODUCTION

Functional dyspepsia (FD) consists of a complex of symptoms, including epigastric pain or burning, post-prandial fullness, or early satiety, which cannot be found by routine examination as organic, systemic evidence, or metabolic diseases (1). And Rome IV consensus proposed to distinguish post-prandial distress syndrome (PDS; meal-related dyspeptic symptoms, characterized by post-prandial fullness and early satiation) from epigastric pain syndrome (EPS; meal-unrelated dyspeptic symptoms, characterized by epigastric pain and epigastric burning) (2). The general population's prevalence is in the range of 11.5–29.2% (3, 4). And ingestion of a meal is an essential trigger for symptom occurrence (5–7). Dyspepsia, which is the most common and representative symptom of gastrointestinal symptom, can lead to decreased quality of life and depression in patients, and studies have shown that the quality of life of patients with FD is significantly lower than that of patients undergoing gastroscopy for other reasons (8, 9). Besides, FD symptoms are prone to recurrent attacks, which seriously affect patients' quality of life and aggravate patients' economic burden. According to statistics, the UK's annual cost of indigestion is 1 billion pounds, while in the US, the average additional cost per person with FD is more than 5,000 dollars per year (10, 11).

Moreover, the symptoms of PDS often overlap with those of EPS. An epidemiological survey in Italy showed that 67.5% of patients diagnosed with FD were PDS, and 48% were EPS. As a kind of FGIDs, FD often overlaps with other disease symptoms in FGIDs because of its common physiological and pathological mechanisms. Studies have shown that patients with overlapping symptoms have a higher frequency and severity (12). Although it has some medicine can well improve patients' symptoms, it is difficult to compare the therapeutic effect of intervention measures with the existing methods of reporting the outcome, and it is a lack of clinical evaluation tools that can be used to evaluate patients' symptoms and treatment (13, 14).

The patient-reported outcome (PRO) assessment records the patient's experience of the condition in a structured form that directly states the patient's health status rather than the clinician's or anyone else's interpretation (15). Scale as a form of expression of PROs, by describing the patient can feel accepted some treatment measures after the change of the domestic symptoms of its health condition or disease, can pay more attention to themselves, highlight the actual effect of intervention effect, make the results more authenticity and reliability, is one of the commonly used methods of efficacy evaluation at home and abroad at present (16). In FGIDs clinical trials, its primary purpose is to improve all patients' signs and symptoms (2). Also, FDA proposed that for Irritable bowel syndrome (IBS), the measurement of symptoms and signs is the only existing measure that can fully determine the therapeutic effect in clinical trials (25).

Considering the higher clinical incidence and the overlap between its symptoms, we would like to develop a symptom scoring scale for PDS with overlapping symptoms of FGIDs. By searching the existing symptom scoring scales for PDS, we found still lacks the scale about PDS symptoms with overlapping symptoms in China. Therefore, we will develop a patient-filled PDS symptom scoring scale for symptom scoring to evaluate the effectiveness of therapeutic interventions for PDS. The objective is to reduce reporting bias and result variance to ensure the authenticity and reliability of clinically relevant results.

Aim

The scale will apply to future evaluation of the effectiveness of interventions for treating patients with PDS. The scale will also be helpful for studies in PDS with overlapping symptoms of FGIDs.

METHODS AND STUDY DESIGN

Study Design

This study has two components (see **Figures 1**, **2**):

(1) Phase 1: Develop a visual analog scoring (VAS) scale for dyspepsia symptoms: ① Build the original entry pool and scale structure through a systematic literature review and group discussion; ② Develop a draft of the scale through core group discussion and expert consultation; ③ Formal version of the scale was formed through investigation and evaluation of the first draft of the scale.

(2) Phase 2: Evaluate the reliability, validity, and responsiveness of the VAS scale for dyspepsia: ① Determine the study subjects; ② Collect the scale data; ③ Evaluate the feasibility, reliability, validity, and responsiveness of the scale.

Methods

Set up a Research Group

This study has two groups. One is a core working group consisting of researchers, experts in clinical digestion, clinical evaluation methodology, and professional statisticians. The other is the scale investigation group composed of researchers and trained investigators.

Phase 1: Develop a VAS Scale for Dyspepsia Symptoms

(1) Step 1:Build the original entry pool and scale structure

By searching the book of internal medicine and digestive medicine, the scales and guidelines of PDS/FD, the existing possible symptoms of PDS were extracted, and the sorted symptoms were normalized. The core working group will pick out the most appropriate symptoms as an item.

By searching the existing scale scoring methods, we decide to use the VAS as the scale scoring method, a 10 cm line segment whose line segment scale represents the degree of symptoms. In clinical practice, a VAS is less affected by other factors in evaluating symptoms, and it can reflect the actual percentage of improvement results, which is widely used in clinical studies.

(2) Step 2: Expert consultation

RAND/UCLA appropriateness method (RAM) was adopted, which overcomes the disadvantages of the Delphi method in which experts do not meet so that it is difficult to reach consensus on controversial issues and participants' opinions are too dispersed in the nominal group method (17). We preliminarily consider using two rounds of expert consultations.

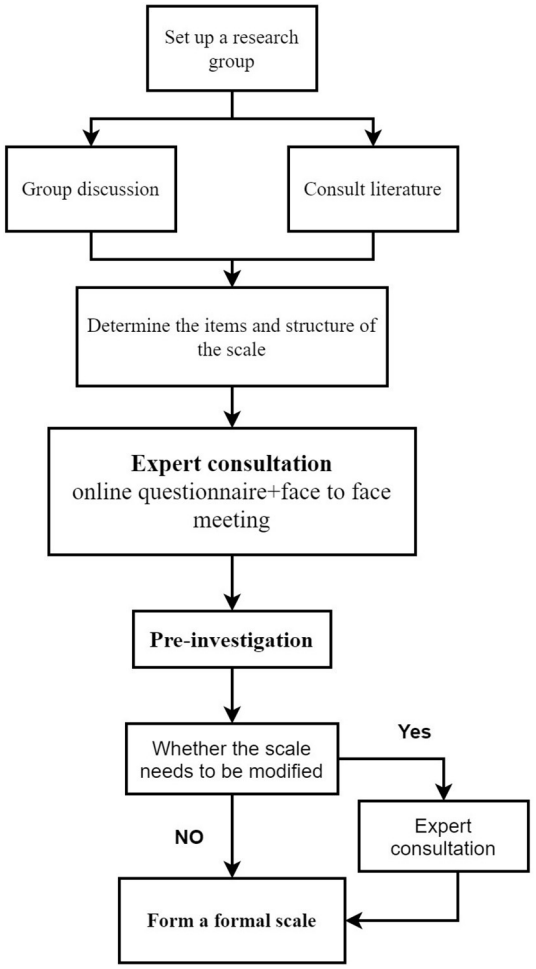


FIGURE 1 | Research flow chart of developing a scale.

① The first round of expert survey

We send an e-mail to invite gastrointestinal experts with senior titles, including the vice senior and senior titles. In the e-mail, we will introduce the background, purpose, and significance of this research in simple language. We will then invite the experts to fill a questionnaire, including a 4-point Likert type scoring in rating the importance of items to the scale and suggestions on modification, supplement, and deletion.

② The second round of expert survey

The second round of experts includes gastrointestinal, methodology, and statistical. An experienced facilitator/coordinator will conduct a face-to-face meeting. At the meeting, all experts were given previous individual ratings from other experts. Each expert will give their opinions on each item's appropriateness and discuss according to the expert opinions collected last time to determine whether the items in question need to be modified, supplemented, or deleted. Before the end of the discussion, each participant will review their previous scoring results again and modify them to form the scale's first draft, and then they will evaluate the scale's draft in a 4-point Likert type scoring.

If the experts still dispute the second round of expert consultation results, the third round of evaluation would be conducted by e-mail.

(3) Step 3: Pre-investigation

The primary entries were filtered through core working group discussions and expert consultations. Content validity index (CVI) was used to evaluate the scale's content validity, and the final draft of the scale was formed. The scale investigation group will then pick out 30 patients with PDS from the Gastroenterology Department outpatient department and the hospital's gastroscopy room by purposed sampling. Semi-structured interviews were used to ask the respondents about the following questions: ① past history and present history; ② the existing symptoms and symptom severity score; ③ score the scale and explain the reasons; ④ comprehension of the question in the scale; ⑤ the processes to retrieve relevant information from memory (i.e., what does the respondent need to recall to be able to answer the question; what strategies does the respondent use to retrieve the information). After a semi-structured interview, the respondent will be invited to fill the scale.

The scale draft items were screened and modified again through pre-investigation. If the revision of the scale is involved in the pre-survey, we will consult experts again. And form a formal version of the scale.

Phase 2: Evaluate the VAS Scale for Dyspepsia Symptoms

Patient Selection

(1) Inclusion criteria

① Meet the diagnostic criteria of PDS;
② Age between 18 and 70 years old (including 18 and 70), male or female;
③ Each subject is informed and voluntarily signed the informed consent form (ICF).

(2) Exclusion criteria

① Patients who cannot fill scales or record their symptoms;
② Pregnant or lactating females.

Sample Size

COSMIN recommended that the sample size should be seven times the number of items, and the sample size should be $\geq$100 cases (18). Assuming a dropout rate of 20%, we take 10 times the number of items. Suppose the number is $<$100 cases, then 100 cases are selected.

Observation Period

This study lasted for 4 weeks (28 $\pm$ 2 days).

Questionnaires

(1) Visual analog scoring scale for dyspepsia symptoms (VAS scale)

Based on a literature survey, the Rome IV definitions, core working group, expert consultation, and pre-investigation, a VAS scale was constructed. The scale investigated the daily symptom

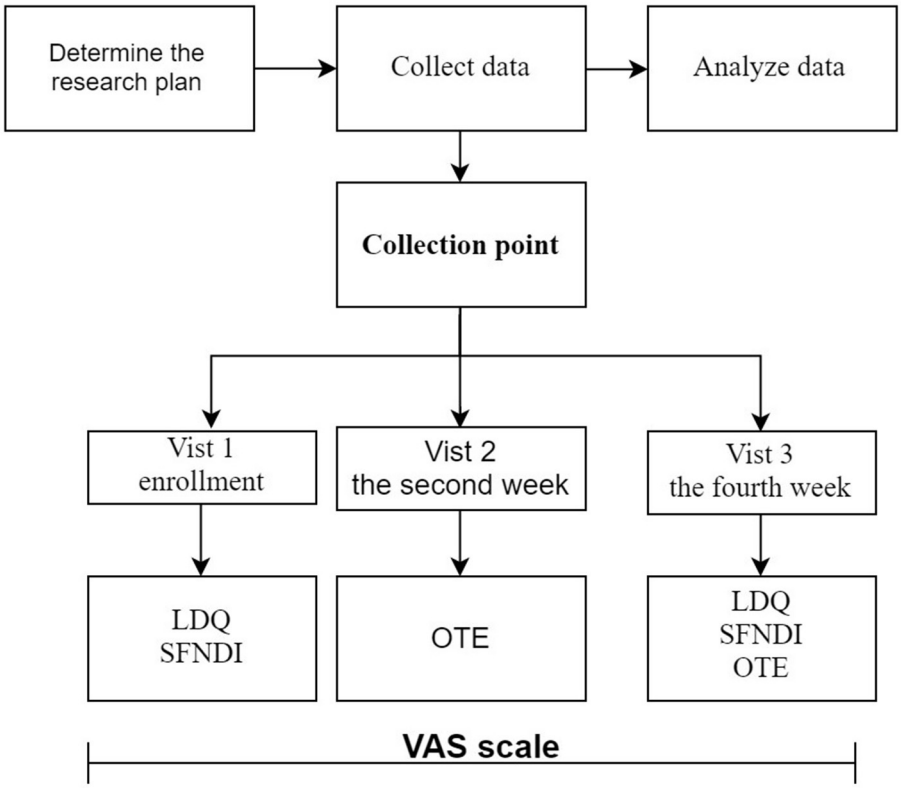


FIGURE 2 | Research flow chart of the scale evaluation.

score of the respondents, the rating of the items is expressed as visual analog scoring (ranging from asymptomatic to unbearable) accompanied by "smiley faces," and the weekly average of each symptom was taken as the weekly score (0–10), the higher the score was, the more severe the symptoms were.

(2) Overall evaluation scale (OTE)

The overall treatment efficacy is evaluated using a 7 point Likert Overall Evaluation Scale (OTE). The clinical investigators asked the subjects the following questions at the visit: "In the last week, how much have your dyspeptic symptoms been alleviated as compared to pre-treatment?" There are seven options: ① the symptoms improved significantly, ② the symptoms improved, ③ the symptoms improved slightly, ④ the symptoms did not change, ⑤ the symptoms aggravated slightly, ⑥ the symptoms aggravated, ⑦ the symptoms aggravated significantly. At the last visit time point of the treatment cycle, patients who selected ①–② were defined as treatment responders, and those who selected ③–⑦ were defined as non-responders.

(3) Leeds Dyspepsia Questionnaire (LDQ)

The LDQ is an eight-item symptom-based questionnaire assessing dyspepsia's severity according to the frequency and the severity of various upper GI symptoms (19).

(4) Short Form-Nepean Dyspepsia Index (SFNDI)

The scale has 10 items that describe how stomach pain, discomfort, or other upper abdominal symptoms have affected the life over the past 2 weeks. Discomforts were rated on a 5-point Likert scale from 1 (no effect) to 5 (significant effect).

Collection Point

The VAS scale was filled out daily by the respondents. Investigators filled out the OTE scale every 2 weeks, the time of the 2nd week and the 4th week after enrollment; And LDQ and SFNDI were completed every 4 weeks, the time of enrollment, and the 4th week of enrollment.

Statistical Analysis

The VAS scale uses VAS to score symptoms in an asymptomatic to unbearable. These were numerically transformed into a 0–10 score range and averaged for each symptom weekly (0–10). We set up the symptoms of post-prandial fullness and early satiation, the core symptoms of PDS, as cardinal symptoms of scale and be included in the VAS diary score. The inclusion of accessory symptoms in the scale is helpful for researchers to understand the patients' epidemiology and improve the symptoms by the intervention, which is more conducive to the positioning of the intervention and the potential target population of the subjects.

(1) Feasibility evaluation

Actual completion and average completion time of the scale were investigated.

(2) Construct validity

The construct validity of the VAS scale was assessed by the content validity index (CVI). First, correct for chance agreement, which can avoid two or more experts agree on evaluating the relevance of items due to their random selection of options. CVI is composed of item-level CVI (I-CVI) and the scale-level CVI (S-CVI). I-CVI evaluates the content validity of each item, and I-CVI $\geq$ 0.78 is considered to have good content validity; while the S-CVI is evaluating the content validity of the entire scale, for the unanimous S-CVI (S-CVI/UA) should be no $<$0.8, and the average S-CVI (S-CVI/ AVE) should reach 0.90.

(3) Criterion validity

Criterion validity is evaluated by comparing groups with different theoretically expected VAS domain score distributions. OTE is compared with respect to post-prandial fullness and early satiation using the Mann–Whitney test. Cohen's d is also reported to quantify the degree of differentiation between groups.

(4) Internal consistency

The relevance of items in each VAS scale symptom domain is evaluated by the model measured at visit 2. A more direct assessment was also carried out through internal consistency measures. Cronbach's α was calculated. Generally, α values $>$0.6 or ideally $>$0.8 are sought.

(5) Test-retest reliability

The patient's VAS scale is filled out every day. The basic steady-state is ideal for assessing the test-retest reliability, so visit 1 and visit 2 are used to assess the test-retest reliability, and the Pearson correlation coefficient is used to measure the correlation between the two scores.

(6) Convergent validity

The convergent validity concept adds credibility to the VAS scale by showing that it is related to other dyspepsia symptom burden measures. The VAS scale at visit 3 was correlated with the OTE, with the SF-NDI, and with the LDQ domains corresponding to early satiation and/or post-prandial fullness. Pearson correlation coefficient is used to measure the correlation between them.

(7) Responsiveness

Evaluate the response degree based on the change in the respondent's VAS scale score before and after treatment.

Data Management

All data will be completed directly by participants using an online questionnaire and stored in an online crowdsourcing platform in mainland China, which provides functions equivalent to Amazon Mechanical Turk. Data collected through the EDC will be entered directly without a paper copy. Once all data monitoring, validation, and cleanup activities have been completed, the final EDC database's output, along with any paper records, will be archived in a secure storage facility for 5 years.

Quality Control and Assurance

A pre-specified standard operating procedure will be trained before the research, which including eligibility criteria, intervention, details in filling scale, assessment of outcomes, data management. An inspection plan will be designed for quality control. Apart from health education, patients prioritize using an online questionnaire to improve compliance. The research assistants can also track patient filling in time from the background.

ETHICS AND DISSEMINATION

Ethical Considerations

Ethical approval for this study was granted by the Clinical Research Ethics Committee, Xiyuan Hospitals, China. This trial has been registered in ChiCTR (ChiCTR2100044489).

Dissemination and Implementation

Upon completion of the VAS scale evaluation, the use of the VAS scale will be published and disseminated.

DISCUSSION

There is still a lack of available published criteria for evaluating the effectiveness of PDS interventions. By describing the changes in patients' health status or disease symptoms after receiving the intervention, the patient-reported outcome scale can pay more attention to themselves, highlight the intervention's actual effect, and make the results more authentic and reliable. By establishing a symptom scoring scale reported by patients daily, we take the average of each symptom as the weekly score, which has the advantage of prospective records and avoids the potential false recall. Also, taking the average of each symptom within a week can make the results more reliable. For the scale scoring, we adopted the VAS, which was represented by a line segment of 100 mm in length. The VAS score was less affected by other factors in evaluating symptoms, reflecting the actual percentage of improvement results. Although verbal symptom description is used in most PRO scales to describe the pattern and severity of FGID symptoms and is the outcome parameter in the PRO development process, it is not suitable for all groups of people because of the differences in the level of writing cognition and thinking ability (14, 20–23). As an alternative, pictures have great potential to promote understanding and recall of new information (24). We use the smiley face to help the patient understand the symptoms' impact on her discomfort, making the results more reliable. As the whole investigation period is as long as 4 weeks, how to prevent patients from falling out is a big problem. To solve this problem, we adopt the form of an online questionnaire survey. Researchers in the background visit and push the questionnaire, improving patient compliance and reducing unnecessary workforce and material resources. Besides, there was no pharmacological intervention for the enrolled patients, and we were unable to determine the minimal clinically important difference of the scale, which is the patients achieved the minimum improvement value. There needs further research in the future.

CONCLUSION

We expect this scale to solve the two major problems of limited tools for evaluating PDS interventions' efficacy

and lack of authentic and reliable tools for evaluating the efficacy. This scale can truly and reliably reflect the improvement of patients' symptoms. Because FGIDs often overlap in symptoms, the scale focuses on the main symptoms of PDS and includes the symptoms that may occur with PDS as accessory symptoms. Moreover, giving priority to collecting and reporting the possible symptoms of patients helps researchers understand their epidemiology and the improvement of each symptom by intervention measures, which is more conducive to the positioning of intervention measures and potential target subjects. Furthermore, this scale improves trial reporting, reducing research waste by prioritizing the collection and reporting of critical results for all relevant stakeholders.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Xiyuan Hospital, China Academic of Chinese Medical Sciences. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FL conceived and designed the study. FL and MX wrote the protocol and manuscript, respectively. YaZ wrote the statistical analysis plan. All authors made significant contributions to the conception and design of the study protocol. All authors gave final approval of the manuscript and agreed to be accountable for all aspects of the work.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Performance Comparison of Public Hospitals Between 2014 and 2018 in Different Regions of Guangdong Province, China, Following 2017 Medical Service Price Reforms

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This study analyzed performance of public hospitals and regional differences in performance following reform of medical service prices in Guangdong province, China. From three cities in four regions, we randomly selected a total of 12 traditional Chinese medicine hospitals and 12 general tertiary hospitals. Six questionnaires were completed by the hospitals, using 2014–2018 internal data. Principal components analysis was used to compare performances of the hospitals and regions following price reform. The extent to which medical service prices were adjusted varied considerable for different procedures in the same region and for the same category of procedures among regions. After reform, compensation for medical services in public hospitals reached the target of 80%, except in the Western region. However, annual growth of costs to patients was generally above 4%; the burden on patients was not alleviated by fee control. Reforms were more effective for comprehensive than Chinese traditional medicine hospitals. Performance scores of general hospitals in the Pearl River Delta, Eastern, Western, and Northern regions were 1.24, 1.16, −0.22, and −1.01, respectively. This is consistent with ranking by level of economic development of each region. The government should implement a regional medical service pricing mechanism. Additionally, comprehensive and traditional Chinese medicine hospitals should each have appropriate pricing policies. Future policies should focus on controlling costs incurred by patients.

Keywords: public hospitals, medical service prices, performance, regional differences, China

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INTRODUCTION

In recent years, the Chinese government has enacted significant medical service price reforms in public hospitals to solve the problem of expensive medical treatment. The price of medical services is the monetary expression of the medical service's value, including outpatient, hospitalization, examination, treatment, testing, surgery, and so on. Previous studies have shown that medical service prices are closely related to quality of life (1, 2). Prior to the medical service price reform, patients who received drugs from urban public hospitals in the Guangdong Province of China were required to pay 12–15% of the drug price. However, on July 1, 2017, public tertiary hospitals in

Guangdong Province enacted medical service price reforms, by abolishing drug costs to patients. The policy stipulates that 80% of the income from drug reductions will be compensated by adjusting the hospital medical prices. In addition, the government subsidies 10%, and the hospital itself bears 10%. The policy optimizes the income structure of hospitals by reducing the proportion of drug revenue and increasing the income of technical services such as diagnosis, surgery and treatment (3).

The price adjustment policy affects a large number of medical services, and the adjustment range has changed greatly (4). This has far-reaching impact on hospitals, patients, and medical insurance funds (5). In this reform, the adjustment and formulation of local medical service prices are the responsibility of prefecture-level cities. Therefore, the prices of medical services may vary among cities and the implementation of policies may vary by region.

There exists relevant research on the implementation in other provinces of China. Zhang found that hospitals' income structure improved significantly after the price adjustment in Sichuan Province (6). A survey of Qingdao public hospitals found that hospital operating costs were more reasonable after the price reform (7). Tang and colleagues showed that the Nanjing government has a good control over price adjustments, and the compensation mechanism is reasonable (8).

Different countries have different pricing mechanisms for medical services. The price of medical services in some countries is controlled by the government, such as Canada, Germany, and Japan. In other countries, the price of medical services is negotiated by doctors, medical institutions, and insurance companies, such as in the United States. In 1989, Professor Xiao of Harvard University established a Resource-Based Relative Value Scale (RBRVS) by which to estimate the price of more than 7,000 medical service items. Subsequently, the RBRVS model was widely used by other countries (9–13). In 2006, the United States introduced multiple procedures for payment reduction (MPPR). When a patient receives multiple related procedures (e.g., CT, MRI), full price is charged for the most expensive procedure, with the other procedures being charged at a discount (14–17). In Japan, hospitals charge patients according to the Medical Insurance Points Table, with a score of 10 Yen per point (18, 19). In the UK, 97% of health care funding is obtained from taxes paid by residents to the government. Almost all medical service professionals are directly employed by the government, and residents receive free medical care at the point of service (20–22).

There are great differences between China and other countries in the price management model of medical services. Haiyin and colleagues suggested that China's medical service price reform has strong management and control capabilities, but the concept of performance-based payment, as used in the United States, is also of potential value (23).

To date, no studies have used hospital data to analyze the price of Chinese medical services. In China, most researchers have engaged in theoretical discussions. Some researchers have used a small number of indicators, such as compensation rate and balance rate, to conduct cross-sectional analysis of a hospital or region (24–26). However, these studies rarely compared differences among the regions involved. In addition, the use of statistical methods is rarely seen in the literature on the price of medical services. In the current study, the internal data of 24 hospitals in 12 cities in Guangdong Province in the past 5 years were assessed using principal components analysis to compare regional differences in reform performance, including in-depth analysis of differences in the implementation effects of policies in different regions. This study thereby addresses a current research gap regarding China's current medical service price reforms.

There are three advantages to the principal components analysis used in this study. First, statistical results permit differences among regions in the effects of reforms to be clearly elucidated. Second, performance comparisons among the same type of hospitals enables testing of the extent of each hospital's policy implementation. Third, it is possible to characterize differences between general hospitals and Chinese medicine hospitals. By this approach, we illustrate the shortcomings in the implementation of the policy, and propose improvement measures.

MATERIALS AND METHODS

Data Source

Guangdong Province can be divided into the Pearl River Delta region (e.g., Guangzhou, Foshan, Zhongshan), the Eastern region (e.g., Shantou, Chaozhou, Jieyang), the Western region (e.g., Yunfu, Maoming, Yangjiang), and Northern regions (e.g., Meizhou, Zhaoqing, Qingyuan) based on geographic, but with the regions varying in economic development. In this study, three cities were randomly selected from each region, and within each city, municipal people's hospitals and municipal traditional Chinese medicine hospitals were selected as research objects. Therefore, 12 comprehensive tertiary hospitals and 12 traditional Chinese medicine hospital were considered in this study. These hospitals have robust administrative and information systems, and thus provided authentic and reliable data.

With the agreement of the government and the hospitals, we designed questionnaires, and asked each hospital to extract data from its internal information system and financial statements. In the process of questionnaire design, we referred to other provinces' price assessment methods and related literature (27–29). After two rounds of group discussions, six questionnaires were initially generated that addressed the following topics: hospital drug revenue, basic status of hospital medical service price compensation, hospital medical income classification, hospital workload status, patient expenses, and charges for medical procedures. After preparing the questionnaires, they were further revised and improved in consultation with six relevant experts who are well-known in the field of health management. Then, we selected three hospitals in which to conduct a preliminary survey using the prepared questionnaires. It was verified that the questionnaires could be implemented in practice and fully collected the information required for the project. The hospitals were required to provide the completed questionnaire and financial statements for 2014–2018.

TABLE 1 | Performance evaluation indicators.

Indicators	Meaning
Medical service price compensation rate	Medical service price compensation income/(pharmaceutical income * actual drug addition rate) * 100%
Medical income growth rate	(Total medical income of a hospital in 2018 − Average medical income in 2014-2016)/Average medical income in 2014-2016 *100%
Decrease in medicine proportion	The proportion of hospital drug revenue in 2018 − the average proportion of drug revenue in 2014-2016
Hospitalization growth rate	(Total number of hospitalizations in 2018 − Average number of hospitalizations in 2014-2016)/Average number of hospitalizations in 2014-2016 * 100%
Per capita outpatient cost growth rate	(2018 per capita outpatient expenses − per capita outpatient expenses in 2014-2016)/per capita outpatient expenses in 2014-2016 * 100%
Per capita hospitalization cost growth rate	(2018 per capita hospitalization expenses − per capita hospitalization expenses in 2014-2016)/per capita hospitalization expenses in 2014-2016 * 100%

TABLE 2 | Average price adjustment range of public hospitals in various regions of Guangdong province (%).

Regions	Diagnosis	Nursing	Bed	Treatment	Surgery	Assay	Examination	Chinese medicine
Pearl River Delta	57.45	35.15	15.36	26.70	41.95	−5.50	−4.15	8.32
Eastern region	17.80	37.77	11.31	17.05	27.92	−1.35	−1.87	20.51
Western region	10.29	41.97	11.75	11.00	24.09	−3.10	−2.96	18.56
Northern region	10.62	33.15	−9.29	6.79	19.88	−6.05	−15.22	10.74

Data Analysis

There was a 100% response rate by the hospitals, but some hospitals provided incomplete data, such that only 60.5% of data were initially complete. To address missing data, we contacted the hospitals by phone and email and thereby completed the missing items. However, the data of four hospitals differed greatly from expectations. We personally traveled to these hospitals to conduct field surveys and obtain data. Before data analysis, we ensured 100% integrity and completeness of the 24 hospitals' data. As the price reforms were enacted on July 1, 2017, we selected the data of the first 3 years before reforms (2014, 2015, and 2016) and the year after reforms (2018) for analysis. This study primarily used principal components analysis to compare among-region differences (30–32).

Principal components analysis was used to measure the price reform performance scores of hospitals. First, we identified six principal components indicators. From the perspective of government evaluation, medical service price compensation and proportion of revenue derived from medicines were selected. From the perspective of hospital operation, the growth rate of hospital medical income and the growth rate of hospitalizations were selected. From the perspective of patient burden, the average outpatient expenses and the average hospitalization expenses were selected. The specific meanings of the six indicators are shown in **Table 1**. The impact of the price index was considered and excluded from the measurement of the indicator. Second, all indicator data were standardized as z-scores. Finally, principal component analysis was performed on the normalized data. Components with eigenvalues >1 were extracted until the cumulative variance explained exceeded 70%. The score of the principal component was the corresponding principal component analysis multiplied by the arithmetic square root of the corresponding variance. The composite score is obtained by summing the actual scores of all factors. The actual score of the factor is equal to the actor variance percentage multiplied by the initial score. The 24 hospitals were ranked in terms of reform performance via the principal components analysis. Further, regional performance differences were compared.

RESULTS

Price Adjustment Range of Different Service Items in Different Regions

The commonalities among regions were that the prices of medical nursing, treatment, surgery, and Chinese medicine all increased, while the prices of medical examinations decreased. However, there were differences in the price adjustments for the same medical service items in different regions. The key price adjustments for medical service items also differed among regions (**Table 2**).

Indicator Analysis

Table 3 shows that the compensation rates in the Pearl River Delta, Eastern, and Northern regions were all above or close to the target of 80%; the Western region did not attain the target. After the price adjustments, the medical and hospitalization-related income of hospitals in all regions increased steadily, and the hospitals operated effectively. In addition, the proportion of income derived from medicines decreased significantly. However, the average cost of outpatient and inpatient admissions continued to show an increasing trend, and growth in some areas was large, such as the average cost of outpatient clinics in the Pearl River Delta region and the Eastern region, and the average cost of hospitalization in the Western region.

TABLE 3 | Index values of different regions (%).

Regions	Compensation rate	Medical income growth rate	Hospitalization growth rate	The decreased proportion of drug costs	Outpatient cost growth rate	Hospitalized patients' cost growth rate
Pearl River Delta	79.50	10.62	7.99	−4.71	20.12	3.56
Eastern region	84.49	9.06	7.58	−6.15	15.78	4.32
Western region	74.38	15.48	7.49	−4.15	4.26	11.36
Northern region	96.29	15.81	12.28	−6.26	4.38	6.10

TABLE 4 | Rotating component matrix and coefficient matrix after conversion.

Index	Rotating component matrix			Component score coefficient matrix		
	F1	*F2*	*F3*	*F1*	*F2*	*F3*
Compensation rate	0.12	0.80	−0.11	0.07	0.52	−0.01
Medical income growth rate	0.88	−0.03	0.04	0.60	0.00	0.21
The decreased proportion of drug costs	0.03	−0.86	0.02	0.01	−0.57	−0.04
Hospitalization growth rate	0.58	0.24	−0.02	0.39	0.17	0.12
Outpatient cost growth rate	−0.01	−0.16	0.95	0.18	−0.04	0.86
Hospitalized patients' cost growth rate	−0.68	0.27	0.50	−0.36	0.20	0.35

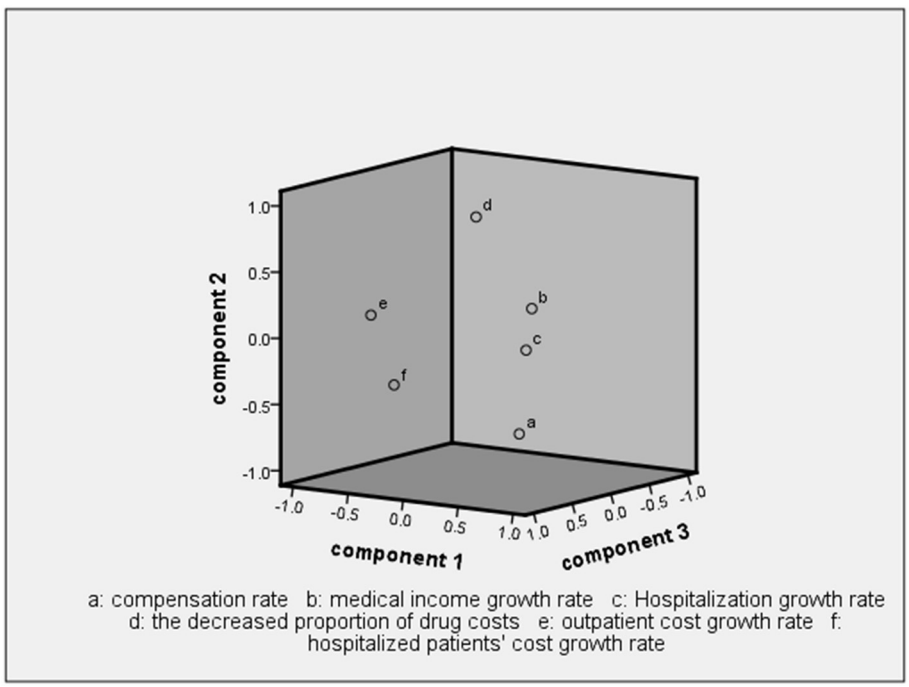


FIGURE 1 | Component plot.

Principal Components Analysis

Three principal components were obtained with eigenvalues of $\lambda_1 = 1.77$, $\lambda_2 = 1.54$, and $\lambda_3 = 1.02$, which together explained 71.14% of the underlying variance (**Table 4**). That is, the three principal components could represent the six initial indicators when analyzing post-reform performance. Therefore, the first three principal components were extracted and are referred to as F1, F2, and F3 hereafter (**Figure 1**).

Performance Ranking of Hospitals

As shown in **Table 5**, the performance scores and rankings of the 24 hospitals were obtained by principal components analysis. The performance of comprehensive hospitals was better

TABLE 5 | Twenty-four hospital performance rankings.

Hospitals	F1	F2	F3	Comprehensive score	Performance ranking
Chinese Medicine Hospital A (Pearl River Delta)	0.00	2.50	1.18	0.87	1
General Hospital A (Pearl River Delta)	2.68	0.26	0.15	0.80	2
General Hospital A (East)	2.26	0.25	0.32	0.72	3
General Hospital B (Pearl River Delta)	0.92	0.71	0.18	0.46	4
General Hospital A (East)	0.03	−0.06	1.32	0.25	5
General Hospital B (East)	−0.98	1.24	0.69	0.19	6
General Hospital B (West)	−0.44	0.19	1.13	0.15	7
Chinese Medicine Hospital A (East)	−0.59	0.87	0.37	0.14	8
General Hospital A (West)	0.12	−0.14	0.49	0.09	9
General Hospital C (North)	1.17	0.86	−2.56	0.03	10
Chinese Medicine Hospital B (West)	−0.09	−0.32	0.68	0.03	11
Chinese Medicine Hospital C (West)	−0.51	0.50	−0.06	−0.02	13
Chinese Medicine Hospital A (West)	0.15	−0.56	0.39	−0.03	14
Chinese Medicine Hospital C (North)	−0.52	−0.32	0.73	−0.08	15
Chinese Medicine Hospital A (North)	0.47	−1.43	0.15	−0.21	16
Chinese Medicine Hospital C (Pearl River Delta)	−0.88	−0.25	0.30	−0.23	17
Chinese Medicine Hospital B (Pearl River Delta)	0.38	−1.18	−0.29	−0.26	18
Chinese Medicine Hospital B (East)	−0.30	0.31	−1.51	−0.29	19
Chinese Medicine Hospital B (North)	−0.30	−0.96	−0.18	−0.36	20
General Hospital B (North)	−0.74	0.94	−2.35	−0.41	21
General Hospital C (West)	−1.38	−0.65	0.33	−0.46	22
General Hospital A (North)	−1.62	0.08	−1.19	−0.63	23
Chinese Medicine Hospital B (East)	0.12	−2.53	−0.51	−0.71	24

than that of traditional Chinese medicine hospitals. In addition, the F1 and F3 scores of the general hospitals were higher than F2. This shows that the reforms affected general hospitals predominately in the growth of medical income and inpatient numbers, and the average outpatient and inpatient expenses. The scores for F2 were generally higher than scores for F1 and F3 in traditional Chinese medicine hospitals. This shows that the Chinese medicine hospital has achieved significant results in the compensation rate and the decline in the proportion of medicines.

TABLE 6 | Reform performance of various regions in Guangdong province.

Regions	General hospital total score	Chinese medicine hospital total score
Pearl River Delta region	1.24	0.37
Eastern region	1.16	−0.87
Western region	−0.22	−0.02
Northern region	−1.01	−0.65

Reform Performance in Different Regions

For comprehensive hospitals, the reform performance scores of the Pearl River Delta region were highest, followed by the Eastern region, Western region, and Northern region. For traditional Chinese medicine hospitals, the reform effect was best in the Pearl River Delta region, followed by the Western region, Northern region, and Eastern region. The ranking of the reform effects for comprehensive hospitals was consistent with the regional economic level. The specific rankings are shown in **Table 6**. **Figure 2** shows the distribution of scores for component 1, component 2, and component 3 of each general hospital. Meanwhile, **Figure 3** shows the distribution of scores for the three components of each traditional Chinese medicine hospital.

DISCUSSION

Based on principal components analysis, we calculated the performance of 24 public hospitals in 12 cities, and compared the overall performance of four regions, focusing on the relationship between regional differences and price reform performance. Further, the effectiveness of the medical service price reform in the province was analyzed, as well as the advantages and disadvantages of the reform. Compared with the existing literature (24–26), the sample selected for this study was sufficiently large, the data more complete and reliable, and the analysis was not restricted to a certain hospital or region. Moreover, this study is the first to explore the specific performance differences related to medical service price adjustment policies in different regions.

This study showed that different service items in different regions exhibited significantly different adjustments in the medical service price. This may be related to differences in economic and basic health status in different regions. The level of regional economic development will affect local public hospitals, including the basic medical equipment available, medical environment, skill of employees, and the amount of attention

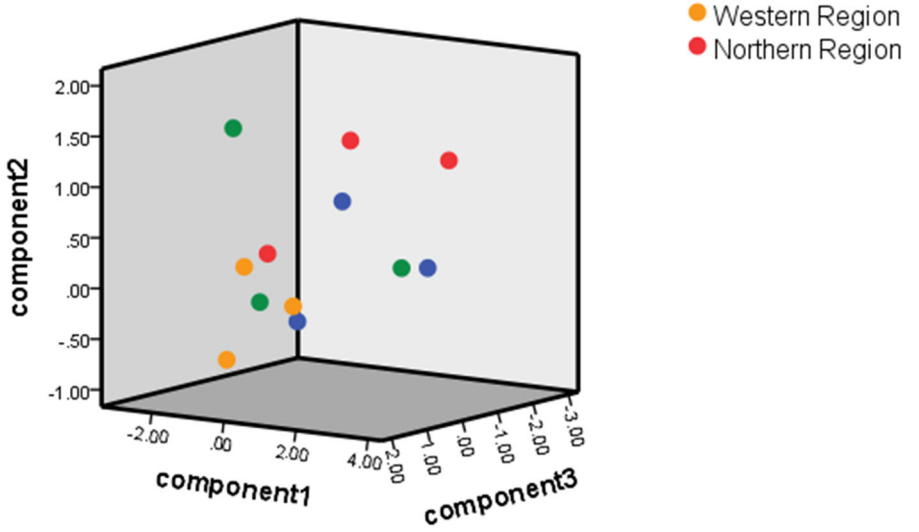


FIGURE 2 | General hospital.

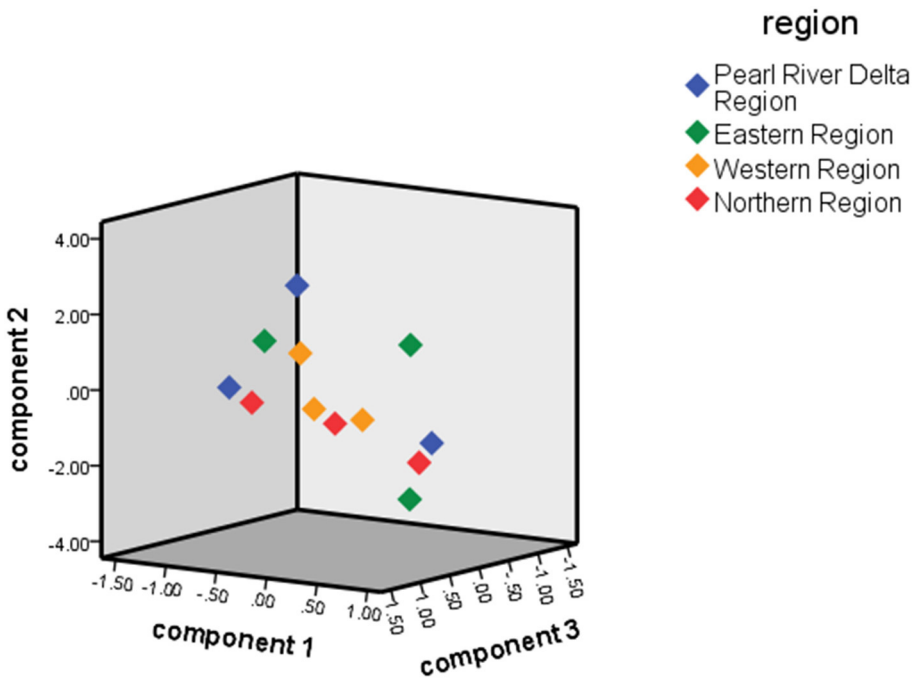


FIGURE 3 | Traditional Chinese medicine hospital.

each patient receives (33). The government needs to consider the status quo of public hospitals when formulating price policies. In addition, when a new price policy is implemented, changes in medical prices will affect the operation and development of public hospitals. A study of Norwegian hospitals found that medical prices fluctuated by 10% and the number of patients increased by 0.8–1.3% (34). Therefore, regional economic development, hospital tapes policy intentions, and medical prices

are often in a process of balance and coordination, and tend to be rationalized.

The Pearl River Delta region is located in the south-central part of Guangdong Province and is one of the most developed regions in China (35). The number of public hospitals in the Pearl River Delta region accounts for more than 60% of the total public hospitals in Guangdong Province. The service quality of hospitals is much higher than in the other three regions. The higher economic level and quality of medical care in the Pearl River Delta region has led to generally higher basic fees for public hospitals than in the other three regions. However, its high medical expenses are predominately generated via examinations and consumables, while the cost of technical services such as diagnosis, treatment, and surgery is relatively low. Therefore, the local government generally increased the cost of diagnosis, treatment, nursing, surgery, and so forth, and lowered inspection costs in the Pearl River Delta region during the price reform.

Compared with the Pearl River Delta region, the lower economic levels of the other three regions led to lower hospital fees. These local governments are more concerned regarding how to improve the hospital profitability in order to maintain the normal development of public hospitals. Therefore, local governments have considered not only excessively burdening the people via fees, but also slightly increasing the price of surgery, treatment, and nursing. Among them, the focus has been on raising the price of Chinese medicine services that include government subsidies and preferential policies. At the same time, local governments in the Eastern and Western regions have only slightly lowered the prices of inspections to ensure the normal operation of the hospitals.

The results showed that the performance scores of general hospitals and traditional Chinese medicine hospitals in the Pearl River Delta region were higher than those of the other regions. The Pearl River Delta region is the center of politics, culture, and economy in Guangdong Province (35). Public hospitals in the Pearl River Delta region may be more susceptible to policy. The comprehensive analysis of general hospitals, and the regional performance rankings are consistent with regional economic strength rankings, which indicates that the local economic level is related to the effect of reforms on local general hospitals. Riedel made similar observations, and found that the development of German hospitals faced severe challenges. An important point is that hospital reform and development are constrained by local economic development (36). At present, public general hospitals in China rely primarily on medical income to maintain hospital operations. Therefore, the services provided by the comprehensive hospitals that are most affected by the policy are likely to be severely affected. In addition to Germany, public hospitals in Japan are also generally facing financial deficits. Konosuke confirmed this and suggested that the extent of public hospital development is related to local purchasing power (37). However, prior studies only described the operation of public hospitals in particular locations, and did not engage in in-depth analysis of the differences in policy effects among regions. The current study add such research content. Overall, for regions with different levels of economic development, the same policy may not be applicable, and the effects of policies will be different. Our subsequent studies will assess how to formulate and improve policies for public hospitals in regions with different levels of economic development.

Compared with general hospitals, the reform performance of traditional Chinese medicine hospitals is affected not only by local economics, but also by local government support policies. The more the local government attaches importance to the development of traditional Chinese medicine hospitals, the greater the support it provides.

The development of local traditional Chinese medicine hospitals is better than general hosipitals. However, under the influence of support policies, the medical prices and patient-incurred expenses of traditional Chinese medicine hospitals also increased rapidly. The financial burden on patients in Chinese medicine hospitals has increased. Therefore, the government need to find balance when supporting the development of traditional Chinese medicine hospitals.

Results showed that the policy effect of controlling fees is not straightforward, and the burden on patients continues to increase on a yearly basis. As can be seen from **Table 3**, the average growth rate of patients' fees is still high, far exceeding the growth rate of the national consumer price index (2.1%) in 2018. The cost of medical treatment for residents has not decreased, and the effect of controlling fees is not satisfactory. The average outpatient expenses in the Pearl River Delta region reached 20.12% of the total medical costs, and the average hospitalization expenses in the Western region reached 11.36% of the total medical costs. These are much higher than expected for the policy developers, adding a considerable burden to patients. Therefore, although the reforms reduced the cost of medicines and inspections, the overall cost of medical care has increased for some patients. Tianlin also found that the cost borne by patients did not significantly decrease after medical service price adjustment in a study of Qingdao City, Shandong Province (7). In addition, Cooper found that hospital medical service prices rose by 42% between 2007 and 2014, and patient-borne costs rose sharply in the US. He suggested that policy makers should consider a range of options to address hospital price increases, including antitrust enforcement, management of pricing, and the use of reference pricing (38). Overall, governments need to develop more effective measures to control the growth of medical expenses.

Principal components analysis showed that the effect of reforms were significantly better on comprehensive hospitals than traditional Chinese medicine hospitals. This may be because the proportion of income derived from inspections and drugs in general hospitals is much larger than that of traditional Chinese medicine hospitals, but the proportion of income derived from technical aspects such as surgery, treatment, and nursing is much lower. After the implementation of the policy, the average cost of patients in general hospitals increased less than that of traditional Chinese medicine hospitals. This also shows that the comprehensive hospitals were greatly affected by the policy, and such hospitals face greater difficulties and challenges than do Chinese medicine hospitals. Similar observations have been made by other researchers. Tang found that the cost of service-dependent hospitals and drug-dependent hospitals was significantly different in a study of public hospitals in

Nanjing (8). He proposed that different pricing policies should be developed for different types of hospitals. At present, in China, an identical policy is implemented concurrently across the country or province. Therefore, policies can have different effects in different places and under different conditions. In this case, hospitals are facing increasing pressure, and the contradiction in the requirements of local governments and local medical institutions is prominent.

Tables 2, **3** show that the cost of diagnosis, treatment, surgery, and nursing, which reflect the value of the technical labor of medical professionals, is rising, and inspection costs are reducing. This encourages hospitals to develop technical medical specialties, especially orthopedics and physiotherapy. After the reform, more hospitals are willing to carry out medical surgery that requires advanced technology because they now have sufficient income. The policy has somewhat reduced the occurrence of over-examination in hospitals, because the profit associated with inspections has been reduced. From this perspective, the change to hospitals' income structures was benign, and the value of the labor of medical professionals has been recognized and valued. Li proposed that county-level public hospitals tend to have a reasonable income structure after adjusting for medical services (24). Wei suggested that the significance of this price adjustment is to make the price of medical services reflect the labor value of medical staff (5). Moreover, both researchers believed that the policy would have a positive impact on the internal management and performance of hospitals. This is consistent with the results of the current study.

There are also several limitations to this study. First, although principal components analysis was suitable for comparing the effects of reforms among hospitals or regions, the effects of reforms at the individual hospital level was not studied in depth. In future, it is necessary to further study the specific impact of the price adjustment policy within individual hospitals. Second, this study did not assess the different responses of local governments in implementing policies. Third, this we proposed that regional differences in economic development will influence the effects of policy changes, but the specific effects have not been thoroughly studied. These aspects represent important future research directions of our research team.

CONCLUSIONS

At present, the reform of medical service prices has achieved some acceptable results in public hospitals in Guangdong Province, but there remain issues. According to the analysis reported here, the following questions and suggestions are proposed: First, the current government's pricing policy does not distinguish between hospital types, such as general hospitals, traditional Chinese medicine hospitals, and specialized hospitals, which is unfair to hospitals. Different types of hospitals carry out different services, so the effects of policies often vary widely. Therefore, formulating appropriate policies is a powerful measure by which to resolve current contradictions regarding different types of hospitals in regions with different levels of economic development. Second, the price adjustment of medical services improved the internal income structure of hospitals, but did not reduce patients' expenses. Therefore, the government's subsequent policy development could usefully focus on the control of patient-borne costs. Third, the current price of medical services varies among cities, which will lead to the flow of patients between cities, and put pressure on local medical institutions. Therefore, we recommend implementing a given price policy among cities with similar economic and healthcare levels, eventually forming a regional medical service pricing mechanism. Fourth, few studies have applied advanced statistical methods to the field of medical service pricing. Therefore, we recommend using such methods within this field.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

W-QL participated in research and report preparation. Y-BW is responsible for full text guidance. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Catastrophic Health Expenditure and Its Determinants Among Households With Breast Cancer Patients in China: A Multicentre, Cross-Sectional Survey

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Background: Although numerous studies have examined catastrophic health expenditures (CHE) worldwide, most focus on the general population, not on specific vulnerable groups. We aimed to analyse the extent and the influencing factors of CHE in households with breast cancer patients in China, and explore the ability of different insurances to protect these households from CHE.

Methods: A multicentre, cross-sectional interview surveys was conducted in households with breast cancer patients across seven provinces/municipalities in China. CHE were defined as out-of-pocket expenditures $\geq$ 40% of households' non-food expenditures. Chi-square tests and logistic regression analysis were performed to identify the determinants of CHE in household with breast cancer patients.

Results: In the 639 participating households with breast cancer patients, the mean out-of-pocket (OOP) expenditure accounted for ∼55.20% of the mean households' non-food expenditures. The overall incidence of CHE was 87.95 and 66.28% before and after insurance compensation, respectively. The logistic regression model revealed that education, disease course, health insurance, treatment method, and income were significant predictors of CHE.

Conclusions: The results indicated that medical insurance protects some households with breast cancer patients from the impact of CHE. However, their reimbursement rates were relatively low. Therefore, breast cancer still had a significant catastrophic effect on the economy of households. Policy efforts should focus on improving insurance compensation rates and relieving the economic burden of critical illnesses such as breast cancer.

Keywords: catastrophic health expenditures, insurance, breast cancer, China, economic burden

BACKGROUND

According to GLOBOCAN statistics, in 2018, there were 18.1 million new cancer cases and 9.6 million deaths worldwide; among women (8.6 million new cases and 4.2 million deaths), breast cancer was the most commonly diagnosed (24.2%) cancer and the leading cause (15.0%) of cancer deaths (1). In China, breast cancer was also the most commonly diagnosed (1.778 million) cancer and the fifth most common cause of cancer death (0.858 million) among women (2). The high incidence and mortality rates of breast cancer in Chinese women can result in CHE and impose a substantial financial burden.

Despite the considerable improvement in health outcomes, the financial catastrophe caused by the excessive spending on healthcare services appears to be a threat to the health system (3). Generally, healthcare expenditure is considered as "catastrophic" when the OOP health spending greatly exceeds a certain proportion of households' income or capacity to pay (CTP) (4, 5). CHE may lead to a reduction in expenditures on basic commodities (6), even for patients choosing to abandon health care services, thus suffering from illness deterioration (7, 8).

Studies on CHE have been conducted globally, mostly using microdata to evaluate residents' economic burdens. Xu et al. reported that, annually and worldwide, over 150 million people suffer from financial catastrophe and approximately 100 million become impoverished owing to healthcare expenditures (9). Moreover, Another study conducted in 133 countries showed that, in just 5 years (i.e., from 2005 to 2010), CHE rose from 9.7 to 11.7% (10). Although many studies have examined CHE, most focused on whole populations, not specific vulnerable groups.

In China, owing to the complexity and severity of breast cancer, the costs associated with its diagnosis and treatment are usually higher than those of other diseases, showing a high OOP expenditure and leading to countless CHE incidents. Nationally, the basic health insurance system comprises the Urban Employee Basic Medical Insurance (UEBMI) and the Urban and Rural Resident Basic Medical Insurance (U&RRBMI), with the first offering a higher reimbursement rate compared to the latter (11). However, the reimbursement rate of UEBMI is only 55%.

Despite these facts, few studies have evaluated CHE, its influencing factors in households with breast cancer patients, and the impact of different insurances on CHE in China. Thus, we aimed to provide new information about the extent of the effect and the relevant factors of CHE in households with breast cancer patients; furthermore, we aimed to explore the ability of the medical insurance to protect Chinese residents from CHE. Our findings may contribute to improving and adjusting the related healthcare policies, which may evoke a reduced economic burden of disease on families affected by breast cancer.

METHODS

Context

The Cancer Screening Program in Urban China (CanSPUC), a key national project supported by the Chinese government, was initiated in 2012. It has served to conduct evaluations of personal cancer risk, clinical cancer screening, health economic evaluation, and follow-up work during the past years. Specifically, it primarily aimed to explore how to appropriately implement the screening of high risk populations and the early diagnosis of major cancers in Chinese urban populations. By 2018, it covered 20 provinces/municipalities in China (12).

Data Collection

A multicenter cross-sectional survey was conducted from January 2018 to June 2019 as part of CanSPUC. Geographic regions/provinces were grouped into eastern, central and western in line with the classification of economic development zones by the Chinese National Bureau of Statistics. Nine tertiary hospitals, were selected from these zones considering cancer patient volumes and completeness of medical records, including Guangdong Cancer Hospital (eastern); Anhui Cancer Hospital, Heilongjiang Cancer Hospital, Shanxi Cancer Hospital (central); Guangxi Cancer Hospital, Yunnan Cancer Hospital, the Regional Cancer Hospital and two city hospitals in Inner Mongolia (western).

Cancer patients diagnosed initially over the period from 01 January 2015 to 31 December 2016 were eligible for CanSPUC program. Eligible study participants were identified from the hospital records and then approached for a survey. The questionnaire was administered through face-to-face interviews. The survey was coordinated by the National Cancer Center. The interviewers were trained prior to deployment and required to check completeness of the questionnaire before concluding each interview. The questionnaire for this survey collected data regarding demographic characteristics, household income and expenditure, medical expenses for cancer treatment, and insurance compensation. A total of 2,565 patients were investigated, including lung cancer, breast cancer, colorectal cancer, oesophageal cancer, stomach cancer and liver cancer.

Regarding household income and expenditure, respondents were asked to describe them for both 2015 and 2016. Regarding medical expenses for cancer treatment, respondents were asked to describe this variable over a 2-year period (i.e., 2 months before and 22 months after the diagnosis); these costs included payments for hospital diagnosis, treatment, and medicines (prescription and non-prescription drugs) purchased from pharmacy retail stores. Household consumption expenditure includes the amount spent on food, clothing and daily necessities, communication and transportation, Housing, water, electricity and fuel, cultural recreation and entertainment, medical care and other consumption spending.

Among these, Breast cancer patients were selected as subjects of this study. Inclusion criteria were as follows: (1) having been diagnosed for the first time with primary breast cancer, (2) having been initially diagnosed between 1 January 2015 and 31 December 2016, and (3) having subsequently received cancer treatment. The exclusion criterion was having cancers in multiple organs. In total, 639 households that had a breast cancer patient were selected, including Guangdong (19.9% of the total sample), Anhui (7.2%), Heilongjiang (12.1%), Shanxi (14.4%), Guangxi (12.1%), Yunnan province (17.9%), and Inner Mongolia (16.4%). Regarding household income and expenditure, owing to

difficulties in articulating a clear cut-off point for the income and expenditure data, we calculated average income and expenditure across the 2 years to match the breast cancer treatment cost data. Regarding medical expenses, we calculated average medical expenses across the 2 years.

Data were double-entered into EpiData 3.1 to ensure accuracy and analysed using Stata 15.

TABLE 1 | Participant characteristics.

Sociodemographic characteristics	Number	Percent (%)
Gender		
Male	5	0.78
Female	634	99.22
Age (years)		
≤60	467	73.08
>60	172	26.92
Education level		
None	29	4.54
primary school	105	16.43
Junior and Senior high school	343	53.68
University and above	162	25.35
Marital status		
Married	563	88.11
Rest 1	76	11.89
Course of disease		
<1 year	75	11.74
1–2 year	564	88.26
Household size		
≤3	377	59.00
>4	262	41.00
Insurance		
UEBMI	317	49.61
U&RRBMI	303	47.42
Rest 2	19	2.97
Income level (RMB)		
≤80,000	444	69.48
>80,000	195	30.52
Treatment method		
Surgery alone	220	34.43
Radical surgery	101	15.81
Radiotherapy alone or chemotherapy alone	52	8.14
Surgery and postoperative adjuvant chemotherapy	229	35.84
Neoadjuvant chemotherapy and surgery	19	2.97
Rest 3	18	2.82

Rest 1 represents unmarried, divorced and widowed. Rest 2 stands for Public medical, commercial insurance and uninsured. Rest 3 stands for symptomatic treatment, concurrent radiotherapy and chemotherapy and oral medication. The UEBMI represents Urban Employee Basic Medical Insurance. UEBMI is a government-run mandatory insurance program based on employment. Because there is no guarantee for urban residents without formal employment, the government launched the Urban Resident Basic Medical Insurance (URBMI) plan in 2007. For uninsured rural residents, the New Cooperative Medical Scheme (NCMS) was implemented in 2003. U&RRBMI includes URBMI and NCMS. The RMB is the abbreviation of Ren Min Bi, which is the currency of China.

Measuring CHE

Based on prior studies (5, 6, 13), CHE was defined as OOP equal to or greater than a threshold level of 40% of household's CTP. In this research, OOP covered only direct medical expenditures. CTP was defined as households' non-food expenditure; we also used CTP as the denominator to calculate CHE, which allowed us to partly avoid measurement bias; such bias is often neglected when examining poverty-ridden families. Based on prior research (14, 15), we used the indicator E to demonstrate whether CHE occurred. In the equation below, the indicator *Ei* defined whether CHE occurred:

$$Ei = \begin{cases} 0, & \frac{oop}{xi - f(x)} < Z \\ 1, & \frac{oop}{xi - f(x)} > Z \end{cases}$$

Where *i* is household *i*, *xi* is the total consumption expenditure, *f(x)* is the food expenditure, and *Z* is the threshold of CHE. Based on this definition and prior research (14, 15), the incidence and intensity were calculated as follows:

$$Headcount = \frac{1}{N}\sum_{i=1}^{N} Ei$$

$$Overshoot = \frac{1}{N}\sum_{i=1}^{N} Ei\left(\frac{oop}{xi - f(x)} - Z\right)$$

$$MPO = \frac{Overshoot}{Headcount}$$

In these formulas, *N* is the sample size. Headcount was CHE incidence, which is the percentage of households with breast cancer patient whose OOP expenditures exceeded the given threshold. Overshoot is the average distance, it reflects the intensity of CHE in the overall households with cancer patients. MPO is the mean relative distance, it indicates the intensity of CHE in the households suffering from CHE (14, 16).

Statistical Analysis

The demographic profile of the breast cancer patients was described using the frequency and percentage for categorical variables (e.g., education level, marital status, and insurance type). The chi-squared test was applied to examine the associations between CHE and other variables including gender, age, education level, marital status, course of disease, household size, insurance, income level and treatment method. The statistically significant variables were then entered into the multivariate logistic regression. $P < 0.05$ was considered statistically significant.

A study has shown that the asymptotic quality of the standard maximum likelihood (ML) model can eliminate sample size problems (17); however, some researchers, specifically Hart and Clark (18, 19), suggested that reasoning problems began to occur when the sample size was <30; Eliaison, in turn, recommended a sample size of higher than 60 participants. Therefore, our sample size, which comprised 639 households with breast cancer patients, was adequate to meet the aforementioned requirements.

TABLE 2 | Incidence of CHE before and after insurance compensation.

Sociodemographic characteristics	CHE		*p*
	Before insurance compensation	After insurance compensation	
Gender			
Male	100.00%	60.00%	0.745
Female	87.85%	66.88%	
Age (years)			
≤60	87.58%	66.81%	0.990
>60	88.95%	66.86%	
Education level			
None	89.66%	86.21%	0.000
primary school	91.43%	76.19%	
Junior high school and Senior high school	89.21%	67.64%	
University and above	82.72%	55.56%	
Marital status			
Married	87.39%	66.61%	0.753
Rest 1	92.11%	68.42%	
Course of disease			
<1 year	81.33%	52.00%	0.004
1–2 year	88.83%	68.79%	
Household size			
≤3	88.06%	64.46%	0.127
>4	87.79%	70.23%	
Insurance			
UEBMI	85.80%	58.04%	0.000
U&RRBMI	90.43%	75.91%	
Rest 2	84.21%	68.42%	
Income level (RMB)			
≤80,000	91.89%	74.77%	0.000
>80,000	78.97%	48.72%	
Treatment method			
Surgery alone	82.27%	57.73%	0.000
Radical surgery	84.16%	56.44%	
Radiotherapy alone or chemotherapy alone	90.38%	73.08%	
Surgery and postoperative adjuvant chemotherapy	93.89%	76.42%	
Neoadjuvant chemotherapy and Surgery	94.74%	84.21%	
Rest 3	88.89%	77.78%	
Total	87.95%	66.82%	

RESULTS

The general characteristics of breast cancer patients and their families are shown in **Table 1**. Overall, 0.78% patients were male and 99.22% female, and their average age was 53.9 years [importantly, a study showed that the annual incidence of male breast cancer amounts to <1% of all breast cancer patients (20)]. Most patients completed junior and senior high school (53.68% of the total sample), followed by university and higher degrees (25.35%), primary school (16.43%), and none (4.54%). Regarding marital status, 88.11% of the respondents were married. Regarding disease course, 88.26% of the respondents had cancer for 1–2 years. Regarding household size, 59% of the households comprised less than four people. Regarding type of medical security, those under the UEBMI were 49.61% of the sample, and under the U&RRBMI were 47.42%. Regarding treatment method, surgery alone accounted for 34.43% of the sample and surgery and postoperative adjuvant chemotherapy accounted for 35.84%.

CHE incidence and intensity—defined by Headcount and Overshoot—for all households before and after insurance compensation are depicted in **Table 2** and **Figure 1**. The Headcount of households with breast cancer patients before insurance compensation was 87.95%; after compensation, it was 66.82% ($p = 0.000$). Thus, insurance was shown to reduce the incidence of CHE by 21.13%.

Meanwhile, the Headcount of households with breast cancer patients protected by the UEBMI were 85.80 and 58.04% before and after insurance compensation ($p = 0.000$), respectively; Thus, the UEBMI was shown to reduce the incidence of CHE by 27.76%. The Headcount of households with breast cancer patients protected by the U&RRBMI were 90.43 and 75.91% ($p = 0.000$) before and after insurance compensation, respectively; thus, the U&RRBMI was shown to reduce the incidence of CHE by 14.52%.

As shown in **Figure 1**, the MPO were 28.67 and 22.75% before and after insurance compensation, respectively. Moreover, households that faced CHE at 40% of the total expenditure averagely devoted 62.75% (22.75 + 40%) of their earnings to afford health services. The Overshoot of households with breast cancer patients were 25.21 and 15.20% before and after insurance compensation, respectively. Breast cancer households that actually had experienced catastrophe at the 40% threshold spent an average of 22.75% (MPO) over this threshold. Thus, these households spent an average of 62.75% of all non-food expenditures on OOP medical expenses.

Patients with breast cancer who had no education, longer course of disease, U&RRBMI insurance, lower income level and more expensive treatment method tended to have higher incidence of CHE than the others (**Table 2**). The logistic regression model further confirmed that education, course of disease, insurance, income level and treatment method were significant predictors of CHE (**Table 3**).

DISCUSSION

To the best of our knowledge, this was the first study that examined CHE incidence and analysed and compared CHE incidence and intensity before and after insurance compensation among households with breast cancer patients in China. Our research found that OOP expenditures for breast cancer patients led 66.82% of our sample to incur in CHE. The incidence of CHE in our study were significantly higher than Malaysia (at 47.8%) (21), South Korea (39.8%) (22), and eight Southeast Asian countries (48%) (23). Concomitantly, the CHE rates in our study

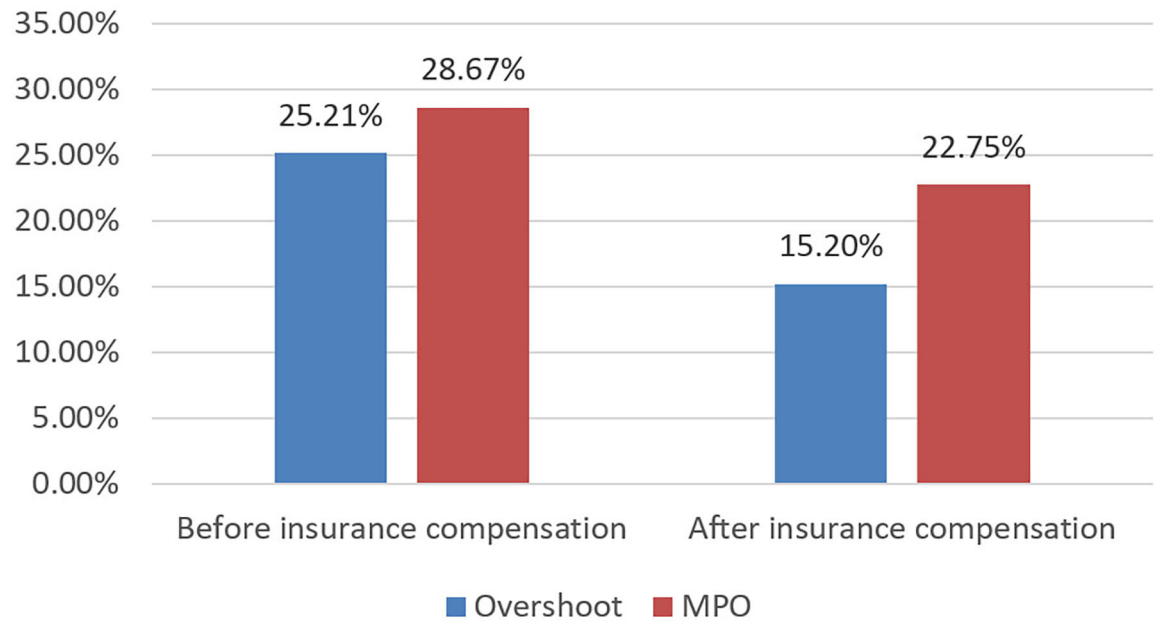


FIGURE 1 | Intensity of CHE before and after insurance compensation. The Overshoot is the average distance, it reflects the intensity of CHE in the overall households with cancer patients. The MPO represents mean relative distance, it indicates the intensity of CHE in the households suffering from CHE.

TABLE 3 | Multivariate logistic regression model of determinants of CHE.

Determinants	OR	SE	p	95% CI	
Education level (ref: none)					
primary school	0.299	0.184	0.049	0.089	0.996
Junior and Senior high school	0.261	0.152	0.022	0.083	0.821
University and above	0.274	0.168	0.036	0.082	0.916
Course of disease(ref: <1 year)					
1–2 year	2.74	0.776	0.000	1.574	4.778
Insurance (ref: UEBMI)					
U&RRBMI	1.677	0.368	0.018	1.091	2.579
Rest 2	1.400	0.755	0.532	0.486	4.030
Income level (ref: ≤80,000)					
>80,000	0.306	0.064	0.000	0.202	0.463
Treatment method (ref: surgery alone)					
Radical surgery	0.717	0.190	0.210	0.467	1.206
Radiotherapy or chemotherapy	1.724	0.628	0.135	0.843	3.523
Surgery and adjuvant chemotherapy	2.377	0.532	0.000	1.532	3.686
Neoadjuvant chemotherapy and surgery	4.131	2.831	0.038	1.078	15.83
Rest 3	3.131	1.922	0.063	0.940	10.42
Cons	0.578	0.703	0.411		

were slightly lower than those in Iran (67.9%) (24). Additionally, the overall CHE incidence in the general population was only of 13.0%, a value confirmed by another Chinese study (25). Thus, OOP expenditures regarding breast cancer treatments impose a serious economic burden on most households with breast cancer patients in China.

Our results also illustrated that insurance is capable of protecting some households with breast cancer patients from the impact of CHE; however, the overall incidence of CHE remained very high. Specifically, the impact of UEBMI on CHE was greater than that of U&RRBMI; particularly, patients with U&RRBMI were more likely to experience CHE. A prior study, which showed that the UEBMI and U&RRBMI have different deductibles, limit lines, and reimbursement rates, may explain this result (11). Therefore, stakeholders and decision-makers regarding breast cancer in China should not only endeavour to expand the scope and depth of these health insurances but also reduce the differences between the UEBMI and U&RRBMI, as this may help relieve patients' and their families' OOP medical expenditures.

Additionally, in our study, the factors associated of CHE in households with breast cancer patients included education, disease course, health insurance type, treatment method, and income. Particularly, having no education, a longer disease course, an expansive treatment method, and low income were factors that had a significant impact on CHE. Concurring with our results, a study conducted in 10 countries in Southeast Asia showed that education, income, and health insurance type were all determinants of CHE (23). They further found that cancer stage also influenced the occurrence of CHE, in that the likelihood of CHE increased as the cancer stage became higher. We deemed that this variable was like the treatment method

variable we utilised; thus, cancer stage and treatment methods may affect the OOP expenditure of households with breast cancer patients, thereby affecting the occurrence of CHE.

However, it is hard for researchers and other stakeholders to change the education, disease course, and income variables of households with breast cancer patients; nonetheless, we can enhance the financial protection provided by insurances and relieve treatment costs for breast cancer to help reduce the incidence of CHE. Currently, the coverage of the basic Chinese health care insurances we studied can be deemed as high; however, they have a somewhat limited impact on OOP health expenditures. Particularly, reimbursement rates are the highest for the UEBMI (at 55%), followed by the URBMI (40%), and the New Rural Cooperative Medical Scheme (30%) (11). For households with breast cancer patients, these reimbursements ratios hinder the ability of these insurances to protect people from incurring in CHE. Therefore, the Chinese government should further optimise and adjust these programs to reduce CHE, specifically for households with critical diseases such as breast cancer that are related to high OOP health expenditures.

According to our findings, the CHE rates for households with breast cancer patients owe not only to the low reimbursement levels mentioned above but also to high medical costs; this finding is in line with the literature (26). In China, these high medical costs may be because of insufficient governmental financial input and the fee-for-service payment mechanism (27–30). The Chinese government had taken full responsibility for financing public hospitals at the end of the 1970s. However, the subsidies of government have been reduced to less than one-third of the income of public hospitals in the past three decades. Accordingly, a study showed that public hospitals need to heavily rely on OOP for cost recovery (29). Meanwhile, the fee-for-service methodology has been shown to encourage doctors to provide excessive medical treatments (29, 30). Moreover, the National Bureau of Statistics showed that the national health expenditure per capita increased from 1,314 Yuan in 2009 to 4,236 Yuan in 2018 (31). Therefore, policy-makers should endeavour to develop policies that help control the cost of medical procedures; we suggest potential reforms in the insurance payment method to reduce patients' economic loss.

Our study has several limitations. First, we defined OOP regarding only direct medical expenditures, excluding direct non-medical costs. Second, we evaluated CHE only in households that received treatment, excluding households that could not afford the treatment; thus, these variables in households with breast cancer patients might, to some extent, have been underestimated. Third, owing to data availability, we did not include not all potential influencing factors of CHE, such as some unobservable household characteristics; this may lead to potentially biassed estimation of the influencing factors of CHE.

CONCLUSIONS

OOP health expenditure for breast cancer patients was shown to be financially catastrophic for most households in our sample. Moreover, medical insurance was shown to protect some Chinese households with breast cancer patients from the impact of CHE. However, the insurance reimbursement rates were relatively low, and the overall CHE incidence remained very high. Some socioeconomic and non-socioeconomic factors were shown to significantly affect CHE in the studied households. Albeit we cannot change these non-socioeconomic factors, policies aimed at reducing CHE can address the socioeconomic factors related to healthcare outcomes in households of patients with critical diseases such as breast cancer.

DATA AVAILABILITY STATEMENT

The data of the current study are available from the Chinese Academy of Medical Sciences upon reasonable request. Requests to access these datasets should be directed to lgx6301@163.com.

ETHICS STATEMENT

This study was approved by the Ethics Committee of the Cancer Institute and Hospital, Chinese Academy of Medical Sciences (15-070/997).

AUTHOR CONTRIBUTIONS

JH and W-qC: acquisition of data and conceived the research idea. J-fS, W-qF, and XZ: conception and design, analysis and interpretation of data. C-yS: writing and drafting of the manuscript, analysis and interpretation of data, and statistical analysis. G-xL: critical revision of the manuscript for important intellectual content, and conceived the research idea. All authors have read and approved the final manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Value of Perampanel as Adjunctive Treatment for Partial-Onset Seizures in Epilepsy: Cost-Effectiveness and Budget Impact Analysis

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Introduction: China has ~6 million patients with active epilepsy every year, around 60% of whom suffer from partial-onset seizures. Perampanel (PER) is a novel anti-epileptic drug for partial-onset seizures. PER has been included in the latest Chinese National Reimbursement Drug List (NRDL) in 2020. However, there is still a lack of evaluation evidence on the value of PER in China.

Methods: This study selected a health system perspective. A Markov model was established to simulate the lifelong transition of different response levels and calculate the number of seizures in Chinese patients. Based on the utility value and mortality risk, the life years and quality-adjusted life years (QALYs) of patients using PER vs. lacosamide (LCM) were estimated. Efficacy data were derived from clinical trials and the literature. Cost data (in US dollars) included drug costs and medical service costs. A lifetime horizon was adopted. Health outcomes and costs were discounted at an annual discount rate of 5%. Deterministic sensitivity analysis, probability sensitivity analysis, and scenario analysis were performed. The impact of the inclusion of PER in the NRDL on the medical insurance budget over 3 years (2021–2023) was also estimated.

Results: Cost-effectiveness analysis indicates that 8 mg/day of PER increases QALYs by 0.054 and saves costs by $2,390 compared with 400 mg/day of LCM. 4 mg/day of PER increases QALYs by 0.010 and saves costs by $860 compared with 200 mg/day of LCM. Deterministic sensitivity analysis reveals that utility value and the extreme discount rate are the factors with the greatest impact on the incremental cost-effectiveness ratio. Probabilistic sensitivity analysis and scenario analysis show that the results are robust. Budget impact analysis indicates that after inclusion of PER in the NRDL, the incremental budget would be $1.28, $2.83, and $4.56 million from 2021 to 2023, respectively, but covering more eligible epileptic patients in the same time (1,918, 4,287, and 8,983, respectively).

Conclusion: PER (8 or 4 mg/day) is of relatively high value as an add-on therapeutic regimen for partial-onset seizures in China because of its dominate advantage of cost-effectiveness over LCM and acceptable budget impact.

Keywords: value, perampanel, cost-effectiveness, budget impact, epilepsy, partial-onset seizures

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INTRODUCTION

Epilepsy is a chronic non-communicable disease of the brain that affects people of all ages. There are ∼50 million patients with epilepsy worldwide, making it one of the most common neurological diseases in the world (1). Nearly 80% of epileptic patients live in low- and middle-income countries. China has ∼6 million patients with active epilepsy (AE, defined as two or more unprovoked seizures in the past year) every year, and 60% of them suffer from partial-onset seizures (2, 3) with a mortality risk of 2–3 times that of the general population (4).

Epilepsy accounts for 5% of the global economic burden of mental illnesses (5). Long-term administration of anti-epileptic drugs (AEDs) and other costs of diagnosis and treatment impose a heavy economic burden to families. In 2009, a study conducted in Southwest China showed that the average annual cost (in US dollars) of epileptic patients was $773, in which the cost of AEDs amounted to $243 (6). In 2015, another study on the disease burden in central China showed that the average annual cost of epileptic patients reached $949 (7). Moreover, the stigma of epilepsy brings about a serious psychological burden to patients and their families, which discourages the patients from seeking treatment and reduces their quality of life (1). As for children and adolescents, suffering from epilepsy imposes a lifelong impact on their social, emotional, and occupational development (8). Therefore, the prevention and treatment of epilepsy is not only a medical problem, but also a vital public health and social problem.

Epilepsy is a treatable disease, with AEDs being the preferred therapeutic option and the most important treatment approach. Up to 70% of epileptic patients achieve seizure remission for a relatively long time through proper diagnosis and standardized use of AEDs (9). However, in developing countries, most epileptic patients cannot receive reasonable and effective treatment. In China, the treatment gap for AE patients is ∼60% (3, 10). Epileptic patients therefore have significant unmet medical needs.

As recommended drugs for the treatment of refractory focal epilepsy in adults, third-generation AEDs including perampanel (PER) and lacosamide (LCM) show advantages in terms of efficacy, safety, and tolerability over first- and second-generation AEDs (11). PER (Fycompa®, Eisai Co., Ltd., Tokyo, Japan) is a first-in-class non-competitive highly selective α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor antagonist. Several multi-center, randomized-controlled, phase III clinical trials have shown that compared with placebo, PER (4–12 mg/day) considerably reduces seizure frequency and improves response rate with acceptable tolerability in epileptic patients (12–15). LCM is one of the sodium channel blockers in AEDs. Two phase III clinical trials have shown that compared with placebo, LCM substantially reduces seizure frequency with good tolerability (16, 17). In the 2018 guidelines from the American Academy of Neurology and the American Epilepsy Association (AAN/AES), the grades of evidence-based recommendation for PER and LCM are A and B, respectively (11). Cost-effectiveness (CE) evidence and budget impact analysis (BIA) of PER have been reported in other countries (18, 19). Some studies have also explored the CE of LCM as an add-on to conventional AED therapy (20, 21). All these studies have demonstrated that PER or LCM as an add-on therapy for uncontrolled or refractory epilepsy is a cost-effective regimen (18, 20, 21).

In 2019, China approved PER for add-on therapy in adults and children over 12 years of age with partial-onset seizures (with or without secondary generalized seizures). In December 2020, PER was included in China's latest National Reimbursement Drug List (NRDL; LCM was released to the market in 2018 and included in the NRDL in 2019). Due to the limitations of the public budget, economic efficiency has become one of the most important factors for inclusion in the NRDL of China since 2018.

The economic efficiency of LCM compared with conventional therapy was proven in 2010. Bolin et al. showed that LCM was cost-effective as an add-on therapy for uncontrolled partial-onset seizures (21). In 2018, the economic efficiency of PER as an add-on therapy for primary systemic tonic-clonic seizures was confirmed in Spain (18). However, the economic efficiency of PER therapy for partial-onset seizures in China remains unknown, and there is a lack of comparison between PER and LCM. From the perspective of resource allocation, even if the drugs are economical, whether they can be afforded by public funds is still the threshold for inclusion. According to the Institute for Clinical and Economic Review (ICER) Value Framework 2.0, the economic efficiency and affordability of a drug should be simultaneously included in its value evidence (22). Since 2019, the evidence from CE analysis (CEA) and BIA has also become economic evidence that is compulsory to be submitted for inclusion in the NRDL of China.

The aim of this study is to evaluate the value of PER as an add-on regimen to the treatment of partial-onset seizures in China and provide evidence on both its CE and affordability.

MATERIALS AND METHODS

Model Structure

As epilepsy is a lifetime chronic disease, we used the Markov model to evaluate lifelong effectiveness and costs of PER + AEDs vs. LCM + AEDs in patients with partial-onset seizures in China. The health state was classified according to seizure frequency, namely: ≥53 times/year, 13–52 times/year, 1–12 times/year, and no seizures. The seizure frequency was dependent on the response level after medication (the scale of the decrease in baseline number of seizures). More specifically, distribution of response levels over each cycle period were mapped to health states defined by seizure frequency. The mapping calculation was based on clinical trials. There are six response levels: seizure-free, response rate of 75–99%, response rate of 50–74%, response rate

Abbreviations: CEA, cost-effectiveness analysis; BIA, budget impact analysis; ICER, incremental cost-effectiveness ratio; NRDL, National Reimbursement Drug List; AE, active epilepsy; AED, antiepileptic drug; PER, perampanel; LCM, lacosamide; LY, life year; QALY, quality-adjusted life years; DDD, defined daily dosages; KOL, Key Opinion Leader; DSA, deterministic sensitivity analysis; PSA, probabilistic sensitivity analysis; CEAC, cost-effectiveness acceptability curve; ZNS, zonisamide; URRBMI, Urban Rural Resident Basic Medical Insurance UEBMI, Urban Employee Basic Medical Insurance.

<50%, increased seizures, and maintenance therapy (including patients withdrawn from the trial due to adverse reaction or other reasons). The cycle period of the model was set to 4 months (consistent with the medication regimen). This model adopted a lifetime horizon, and the cycle of the model was terminated when the proportion of dead patients reached 99.9%. According to latest guidelines for pharmacoeconomic evaluation in China (23), health outputs and costs were discounted at an annual discount rate of 5%.

In particular, two dose comparison groups were set up in this study, namely PER 8 mg/day vs. LCM 400 mg/day and PER 4 mg/day vs. LCM 200 mg/day, as adjunctive treatment. This design was based on comprehensive consideration of the defined daily dose (DDD) recommended by the World Health Organization (WHO) (24), the availability of clinical trial data (12, 16), and the actual clinical dose used in China indicated by clinicians (25).

The model structure is shown in **Figure 1**.

Health Outcomes and Data Sources

Health outcomes included the number of epileptic seizures, life years (LYs), and quality-adjusted life years (QALYs).

For the first cycle in the model, response rates were derived from clinical trials 335 (trial registration number: NCT01618695, sample size: 704) and EP0008 (trial registration number: NCT01710657, sample size: 548), both of which include reasonably large sample sizes in Chinese populations (199 Chinese in trial 335, 406 Chinese in trial EP0008). The baseline seizure distribution of patients by health state was displayed in **Table 1**, as LCM 4 mg/day and LCM 8 mg/day was assumed to have the same baseline seizure frequency with PER 4 mg/day and PER 8 mg/day, respectively. Other baseline information of patients involved in the clinical trials is listed in **Supplementary Table 1**. Because the two trials were not head-to-head trials, we used an indirect comparison method in this study and acquired the risk ratio values of PER and LCM response rates with conventional therapy as the bridge. Because LCM lacked data on the proportion of patients with increased epileptic seizures, we assumed the proportion of patients whose seizures increased by <25% to be equal to that of the PER group. We obtained the proportion of patients whose seizures increased by ≥25% from the data reported in another clinical trial of LCM (26). The initial distributions of response rates are detailed in **Table 2**.

From the second cycle, transition probabilities of response rate were obtained from long-term follow-up data (27). The model converted 5-year transition probabilities according to the following equation (28):

$$P_{4month} = 1 - \exp[(1/15)^* [\ln(1 - P_{5year})]]$$

TABLE 1 | Baseline seizure distribution in Markov model, %.

	≥53 times/year	13–52 times/year	1–12 times/year	Seizures free
PER 8 mg/day (*N* = 48)	87.76	12.24	0	0
LCM 400 mg/day (*N* = 133)	87.76	12.24	0	0
PER 4 mg/day (*N* = 43)	86.67	13.33	0	0
LCM 200 mg/day (*N* = 135)	86.67	13.33	0	0

PER, perampanel; LCM, lacosamide.

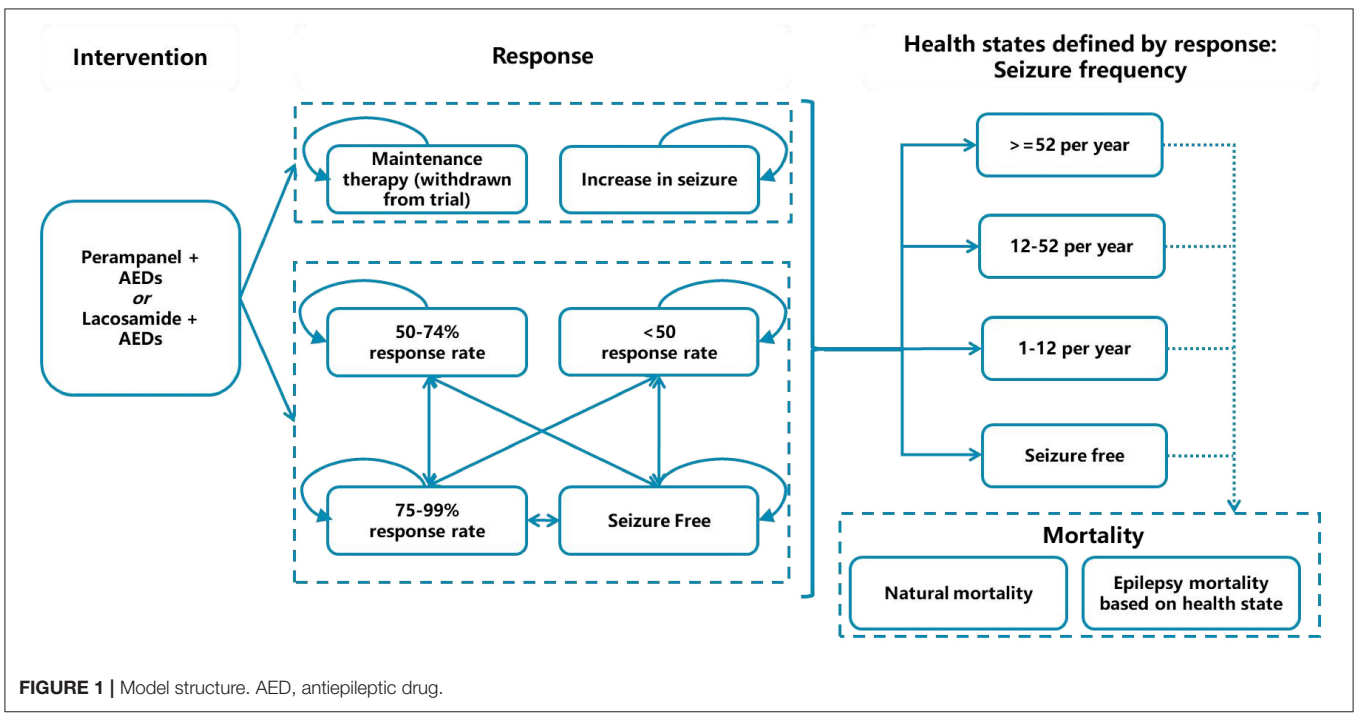


FIGURE 1 | Model structure. AED, antiepileptic drug.

TABLE 2 | Response distribution in the first cycle, %.

	Maintenance therapy	Increase in seizure	<50% Response	50–74% Response	75–99% Response	Seizure free
PER 8 mg/day (*N* = 48)	9.43	26.42	20.75	22.64	13.21	7.55
LCM 400 mg/day (*N* = 133)	16.33	28.17	0.92	33.64	17.62	3.31
PER 4 mg/day (*N* = 43)	6.52	28.26	41.30	4.35	13.04	6.52
LCM 200 mg/day (*N* = 135)	8.64	22.20	20.38	26.43	18.49	3.85

PER, perampanel; LCM, lacosamide.

TABLE 3 | Inputs in the CE model.

	Base case	DSA Range[a]	Distribution	Source
Relative risks of mortality				
≥53 seizures/year	10.16	2.94–35.18	–	(30)
13–52 seizures/year	8.64	2.88–25.93	–	(30)
≤12 seizures/year	7.21	2.52–20.6	–	(30)
Drug costs per 4 months ($)				
PER 4 mg/day	878	±10%	Gamma	MENET, 335 clinical trial
AEDs – PER 4 mg/day group	692	−20%–0%	Gamma	
PER 8 mg/day	1,754	±10%	Gamma	MENET, 335 clinical trial
AEDs – PER 8 mg/day group	827	−20–0%	Gamma	
LCM 200 mg/day	1,484	−20–0%	Gamma	MENET, (16)
AEDs – LCM 200 mg/day group	695	−20–0%	Gamma	
LCM 400 mg/day	2,968	−20–0%	Gamma	MENET, (16)
AEDs – LCM 400 mg/day group	549	−20–0%	Gamma	
Medical costs per 4 months ($)				
≥53 seizures/year	571	±20%	Gamma	Health care documents[b], KOL
13–52 seizures/year	441	±20%	Gamma	Health care documents, KOL
≤12 seizures/year	273	±20%	Gamma	Health care documents, KOL
Seizure free	180	±20%	Gamma	Health care documents, KOL
Health Utilities per 4 months				
≥53 seizures/year	0.619	±0.15	Beta	(31)
13–52 seizures/year	0.628	±0.12	Beta	(31)
≤12 seizures/year	0.673	±0.14	Beta	(31)
Seizure free	0.711	±0.14	Beta	(31)

[a] *To echo the medical pricing reform in China, we assumed the drug prices could only decrease and the service item prices increase. In addition, we assumed a narrower range (±10%) of Perampanel price according to the lowest price provided by Eisai Co., Ltd.*

[b] *The health care documents from the 9 provinces medical security bureaus.*

CE, cost-effectiveness; DSA, deterministic sensitivity analysis; PER, perampanel; LCM, lacosamide; AED, antiepileptic drug.

where P_{5year} denotes the 5-year probability, P_{4month} denotes the 4-month probability, and 4 months accounts for 1/15 of 5 years. Neligan et al. only reported the probability of response rates transitioning from <50 to 50–99% (27). Here, we allocated the transition of response rates from <50 to 50–74% or 75–99% according to the proportion of patients corresponding to the response rates of 50–74% and 75–99% in the trial EP0008 (16). The transition probabilities of response rates are listed in **Supplementary Table 2**.

Natural mortalities were obtained from the life table of natural mortalities in China published by the WHO (29). The seizure-free population was considered to have the same mortality risk as the general population. Mortality risks for different seizure frequencies were based on the data reported by Nilsson et al. (30), and the RR values are listed in **Table 3**.

Costs

From a health system perspective, only direct medical costs were taken into account in this study, including drug costs and medical service costs (covering outpatient, emergency, and inpatient treatment costs). For drug costs, the unit price of drugs was multiplied by their daily dose to obtain the unit cost. AED costs were derived from the unit price multiplied by the use ratio of various drugs in clinical trials (335, EP0008). The unit price of drugs was derived from the median national price in the China Drug Bidding Database (shuju.menet.com.cn). In all

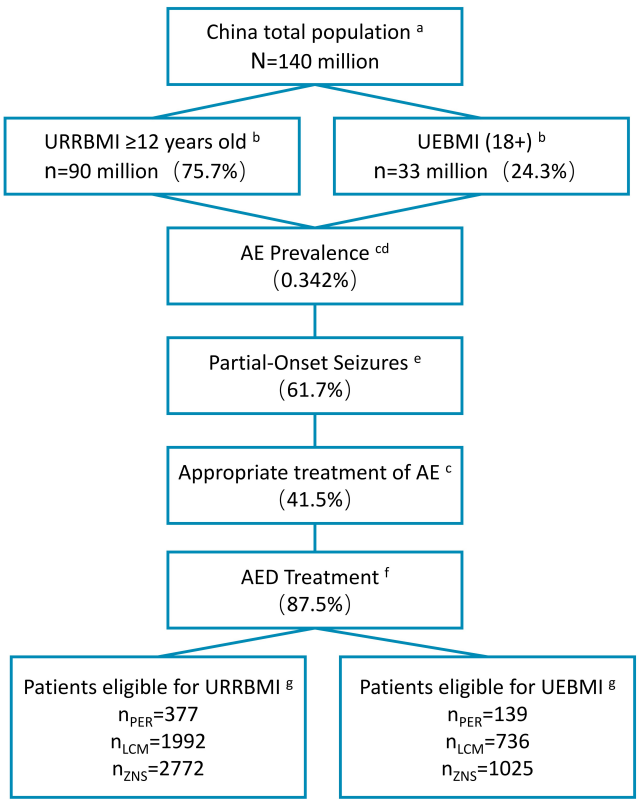


FIGURE 2 | Patient disposition in BI model (2020). [a]Data from the National Bureau of Statistics of China (data.stats.gov.cn). [b]Basic medical insurance participation data from reports of medical insurance bureau (nhsa.gov.cn), and proportion of people over 12 years old from 2010 Census Report (data.stats.gov.cn). [c]Prevalence of active epilepsy and rate of standardized treatment from Ding et al. (10). [d]Annual growth rate of the prevalence during 2021–2023 from Song et al. (34) [e]Proportion of patients with partial seizures from Yu et al. (2). [f]Standardized treatment rate of drugs from investigation results of 18 clinical experts. [g]Market shares of three drugs provided by Eisai Co., Ltd. (**Table 4**). BI, budget impact; URRBMI, Urban Rural Resident Basic Medical Insurance; UEBMI, Urban Employee Basic Medical Insurance; PER, perampanel; LCM, lacosamide; ZNS, zonisamide.

cases, it was included as the price of the largest sales specification and converted into the unit price of the smallest dose. Medical service costs were derived from the unit price multiplied by the frequency of medical visits, and details are displayed in **Supplementary Table 3**. Because of the lack of data on medical visits for epilepsy, the items of medical services and the frequency of medical visits were acquired from the opinions of 18 clinicians from different hospitals in China. The unit price of medical services was derived from the median of documented data in the medical insurance bureaus of nine provinces and cities in China. Because the service prices were inconsistent among different levels of hospitals, we adjusted the service prices according to the proportion of medical visits to second- and third-level medical institutions (32).

All costs used in this study were converted from Chinese yuan to US dollars [1 dollar = 6.5408 yuan (33)]. Details are provided in **Table 3**.

TABLE 4 | Market share (Before and after the inclusion of PER in the NRDL), %.

Drugs	Before				After		
	2020	2021	2022	2023	2021	2022	2023
PER	0.06	0.14	0.24	0.34	0.35	0.7	1.25
LCM	0.32	0.66	1.15	1.61	0.62	1.09	1.42
ZNS	0.48	0.41	0.34	0.29	0.39	0.31	0.24
Total	0.86	1.21	1.73	2.24	1.36	2.1	2.91

Market shares are derived using the overall market of oral anti-epileptic products as the prediction baseline and the data of PER in the baseline year (2020) as the data in Q1 of that year. The impact of ± 10% variation in the annual market share data of various drugs on the BI results after inclusion of PER in the NRDL is observed in DSA.
NRDL, National Reimburesement Drug List; PER, perampanel; LCM, lacosamide; ZNS, zonisamide.

Health Utilities

Health state utility values were acquired from the National Health and Wellness Survey of Kantar Health (31). Details are summarized in **Table 3**.

Base-Case Analysis

Costs were calculated by simultaneously taking into account the usage of all drugs (including PER, LCM, and AEDs) and medical service resources by the patients in different states. Finally, the number of seizures, LYs, QALYs, and incremental CE ratio (ICER) related to PER + AEDs vs. LCM + AEDs were obtained.

Uncertainty Analysis

We performed one-way deterministic sensitivity analysis (DSA) using the 95% confidence interval reported in the literature as the variation range. The discount rate ranged from 0 to 8% (23). The impact of the extreme discount rate (effectiveness: 8%, cost: 0%; effectiveness: 0%, cost: 8%) on the results was taken into account. Assuming that the distribution proportion of PER entering maintenance therapy, response rate of 75–99%, and seizure-free state fluctuates by 20% for DSA. The variation range of other parameters that lacked documented reports was assumed based on KOL (Key Opinion Leader) opinions.

Probabilistic sensitivity analysis (PSA) was performed using Monte Carlo simulation with 10,000 iterations. The standard deviation of utility values was derived from the literature (31). The standard deviation of costs was obtained from the standard deviation of AED prices and the distribution range of KOL opinions. Parameter distributions came from classical assumption (28). The parameter characteristics of mortality, cost, and utility value are listed in **Table 3**. In addition to the parameters listed in **Table 3**, we assumed that LY conforms to a normal distribution, with its mean and standard deviation derived from the model.

In basic analysis, we assumed that there was no transition from <50% response rate to increase in seizure. However, we found this assumption was uncertain compared with other studies. Considering that the transition patterns of response rates are the basis of the cycle in the model, we designed a scenario analysis according to the pharmacoeconomic study of Tremblay et al. (18): assuming that there are probabilities for

TABLE 5 | Inputs in the BI model.

Parameters	Base case	DSA range	Source
Epidemiology			
AE prevalence, 2013 (%)	0.24	0.22–0.33	(10, 35, 36)
Annual growth rate of prevalence(%)	5.20	±30%	(34)
Proportion of clinical dose used by patients[a] (%)			
Proportion of patients taking PER 4 mg/day	60.00	50.00–80.00	KOL
Proportion of patients taking LCM 200 mg/day	68.42	50.00–80.00	KOL
Drug costs[b]			
Annual cost of PER	1,211	±10%	MENET
Annual cost of AEDs-PER	762	−30–0%	MENET, 335 clinical trial
Annual cost of LCM	1,924	−30–0%	MENET, (16)
Annual cost of AEDs-LCM	592	−30–0%	MENET, (16)
Annual cost of ZNS	700	−30–0%	MENET
Annual cost of AEDs-ZNS[c]	670	−30–0%	MENET
Annual cost of AEDs	710	−30–0%	MENET, 335 clinical trial
Direct medical costs[d]	–	–	–

[a] *Assuming that the proportion of other AEDs administered by the patients taking ZNS is the average of PER and LCM, because ZNS lacks available clinical trial data.*
[b] *The sum of the use ratio of PER 8 and 4 mg/day is 100%, which is similar to LCM. These data are derived from opinions of 18 KOLs.*
[c] *Drug costs are weighted according to KOL opinions.*
[d] *Medical service costs in the BI model are exactly the same as used in the CE model (omitted here), except for the parameter range of ±30% in DSA.*
BI, budget impact; DSA, deterministic sensitivity analysis; AE, active epilepsy; PER, perampanel; LCM, lacosamide; ZNS, zonisamide; AED, antiepileptic drug.

TABLE 6 | Base case analysis results.

	Absolute		Incremental		Absolute		Incremental	
	PER 8 mg/day	LCM 400 mg/day		Change%	PER 4 mg/day	LCM 200 mg/day		Change%
Seizures	467	608	−141	−23.22	717	789	−72	−9.14
LYs	4.940	4.879	0.061	1.26	5.17	5.158	0.012	0.24
QALYs	3.137	3.083	0.054	1.75	3.278	3.268	0.010	0.31
Drug costs	9,144	11,462	−23,18	−20.22	7,304	8,229	−925	−11.24
Medical costs	7,001	7,073	−72	−1.01	7,400	7,335	65	0.89
Total costs	16,145	18,535	−2,390	−12.89	14,704	15,564	−860	−5.52

PER, perampanel; LCM, lacosamide; LY, life year; QALY, quality-adjusted life years.

patients with a response rate of <50% transitioning to the state of increased seizures, and the transition is expressed by the following equation:

$P < 50\%$ to increase in seizures $= P$ increase in seizures * (1 – P responsive).

Budget Impact

We analyzed the impact of the inclusion of PER in the NRDL on the medical insurance budget in 2021–2023. The target population comprised participants in basic medical insurance aged ≥12 years with partial-onset seizures and undergoing standardized drug treatment (**Figure 2**). Taking into account the substitution of other similar drugs by PER, we added zonisamide (ZNS) as a reference drug in addition to LCM. The market share of the three drugs in 2020–2023 was obtained by Eisai Co., Ltd. based on the actual market situation (**Table 4**). Cost data were derived from the CEA results, and the distribution proportion of patient health states before and after treatment is summarized in **Supplementary Table 4**. For the two groups of daily doses, we obtained the use ratio of clinical patients for different daily doses of PER and LCM by consulting KOL, and this set of data was used for weighting in the cost calculation. The medical insurance reimbursement policy is provided in **Supplementary Table 5**. DSA was performed on epidemiological parameters, use ratio of clinical doses, and cost parameters that may affect budget impact (BI). The distribution ranges of the parameters are given in **Table 5**.

RESULTS

Base-Case Analysis

The results of base-case analysis (**Table 6**) show that PER has an dominate advantage over LCM in terms of CE. Compared with LCM 400 mg/day, PER 8 mg/day reduces the number of seizures per capita by 141 times, with an incremental LY of 0.061, an incremental QALY of 0.054, and a direct medical cost

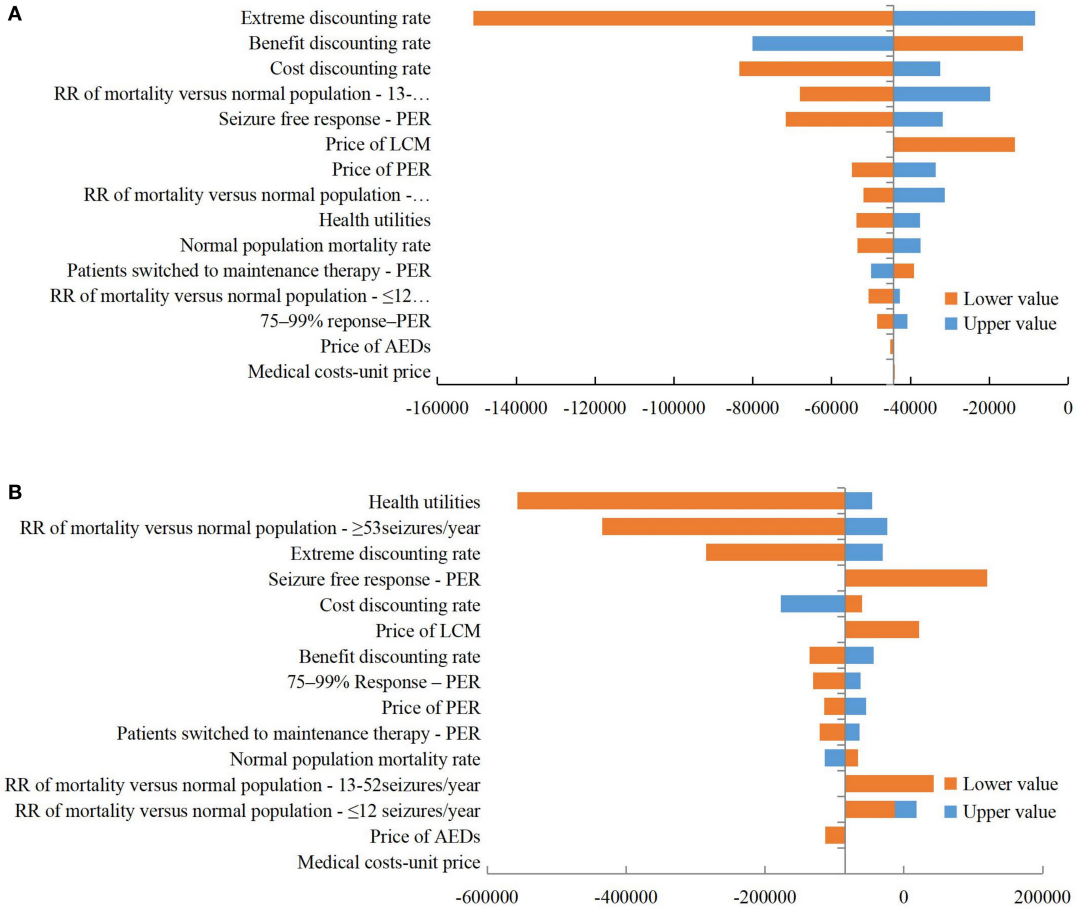


FIGURE 3 | Tornado diagram of deterministic sensitivity analysis. **(A)** PER 8 mg/day vs. LCM 400 mg/day; **(B)** PER 4 mg/day vs. LCM 200 mg/day. ER, perampanel; LCM, lacosamide; RR, relative risk; AED, antiepileptic drug.

saving of $2,390. Compared with LCM200 mg/day, PER 4 mg/day reduces the number of seizures per capita by 72 times, with an incremental LY of 0.012, an incremental QALY of 0.010, and a cost savings of $860.

Uncertainty Analysis

Deterministic Sensitivity Analysis

The DSA results (**Figure 3**) show that the ICER of PER 8 mg/day vs. LCM 400 mg/day group ranges from $150,911 to $8,418/QALY, with the extreme discount rate having the greatest impact on ICER. The ICER of PER 4 mg/day vs. LCM 200 mg/day group ranges from $556,653 to $119,970/QALY, with the utility value having the greatest impact on ICER. The price of AEDs and the unit price of medical services have little impact on ICER in both groups.

Probabilistic Sensitivity Analysis

The PSA results (**Figure 4**) show that the different dose groups of PER have a large probability of being economical at various levels of willingness-to-pay. The one-to-three times gross domestic product (GDP) per capita was $10,838–$32,515 in China in 2019 (data.stats.gov.cn).

Scenario Analysis

The results of scenario analysis (**Table 7**) show that compared with LCM 400 mg/day, PER 8 mg/day achieves an incremental QALY of 0.039 and a cost saving of $2,747, which is still the regimen with dominate advantage. However, compared with PER 4 mg/day, LCM 200 mg/day results in an incremental QALY of 0.005 and an incremental cost of $554. The ICER is $105,194/QALY, higher than three times GDP per capita [$32,515], indicating that LCM is not cost-effective. This result may be attributed to the relatively small incremental QALY, which may not meet the minimal clinically important difference.

Budget Impact Analysis

Base-Case Analysis

After the inclusion of PER in the NRDL, it is expected that the target population using PER will increase by 1,918; 4,287; and 8,983 in 2021–2023, respectively, with a total population

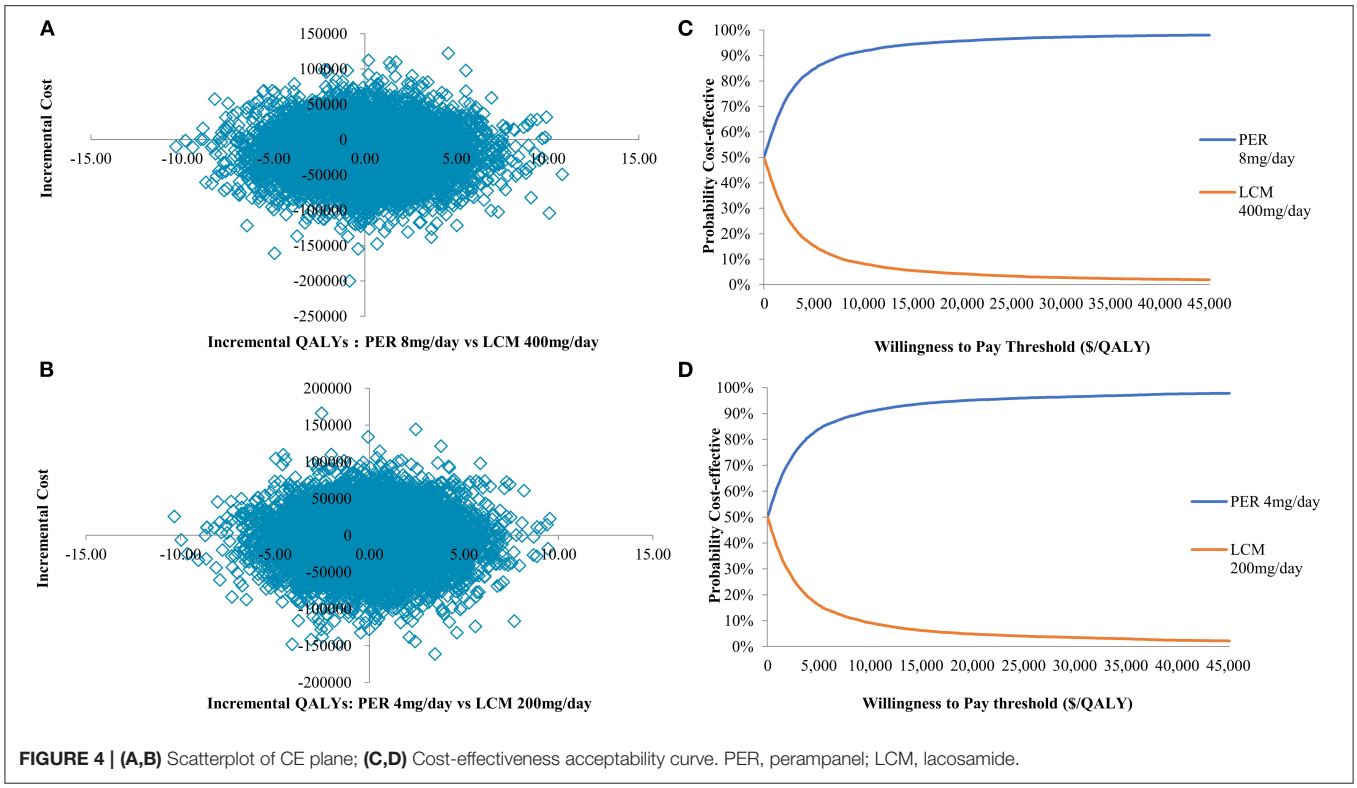


FIGURE 4 | (A,B) Scatterplot of CE plane; **(C,D)** Cost-effectiveness acceptability curve. PER, perampanel; LCM, lacosamide.

TABLE 7 | Scenario analysis results.

	Absolute		Incremental		Absolute		Incremental	
	PER 8 mg/day	LCM 400 mg/day		Change%	PER 4 mg/day	LCM 200 mg/day		Change%
Seizures	530	633	−103	−16.23	854	873	−19	−2.16
LYs	4.912	4.868	0.044	0.90	5.122	5.127	−0.005	−0.09
QALYs	3.111	3.072	0.039	1.24	3.233	3.238	−0.005	−0.16
Drug costs	7,198	9,947	−2,749	−27.63	5,800	6,496	−696	−10.71
Medical costs	7,137	7,135	2	0.03	7,649	7,507	142	1.89
Total costs	14,335	17,082	−2,747	−16.08	13,449	1,4003	−554	−3.95
					ICER per seizure avoided ($/seizure)	29.41		
					ICER per LY ($/year)	116,275.56		
					ICER per QALY ($/QALY)	105,193.94		

PER, perampanel; LCM, lacosamide; LY, life year; QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio.

increase from 6,557 to 21,774. In contrast, the target populations of LCM and ZNS will decrease by a total of 3,531 in the 3 years.

Before and after the inclusion of PER in the NRDL, the absolute BI over 2021–2023 will be $17.30, $27.78, and $39.08 million and $18.58, $30.61, and $43.65 million, respectively (**Table 8**). The incremental BI (including drug and medical service costs) over the 3 years will be $1.28, $2.83, and $4.56 million, respectively, accounting for 0.00037, 0.00082, and 0.00132% of the total expenditure of national medical insurance in that year (total medical insurance expenditure was acquired from medical insurance bureau reports. Among them, drug costs will increase by $1.39, $3.02, and $4.99 million, whereas medical service costs will be reduced by $0.10, $0.19, and $0.42 million (**Figure 5**). Medical insurance reimbursement costs per capita (including drug and medical service costs) will increase by $110.72, $151.59, and $169.14.

Deterministic Sensitivity Analysis

The BI results are relatively robust. The factors that have the greatest impact on the results are the market share after inclusion of PER in the NRDL, the prevalence of AE, and the distribution of patients using different daily doses of PER (4/8 mg). The price of PER also has a relatively large impact on the results (**Figure 6**).

TABLE 8 | Budget impact (Before and after the inclusion of PER in the NRDL), million USD.

Costs	Before the inclusion of PER in the NRDL					After the inclusion of PER in the NRDL			
	2020	2021	2022	2023	3-Year total	2021	2022	2023	3-Year total
URRBMI&UEBMI									
Total	10.61	17.30	27.78	39.08	94.77	18.58	30.61	43.65	103.45
Durg	5.60	9.33	15.16	21.25	51.34	10.72	18.18	26.23	60.73
Direct medical	5.01	7.96	12.62	17.83	43.43	7.86	12.43	17.41	42.71
URRBMI	7.14	11.83	19.17	27.15	65.29	12.74	21.12	30.42	71.42
UEBMI	3.47	5.46	8.61	11.93	29.48	5.84	9.49	13.23	32.03

PER, perampanel; NRDL, National Reimburesement Drug List; URRBMI, Urban Rural Resident Basic Medical Insurance UEBMI, Urban Employee Basic Medical Insurance.

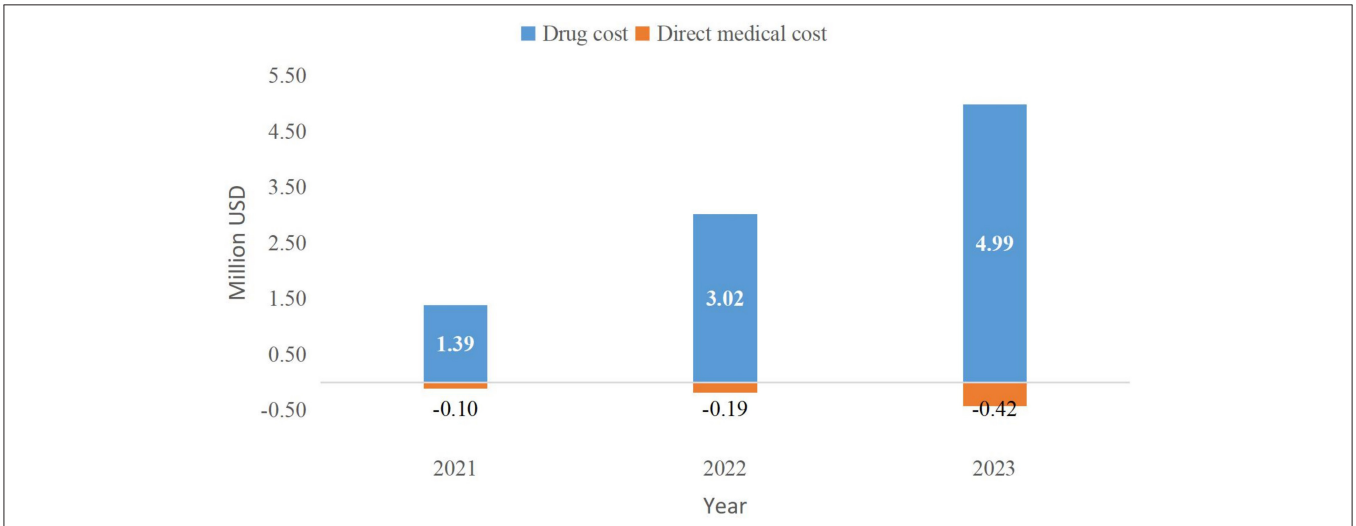


FIGURE 5 | Incremental budget impact of the inclusion of PER in the NRDL (2021–2023). NRDL, National Reimburesement Drug List.

DISCUSSION

This is the first study to calculate the value of PER as an add-on regimen to the treatment of patients with partial-onset seizures in China with respect to CE and medical insurance affordability. Currently, there are limited documents on the economic evaluation of PER. An economic evaluation based on the perspective of Spain showed that the ICER of PER as an adjuvant therapy to AEDs was €16,557/QALY over a 33-year study period; with the willingness-to-pay of €30,000/QALY, PER had an 89.3% probability of being the cost-effective option for primary generalized tonic-clonic epileptic seizures (18). Here, our study from the perspective of China's health system shows that using PER as an adjuvant therapy to AEDs has an dominate advantage over LCM in terms of CE. This result is also relatively stable within the one-two-three times GDP per capita of $10,838–$32,515. Moreover, the time horizon of our model is the patient's lifetime. Based on the BIA, this study is in agreement with the results of Tremebly et al. (19) for PER; that is, PER as an add-on brings about an increase in BI year by year while also resulting in a medical service cost savings. This result is mainly attributed to the improvement of health state after the use of PER, which in turn reduces the direct medical costs. In clinical trials 304, 305, and 306 with PER, 4.4% and 3.5% of the patients achieved a seizure-free state owing to an add-on therapy with PER at 4 or 8 mg/day (1.0% in the AEDs placebo group) (37), whereas in the clinical trial 335, the proportion of seizure-free patients in the Chinese population was even higher in the PER group (8.8 vs. 0%).

This study is novel in several ways. First, this study simulates the lifetime effectiveness and cost data of patients through a Markov model, with full consideration of long-term simulation and health state classification of epileptic patients. Epilepsy is a chronic disease that may be lifelong (1). It is therefore necessary to investigate the long-term health outcomes of epilepsy and distinguish the costs from different frequencies of epileptic seizures. In an economic evaluation of LCM compared with conventional therapy, Simoens and Bolin et al. adopted a decision tree model to simulate the outcomes of short-term therapy in epileptic patients without considering the seizure-free state (20, 21). Furthermore, no head-to-head studies on PER and LCM have been found, which is also one of the innovative points of this study.

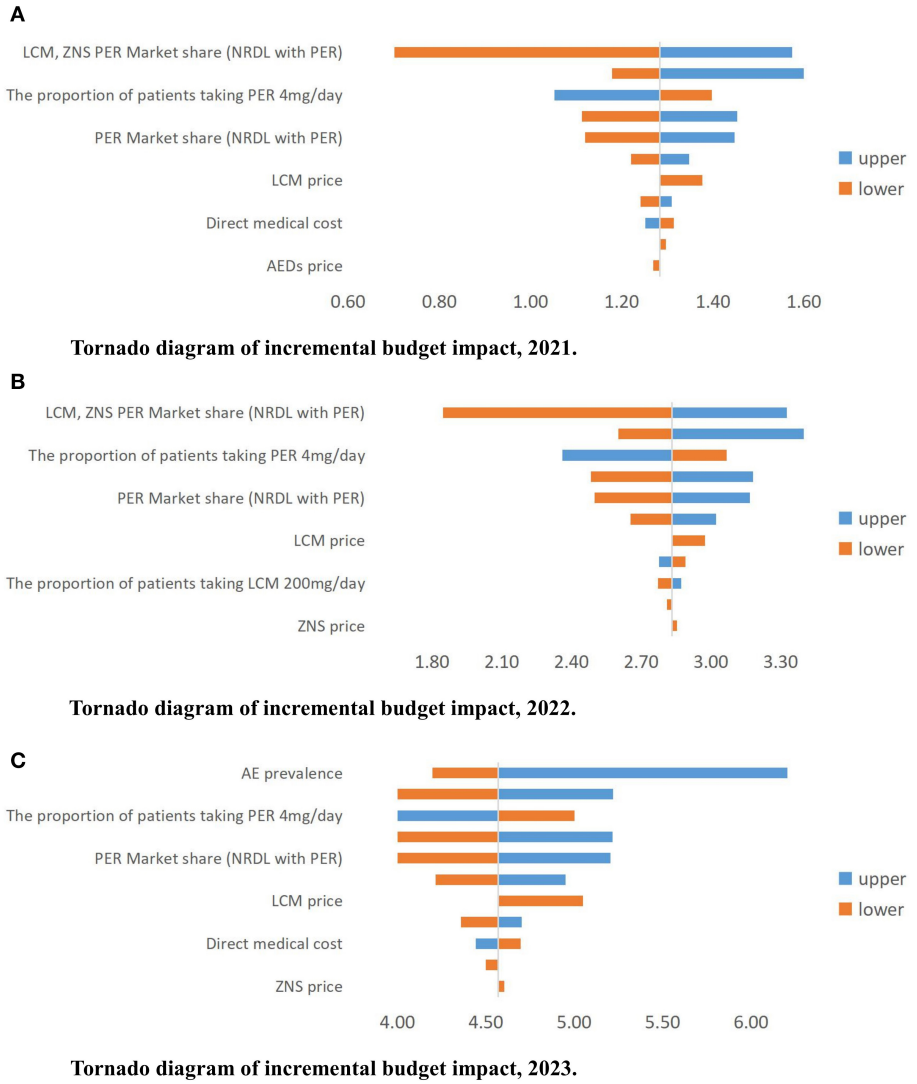


FIGURE 6 | (A–C) Tornado diagram of incremental budget impact, 2021–2023 (million USD). AE, active epilepsy; PER, perampanel; LCM, lacosamide; ZNS, zonisamide; NRDL, National Reimburesement Drug List; AED, antiepileptic drug.

Second, this study gives a comprehensive consideration to the daily dose of drugs. The WHO recommends the adult daily doses of PER and LCM to be 8 and 300 mg/day, respectively (24). Clinical trial 335 of PER involved three daily dose groups of 4, 8, and 12 mg, respectively (12). However, clinical trial EP0008 of LCM only consisted of two daily dose groups of 200 and 400 mg, respectively (16). According to KOL opinions, we finally determine to explore the CE of PER 8 mg/day vs. LCM 400 mg/day and PER 4 mg/day vs. LCM 200 mg/day. We did not include PER 12 mg/day in the analysis because this dose is mainly used in patients with refractory epilepsy as indicated by KOL. In the BIA, the distribution of patients using different doses is taken into account comprehensively in accordance with the actual use ratio in the clinic given by KOL, aiming to be more in line with the real-world situation.

Third, this study also takes into account multiple aspects of cost data to better reflect the current situation in China. All the drugs analyzed in this study are included in the latest NRDL (announced by medical insurance bureau at the end of December 2020). Considering the fairness of the control and the origin of efficacy data from original drugs, we obtain the price of LCM from the price of the original drug, whereas for the remaining AEDs, both original and generic drugs are taken into account to make the price close to the market. In China, the price of medical services is set by medical insurance bureaus of various provinces and cities, leading to the differences in medical service price across regions. Here, we select nine provinces and cities based on their geographical locations in East, Central, and West China, and then take the medians of their prices. In addition, considering that epileptic patients usually visit second- and third-level medical institutions, we have the

prices of second- and third-level medical institutions weighted according to the proportion of the number of medical visits (32). In the BIA based on the perspective of medical insurance payers, we not only distinguish the difference in the reimbursement of various insurance categories (URRBMI and UEBMI), but also consider the difference in the reimbursement policies of outpatient, emergency, or inpatient, and Class A or Class B of drugs.

Our study is not without limitations. First, the lack of local data in China may introduce potential bias in the results. For example, because no data are available on the utility value and mortality risk caused by epilepsy in the Chinese population, the utility value (31) and mortality risk (30) of foreign population are used in this study. There are also no data on the long-term transition probability of epileptic patients in the Chinese population. We therefore use the transition of response rates in epileptic patients of a 5-year follow-up investigation conducted in the United Kingdom (27). Moreover, with regard to whether there will be a certain probability for epileptic patients with a response rate of <50% transitioning to increased seizures during actual drug use in the clinic, we take this situation as a scenario analysis for supplementation, because follow-up data are lacking for the Chinese population.

Further, we have to make certain assumptions because of the objective lack of some data. For example, LCM lacks the proportion of patients with increased seizures reported in clinical trials. We therefore assume that the proportion of patients whose seizures increased by <25% is equal to that of the PER group, whereas the proportion of patients whose seizures increased by ≥25% is based on another clinical trial (26). In the BIA, reports on the annual growth rate of the prevalence of AE is lacking. Thus, we select the annual growth rate of the lifetime prevalence of epilepsy reported in a meta-analysis in China (34) and perform a sensitivity analysis on this parameter. In addition, because no available clinical research reports on ZNS are found, we assume in the BIA that the proportion of AEDs and therapeutic efficacy of patients in the ZNS group are at the average levels of PER and LCM. We consult pharmacoeconomic experts and clinicians to deal with all the assumptions as much as possible.

Finally, some factors are not taken into account in this study, such as compliance and adverse reactions. Frequent administration of AED affects patient compliance. When AED is administered once a day, patient compliance is 87%; when AED is administered twice a day, patient compliance drops to 81% (PER once a day and LCM twice a day) (38). However, because the two drugs are both add-on therapy in this study and the daily administration frequency of AEDs also affects compliance, the measurement of compliance value is not included in the model. Previous research has reported that PER and LCM cause relatively mild adverse reactions in a short term (12, 16), whereas ZNS is currently a generic drug in the Chinese market which lacks reliable research reports. Long-term adverse reactions to PER and LCM need to be determined through further follow-up monitoring of the Chinese population.

CONCLUSION

Our study demonstrates that PER is valuable as an add-on therapy for patients with partial-onset seizures in China. PER has a dominate advantage of CE compared with LCM (8 vs. 400 mg/day; 4 vs. 200 mg/day), and its incremental BI for medical insurance payers is relatively acceptable. In this study, the BIA as a supplement to CEA achieves a relatively comprehensive evaluation of the value of PER in the treatment of partial-onset seizures in China. China has not yet developed a value framework that integrates CE and BI proposed by foreign researchers (22). Nevertheless, evidence on the CE and affordability of drugs has received increasing attention in this country. The present study also provides a reference for stakeholders to judge the value of PER.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://clinicaltrials.gov/ct2/show/NCT01618695?term=NCT01618695&draw=2&rank=1; https://clinicaltrials.gov/ct2/show/results/NCT01710657?term=NCT01710657&draw=2&rank=1.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

DZ and XL were mainly responsible for research model building, data collection, and manuscript writing. WT was responsible for research design, model building, and manuscript review and modification. XK, WD, and YR contributed to the collection of model data and model building. HX provided beneficial help to the initial model building. JD confirmed the clinical and epidemiological inputs. All authors have contributed substantially to the study and approved the final submitted version of the manuscript.

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SUPPLEMENTARY MATERIAL

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Paricalcitol versus Calcitriol + Cinacalcet for the Treatment of Secondary Hyperparathyroidism in Chronic Kidney Disease in China: A Cost-Effectiveness Analysis

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Background: Chronic Kidney Disease (CKD) is a global chronic disease with increasing prevalence in recent years, particularly CKD accompanied by Secondary Hyperparathyroidism (SHPT) leads to reduced quality of life, increased mortality, a considerable economic burden for patients and society. The aim of this study was to investigate the cost-effectiveness analysis of paricalcitol vs. calcitriol + cinacalcet for CKD patients with SHPT in China in 2020.

Methods: A Markov model was conducted employing data derived from published literature, clinical trials, official sources, and tertiary public hospital data in China, based on a 10-year horizon from the perspective of the healthcare system. Calcitriol + Cinacalcet was used as the reference group. CKD stage 5 (CKD-5) dialysis patients suffering from SHPT were included in the study. Effectiveness was measured in quality-adjusted life years (QALYs). The discount rate (5%) was applied to costs and effectiveness. Sensitivity analysis was performed to confirm the robustness of the findings.

Results: The base case analysis demonstrated that Patients treated with paricalcitol could gain an increase in utility (0.183 QALYs) and require fewer expenditures (6925.612 yuan). One-way sensitivity analysis was performed to showed that impact factors were the price of cinacalcet, the hospitalization costs of patients with paricalcitol and calcitriol, the costs and utilities of hemodialysis and the costs of calcitriol, the costs of paricalcitol regardless of period. Probabilistic simulation analysis displayed when willingness-to-pay was ¥217113, the probability that Paricalcitol was dominant is 96.20%.

Conclusion: The results showed that paricalcitol administrated to treat patients diagnosed with Secondary hyperparathyroidism in Chronic Kidney Disease, compared to calcitriol and cinacalcet, might be dominant in China.

Keywords: paricalcitol, calcitriol, cinacalcet, secondary hyperparathyroidism, chronic kidney disease, cost-effectiveness analysis

BACKGROUND

Chronic Kidney Disease (CKD) is a global chronic disease with gradually renal function loss. The number of individuals diagnosed with CKD and who die from CKD in China ranks top worldwide (1). The prevalence of CKD, even exceeding that of diabetes mellitus (2), has increased progressively from 10.8 to 11.6% during 2012–2018 in China (3, 4). The aging population deteriorates the prevalence of CKD in China, as well as a physiological decline in renal function and rising prevalence of Hypertension and Diabetes (3, 5). A cross-sectional survey conducted in China revealed that ∼3 million CKD patients arrived in the end-stage renal disease (ESRD) stage over 3 years (4), where CKD patients are necessary to receive renal replacement treatment (RRT) (6). A large population of potential patients exists in China (4), as estimated, the prevalence of ESRD grown at a rate of 1.95% from 2015 to 2020 in Nanjing (7), a medium-sized city of China, imposing enormous pressure on the health care system due to productivity loss and premature death (8, 9).

Secondary hyperparathyroidism (SHPT) is a common serious complication in dialysis patients (10), over 70% advanced CKD patients are diagnosed with SHPT (11). As reported, about 60% of maintaining hemodialysis patients were affected by different levels of severity of SHPT, where the standard-reaching rate was about merely 55% (12). Due to renal dysfunction resulting in increased endogenous calcitriol and serum calcium, while decreased serum phosphorus (13), SHPT is characterized by increased serum parathyroid hormone (PTH) and parathyroid hyperplasia (14), risk factors of cardiovascular disease and fracture, resulting in lower quality of life, and higher mortality (10, 15, 16).

In 2017, total Medicare expenditure for CKD and ESRD in the US was high, approaching over 120 billion dollars (17). The same situation occurs in China in that the medical spending of CKD patients was 27.646 billion RMB in 2016, accounted for 6.50% of total health spending. For dialysis patients, the medical expenditure approached 911 million RMB, 75.6% of that was covered by urban basic health insurance. The economic burden of ESRD rises over time (9). It has been established that the medical expenditures of ESRD are multiplying at a mean annual rate of 5.8% in Nanjing (7). Treatment of CKD and ESRD is a heavy burden for patients, for family, and the health care system. Undoubtedly, Complications like SHPT, CVD exacerbate the economic burden for dialysis patients as well (18–20).

Based on the guideline-recommended by Kidney Disease: Improving Global Outcomes (KDIGO), Vitamin D Receptor Activators (VDRA) and calcimimetics are the optimal strategies of SHPT treatment, complemented to decrease PTH, prevent hypocalcemia, improve survival, and reduce cardiovascular disease (15, 21). Approximately 60% of patients undergoing hemodialysis and peritoneal dialysis were treated with Calcitriol, a non-selective Vitamin D (18). However, the adverse effects of Calcitriol due to non-selective mechanisms, hyperphosphatemia, and hypercalcemia causing vascular and soft tissue calcification (13)—the risk factors of mortality, restricts the effectiveness of calcitriol on the treatment of SHPT (10, 22, 23). Cinacalcet, the first and the only calcimimetics launched in China, approving for the treatment of maintaining dialysis (12). It has been documented that Cinacalcet has the advantage of quick onset in declining serum calcium, serum phosphorus, and PTH, meanwhile, reduce volume and size of parathyroid glands, hardly causing hyperphosphatemia and hypercalcemia (15, 24). Cinacalcet was commonly adopted when Vitamin D was poorly controlled (12).

Paricalcitol, a synthetic analog of vitamin D, less hypercalcemia and hypercalcemia, effectively decreases PTH, particularly administrated intravenously compared to the Calcitriol (15, 25, 26). As reported, in the long term, paricalcitol has a significant survival advantage and decreases hospitalization (4, 27–29). Notably, paricalcitol could be effective for calcitriol-resistant hemodialysis patients (23, 30).

Therefore, here we choose calcitriol and cinacalcet as references to explore the cost-effectiveness analysis of Paricalcitol. The cost-effectiveness of paricalcitol has been proved in Italian, US, UK, Brazil, German (13, 31–34). We aim to explore the cost-effectiveness of paricalcitol in China.

METHODS

Model Design

A Markov model (**Figure 1**) was conducted by Microsoft® Excel (Excel 2019 version) based on the model Nujiten (31) published. We invited local experts to confirm the Markov model is reasonable by requiring nephrology and pharmacoeconomics specialists' advice. The Markov model was selected for the following reasons: Markov model allows us to assess the cost-effectiveness of paricalcitol in the long term by defining a series of health states and health state transitions between these states to simulate disease process and combining consumable costs with health outcomes in every health states (35), moreover, it could take complications into considerations (31).

We assumed that a hypothetical cohort of 10,000 patients step into the model to calculate the standard error to make probabilistic sensitivity analysis and set that each cycle of the model was 1 year. All patients were in the "peritoneal dialysis" state (PD) or "hemodialysis" (HD) state at the beginning, the proportion distribution was extracted from the annual report on kidney in China (18). Patients could transfer to "Transplantation"

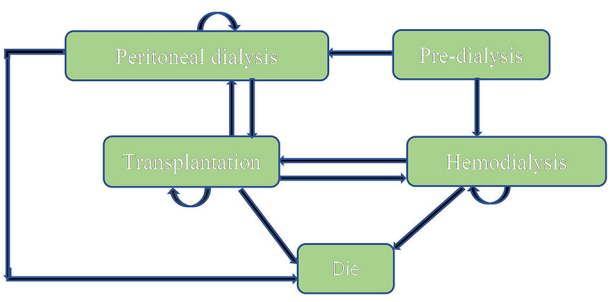


FIGURE 1 | Markov model bubble diagram.

state or "Dead" state, also could stay the original state after 1-year cycle. "Transplantation" and "peritoneal dialysis," "Transplantation," and "hemodialysis" were possible to convert each other. Importantly, "Dead" was an absorbed state and could not move back to other states. We hypothesized that the time horizon of 10 years since a study conducted in China (n = 153) reported that the survival rates from 5 years to 10 years for hemodialysis and peritoneal hemodialysis elderly patients dropped to 18.4 and 2.6% (36), which was appropriate because it covered the entire process from the moment they were diagnosed. The annual discount rate of costs and health outcomes was 5%.

Cost Assessment

As shown in **Table 1**, the medical costs incorporated in this model included the costs of management of SHPT (paricalcitol, calcitriol, and cinacalcet), the costs of inpatient due to common complications (cardiovascular disease, fracture, and a series of complications), and the costs of management of ESRD (peritoneal dialysis, hemodialysis, transplantation) from the perspective of the health care system. The total cost per one patient was assessed once a year. All costs were presented and measured as Renminbi (RMB) in 2020.

Costs of Management of SHPT

The cost and dosage for each drug were obtained from official sources and published literature. Calcitriol was given twice daily, each dose is 0.25 ug. The dose of cinacalcet is 44.7 mg once daily (38). The daily dose of paricalcitol could not be stable until after 18 weeks based on the literature (25). Paricalcitol was administrated by three times a week before meeting the standard, after that altering to once weekly (37). The cost of each drug recorded in detail were summarized in **Table 2**.

Costs of Hospitalization

The costs of hospitalization of CKD-5 patients were from a tertiary public hospital, located in Jiangsu Province in China during 2019–2020. Jiangsu province is located on the southeast coast of China. The eastern region like Jiangsu ranks top in the medical resources density index and healthcare services utilization in China in 2016, therefore, it is a good representative.

TABLE 1 | Inputs to model for base case analysis and sensitivity analysis.

Costs (yuan/year)	Base case analysis	One-way sensitivity analysis		Distribution	References
		min	max		
Drug costs					
Paricalcitol 1st year	21766.86	10448.09	26120.23	Gamma ($\alpha = 10000.00$, $\beta = 2.18$)	(25, 37)
Paricalcitol beyond 1st year	18562.86	8910.17	22275.43	Gamma ($\alpha = 10000.00$, $\beta = 1.86$)	(37)
Calcitriol	3942.00	1892.16	4730.40	Gamma ($\alpha = 10000.00$, $\beta = 0.39$)	Official sources
Cinacalcet	27740.00	13315.20	33288.00	Gamma ($\alpha = 10000.00$, $\beta = 2.77$)	(38)
Renal replacement costs					
Kidney transplantation 1st year	188697.90	150958.32	226437.48	Gamma ($\alpha = 560.06$, $\beta = 336.92$)	Hospital data
Kidney transplantation beyond 1st year	99228.25	47629.56	119073.89	Gamma ($\alpha = 194.63$, $\beta = 509.83$)	Hospital data
HD	67200.00	32256.00	80640.00	Gamma ($\alpha = 10000.00$, $\beta = 6.72$)	(39)
PD	51600.00	24768.00	61920.00	Gamma ($\alpha = 10000.00$, $\beta = 5.16$)	(39)
Inpatient costs					
Calcitriol + Cinacalcet	19375.57	15500.46	23250.68	Gamma ($\alpha = 58.26$, $\beta = 332.59$)	Hospital data
Paricalcitol	19557.85	15646.28	23469.42	Gamma ($\alpha = 10.90$, $\beta = 1793.48$)	Hospital data
Utility (QALY/year)					
HD	0.60	0.54	0.66	Beta ($\alpha = 1638.584$, $\beta = 1092.39$)	(40)
PD	0.60	0.54	0.66	Beta ($\alpha = 1638.584$, $\beta = 1092.39$)	(40)
Kidney transplantation	0.84	0.76	0.92	Beta ($\alpha = 7238.162$, $\beta = 1378.70$)	(32)
Dead	0	—	—	—	—
Discount rate	5%	0%	8%	—	—
Risk adjustment	0.23				(32)

TABLE 2 | The costs of SHPT management including paricalcitol, calcitriol, and cinacalcet.

Item / Medications	Cost/tablet (¥)	Weekly cost (¥)	Annual cost before up-to-standard (¥)	Annual cost after up-to-standard (¥)
Paricalcitol	178	534	21766.86	18562.86
Calcitriol	5.4	75.6	3942	3942
Cinacalcet	38	532	27740	27740

The reason why we choose a single tertiary public hospital is that the few hospitals administrate expensive paricalcitol and cinacalcet, we used the data to show Chinese practical clinical setting by cost. The inclusion criteria of CKD-5D patients are as follows: (1) CKD-5D patients diagnosed with SHPT; (2) Eighteen years of age and above; (3) CKD-5D patients are accompanied by other common complications; The exclusion criteria are as follows: (1) Cross-use of paricalcitol, calcitriol, and cinacalcet during the hospital stay. (2) The patients with other diseases have no association with SHPT, such as depression and tumors.

The annual number of hospitalizations was derived from a US-setting study (28). The average annual number of hospitalizations of paricalcitol, calcitriol was 2.40, 2.61, respectively. Here, we assume that Cinacalcet was consistent with calcitriol, which was a conservative approach toward cinacalcet to perform an analysis in this study due to unavailable data.

Costs of Management of ESRD

The costs of transplantation of CKD-5 patients were from a tertiary public hospital, located in Jiangsu Province in China during 2019–2020. The direct medical cost involved kidney source fees, bed charges, nursing care fees, operating expenses, laboratory fees, inspection fees, drug fees, and other fees (material fees) in the first year of receiving kidney transplantation. The medical costs during next year focused on following-up visit costs, including drug fees, laboratory fees, inspection fees, and other fees (material fees).

Transition Probabilities Including Mortalities

The majority of transition probabilities between health state was from an Italian study (31), partly corrected by the local proportion of HD and PD patients in China (18). In details, the annual probabilities change from kidney transplantation to dialysis was 5.00% (41), as official data in China reported (18), 91.46% of kidney transportation would choose hemodialysis, others would receive peritoneal dialysis. Therefore, we can calculate that 4.60% of kidney transplantation patients receive hemodialysis and 0.40% of that choose peritoneal dialysis. The transition probabilities were shown in **Tables 3**, **4**.

The mortalities data were from same literature (31), widely used in the different clinical settings (31–33), that the mortality rate of paricalcitol decreased by 15% (27), compared to those treated with calcitriol. This historical cohort study enrolling a large number patients revealed that paricalcitol have greater survival advantage over calcitriol.

Utility

The health utility scores of ESRD patients from the Singapore cross-sectional survey (40) were adopted where the Chinese population accounts for over half the proportion. However, we judged that the health utility score of kidney transplantation population from the UK setting (32) could be applied to the Chinese kidney transplantation population due to unavailable data. Those are measured based on EQ-5D. Health outputs were expressed in terms of quality-adjusted life years (QALYs), which can assess intervention strategy in terms of life time and life quality to reflect the health state of subjects better.

Base Case Analysis

Base case analysis results were expressed as incremental cost-effectiveness ratio (ICER), which was calculated as incremental costs/incremental QALYs. Based on the World Health Organization (WHO) recommendations, if the ICER < per capita Pross Domestic Product (GDP), the treatment strategy is totally cost effective; if the per capita GDP < ICER < three times per capita GDP, the therapy strategy is acceptable in terms of economic evaluation; if the ICER > three times per capita GDP, we can consider that the therapy strategy is not cost effective. In this study, we assumed that the paricalcitol regimen was cost-effective when the ICER was less than three times per capita gross domestic product (GDP). According to the latest data from the 2020 National Economic and Social Development Statistical Bulletins, the per capita GDP was 7.2447 yuan (42).

TABLE 3 | Transition probabilities between different states in patients with calcitriol and cinacalcet.

	HD	PD	Transplantation	Die
1 year				
HD	0.829	0	0.033	0.138
PD	0	0.867	0.033	0.100
Transplantation	0.0460	0.00403	0.920	0.030
>1 year				
HD	0.829	0	0.033	0.138
PD	0	0.817	0.033	0.150
Transplantation	0.0460	0.00403	0.934	0.016

TABLE 4 | Transition probabilities between different states in patients with paricalcitol.

	HD	PD	Transplantation	Die
1 year				
HD	0.8576	0	0.0254	0.117
PD	0	0.8896	0.0254	0.085
Transplantation	0.0354	0.0031	0.9355	0.026
>1 year				
HD	0.8576	0	0.0254	0.117
PD	0	0.8466	0.0254	0.128
Transplantation	0.0354	0.0031	0.9475	0.014

TABLE 5 | Expected costs and QALYs of two treatment strategies, incremental costs, and incremental QALYs between two treatment strategies, ICERs.

	Costs (Yuan)	Utility (QALYs)	ΔC	ΔU
Paricalcitol	472596.007	2.855	−6925.612	0.183
Calcitriol + Cinacalcet	479521.619	2.672		

Sensitivity Analysis

The one-way sensitivity analysis and probabilistic simulation analysis were conducted to ensure the robustness of the results. One-way sensitivity analysis was performed by changing a parameter every time to highest or lowest values. A Tornado graph was used to shows the influential variables—the results of one-way sensitivity. Due to unavailable 95% confidence interval (CI), the inpatient expenditures were set to fluctuate between −20 and +20%, the range of utility started from −10 to +10%. Of note, we assume that the price of medicines and devices (including transplantation costs and dialysis costs) involved in disease progression exhibited a mean decrease of 52% because the centralized tender system of medicines and medical devices is being established in China (43).

Probabilistic simulation analysis was conducted by varying all parameters within set different distributions simultaneously in 1000 Monte Carlo simulation iterations to illustrate the results of uncertain analysis and build a cost-effectiveness acceptability

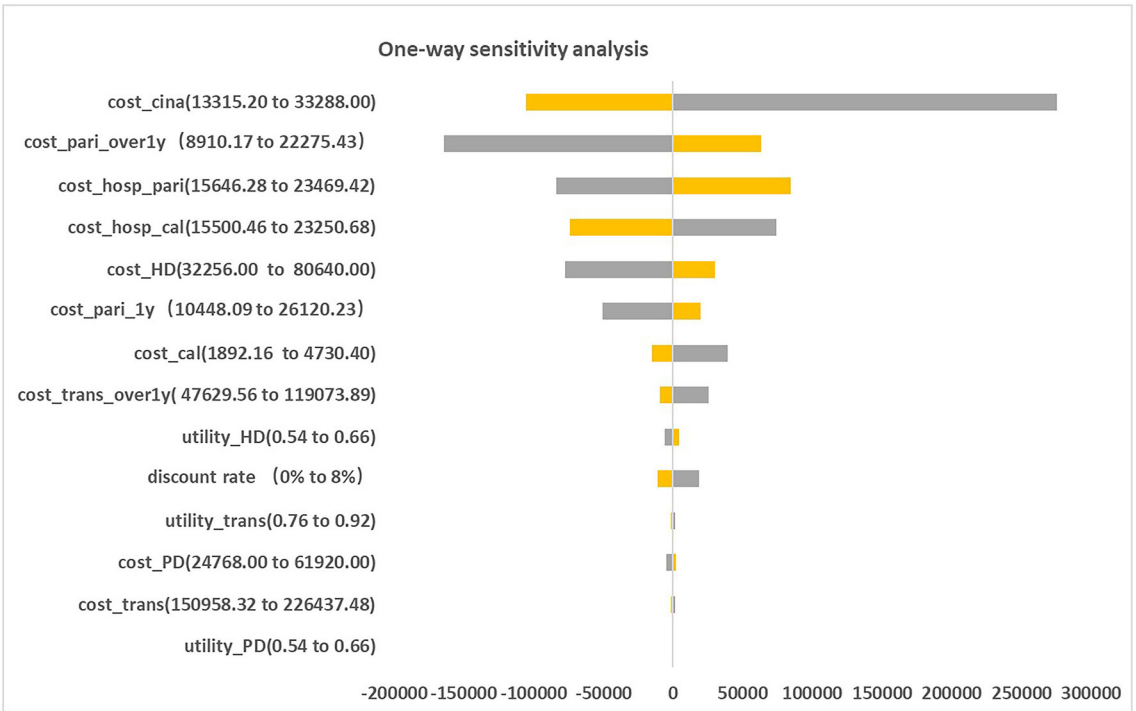


FIGURE 2 | Tornado diagram for two therapies: paricalcitol vs. calcitriol and cinacalcet.

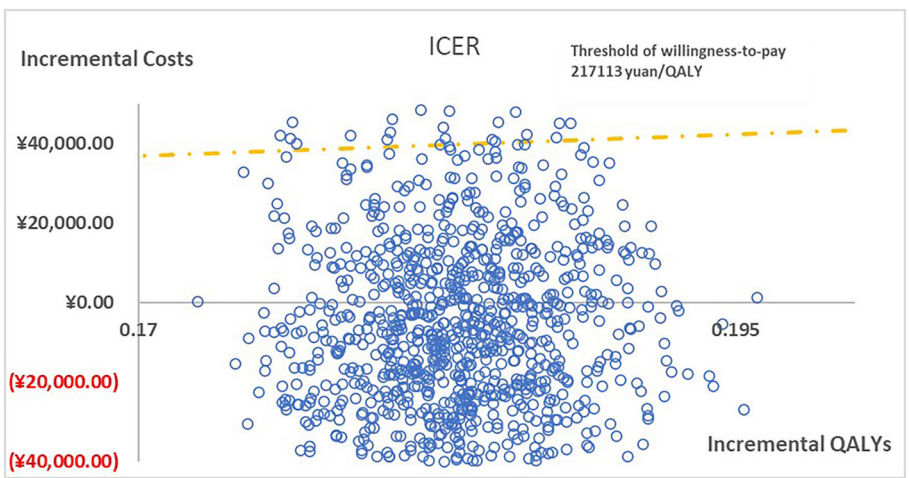


FIGURE 3 | The cost-effectiveness plane illustrated ICERs between paricalcitol and calcitriol + cinacalcet in 1,000 iterations of Monte Carlo simulation.

curve. In this study, we set costs, utility followed gamma distribution (31, 33), beta distribution, respectively. The value of willingness-to-pay was defined as three times GDP per capita, which was 21.7113 yuan. Here we report that EVPI (expected value of perfect information), interpreted as the average of maximum net monetary benefits, estimates the expected values of uncertainty by combining perfect information with the current known information. We still assume that the benefit patients cohort is 10,000 patients.

RESULTS

Base Case Analysis

The results of the base case analysis were summarized in **Table 5**. Total costs of CKD-5D patients accompanied with SHPT, treated with paricalcitol (472596.007 yuan) paid lower than those with calcitriol and cinacalcet (479521.619 yuan), total utilities as well (2.855 QALYs vs. 2.672 QALYs), in 10 years in the Chinese Healthcare System. Compared to regimen Calcitriol and Cinacalcet, patients who choose Paricalcitol as a regimen need to pay <6925.612 yuan, but gain an increase in Utility (0.183 QALYs). Paricalcitol was dominant as compared to calcitriol and cinacalcet.

Sensitivity Analysis

Figure 2 presented the tornado diagram of one-way sensitivity analysis showing the ICERs in descending order were sensitive to which parameters. In this present study, parameters that might affect ICER. The results showed that this model was relatively robust. The most impactful factor on the total outcome was the price of cinacalcet. The results of probabilistic simulation analysis and were displayed in **Figures 3**, **4**. When willingness-to-pay was 217113 yuan, 96.20% of patients were willing to pay for paricalcitol. **Figure 5** displayed the EVPI altering at a variety of willingness-to-pay thresholds.

DISCUSSION

This is the first study that revealing the cost-effectiveness of paricalcitol in China healthcare system settings. The findings of base case analysis showed that paricalcitol was preferred for CKD-5D patients accompanied with SHPT in China compared to the combination use of calcitriol and cinacalcet, with ICER was negative. This study shows that CKD-5 individuals with SHPT administrated by paricalcitol are an optimal strategy for CKD patients with SHPT in China. The one-way sensitivity analysis suggested that the price of cinacalcet was the most influential factor, the probabilistic sensitivity analysis showed that the probability of paricalcitol was dominant is 96.20% when the threshold of willingness-to-pay was 217113 yuan. Our findings are in line with the previous results done in CKD patients with SHPT from other national studies.

On the other hand, the one-way sensitivity analysis results revealed our model was relatively robust. The main reason that led to this phenomenon was that the magnitudes of decrease in

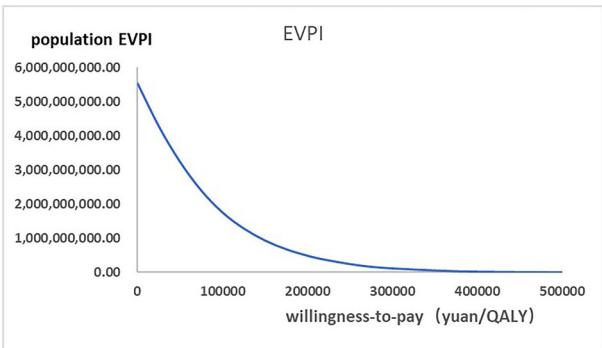


FIGURE 5 | The expected values combining current information and perfect information were shown in the EVPI graph at a variety of willingness-to-pay thresholds.

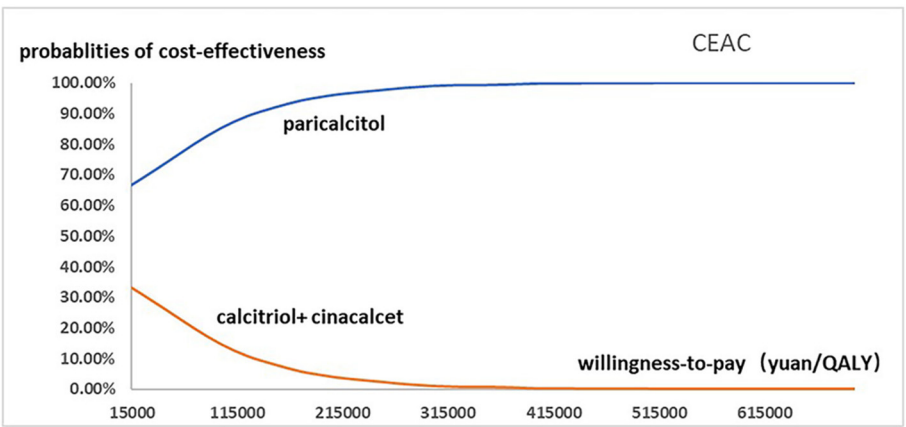


FIGURE 4 | The cost-effectiveness acceptability curve used for probabilistic simulation analysis was drawn to show the probability that paricalcitol vs. calcitriol and cinacalcet was cost-effective at a variety of willingness-to-pay thresholds.

costs of cinacalcet in the model were large (52%). Furthermore, we found it particularly depended on the dosage of paricalcitol after achieving the therapeutic range.

It has been reported that paricalcitol could extend survival and decrease the number of hospitalizations (26, 28). Other advantages have been gradually recognized. For renal transplant recipients, a clinical trial reveals that paricalcitol could decrease proteinuria, which could reduce the risk of kidney transplantation failure (44). Paricalcitol currently is approved to be used in adults, while clinical trials had proven to be effective for children regardless of oral and intravenous (45, 46), besides this, some studies showed that paricalcitol could potentially treat cardiac dysfunction and diabetic nephropathy (47, 48), which suggests the scope of the applicable population should be extended. Furthermore, patients preferred to receive the injection of paricalcitol in the process of getting dialysis due to convenience (11), compared to taking oral calcitriol every day, which can reduce the probability of forgetting to take drugs and increase medication adherence to better control SHPT (49).

With an increase in time of dialysis, vitamin D therapy may be ineffective, parathyroidectomy (PTX) could be considered (50), contributing to improving quality of life (51) and reducing all-cause mortality in ESRD patients with SHPT (52). There are few studies to discuss the cost-effectiveness of PTX, usually compared with cinacalcet (53, 54), which provided new ideas that the cost-effectiveness of PTX for refractory secondary hyperparathyroidism could be investigated in China. Additionally, here we try to discuss more on cinacalcet and other calcimimetics. Cinacalcet has significantly apparent treatment efficacy for severe SHPT patients, it can be used to decrease PTH before receiving PTX and it is a substitute PTX treatment strategy as well (55). Notably, cinacalcet reduces the risk of undergoing PTX (19), also could obtain favorable outcomes for patients with recurrent SHPT after receiving parathyroidectomy (56). Therefore, cinacalcet, a potential therapeutic agent, should be further assessed. A randomized clinical trial (57) demonstrates a novel calcimimetics called etelcalcetide is not inferior to cinacalcet for moderate and severe SHPT patients, in addition, etelcalcetide is administrated intravenous injection to improve adherence and reduce the probability of gastrointestinal adverse effects. However, etelcalcetide has not been launched in China, which is expected to improve cost-effectiveness of medication therapy soon.

However, there are existing problems in terms of treating SHPT in China. Firstly, only 20% of ESRD patients received RRT in China, especially concentrated in large and medium-sized cities (58), which indicated that there are significant geographic differences in ESRD treatment, besides the large population base of CKD patients with SHPT, which may lead to accelerated conditions due to the lack of timely and adequate treatment. Moreover, ESRD patients with complications might achieve worse outcomes, like productivity loss, the absence of caregivers, and even premature death (9). Based on China Kidney Disease Network 2016 annual data report (18), patients with CKD, particularly with SHPT, are associated with increased risk of morbidity and mortality in cardiovascular disease (49), which causes higher medical costs compared to other complications. However, high healthcare costs can not contribute to ideal therapeutic efficacy. According to this study, governments and the relevant departments should pay close attention to optimize medical resource allocation, to reduce the burden of patients. Besides that, over 80% of ESRD patients choose HD as renal replacement treatment in Asia, which parallel to the global conditions, to achieve maximum outcomes of ESRD patients (59). However, HD has worsened outcomes and higher costs than renal transplantation (59), which prompted us to conduct a cost-effectiveness analysis between HD and renal transplantation to provide optimal clinical decisions, which may update awareness and prescribing habits of doctors without considering kidney donations.

This study has several limitations. First, we did some assumptions far away from the real world. Especially, the dosage of drugs, health utility scores of kidney transplantation, and transition probabilities in different health states were not derived from Chinese populations. We could not obtain available data due to no similar studies had been conducted in China. For example, a study revealed that the 1-year survival rate was higher, while the 5-year survival rate was lower than that we adopted (60), whereas we could not confirm that specific clinical setting of the study so that we could not support that. However, according to the requirements of the International Conference on Coordination for Human Drugs (ICH), paricalcitol was approved by National Medical Products Administration (NMPA) in China without local clinical trials, which could demonstrate that the efficacy and safety of paricalcitol in Chinese populations was as same as those in other countries. Therefore, it is reasonable that we adopted the data from published literature from Italia. Second, merely paricalcitol, calcitriol, and cinacalcet were included in the analysis, a possible future of improvement could also incorporate Erythropoietin-treated anemia (a common complication of CKD) and phosphate binders into the analysis. We should be aware of the importance of phosphate control which is significant to mortality and treatment outcomes, moreover, calcium-containing phosphate binders were no longer recommended by China guideline (12) to prevent vascular and soft tissue calcification. Third, we accounted for direct costs using a healthcare perspective, we did not include indirect costs (like productivity loss due to ESRD patients are usually all unproductive, it will be offset from the perspective of the healthcare system and transportation costs) and other costs such as the costs of treating adverse effects. The reason why we did not take adverse effects costs into account is that the adverse effect of paricalcitol, calcitriol and cinacalcet are usually managed by adjusting dosages, which needs real-world data to calculate, we have sufficient data to calculate, which need further exploration.

CONCLUSION

The results demonstrated that paricalcitol used for the treatment of secondary hyperparathyroidism in Chronic Kidney Disease when compared to calcitriol and cinacalcet,

would be cost-effective from the perspective of the healthcare system in China over 10 years.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

ZZ, LC, and XL designed the whole study. ZZ, HW, LC, and XX were responsible for collecting and analyzing data. ZZ, LC, WF, XW, and XH contributed to preparing the original draft. ZZ, XX, and XL took the responsibility of review and editing. All authors have read and agreed to the published version of the manuscript.

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Cost-Effectiveness Analysis of Triple Combination Preparations in the Treatment of Moderate-to-Severe Chronic Obstructive Pulmonary Disease

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Objectives: This study analyzed the long-term cost-effectiveness of fluticasone/umeclidinium/vilanterol triple combination (FF/UMEC/VI) vs. budesonide/formoterol double combination (BUD/FOR) in the treatment of moderate-to-severe chronic obstructive pulmonary disease (COPD) and provides evidence for COPD treatment decisions.

Methods: From the perspective of the healthcare system, a Markov model was established that consists of four states—stable period, non-severely deteriorating period, severely deteriorating period, and death—according to real-world COPD progression. The model period comprises 6 months, with a cycle length of 14 years. The initial state, transition probabilities, costs, and utility data were collected from the FULFIL trial, published literature, hospital record surveys, and *China Health Statistics Yearbook*. The discount rate was 5%, and the threshold was set as the Chinese per capita GDP in 2020 (¥72,447). The cost, utility, transition probabilities, and discount rate were calculated through TreeagePro11 software. The results were analyzed *via* one-way factor analysis and probability sensitivity analysis.

Results: The baseline study shows that the 14-year treatment for FF/UMEC/VI and BUD/FOR groups are ¥199,765.55 and ¥173,030.05 with effectiveness at 8.54 quality-adjusted life years (QALYs) and 7.73 QALYs, respectively. The incremental cost-effectiveness ratio is ¥33,006.80/QALY, which is below the threshold. A tornado diagram of a one-way sensitivity analysis shows that the top three factors that affected the results are the non-severe deterioration rates of FF/UMEC/VI, the cost of FF/UMEC/VI and the non-severe deterioration rates of BUD/FOR. Probabilistic sensitivity analysis shows that FF/UMEC/VI (compared to BUD/FOR) can be made cost-effective under the willingness-to-pay (WTP) threshold (¥38,000). Furthermore, the likelihood of cost-effectiveness increases with a higher WTP.

Conclusions: Compared with the double combination (BUD/FOR), the triple combination (FF/UMEC/VI) is more cost-effective under the Chinese per capita GDP threshold.

Keywords: chronic obstructive pulmonary disease, economic evaluation, cost-effectiveness analysis, triple combination preparations, Markov model

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a kind of chronic bronchitis and/or emphysema characterized by airflow obstruction that can further develop into the common chronic diseases of pulmonary heart disease and respiratory failure. COPD is related to an abnormal inflammatory reaction to harmful gases and particles and has high disability and mortality rates (1). It is also one of the most rapidly growing causes of death in developed countries. While the mortality rates of cardiovascular and cerebrovascular diseases have fallen sharply during the period from 1990 to 2010, the mortality rate associated with COPD has increased by 163% (2). In China, more than one million COPD patients die every year (3), and COPD is the fourth leading cause of death worldwide (4).

COPD severely affects quality of life and imposes substantial burden on patients, their families, and society, which in turn severely impacts public health and the economy (5). The results of a survey on disability adjusted life years (DALYs) due to a total of 306 diseases in 188 countries showed that DALY loss due to COPD ranked 7th in the world in 2013, 6th in economically developed countries, and 10th in developing countries (6). Data from the World Bank and the World Health Organization indicates that by 2020, the economic burden of COPD will rank it as the 5th most expensive disease in the world. *The New European Lung White Book* points out that the direct and indirect economic burden caused by COPD is expected to exceed €100 billion in 2013, which is significantly higher than €3.86 billion in 2003 (7). In 2006, The Chinese Center for Disease Control and Prevention noted that COPD ranked second in terms of burden from chronic diseases in China (8). There are currently 100 million patients with COPD in China, and COPD has become the third most common chronic disease in China after hypertension and diabetes mellitus. The prevalence rates of COPD among adults over 20, 40, and 60 years old are 8.6, 13.7, and over 27%, respectively (9). According to the 2015 Global Burden of Disease Report, COPD ranked third in terms of causes of disease death in China after cerebrovascular disease and ischemic heart disease, and the number of deaths accounted for 9.7% of overall deaths (10).

The 2020 Global Initiative for Chronic Obstructive Lung Disease (GOLD) states that COPD treatment goals are to prevent disease progression, relieve symptoms, improve exercise capacity, improve health status, prevent and treat complications, prevent exacerbations, and reduce mortality (11). The current main treatments for COPD are drug and non-drug interventions. Drug therapy is an essential method for addressing COPD, as this can help to prevent and control symptoms, reduce the frequency of acute exacerbations, and improve the quality of life and exercise tolerance of patients. The "China Chronic Obstructive Pulmonary Diagnosis and Treatment Guidelines (2013)," "NICE: Chronic Obstructive Pulmonary Disease in over 16s: Diagnosis and Management," and other guidelines mention that drug treatment can relieve symptoms experienced by COPD patients and improve their lung function. Furthermore, drug treatment plays an essential role in improving patients' quality of life (12, 13).

Patients with moderate-to-severe COPD often need to use a combination of drugs with three different mechanisms of inhaled corticosteroid/long-acting muscarinic antagonist/long-acting b2-agonist(ICS/LAMA/LABA) at the same time. GOLD also recommends inhaled triple-drug therapy (ICS/LAMA/LABA) for COPD patients with persistent symptoms and exacerbations (11). However, although these treatment options with various underlying mechanisms are widely used, few randomized controlled trials have shown sustained advantages in lung function and patient-reported outcome indicators compared with using ICS/LABA alone. In addition, the triple treatment plan requires the use of more than two inhalation devices, which can lead to dosing errors. Therefore, there is an urgent need to improve the approach used to administer the triple combination of ICS/LAMA/LABA.

At present, there are alternative triple combinations for treating COPD, including fluticasone/umeclidinium/vilanterol (FF/UMEC/VI) and budesonide/glycopyrrolate/formoterol. However, there is insufficient economic evidence to support the use of these triple combinations. Here we developed a Markov model to simulate and analyzed the long-term cost-effectiveness of FF/UMEC/VI and the double combination budesonide/formoterol (BUD/FOR) based on the published results of the Phase III FULFIL study of a COPD triple combination (FF/UMEC/VI) (14). The results provide evidence to support a reasonable treatment strategy for COPD.

MATERIALS AND METHODS

Analytical Method

A Markov model was constructed to evaluate the cost and output of an intervention group and a control group.

Intervention

This study was based on a Phase III, randomized, double-blind, double-simulation, parallel-group, multi-center FULFIL study (GSK: CTT116853; ClinicalTrials.gov: NCT02345161). In the FULFIL study, patients with COPD were defined as being in Gold Initiative for Chronic Obstructive Lung Disease group D (**Appendix II**) (11). It was conducted over a total of 24 weeks and involved 1,810 patients with a mean age of 63.9 years.

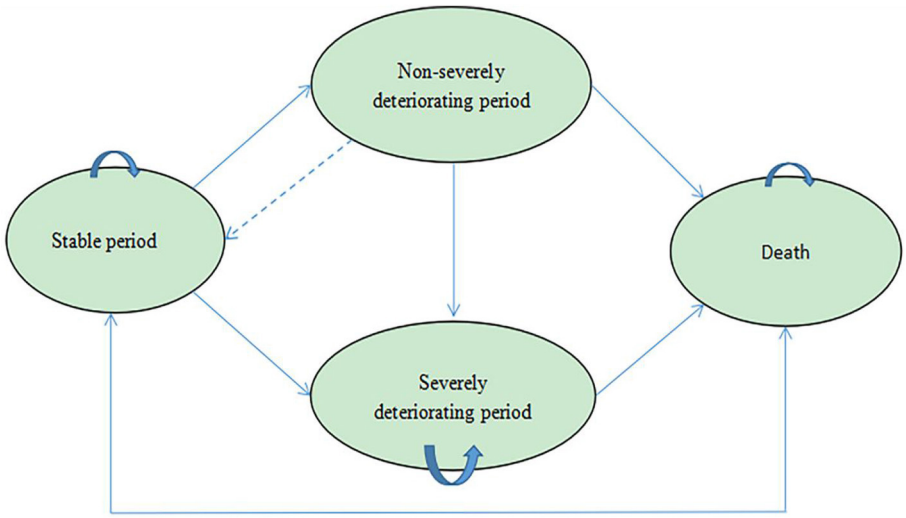


FIGURE 1 | Model structure.

TABLE 1 | Cost parameters.

Project Fees (¥)		Base value	Minimum	Max	Distribution	References
Medicine	FF/UMEC/VI[a]	5,400.00	4,860.00	5,940.00	Gamma: α 606 β 0.1	(see text footnote 1)
	BUD/FOR[b]	2,695.38	2,425.84	2,964.92	Gamma: α 84 β 0.04	(see text footnote 1)
General practitioner		26.00	23.40	28.60	Gamma: α 4 β 0.08	Clinical data
Laboratory test	Spirometry	80.00	72.00	88.00	Gamma: α 384 β 6	Clinical data
Maintenance treatment	Stable period	319.26	287.34	351.19	Gamma: α 384 β 1	(15)
	Non-severe deterioration period	567.01	510.31	623.71	Gamma: α 384 β 0.7	(15)
	Severe deterioration period	20,610.84	18,549.76	22,671.92	Gamma: α 384 β 0.01	(15)

[a] *Fluticasone/umeclidinium/vilanterol triple combination.*
[b] *Budesonide/formoterol double combination.*

In the intervention group ($n = 911$), FF/UMEC/VI, patients mainly used a single ELLIPTA inhaler to deliver once-daily FF/UMEC/VI 100 μg/62.5 μg/25 μg inhalation powder; in the stable period, non-severely deteriorating period, and severely deteriorating period, drugs and oxygen therapy were added to address the patients' symptoms.

In the control group ($n = 899$), BUD/FOR, patients mainly used Turbuhaler to deliver twice-daily BUD/FOR 400 μg/12 μg; in the stable period, non-severely deteriorating period, and severely deteriorating period, drugs and oxygen therapy were added to address the patients' symptoms.

Markov Model Structure

Decision analysis software (TreeAge Pro 2011, Williamstown, MA) was used to establish a Markov model to realize the calculation process, which consisted of four states (**Figure 1**)—stable period, non-severely deteriorating period, severely deteriorating period, and death—according to the real-world disease progression of COPD. The degree of deterioration was divided according to whether additional medical resources were needed: patients in the non-severely deteriorating period only need to have their medication adjusted according to their general practitioner's instructions, while patients in severe exacerbation stages need to be hospitalized for treatment. According to the FULFIL test, the cycle length was 6 months.

Cost Parameters

From the perspective of the healthcare system, all direct medical costs were included in this study, which mainly include drug costs, diagnosis costs and maintenance treatment costs in the stable and deteriorating periods. The costs of medicines were taken from the average bid price of 2020 in China by querying the bid information of www.yaozh.com.[1] The costs of diagnosis and laboratory tests were derived from a real-world clinical data survey. The maintenance treatment cost was based on a previous COPD pharmacoeconomic study (15). The maximum and minimum values of the parameters were based on the basic

[1]YAOZH [EB/OL]. Available online at: https://www.yaozh.com/ (accessed December 30, 2020).

TABLE 2 | Model utility parameters.

Status	Base value	Minimum	Max	Distribution	References
Stable period	0.65	0.64	0.66	Beta: α 5,680 β 3,058	(14)
Non-severe deterioration loss/year	0.01	0.00	0.024	Beta: α 4 β 632	(16)
Serious deterioration loss/year	0.04	0.024	0.06	Beta: α 20 β 954	(16)
Death	0				

TABLE 3 | Transition probability.

Status			Base value	Minimum	Max	Distribution	References
Stable-	Non-severe	FF/UMEC/VI	0.1195	0.1076	0.13145	Beta: α 338 β 2,492	(14)
		BUD/FOR	0.1563	0.1407	0.17193	Beta: α 324 β 1,749	(14)
	Severe	FF/UMEC/VI	0.0148	0.0133	0.01628	Beta: α 4 β 251	(14)
		BUD/FOR	0.0264	0.0238	0.02904	Beta: α 374 β 13,793	(14)
	Death		P_D: Natural mortality				
Non-severe-	Stable		0.5345	0.4811	0.58795	Beta: α 178 β 155	(14)
	Severe		0.4655-P_D				
	Death		P_D: Natural mortality				
Severe-	Severe		1-P_D				
	Death		0.0770	0.0693	0.0847	Beta: α 354 β 4,250	(17)

value ±10% of all costs and the mean value of that cost ±10% (**Table 1**).

Effectiveness Parameters

Quality-adjusted life years (QALYs) were used as the effect indicators of this model. The utility value of each state was extracted and calculated based on previous literature. Non-severe deterioration will cause a loss of 0.01/year of health utility, severe deterioration will cause a loss of 0.04/year of health utility, and the health utility of death is 0 (**Table 2**). The utility of the stable phase was converted from the St George's respiratory questionnaire (SGRQ) score of the FULFIL study population using the published formula (16) (Equation 1).

$$U = 0.9617 - \left(0.0013 \times SGRQ\ total\right) - \left(0.0001 \times SGRQ\ total^2\right) + \left(0.0231 \times male\right) \quad (1)$$

Transition Probability

The transition probability mainly came from clinical trials, the literature, and official Chinese databases. The annual natural mortality rate of the population was obtained from the "National Death Population Status by Age and Sex (2017–2018)" and was transformed into the natural mortality rate of patients during the study period (**Appendix I**). The transition probability of patients from a stable period to non-severe and severe deterioration was calculated from the deterioration of the patient population in the FULFIL study. The mortality rate of severely deteriorated patients comes from the "2008 National Chronic Obstructive Pulmonary Disease Audit in the UK" (17) (**Table 3**).

Willingness-to-Pay Threshold

Concerning the reference threshold value of Chinese medical insurance drug negotiations in recent years, this study set one-time per capita GDP as the threshold value for willingness-to-pay (WTP). According to official data from the National Bureau of Statistics, the 2020 per capita GDP was ¥72,447 in China.[2] When the incremental cost-effectiveness ratio (ICER) is lower than ¥72,447/QALY, the treatment scheme is considered cost-effective.

Cycle Length and Discount Rate

The average life expectancy in China in 2019 (77.3 years), minus the average age of subjects included in the FULFIL study (63.9 years), was used as the basis for the model's operating time limit. Therefore, the study set 28 cycles to simulate the long-term cost-utility of patients 14 years after treatment. The baseline discount rate was 5% according to the *Chinese Pharmacoeconomic Evaluation Guidelines and Guide (2020) Edition* (18).

Sensitivity Analysis

One-Way Sensitivity Analysis

In the one-way sensitivity analysis, the value was assigned with a varied range of ±10% of the basic value; the discount rate's variation range was 0–8%. The key factors that had the most significant impacts on the research results were obtained through one-way sensitivity analysis. The results are presented in a one-way analysis table and an ICER tornado chart.

[2]National Bureau of Statistics (2020). Available online at: https://data.stats.gov.cn/search.htm?s=%E4%BA%BA%E5%9D%87GDP (accessed December 30, 2020).

TABLE 4 | Basic analysis results.

Project	Cumulative cost(¥)	Cumulative effectiveness (QALYs)	Incremental cost	Incremental effectiveness	ICER (¥/QALY)
BUD/FOR[a]	173,030.05	7.73			
FF/UMEC/VI[b]	199,765.55	8.54	26,735.50	0.81	33,006.80

[a] *Fluticasone/umeclidinium/vilanterol triple combination.*
[b] *Budesonide/formoterol double combination.*

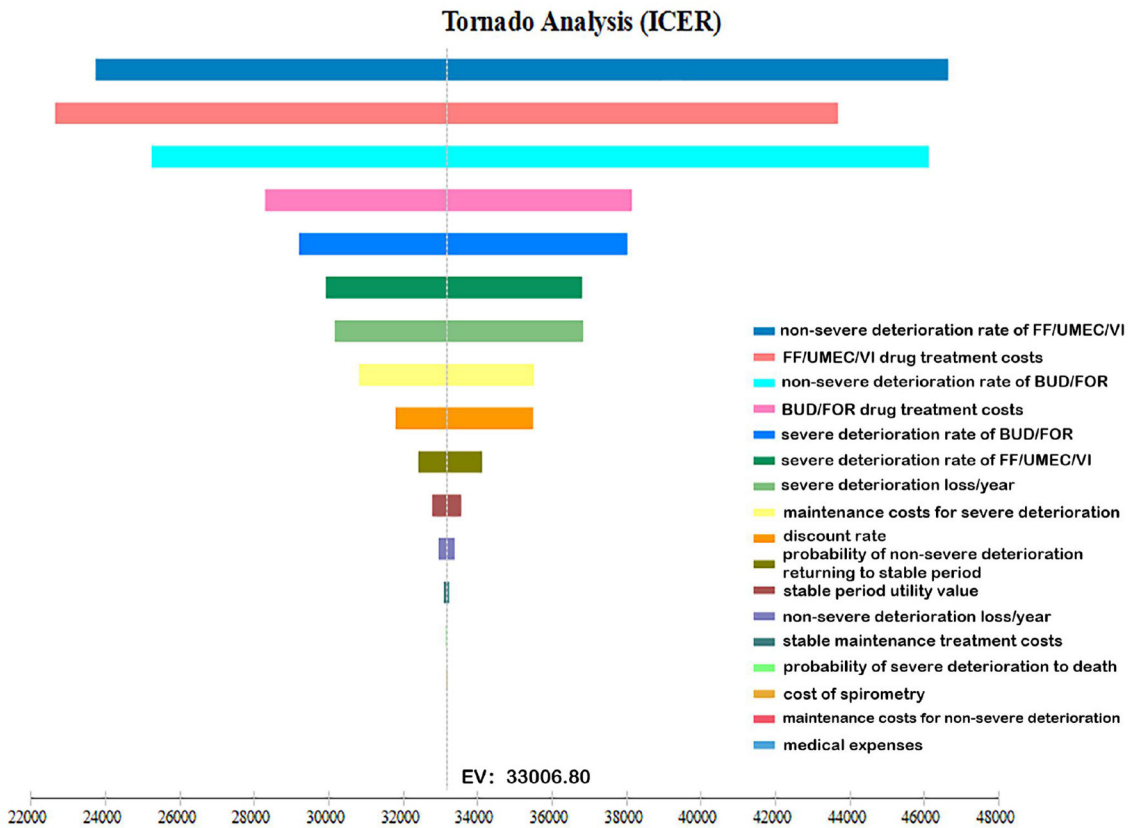


FIGURE 2 | One-way sensitivity analysis tornado diagram. The influencing factors from highest to lowest are: A: non-severe deterioration rate of FF/UMEC/VI; B: FF/UMEC/VI drug treatment costs; C: non-severe deterioration rate of BUD/FOR; D: BUD/FOR drug treatment costs; E: severe deterioration rate of BUD/FOR; F: severe deterioration rate of FF/UMEC/VI; G: severe deterioration loss/year; H: maintenance treatment costs for severe deterioration period; J: discount rate; K: probability of non-severe deterioration returning to stable period; L: stable period utility value; M: non-severe deterioration loss/year; N: stable maintenance treatment costs; O: probability of severe deterioration returning to death; P: cost of spirometry; Q: maintenance treatment costs for non-severe deterioration; R: medical expenses.

Probabilistic Sensitivity Analysis

Monte Carlo simulation was used for probabilistic sensitivity analysis (PSA). The research results for different parameters changing simultaneously were obtained through 1,000 simulations. Based on this stochastic simulation method, the research results from simultaneous changes in multiple parameters and the influence of threshold changes on decision-making were analyzed. The results are presented in Monte Carlo simulation scatter plots, cost-effectiveness acceptability curves, and other charts.

RESULTS

Baseline Results

FULFIL demonstrated clinically meaningful and statistically significant improvements at Week 24 in SGRQ total scores. There was a difference of −2.2 (95% CI −3.5, −1.0; $p < 0.001$) in change from baseline in SGRQ total score for FF/UMEC/VI vs. BUD/FOR (**Appendix II**) (14).

Following cohort simulation with the Markov model, the cumulative costs of the FF/UMEC/VI treatment for each COPD patient was determined to be ¥199,765.55,

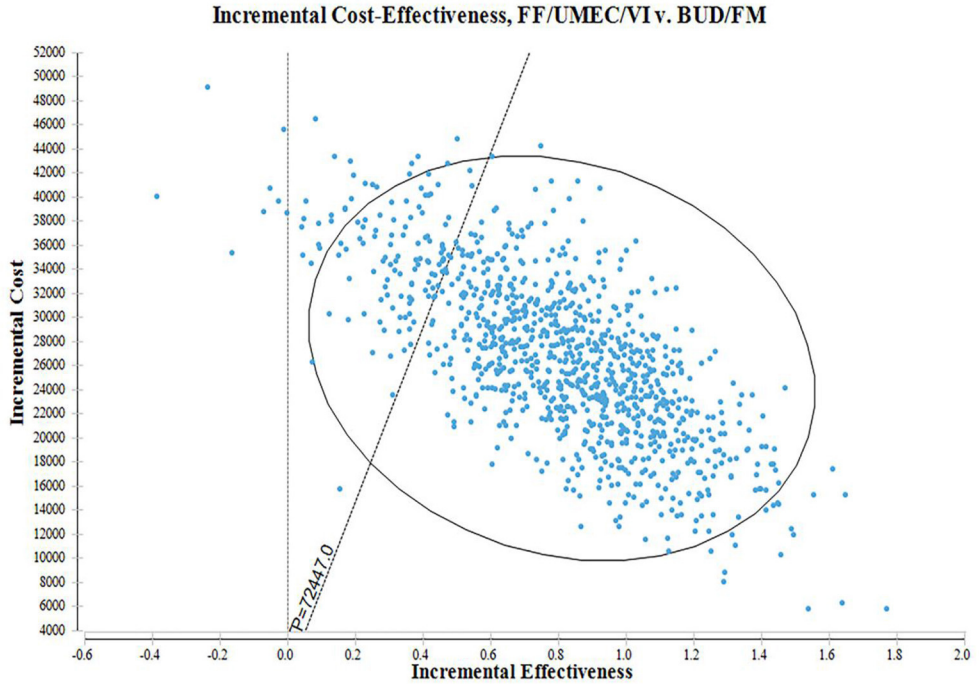


FIGURE 3 | Monte Carlo simulation pseudo-scatter plot. Dotted line: WTP = ¥72,447/QALY.

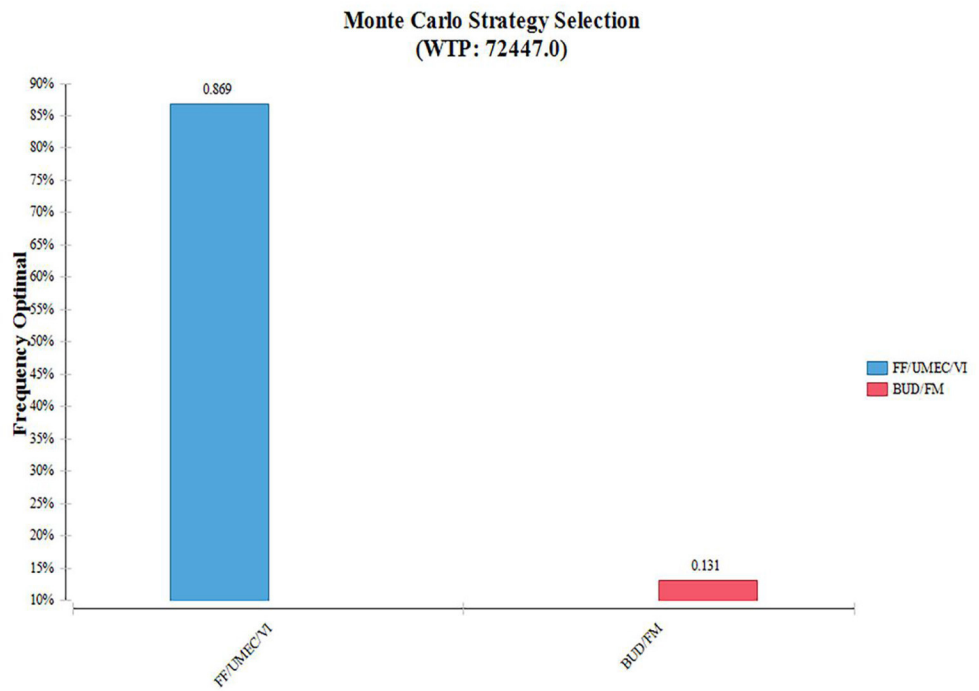


FIGURE 4 | Cumulative cost-acceptable probability of effect. FF/UMEC/VI, fluticasone/umeclidinium/vilanterol; BUD/FOR, budesonide/formoterol.

and total QALY gains were 8.54. The costs of BUD/FOR were ¥173,030.05, and the QALY gains were 7.73. The FF/UMEC/VI group paid ¥26,735.50 more in costs compared to the BUD/FOR group but gained 0.81 extra QALYs. The ICER was ¥33,006.80/QALY, which was less than the set threshold of ¥72,447/QALY, indicating that the

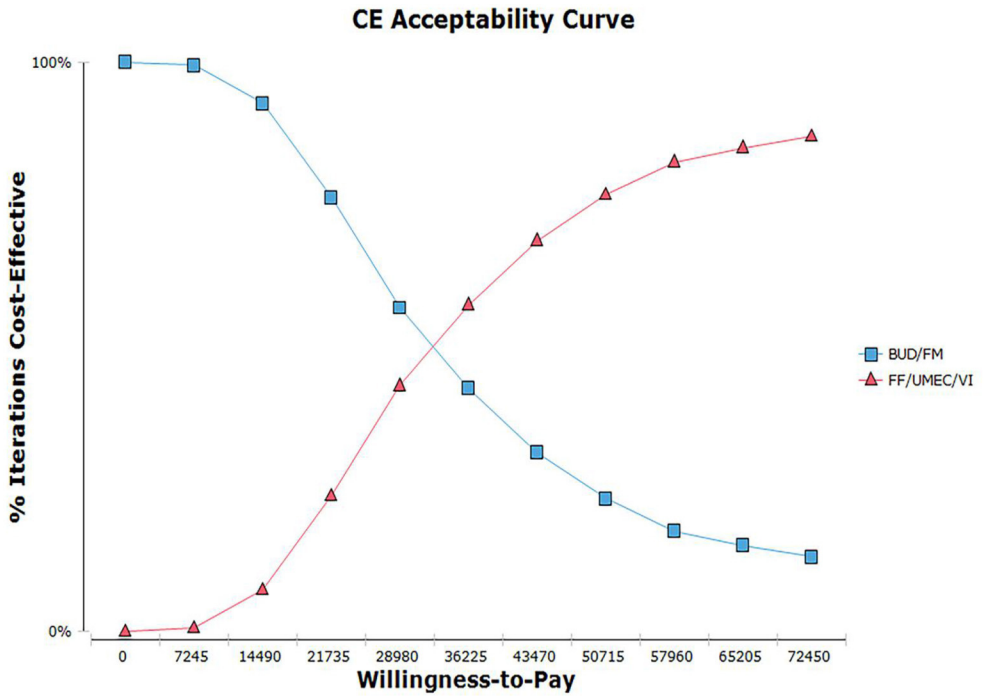


FIGURE 5 | Cost-effectiveness acceptable curve plotting. Willingness-to-pay vs. iterations cost-effective.

FF/UMEC/VI treatment is more cost-effective than BUD/FOR (**Table 4**).

One-Way Sensitivity Analysis

A one-way sensitivity analysis was performed with the changes in cost, utility, transition probability, and discount rates of the two drug treatment options. The ICER tornado chart is shown in **Figure 2**. The top three factors that affected the results are the non-severe deterioration rates of FF/UMEC/VI, the cost of FF/UMEC/VI and the non-severe deterioration rates of BUD/FOR.

PSA

According to the distribution of various parameters, Monte Carlo simulation was used to simulate the research results 1,000 times. The ICER scatter plot is shown in **Figure 3**. A total of 86.9% points fell below the threshold line in **Figure 4**, indicating that in 1,000 simulations, FF/UMEC/VI had a higher probability of offering economic advantages over BUD/FOR.

To further illustrate the relationship between the cost-effectiveness threshold change a cost-effectiveness acceptability curve (CEAC) was drawn, as shown in **Figure 5**. According to the CEAC, when WTP was higher than about ¥38,000, FF/UMEC/VI was more likely to be economically advantageous than BUD/FOR.

DISCUSSION

A variety of COPD treatment drug regimens are currently available, including the most prominent class of bronchodilators and expectorants, corticosteroids, phosphodiesterase-4 inhibitors, and antimicrobials that target airway obstruction. Among bronchodilators, single-agent use and the combination of LABA, LAMA, and inhaled corticosteroids are recommended in the COPD related guidelines. The common diphasic combinations are LABA/LAMA (Indacaterol/Glonoprost, Umeclidinium/Vilanterol, etc.), and LABA/ICS (Salmeterol/Tikasone, Budesonide/Formoterol, etc.); inhalation formulations are more widely used in clinical practice. The triple combination system ICS/LAMA/LABA (Budesonide/Glycopyrronium/Formoterol, Fluticasone/ Umeclidinium/Vilanterol, Beclometasone/ Formoterol/Glycopyrronium) is also continuously being developed and produced and is recommended by GOLD and other guidelines for the treatment of moderate-to-severe COPD.

Regarding triple combination preparations, FF/UMEC/VI can significantly reduce the hospitalization rate and all-cause mortality of COPD patients compared with LAMA/LABA preparations (19, 20). Compared with the commonly used ICS/LABA preparation, FF/UMEC/VI can also significantly alleviate COPD symptoms, improve lung function, and reduce acute exacerbations (21). Schroeder showed that although the cost of FF/UMEC/VI is greater than that of BUD/FOR, the benefit of FF/UMEC/VI is higher than it is for BUD/FOR

or other double combinations in terms of long-term cost effects (22). Papi and Martinez also showed that other triple combination preparations are advantageous compared to double combinations; for instance, the triple combination Beclometasone/Formoterol/Glycopyrronium is associated with a significantly larger reduction in the rate of moderate-to-severe COPD exacerbations compared to the dual bronchodilator combination of Indacaterol/Glycopyrronium over 52 weeks of treatment. Likewise, Budesonide/Glycopyrronium/Formoterol offers greater benefits in reducing moderate/severe and severe exacerbation rates relative to Glycopyrrolate/Formoterol, even among COPD patients with no history of exacerbations in the prior year (23, 24). Thus, the findings of the present study are in line with those of extant literature.

In addition, the effects of cigarette smoking also need to be taken into account when treating COPD with the appropriate pharmacotherapy. Across the world, cigarette smoking is the most commonly encountered risk factor for COPD (11). Cigarette smokers have a higher prevalence of respiratory symptoms and lung function abnormalities and a greater COPD mortality ratee than non-smokers (25). Smoking cessation can significantly reduce morbidity and mortality associated with COPD in conjunction with pharmacotherapy. China has also taken many strategies in tobacco control: In 2006, China signed the World Health Organization Framework Convention on Tobacco Control (WHO FCTC) to combat the tobacco epidemic; Up to data as of January 2018, 18 cities, including Beijing, Shanghai, Hangzhou, and Guangzhou, have introduced local tobacco control regulations, covering nearly 10% of the country's population.[3] The "Health China 2030" plan also set specific targets for tobacco control, with a reduction in the smoking rate to 20% of the population by 2030.[4]

Finally, pharmacist-led intervention and Effective use of the inhaler are crucial for COPD patients, too. Abdulsalim showed that Structured pharmacist-led intervention programme can improve medication adherence in COPD patients and effective use of the inhaler. Better medication adherence is associated with decrease in the number of emergency department visits and length of hospital stay among patients with COPD with improved adherence saving medicine costs and clinical pharmacy time (26–28).

Overall, we found that FF/UMEC/VI is more economical than BUD/FOR from the perspective of Chinese healthcare system. The sensitivity analysis results showed that the baseline analysis results are robust. The conclusions of this study are consistent with the GALAXY-COPD joint risk equation model (29). A systematic literature review about COPD showed that annual total societal costs of COPD ranged from $4398 to $23,049 in Japan and $453 to $12,167 in South Korea. There were no domestic comparison estimates for the remaining countries (Singapore: $2700; Taiwan: $4000; China: $3942; and Thailand: $1105) (30). This was consistent with the findings of our study that COPD imposes a significant financial burden on society, the health insurance segment, patients, etc.

In this study, a classic Markov model was constructed based on the disease outcome of COPD patients in the real world. Due to issues with data availability and to ensure experimental rigor, this study did not use the 1% forced expiratory volume value recommended by the commonly used GOLD guidelines and other COPD studies to classify the disease into several states (e.g., mild, moderate, severe, and extremely severe). Instead, the stable and deteriorating periods simulate the patient's disease progression. Additional real-world data and clinical findings are needed to support methodological refinement for the economic evaluation of COPD treatment options.

This study is subject to several limitations. First, the Markov model was based on a simulation of the patient's ideal state based on certain assumptions. For instance, it was assumed that FF/UMEC/VI and BUD/FOR had the same remission rate for non-severe deterioration, and the mortality rate of non-severe deterioration was based on natural mortality, which impacts extrapolation of the results to a certain extent. Second, the utility value was derived from calculating the formula, and this study only simulated the loss of utility value in patients with worsening conditions, without taking into account the increase in utility value brought about by improvement of the condition. Therefore, we may have underestimated the quality of health output. Third, there are currently no utility value measurement studies for the Chinese population of COPD patients with acute exacerbation and stable disease. It is thus recommended that further research on the quality of life of COPD patients be carried out in future. Fourth, more attention needs to be paid to the impact of long-term glucocorticoid use on increasing the risk of pneumonia and the prognosis of patients with proper inhaler use, these can affect the outcome and cost of treatment for patients.

CONCLUSION

Compared with the double-combination treatment option for COPD, BUD/FOR, our results showed that the triple combination FF/UMEC/VI was cost-effective under the threshold of Chinese per capita GDP. Simulations over 14 years of the model showed that FF/UMEC/VI can increase patient benefits and save on health resources. The 2020 edition of the *Global Chronic Obstructive Pulmonary Disease Initiative* recommends that patients with moderate-to-severe stable stages choose the ICS/LAMA/LABA triple combination for treatment. However, additional real-world data from the Chinese population and more accurate cost data are needed to test this hypothesis.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

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ETHICS STATEMENT

Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

MH conceived and designed the study. YZ, EL, QX, LW, and XJ contributed materials and collected the data. YZ and EL analyzed the data. YZ, EL, QX, and LW wrote the manuscript. YZ and EL contributed equally to this manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.713258/full#supplementary-material

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SYSTEMATIC REVIEW
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Systematic Review and Quality Evaluation of Pharmacoeconomic Studies on Traditional Chinese Medicines

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Objectives: This study was aimed to find and appraise the available published pharmacoeconomic research on Traditional Chinese Medicine (TCM), to identify related issues and make suggestions for improvement in future research.

Methods: After developing a search strategy and establishing inclusion and exclusion criteria, pharmacoeconomic studies on TCM were sourced from seven Chinese and English databases from inception to April 2020. Basic information about the studies and key pharmacoeconomic items of each study were extracted. The quality of each study was evaluated by using the British Medical Journal economic submissions checklist for authors and peer reviewers, focusing on factors such as study design, research time horizon, sample size, perspective, and evaluation methods.

Results: A total of 431 published pharmacoeconomic articles with 434 studies on topics including cost-effectiveness, cost-benefit, cost-minimization, cost-utility, or combination analyses were identified and included in this review. Of these, 424 were published in Chinese and 7 in English. These studies conducted economic evaluations of 264 Chinese patent medicines and 70 types of TCM prescriptions for 143 diseases, including those of the central nervous, cardiovascular, respiratory, gynecologyical, and other systems. The studied TCMs included blood-activating agents (such as Xuesaitong tablet, Fufant Danshen tablet, and Danhong Injection), blood circulation promoting agents (such as Shuxuetong injection, Rupixiao tablet, and Fufang Danshen injection), and other therapeutic agents. The overall quality score of the studies was 0.62 (range 0.38 to 0.85). The mean quality score of studies in English was 0.72, which was higher than that of studies in Chinese with 0.62.

Conclusions: The quality of pharmacoeconomic studies on TCM was relatively, generally low. Major concerns included study design, inappropriate pharmacoeconomic evaluation, insufficient sample size, or non-scientific assessment. Enhanced methodological training and cooperation, the development of a targeted pharmacoeconomic evaluation guideline, and proposal of a reasonable health outcome index are warranted to improve quality of future studies.

Keywords: trad. Chinese medicine, Chinese patent medicines, pharmacoeconomic, system review, quality evaluation

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INTRODUCTION

Pharmacoeconomics is a complex science that provides evidences for the optimal allocation and efficient utilization of medical resources. Since the 1970s, it has been increasingly accepted and applied by health care providers, health policy makers, and medical insurance institutions. It has also formed part of the basis of new drug applications, drug pricing, drug purchasing by medical institutions, National Essential Medicines List formulation, medical insurance, and post-marketing drug evaluation (1–3).

With the increasing popularity of and substantial expenditures on complementary and alternative medicine (CAM) therapies globally, the availability of economic evaluations becomes increasingly important (4, 5). However, the quality of those evaluations has significant influence on the popularization and application of the results. A few systematic reviews on economic evaluations of CAM have described findings and quality of available research and have made recommendations for future research (6–10).

Traditional Chinese Medicine (TCM) as one kind of CAM plays an important role in preventing, treating, and curing disorders and diseases (11, 12). Since 1984, the Drug Administration Law of the People's Republic of China has established the policy governing the development both modern medicines and traditional medicines. In 2020, Chinese patent medicine accounted for more than one third of all the drug approvals in China (13) and for 49.07% of all drugs listed in the National Drug Catalog for Basic Medical Insurance of China (14), equaling the proportion of Western medicines. In recent years, with more attention on economic evaluation of medicines, an increasing amount of pharmacoeconomic research has comprehensively evaluated the efficacy, safety and affordability of TCM. This research provides evidence for the rational use of health resources, essential medicine and state medical insurance catalog selection and national drug price negotiations.

The present study aims to find and appraise the available published pharmacoeconomic studies on TCM, analyze the limitations of the research and make suggestions for improved pharmacoeconomic evaluation on TCM in future.

MATERIALS AND METHODS

Data Sources

This systematic review was conducteded in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We searched the following databases between their inception (years in parentheses) and April 2020: China National Knowledge Infrastructure(CNKI) (1974), Chongqing VIP Information(VIP) (1989), WanFang Database (1998), Sinomed (1978), Pubmed (1966), Embase (1974), and Cochrane Library (2000).

The search keywords was ("Chinese medicine" OR "Traditional Chinese Medicine" OR "Chinese patent medicine" OR "herbal medicine" OR "natural medicine" OR "Chinese Medicinal Materials" OR "Botanical medicine" OR "Chinese herbal pieces" OR "Chinese medicinal granula") and ("pharmacoeconomic" OR "economics" OR "Cost Effectiveness Analysis" OR "Cost Utility Analysis" OR "Cost Benefit Analysis" OR "Cost Minimization Analysis" OR "Markov" OR "Decision Tree" OR "Partitioned Survival Model"). Chinese and English terms for search keywords were used when searching the databases. In addition, the references lists of retrieved articles were also searched.

Study Selection

We included the articles describing pharmacoeconomic evaluation articles on TCM, defined as medicines made according to Chinese medicine theory, such as Chinese patent medicine and Chinese medicine prescription or formula. Articles describing research on traditional Chinese treatment or therapy as interventions such as acupuncture, Guasha or massage or theory papers, reviews, reports, protocols, news, and opinion articles, were excluded. Partial economic evaluations, such as outcome, cost, cost-outcome description, effectiveness (or efficacy) evaluation, and cost analysis, quality of life research, and budget impact analysis were also excluded. Besides, the study country was limited in China and study language was limited in Chinese and English.

Data Extraction and Quality Assessment

All articles included in the study were read in full and independently judged against inclusion and exclusion criteria of the individual phase by two authors (HH Zhang and TY Deng). Any difference during assessment between the two reviewers was discussed or resolved by a third dependent reviewer (N Yang). A data extraction table was designed using Excel software, and information extracted from each article including title, first author's name and affiliation, journal and year of publication, information about disease, sample size, study design, intervention, and information related cost, health outcomes, uncertainty analysis, perspective, evaluation techniques, and other factors. The data were descriptively analyzed using Microsoft Excel.

The five most representative checklists or guidelines for evaluation of pharmacoeconomic research are the British Medical Journal (BMJ) checklist (15), Quality of Health Economic Studies (QHES) instrument (16), Consensus Health Economic Criteria (CHEC) (17), Philips guideline (18), and Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (19). Among them, the BMJ checklist was the first to emerge and to be used. Published in 1996, it includes 35 items to assess the quality of articles on economic evaluation, and to date this has been the mostly cited of these appraisal methods (20). Each item of the checklist requires a "yes," "no,"

Abbreviations: CAM, complementary and alternative medicine; TCM, traditional Chinese medicine; PRISMA, preferred reporting items for systematic reviews and meta-analyses; CNKI, China national knowledge infrastructure; VIP, Chongqing VIP information; BMJ, British medical journal; QHES, quality of health economics studies; CHEC, consensus on health economic criteria; ISPOR, international society of pharmacoeconomics and outputs research; CHEERS, consolidated health economic evaluation reporting standards; CEA, cost-effectiveness analysis; CMA, cost analysis; CBA, cost-benefit analysis; CUA, cost-effectiveness analysis; DT, decision tree.

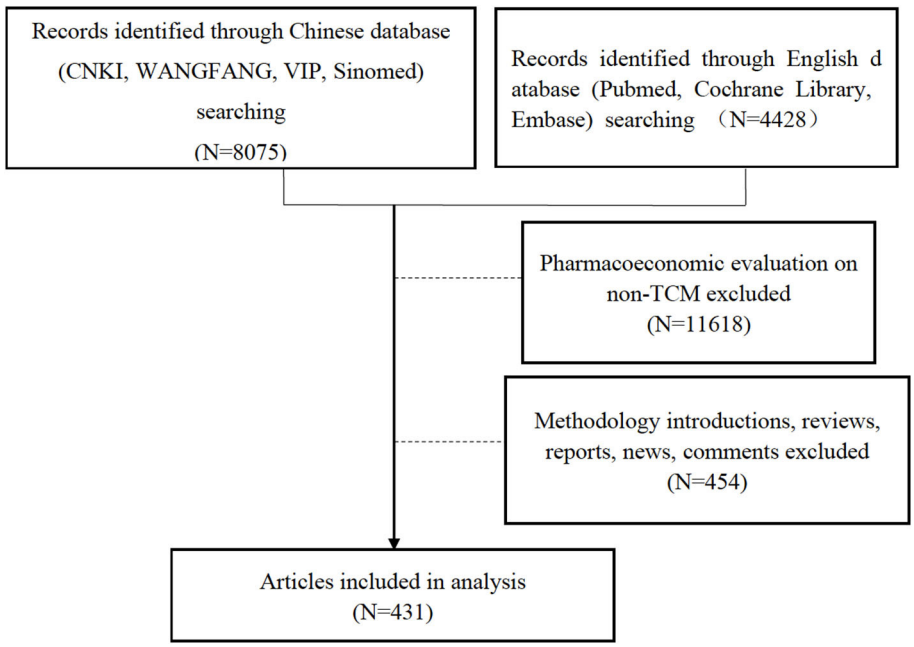


FIGURE 1 | Flow chart of study search and selection.

"unclear," and "not applicable" response, and this broad form of grading means that the checklist may be used to assess various economic evaluations. Due to its wide application, general recognition in the pharmacoeconomic research field, and flexibility of evaluation items, we used BMJ checklist to evaluate the quality of studies included in this review. The percentage of the applicable items on the BMJ checklist meeting by each study represented the quality score of the study.

The 35 checklist items are organized into 10 sections under three headings including study design, data collection, and analysis and interpretation of results. One mark was awarded for each item with a "yes" response, and a mark of zero for "no" or "unclear." Each study was scored based on its maximum possible score on the checklist, excluding items irrelevant to the study. The overall quality score was calculated as the mean of the scores of all included studies. A score <0.90 was taken to indicate high quality. Scores of individual items were also recorded.

RESULTS

Study Description

According to the pre-defined search strategy and selection criteria, the databases were searched and identified articles were screened (**Figure 1**). We eventually included a total of 431 articles including 424 articles in Chinese language and seven articles in English.

The first pharmacoeconomic study on TCM in Chinese was published in Chinese Journal of Pharmacoepidemiology in 1997, and focused on Ahylysantinfarctase and Fufang Danshen injection for cerebral infarction patients (21). The first TCM pharmacoeconomic study in English was published in the Chinese Journal of Integrative Medicine in 2014, and was focusing on Chinese medicine and Western medicine for ischemic stroke patients (22). Since 2002, the number of published pharmacoeconomic studies on TCM has gradually increased (**Figure 2**).

In addition to 25 dissertations, other pharmacoeconomic evaluation literatures on TCM were published in 173 journals, among which 178 were Chinese journals and 5 English journals.

More than 80.97% of the pharmacoeconomic evaluation studies on TCM were carried out by teams with the first author affiliated with a hospital (349), and the remaining studies' first authors were affiliated with universities or research institutions ($n = 72$, 16.71%) or enterprises ($n = 10$, 2.32%). All of the first authors of English articles were affiliated with universities.

Among 431 articles, only 66 (15.56%) were reported as having financial support, including nine nationally funded projects, 22 provincial and ministerial funded projects, 22 municipally funded projects, four university funded projects, four funded projects by the authors' units, three projects supported by a foundation, and two projects supported by Enterprise funding.

Diseases

According to the International Classification of Diseases (ICD-10), the studies focused on a range of 148 kinds of diseases, among which most frequently studied were diseases of the nervous system, cardiovascular system, respiratory system, gynecological, and alimentary systems as shown in **Figure 3**.

Interventions

The medical interventions involved in the studies were complex and diverse. Nearly half of the studies compared

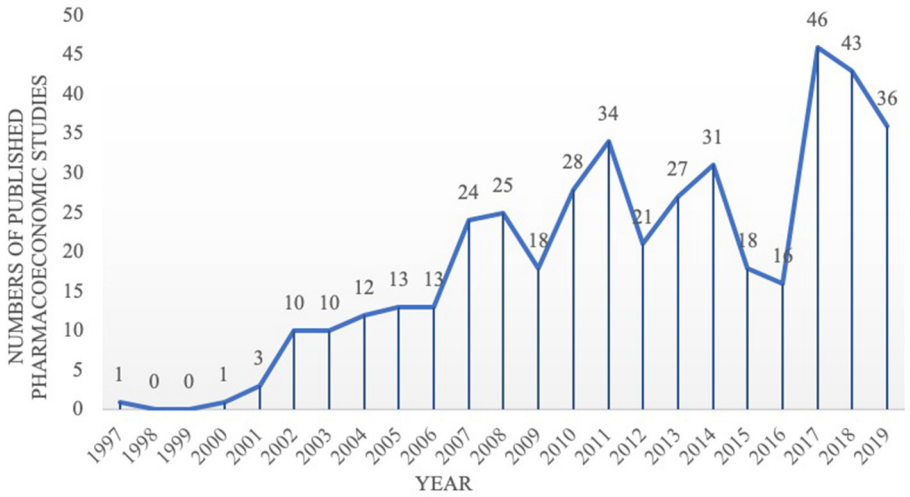


FIGURE 2 | Number of included pharmacoeconomic research publications ($N = 434$).

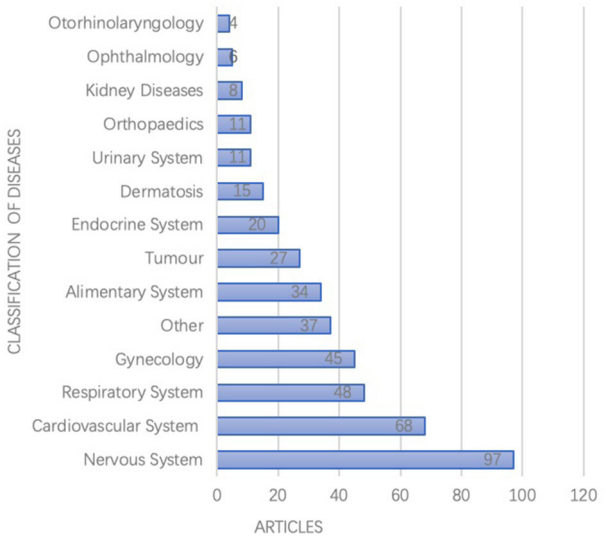


FIGURE 3 | Disease therapies for included pharmacoeconomics researches ($N = 434$).

two interventions, while others compared three or more interventions. However, 186 studies did not describe reasons for choosing the specific program or interventions for comparison. More than a third of the studies used TCM as the control group, and in most of these cases the TCM was not recommended by relevant clinical guidelines (**Table 1**).

The studies included 264 types of Chinese patent medicines and 70 types of TCM prescriptions (such as prescription, pieces decoction, powder, extraction, tincture, and pills). **Table 2** shows the Chinese patent medicines that were the focus of more than eight

TABLE 1 | Number of studies making different types of comparisons between Chinese and Western medicine ($N = 434$).

Treatment comparison	Number of studies	Percentage
Chinese medicine vs. Chinese medicine	164	37.79%
Chinese medicine vs. Western medicine	156	35.94%
Chinese medicine plus western medicine vs. Western medicine	76	17.51%
Chinese medicine plus Western medicine vs. Chinese medicine plus Western medicine	20	4.61%
Chinese medicine prescriptions	15	3.46%
Chinese medicine plus Western medicine vs. Chinese medicine	3	0.7%

pharmacoeconomic studies, in addition to their TCM syndromes and their indications from the perspective of Western medicine.

Study Characteristics

Study characteristics of the 434 studies are presented in **Table 3** including the study design, duration, sample size, and viewpoint/perspective. While 24 studies were based on data from previous research, most were prospective or retrospective clinical trials. Seventeen studies did not specify the study duration, but of the remainder most were <3 months. Excluding the 27 studies in which data were extracted from previous research, the sample size of included studies ranged from 38 to 2,820 and subjects' age ranged from 0 to 90 years old. Most ($n = 377$; 86.87%) of the studies did not specify the perspective of their pharmacoeconomic evaluations.

More than 85% of the studies used cost-effectiveness analysis (CEA), and the remainder study used at least

TABLE 2 | Chinese patent medicines with more than eight pharmacoeconomic studies, the TCM syndromes to which they apply, and the Western medicine indicators for these ($N = 434$).

Chinese patent medicines	Applicable TCM Syndromes	Indications of Western Medicine	Number of studies	Percentage
Xuesaitong tablet	Blood-activating, stasis-dissolving	Stroke, hemiplegia and others	20	4.60%
Fufang Danshen tablet/dropping pill	Blood-activating, stasis-dissolving	Coronary heart disease, angina pectoris	17	3.92%
Shuxuening injection	Blood vessel-expanding, microcirculation-improving	Ischemic cardiovascular, cerebrovascular diseases, coronary heart disease, angina pectoris, cerebral embolism and others	16	3.69%
Danhong injection	Blood-activating, stasis-dissolving	Chest pain, chest tightness, palpitation, cerebrovascular diseases, coronary heart disease, angina pectoris and others	15	3.46%
Qingkailing injection	Heat clearing-detoxication, tranquilizing,allaying excitement	Upper respiratory tract infection, viral cold and others	15	3.46%
Shuxuetong injection	Blood circulation promoting, blood stasis removing, channels and collaterals dredging	Hemiplegia, speech askew, speech astringent, acute cerebral infarction	13	2.99%
Xiyanping injection	Heat clearing-detoxication, relieve diarrhea	Bronchitis, tonsillitis, bacillary dysentery	13	2.99%
Danshen Chuanxiongqin injection	Not provided	Occlusive cerebrovascular diseases	13	2.99%
Rupixiao tablet	Blood circulation promoting, blood stasis removing, hard mass softening and resolving	Lobular hyperplasia of mammary gland, ovarian cyst, uterine leiomyoma	12	2.76%
Fufang danshen injection	Blood circulation promoting, blood stasis removing, pulse-invigorating, heart-nourishing	Coronary heart disease, chest tightness, angina pectoris	12	2.76%
Ciwujia injection	Liver and kidney reinforcing moderately, bone strengthening	Transient ischemic attack, cerebral arteriosclerosis, cerebral thrombosis and cerebral embolism caused by liver and kidney deficiency, coronary heart disease, angina pectoris, neurasthenia, climacteric syndrome	11	2.53%
Shenmai injection	Qi-supplementing, yin-nourishing, normal pulse restoring, collapse remedy	Palpitation, shortness of breath, limb cold, sweating, pulse loss, myocardial infarction, cardiogenic shock	10	2.30%
Xueshuantong injection	Blood circulation promoting	Central Retinal vein occlusion, sequelae of cerebrovascular disease, internal ophthalmopathy, anterior chamber hemorrhage and others.	10	2.30%
Tanreqing injection	Heat clearing-detoxication, phlegm resolving	Fever, cough, expectoration, sore throat, thirst, red tongue, yellow fur; early pneumonia, acute bronchitis, acute attack of chronic bronchitis, upper respiratory tract infection.	9	2.07%
Yinxingdamo injection	Not provided	Coronary heart disease, thromboembolic diseases	9	2.07%
Yanhuning injection	Not provided	Viral pneumonia, upper respiratory tract infection	9	2.07%
Reduning injection	Heat clearing-detoxication, wind dispelling	High fever, head and body pain, cough, yellow phlegm, upper respiratory tract infection	9	2.07%
Aidi injection	Heat clearing-detoxication, blood stasis eliminating	Primary liver cancer, lung cancer, rectal cancer, malignant lymphoma, gynecological malignancies, and others	8	1.84%

one method of cost analysis, such as Cost Minimization Analysis (CMA), Cost Benefit Analysis (CBA), or Cost Utility Analysis (CUA). See **Table 3** for details. Among these studies, 28 studies used modeling research, with six studies using Markov model and 22 studies using a decision tree model. Thirty-one studies used combination analyses, with two or more methods such as CEA, CMA, CUA, or CBA used in one study. Other relevant specific information is shown in **Table 3**.

Cost Scope and Identification

More than 80% of the studies only calculated direct costs, less than one-fifth of the studies included both direct and indirect costs, and the remaining 6% of the studies did not clearly define costs.

Direct costs in these studies were related to the following: drugs ($n = 385$), examination fee ($n = 158$), treatment fee ($n = 78$), hospitalization cost ($n = 42$), nursing cost ($n = 42$), bed fee ($n = 41$), registration fee ($n = 32$), dispensing fee ($n =$

TABLE 3 | Characteristics and uncertainty analysis variables for included pharmacoeconomic studies ($N = 434$).

Study characteristics	Number of studies	Percentage
Study design	407	
Prospective study	248	60.93%
Prospective experimental study	234	57.49%
Prospective observational study	14	3.44%
Retrospective study	159	39.07%
Study duration	407	
<14 d	166	40.79%
15 to 30 d	100	24.57%
1 to 3 m	100	24.57%
4 to 6 m	11	2.70%
7 to 12 m	10	2.46%
12 to 24 m	4	0.98%
Not mentioned	16	3.94%
Sample size	407	
<100 subjects	152	37.35%
101 to 200 subjects	146	35.87%
201 to 500 subjects	86	21.13%
501 to 1,000 subjects	15	3.69%
over 1,000 subjects	8	1.97%
Perspective	434	
Medical institutions	24	5.53%
Patients	9	2.07%
Whole society	11	2.53%
Payers	11	2.53%
Health system	2	0.46%
Not specified	377	86.87%
Evaluation Methods	434	
CEA	369	85.02%
CMA	20	4.72%
CBA	7	1.61%
CUA	7	1.61%
Combination analysis	31	7.14%
Uncertainty analysis variables	289	
Drug prices	190	65.74%
Drug prices and other cost (such as examination fee, examination fee, bed fee, treatment fee, nursing fee, compensation/fee for absence from work.)	67	23.18%
Drug prices and health outcome (such as efficiency rate)	19	6.57%
Other cost (such as examination fee, examination fee, bed fee, treatment fee, nursing fee, compensation for one's absence from work)	7	2.42%
Other variables (such as course of medication, discount rate)	6	2.08%

d, day; m, month.

27), adverse reaction treatment cost ($n = 23$), material cost ($n = 16$ studies), meal ($n = 11$), surgery cost ($n = 9$), disposal cost ($n = 6$), consultation fee ($n = 1$), blood transfusion cost ($n = 1$), instrument loss ($n = 1$), and other expenses ($n = 55$). Indirect costs were related to time cost ($n = 22$), compensation (fee) for one's absence from work ($n = 18$), labor loss ($n = 3$), and funeral expenses ($n = 1$).

Health Outcomes

A total of 226 studies used a single end-point, 156 studies used double end-points, 26 studies used three end-points, and the other 26 studies used four or more end-points at the same time. Of 400 CEA studies with a health-related the final end-points, 264 studies included clinical efficiency/improvement rate, 132 included adverse reactions rate, 47 included efficiency rate of TCM syndromes, 11 included recurrence rate, and 16 included disease or drug withdrawal rate, and 5 included death rate. Fourteen percent ($n = 61$) of studies reported the intermediate end-points as the health-related outcomes, including score/index scale ($n = 41$), biochemical indicators ($n = 22$), physiological indices ($n = 9$), and imaging indices ($n = 9$). Twenty studies reported quality-adjusted life year as a health outcome and one study reported net benefit as a health outcome.

Uncertainty Analysis and Generalizability

Sixty seven percent of the included studies ($n = 289$) carried out an uncertainty price analysis, the main variables of which are shown in Table 3. In 220 (76.12%) studies, uncertainty analysis were conducted by using one-way sensitivity analysis with reducing drug prices by 10–20%, while 69 (23.88%) of studies used multi-way sensitivity analysis for uncertainty.

A total of 102 articles (23.67%) discussed the limitations of their studies, and 12 articles discussed the generalizability of their results. Although 66 studies included children under 18 years of age, none of these acknowledged the related ethical issues.

Quality Assessment of Pharmacoeconomic Evaluation Studies on TCM

The average overall quality score of 431 pharmacoeconomics studies on TCM was 0.62.with a range from 0.38 to 0.85. Scores on most of the studies were from 0.5 to 0.7. The distribution is shown in Table 4. On items 2.5, 2.9, 2.12, 3.2, 3.3, 3.4, and 3.5 the score was below 0.1. On items 1.3, 2.7, 2.8, and 3.14 it was no more than 0.5 and on items 1.4, 2.1, 3.6, 3.7, and 3.8 it was no more than 0.7 (**Table 4**).

The quality of the studies was not significantly improved over the past 20 years, as shown in **Table 5**. The quality of studies with first authors affiliated with universities researchers was much higher than that of studies with first authors affiliated with hospitals. The mean score of the seven studies in English was 0.72, while that of studies published in Chinese journals was 0.62. The scores of studies in English were higher than those in Chinese on items 3.2, 3.2, 3.4 3.5, and 3.14 and scores were relatively high in the Chinese journals on items 1.2, 2.3, 2.7, and 2.8. However, scores on items 2.7, 2.8, 2.9, 3.2, 3.3, and 3.4 were low in both Chinese and English studies, suggesting a need for improvement (**Table 4**).

TABLE 4 | Quality Evaluation Scoring of Included Pharmacoeconomic Studies on TCM (N = 434).

Evaluation items		Scores of the studies published in Chinese		Scores of the studies published in English	
		Number of studies scored	Mean score	Number of studies scored	Mean score
Study Question	1.1 The research question was stated	427	1	7	1
	1.2 The economic importance of the research question was stated	310	0.726	4	0.571
	1.3 The viewpoint(s) of the analysis were clearly stated and justified	58	0.136	4	0.571
Selection of Alternatives	1.4 The rationale for choosing the alternative programs or interventions compared was stated	241	0.564	3	0.429
	1.5 The alternatives being compared were clearly described	385	0.902	7	1
Form of Evaluation	1.6 The form of economic evaluation used was stated	427	1	7	1
	1.7 The choice of form of economic evaluation was justified in relation to the questions addressed	427	1	7	1
Effectiveness Data	2.1 The source(s) of effectiveness estimates used were stated	214	0.501	6	0.857
	2.2 Details of the design and results of effectiveness study were given (if based on a single study)	253	0.811	7	1
	2.3 Details of the method of synthesis or meta-analysis of estimates were given (if based on an overview of a number of effectiveness studies)	22	0.880	0	0
Benefit Measurement and Valuation	2.4 The primary outcome measure(s) for the economic evaluation were clearly stated	427	1	7	1
	2.5 Methods to value health states and other benefits were stated	0	0	1	0.143
	2.6 Details of the subjects from whom valuations were obtained were given	392	0.918	6	0.857
Costing	2.7 Productivity changes (if included) were reported separately**Δ**	44	0.103	0	0
	2.8 The relevance of productivity changes to the study question was discussed**Δ**	57	0.133	0	0
	2.9 Quantities of resources were reported separately from their unit costs**Δ**	0	0	2	0.286
	2.10 Methods for the estimation of quantities and unit costs were described	402	0.941	6	0.857
	2.11 Currency and price data were recorded	417	0.977	5	0.714
	2.12 Details of currency of price adjustments for inflation or currency conversion were given	0	0	0	0
Modeling	2.13 Details of any model used were given	20	0.833	4	1
	2.14 The choice of model used and the key parameters on which it was based were justified	22	0.917	4	1
Adjustments for timing of costs and benefits	3.1 Time horizon of costs and benefits was stated	433	1	6	0.857
	3.2 The discount rate(s) was stated***Δ**	7	0.016	3	0.429
	3.3 The choice of rate(s) was justified***Δ**	7	0.016	3	0.429
	3.4 An explanation is given if costs or benefits were not discounted***Δ**	17	0.040	1	0.143
Allowance for uncertainty	3.5 Details of statistical tests and confidence intervals were given for stochastic data*	25	0.059	4	0.571
	3.6 The approach to sensitivity analysis was given	284	0.665	5	0.714
	3.7 The choice of variables for sensitivity analysis was justified	285	0.667	4	0.571
	3.8 The ranges over which the variables were varied are stated	283	0.663	5	0.714
	3.9 Relevant alternatives were compared	427	1	7	1
Presentation of results	3.10 Incremental analysis was reported	267	0.837	6	0.857
	3.11 Major outcomes are presented in a disaggregated as well as aggregated form	427	1	7	1
	3.12 The answer to the study question was given	427	1	7	1
	3.13 Conclusions followed from the data reported	427	1	7	1
	3.14 Conclusions were accompanied by the appropriate caveats*	77	0.180	7	1

**indicates that the score for studies in English was higher than in Chinese; Δ indicates that the score of studies was relatively low both in Chinese and English articles.*

DISCUSSIONS

Policy orientation and a demand for evidence have influenced a rapid increase over the past decade in number of the published pharmacoeconomic research articles on TCM. However, the volume remains only one tenth of the number of corresponding articles on chemical drugs. Overall, the quality of published pharmacoeconomics evaluation on TCM was relatively and generally low, which was consistent with the results of several studies in 2009 (23), 2015 (24), and 2020 (25). And compared

TABLE 5 | Scoring comparison from different viewpoints for included pharmacoeconomic studies ($N = 431$).

Viewpoint	Number of studies	Score
Year of publication		
Before 2005	50	0.62
2005–2010	108	0.62
2011–2015	132	0.61
After 2015 y	144	0.63
Language of publication		
Studies in Chinese	427	0.62
Studies in English	7	0.72
First author affiliation		
Hospital	349	0.61
University	75	0.68
Enterprise	10	0.64

with the studies of Chen (26), Li (27), Lei (28) in 2004, 2008, and 2010 respectively, the quality of pharmacoeconomics research articles on TCM was also lower than that on chemical drugs.

Three main limitations in quality were identified. Firstly, many of the included studies were not well-designed and lacked clear research perspective. Only four studies described the method of sample size estimation based on China guidelines for pharmacoeconomic evaluation, which would affect cost identification and measurement and thereby the integrity and reliability of the studies (29). Many studies did not report the randomization method, and failed to justify the selected intervention.

Many studies with first authors affiliated with a hospital appeared to not fully understand the basic principles of pharmacoeconomics and did not design their clinical trials appropriately, despite pharmacoeconomic data being relatively easy to obtain in a hospital. Some studies failed to implement and apply pharmacoeconomic research methods correctly. There were limitations or errors in cost identification and measurement in some studies, more than half of which included only drug costs. Due to these issues, some researchers misunderstood or were confused about cost assessment in pharmacoeconomic evaluation. Even in the study of chronic diseases, people generally did not pay enough attention to discount. In addition, the choice of discount rate is also based on different countries and different perspectives, which is also a controversial issue in the field of Pharmacoeconomics.

Some studies assessed TCM as an adjunct to Western medicines, which made the cost difficult to calculate. In addition, the lack of a specific and unique pharmacoeconomic evaluation guideline for TCM was also an important limitation. In 2013, Xie et al. published a "technical specification for pharmacoeconomic evaluation on post marketed Chinese patent medicine (Draft)" in the China Journal of traditional Chinese Medicine (30). This guideline considered the basic ideology and characteristics of traditional Chinese medicine to a certain extent, but did not solve the specific problems in the pharmacoeconomic evaluation of TCM, such as how to map the effectiveness and health outcome of TCM and chemical medicines.

Finally, some TCM clinical trials were found to be limited in terms of sample size, comparison type, or the use of non-scientific assessments. The short durations of most studies were not well-aligned with the chronic nature of disease on which they focused, and did not fully reflect the advantages of TCM in improving long-term clinical efficacy and potential safety. Most of the studies were retrospective, with small samples and no follow-up. Common defects were in protocol design, lack of trial registration, study reporting, and quality control. Frequently used outcome indicators were overall efficiency and recurrence rate, and were not sufficiently specific to reflect outcomes of different types of TCM treatment.

There were some limitations in our study. First, the BMJ checklist was published in the 1990s, and its applicability may deviate to some extent from the current research including pharmacoeconomic evaluations on TCM. Second, this study included only published research and not unpublished research reports. Some outcome indicators were not addressed by the included studies, resulting in low scores for those indicators, which may have impacted negatively on the evaluation results of this study.

CONCLUSIONS

Although limitations and deficiencies are found in the current pharmacoeconomic evaluation of TCM, the body of research still provides a lot of valuable evidence for the rational use of health resources, essential medicine and state medical insurance catalog selection and national drug price negotiations. The following recommendations may improve the quality of research in this area. In the pharmacoeconomics evaluation of TCM, the following recommendations are made.

With regard to the point discussed above, we call for enhanced methodological training and cooperation to improve the quality of research and reporting quality. A pharmacoeconomic evaluation guideline conforming to the theoretical characteristics of TCM should be established to reflect the economic evaluation results of TCM objectively. In addition, importantly, a reasonable health outcome index for TCM should be developed, balancing between the specificity and quantification of TCM indicators, mapping of indicators between Chinese patent medicine, and Western medicines, and enhancing clinical comparability of health indicators.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

MH and NY conceived the study design. HZ and TD searched and selected the articles, extracted, analyzed, and interpreted the data. NY drafted the manuscript. MH and JG critically reviewed

the manuscript. All authors read and approved the final version of the manuscript.

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Impact of the National Health Insurance Coverage Policy on the Utilisation and Accessibility of Innovative Anti-cancer Medicines in China: An Interrupted Time-Series Study

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Objective: The study aimed to evaluate the impact of the National Health Insurance Coverage (NHIC) policy on the utilisation and accessibility of innovative anti-cancer medicines in Nanjing, China.

Methods: We used the adjusted World Health Organisation and Health Action International methodology to calculate the price and availability of 15 innovative anti-cancer medicines included in the National Health Insurance drug list in 20 tertiary hospitals and six secondary hospitals in Nanjing before and after NHIC policy implementation. Interrupted time-series regression was used to analyse the changes in the utilisation of the study medicines.

Results: The price reduction rates of innovative anti-cancer medicines ranged between 34 and 65%. The mean availability rate was 27.44% before policy implementation and increased to 47.33% after policy implementation. The utilisation of anti-cancer medicines suddenly increased with a slope of 33.19–2,628.39 when the policy was implemented. Moreover, the usage rate of bevacizumab, bortezomib, and apatinib significantly increased ($p < 0.001$, $p = 0.009$, and $p < 0.001$, respectively) after policy implementation. With regard to price reduction and medical insurance reimbursement, the medicines became more affordable after policy implementation (0.06–1.90 times the per capita annual disposable income for urban patients and 0.13–4.46 times the per capita annual disposable income for rural patients).

Conclusion: The NHIC policy, which was released by the central government, effectively improved the utilisation and affordability of innovative anti-cancer medicines. However, the availability of innovative anti-cancer medicines in hospitals remained low and the utilisation of innovative anti-cancer medicines was affected by some factors, including the incidence of cancer, limitation of indications within the insurance program, and the

rational use of innovative anti-cancer medicines. It is necessary to improve relevant supporting policies to promote the affordability of patients. The government should speed up the process of price negotiation to include more innovative anti-cancer medicines in the medical insurance coverage, consider including both medical examinations and adjuvant chemotherapy in the medical insurance, and increase investment in health care.

Keywords: innovative anti-cancer medicines, national health insurance coverage, utilisation, affordability, interrupted time series

INTRODUCTION

Cancer has been a major health issue worldwide and is one of the most serious health problems in China. Based on the data from the National Central Cancer Registry in 2019, 2.929 million patients were newly diagnosed with cancer and 2.338 million deaths were reported (1). Cancer accounts for 25% of all cases and deaths worldwide (2). Population growth and increased life expectancy are among the important reasons for the high morbidity of cancer (2).

To address the increase in the risk of cancer, the pharmaceutical industry has focused on the research and development of novel anti-cancer medicines worldwide. In recent years, a number of innovative anti-cancer medicines were approved for marketing every year (3), such as molecular targeted therapy drugs (osimertinib), immunotherapy drugs, programmed cell death protein (PD)-1 inhibitors, and PD ligand 1 inhibitors. Innovative anti-cancer medicines play an important role in the treatment of malignant tumours, bringing hope to patients with cancer who have a higher mortality risk. Moreover, innovative anti-cancer medicines can improve the quality of life; some patients may even achieve normal lives (4). Opinions of the State Council on the Implementing the Healthy China Action clearly stated that by 2022 and 2030, the overall 5-year survival rates of cancer should be >43.3% and >46.6%, respectively (5). Actively advocating for cancer prevention and promoting early diagnosis and treatment, supplemented by the early use of suitable innovative anticancer medicines, can help patients receive better treatment, thereby improving the overall five-year survival rate (6). However, due to patent protection and technology monopoly of innovative drugs, the cost of innovative anti-cancer medicines is usually higher than the catastrophic health expenditure, which imposes a financial burden on patients and hinders access to these medicines (7, 8).

In some developing countries, the financing healthcare systems rely mainly on out-of-pocket payment (OOP), which increases the risk of financial catastrophe in many patients with cancer and their families (9). In China, the high cost of cancer treatment has become a major issue in the area of social security. An empirical study conducted by the National Cancer Centre in 2016 showed that the treatment cost per patient with cancer in China was US$9,739, while the average household income in the same year was US$8,607 (10). Another study in inner Mongolia found that the annual direct medical cost for cancer reached CNY 86,100 after the basic medical insurance reimbursement, which exceeded the "catastrophic health expenditure" defined by the World Health Organisation (WHO) and imposed a heavy economic and mental burden on patients and their families (11). Furthermore, in China, a 1-month supply of Gleevec costs > CNY 23,000, which is not covered by health insurance in most cities in China. A patient with leukaemia named Yong Lu borrowed the idea from the Oscar-winning film *Dallas Buyers Club* and smuggled unapproved, India-made drugs for himself and for >1,000 other patients to obtain medicines at a relatively affordable price. However, any unapproved medications are illegal in China (12). Patients often give up treatment because of financial burden, putting their physical and mental health at risk (13).

In low- and middle-income countries (LMICs), poor availability and high expenditure are among the greatest obstacles to cancer treatment (14). Even in developed countries such as the United States, 29% of cancer survivors reported at least one cancer-related financial problem (15). Statistics have shown that during the median survival period, most cancer patients spend >US$150,000. In fact, only a few patients used innovative anti-cancer medicines. In 2017, 87% of these drugs were used in <1,000 patients nationwide (16). It is important to guarantee the availability and affordability of anti-cancer medicines (17) to measure whether patients can receive medical treatment at an affordable price (18).

The 2011 Political Declaration of the High-Level Meeting of the United Nations General Assembly on the Prevention and Control of Non-Communicable Diseases declared that the global burden and threat of non-communicable diseases including cancer have caused a great social and economic burden. It highlighted the primary role of governments and the responsibilities they need to undertake (19). Thus, to improve the rational use of drugs and promote accessibility and affordability of innovative anti-cancer medicines, the Chinese government implemented a series of policies such as the National Health Insurance Coverage (NHIC) policy for innovative medicines.

For instance, Yang et al. calculated the financial burden of patients with human epidermal growth factor receptor 2-positive breast cancer who used trastuzumab after the implementation of special insurance drug coverage in Jiangsu province. The results showed that the total medical cost had dropped significantly compared to the price before policy implementation. Moreover, the compensation ratio of reimbursement increased from 23.44 to 72.81% after policy implementation (20). Tian et al. evaluated the affordability of three anti-cancer targeted drugs (gefitinib, trastuzumab, and sunitinib) used in urban and

rural residents of Hubei province using the WHO and the Health Action International (HAI) standard survey method. The affordability of the three drugs increased from 64 to 74% after applying a 50% discount and the reimbursement (21). On the other hand, Diao et al. used an interrupted time-series (ITS) design to evaluate the changes in the utilisation of targeted anti-cancer medicines covered by the provincial government health insurance program from 2013 to 2016 in 69 hospitals in Hangzhou, Zhejiang province. The results showed that the inclusion of expensive targeted anti-cancer medicines in government health insurance coverage notably increased the utilisation of these medicines and improved the affordability of patients. However, the financial burden of patients remained high (22).

In April 2017, the Ministry of Human Resources and Social Security of the People's Republic of China initiated the centralised strategic price negotiation with pharmaceutical companies, which gave full play to the advantage of "group purchase" in terms of exchange quantity and price. After the price negotiation, the prices of innovative medicines were reduced and some new medicines were included in the National Insurance Medicine List. Moreover, the pharmaceutical enterprises obtained the market share under the premise of ensuring their business profits (23, 24). A total of 44 new medicines were included in the price negotiation, and a reduction in the price of 36 medicines was successfully negotiated. On average, the price of innovative medicines was reduced by 44%. Among the 36 new medicines, 15 innovative anti-cancer medicines were included in the "National Basic Medical Insurance, Work-Related Injury Insurance and Childbirth Insurance Medicine List (Category B)" (25), which was an important step toward facilitating access to expensive anti-cancer medicines (26).

The NHIC policy has been implemented in Nanjing, Jiangsu province since September 1, 2017. The 15 negotiated innovative anti-cancer medicines were listed in the "Provincial Medical Institution Drugs Centralised Procurement Online and Supervision Platform," along with the medical insurance payment standards. With this, all public medical institutions in Nanjing could purchase the innovative anti-cancer medicines on the centralised platform. Furthermore, to reduce the financial burden of patients with cancer, the local health insurance policy reimbursed 70–90% of the cost of the 15 innovative anti-cancer medicines in Nanjing.

However, there was little evidence for government about the changes in the availability, utilisation, and affordability of these 15 anti-cancer medicines after policy implementation. Thus, in this study, we tried to explore whether the NHIC policy had a positive impact on the price, availability, utilisation, and affordability of anti-cancer medicines in Nanjing City.

Using the WHO/HAI methodology, the study aimed to analyse the impact of the NHIC policy on the availability and affordability of negotiated innovative anti-cancer medicines in 20 tertiary hospitals and six secondary hospitals in Nanjing City, the capital city of Jiangsu province. Furthermore, an ITS analysis was used to analyse the changes in the utilisation of the study medicines.

MATERIALS AND METHODS

Study Design

The study was performed in Nanjing City from January 2016 to December 2018. Nanjing is the capital of Jiangsu province. It has 11 municipal districts and a population of >6.8 million permanent residents. The gross domestic product was CNY 1.17 trillion in 2017 (27). The NHIC policy was implemented on September 1, 2017, in Nanjing, where cancer is ranked as the second leading cause of death (28).

Sample and Data Source

We analysed the monthly sales data of the surveyed anti-cancer medicines from January 2016 to December 2018, which were obtained from the Jiangsu Medicine Information Institute. As primary hospitals are not qualified to prescribe most anti-cancer medicines, they were not included among the study hospitals. Moreover, tertiary and secondary hospitals that did not provide oncotherapy services were also excluded due to the lack of tumour therapy services. Hence, 20 tertiary hospitals and six secondary hospitals, including an oncology department, were included in this study. A total of 15 innovative anti-cancer medicines were evaluated in this survey. The essential features of the 15 drugs are presented in **Table 1**.

Date Analysis

Price

Price was expressed as the median defined daily dose cost (DDDc). A higher DDDc indicated that the medicine was more expensive. We calculated the DDDc by dividing the total amount of medicine into Defined Daily Doses (DDDs) before and after policy implementation.

Availability

Availability of innovative anti-cancer medicines was expressed as the proportion of all survey hospitals that had the study medicines within the time period. Furthermore, we compared the availability of these medicines between tertiary and secondary hospitals before and after policy implementation. The following criteria were used to describe the level of availability (18, 29, 30):

- Absent: 0%, the medicine was not available in any surveyed hospital;
- Very low: <30%, the medicine was available hardly in surveyed hospitals;
- Low: 30–50%, the medicine was available in few surveyed hospitals;
- Fairly high: 50–80%, the medicine was available in many surveyed hospitals;
- High: >80%, the medicine had a good availability and was available in most surveyed hospitals.

Utilisation

Utilisation was expressed as monthly DDDs; the greater the DDDs, the greater frequency of using the medicine. The monthly DDDs were calculated by dividing the monthly sales data in volume into the DDD. As there was no standard DDD for anti-cancer medicines, we accessed the medicine DDD information

TABLE 1 | Baseline information of 15 innovative anti-cancer medicines.

No.	Name	Dosage form	Strength	Indications	Pharmaceutical company
1	Rituximab	Injection	100 mg/10 ml	Lymphoma	Roche
2	Trastuzumab	Injection	440 mg/20 ml	Breast cancer and gastric cancer	Roche
3	Bevacizumab	Injection	100 mg/4 ml	Colorectal cancer and lung cancer	Roche
4	Sorafenib	Tablet	200 mg	Kidney cancer, hepatocellular carcinoma, and thyroid cancer	Bayer
5	Bortezomib	Injection	13.5 mg	Mantle cell lymphoma	Hansoh, Johnson & Johnson
6	Erlotinib	Tablet	150 mg	Lung cancer	Roche
7	Nimotuzumab	Injection	50 mg/10 ml	Nasopharynx cancer	Biotech Pharma
8	Apatinib	Tablet	250, 425 mg	Gastric adenocarcinoma	Jiangsu Hengrui Pharmaceuticals
9	Chidamide	Tablet	5 mg	Peripheral T-cell lymphoma	Chipscreen Biosciences
10	Fulvestrant	Injection	250 mg/5 ml	Breast cancer	AstraZeneca
11	Everolimus	Tablet	5 mg	Kidney cancer	Novartis
12	Lenalidomide	Capsule	10, 25 mg	Multiple myeloma	Celgene
13	Lapatinib	Tablet	250 mg	Breast cancer	GlaxoSmithKline
14	Abiraterone	Tablet	250 mg	Prostate cancer	Johnson & Johnson
15	Recombinant human endostatin	Injection	15 mg/2.4 × 10^5U/3 ml	Lung cancer	Simcere

based on the daily dose and its main indication from the authoritative medicine specification database. ITS regression analysis was used to analyse the changes in the utilisation of anti-cancer medicines within 36 months. When it was difficult or impossible to find a control group, the ITS model considered a quasi-experimental design to analyse the longitudinal effects of the interventions. The ITS model could evaluate whether policy intervention had a transient or long-term impact (31). The NHIC policy was implemented on September 1, 2017. Hence, there were 20 months before intervention and 16 months after intervention. To perform independent tests, utilisation was divided into three parts—(i) the slope of the utilisation before policy implementation, (ii) the change in the level of policy intervention, and (iii) the slope after policy implementation. The following ITS model formula was used:

$$Y_t = \beta_0 + \beta_1 T + \beta_2 D + \beta_3 P + \varepsilon$$

Y_t is the monthly utilisation measured at each T time point. T is the time since the study was initiated (T = 1, 2, 3 ... 36). D is the dummy variable for the two time periods before and after policy implementation ($D = 0$ represents the time period before policy implementation and $D = 1$ represents the time period after policy implementation). P is the time point after policy intervention ($P = 0$ indicates before policy intervention and P = 1, 2, 3, 16 indicates after policy intervention). β_0 is the intercept (which refers to the outcome when the time is 0 at the baseline level), β_1 is the slope of the baseline, β_2 is the level of changes in the intervention, β_3 is the trend change of the outcome caused by the policy intervention, $\beta_1 + \beta_3$ is the slope after the intervention, and ε is the error term (32). The ITS model is presented in **Figure 1**.

The Durbin–Watson test was used to test the first-order autocorrelation of the data (33). It is extremely possible that the observations are independent. The feasible generalised least square method was used to modify the first-order autocorrelation errors if needed (34–36). All analyses were performed using STATA v.14 software (STATA Corporation, College Station, TX, USA), and a $p = 0.05$ was considered significant.

Affordability

Using the WHO/HAI affordability method, the affordability of patients was estimated using the minimum daily income of unskilled government workers by determining the daily income required to purchase the selected courses of treatment for a common acute or chronic condition. Generally, if the outcome was <1, the medicine was affordable for patients. If the outcome was >1, the patients could not afford the medicines. In consideration of the long-term treatment and heavy financial burden of anti-cancer medicines, a study in Hangzhou, Zhejiang province calculated the affordability as the number of average per capita disposable annual income needed to pay for the OOP expenditure of the study medicines based on the standard treatment guideline of a certain regimen used in patients within a particular duration (22). In this study, we assessed the duration of medicine treatment based on the median progression-free survival (mPFS). For trastuzumab, the 1-year mPFS was evaluate based on the treatment guideline (37–48).

OOP expenditure = the total cost of medicine × (1– proportion of reimbursement)

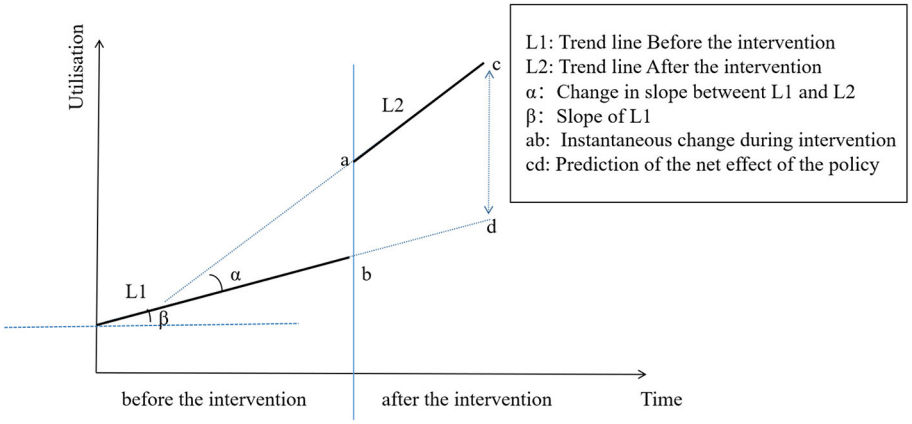


FIGURE 1 | Graphic illustration of the interrupted time-series model and measurement of the policy effect based on trend lines for data points before and after policy implementation.

TABLE 2 | Patient assistance program (PAP) of pharmaceutical companies to increase access to six innovative anti-cancer medicines.

Name	Indication	PAP
Trastuzumab	Breast cancer	8 vials paid by the PAP after 6 vials paid by patient
Bevacizumab	Colorectal cancer	Free after payment of 4 M
Sorafenib	Kidney cancer	Free after payment of 3 M
Bortezomib	Mantle cell lymphoma	Company donates 6 treatment courses after 3 treatment courses paid
Erlotinib	Non-small cell lung cancer	Free after payment of 4 M
Fulvestrant	Breast cancer	Company donates 3 M after 3 M paid

PAP, patient assistance program.
M, Months.

The proportion of reimbursement was based on each drug OOP ratio, defined by the Nanjing Medical Insurance Bureau.

Availability of patients = OOP expenditure of the medicine for mPFS treatment course/per capita annual disposable income

Data on the per capita annual disposable income were obtained from the 2018 and 2019 Nanjing Statistical Yearbook (27, 49).

Before policy implementation, some innovative anti-cancer medicines were included in the patient assistance program (PAP) of pharmaceutical companies. In China, PAP refers to the donation of drugs or funds by pharmaceutical companies to charitable organisations or other third-party, non-profit organisations and is initiated by these organisations to help patients with specific conditions. Patients with low income or a guaranteed minimum income as defined by the local government are included in the PAP. The eligible patients receive a defined free dose of innovative anti-cancer medicines after making an OOP of a defined dose. The six innovative anti-cancer medicines included in the PAP are shown in **Table 2**.

TABLE 3 | Prices of 15 innovative anti-cancer medicines before and after policy implementation (CNY).

No.	Name	Before	After	Rate of change/%
1	Rituximab	4,346.25	2,802.47	−35.52
2	Trastuzumab	999.97	345.45	−65.45
3	Bevacizumab	1,300.00	499.50	−61.58
4	Sorafenib	1,666.67	812.00	−51.28
5	Bortezomib	1,443.43	698.97	−51.58
6	Erlotinib	460.00	195.00	−57.61
7	Nimotuzumab	972.40	486.20	−50.00
8	Apatinib	731.34	462.40	−36.77
9	Chidamide	—	669.90	—
10	Fulvestrant	181.24	79.68	−56.04
11	Everolimus	495.00	296.00	−40.20
12	Lenalidomide	2,104.46	826.49	−60.73
13	Lapatinib	—	245.00	—
14	Abiraterone	—	579.68	—
15	Recombinant human endostatin	544.16	357.00	−34.39

"—" means that this drug could not be available in this time period.

RESULTS

Changes in the Price of Anti-cancer Medicines

Table 3 shows the changes in the DDDc of the study anti-cancer medicines. The rate of change shows the impact of the NHIC policy on the DDDc. As a result of the national price negotiation, the DDDc significantly decreased, varying from 34 to 65%. The price reduction rate was between 34.39 (recombinant human endostatin) and 65.45% (trastuzumab), and mean reduction rate was 50.1%.

TABLE 4 | Availability of 15 innovative anti-cancer medicines before and after policy implementation.

No.	Name	Tertiary hospital/%		Secondary hospital/%	
		Before	After	Before	After
1	Rituximab	85.00	85.00	50.00	33.33
2	Trastuzumab	70.00	50.00	33.33	50.00
3	Bevacizumab	45.00	85.00	33.33	83.33
4	Sorafenib	15.00	50.00	0.00	0.00
5	Bortezomib	40.00	45.00	0.00	33.33
6	Erlotinib	45.00	55.00	0.00	50.00
7	Nimotuzumab	30.00	40.00	0.00	0.00
8	Apatinib	40.00	55.00	0.00	33.33
9	Chidamide	0.00	20.00	0.00	0.00
10	Fulvestrant	10.00	60.00	0.00	16.67
11	Everolimus	20.00	25.00	0.00	0.00
12	Lenalidomide	10.00	35.00	0.00	0.00
13	Lapatinib	0.00	15.00	0.00	0.00
14	Abiraterone	0.00	35.00	0.00	33.33
15	Recombinant human endostatin	80.00	75.00	33.33	50.00

Changes in the Availability of Anti-cancer Medicines

As shown in **Table 4**, some anti-cancer medicines were unavailable before policy implementation. The mean availability of the studied anti-cancer medicines improved after policy implementation of medical insurance coverage (32.67 vs. 48.67% in tertiary hospitals; 10 vs. 25.56% in secondary hospitals). The availability of these medicines in tertiary hospitals was higher than that in secondary hospitals.

Changes in the Level of Utilisation

Chidamide, fulvestrant, lapatinib, lenalidomide, lapatinib, and abiraterone were excluded as these medicines had no purchase records at most time points.

Figure 2 shows the scatter plots of the observed utilisation of the study medicines. The implementation period of the policy intervention was considered September 1, 2017, and the time series was divided into two parts. Based on the results shown in **Table 5**, the utilisation of rituximab increased significantly before policy implementation ($p < 0.001$). When the NHIC policy was implemented, the utilisation rate suddenly increased [range: 33.19 ($p = 0.247$, everolimus) to 2,628.39 ($p < 0.001$, bevacizumab)]. The utilisation rate of bevacizumab, bortezomib, and apatinib significantly increased ($p < 0.05$), while that of trastuzumab, erlotinib, and everolimus decreased, with no significant difference ($p = 0.817$, $p = 0.973$, and $p = 0.152$, respectively). An upward trend was observed in the utilisation rate of nimotuzumab and recombinant human endostatin.

Changes in Affordability of Patients

To compare the affordability of the studied anti-cancer medicines before and after medical reimbursement, we excluded chidamide, lapatinib, and abiraterone because they had zero purchase data before policy implementation. Among the remaining 12 drugs, one indication for each drug was selected to calculate the affordability. **Table 6** shows the affordability during the mPFS treatment course of urban and rural patients before and after policy implementation. Before policy implementation, the affordability rates of patients were 0.64–16.02 times higher than per capita annual disposable income for urban patients and 1.50–37.76 times higher than per capita annual disposable income for rural patients. With the PAP, only fulvestrant could be affordable. After policy implementation, the affordability was obviously improved (0.06–1.90 times higher than that of per capita annual disposable income for urban patients and 0.13–4.46 times higher than that of per capita annual disposable income for rural patients). Therefore, most of the studied anti-cancer medicines could be affordable for patients.

DISCUSSION

Decrease in the Price of Innovative Anti-cancer Medicines

The high cost of medical treatment has been a long-term problem in China. Expensive anti-cancer medicines prevent patients, especially low-income individuals, from seeking medical treatment. Thus, reducing the price of medicines is needed.

The NHIC policy stipulates that the governments should use their bargaining power to effectively reduce the high price of innovative anti-cancer medicines. The price of trastuzumab has decreased by 65.45% (from a daily cost of CNY 999.97 to CNY 345.45) after a series of price negotiations. The policy has significantly reduced the economic burden on patients. However, the discovery and research of innovative medicines are complex and lengthy processes. Pharmaceutical companies invest a lot of talent and financial resources in drug research and development; therefore, it is important to protect innovative profits. The centralised strategic price negotiation underpinned

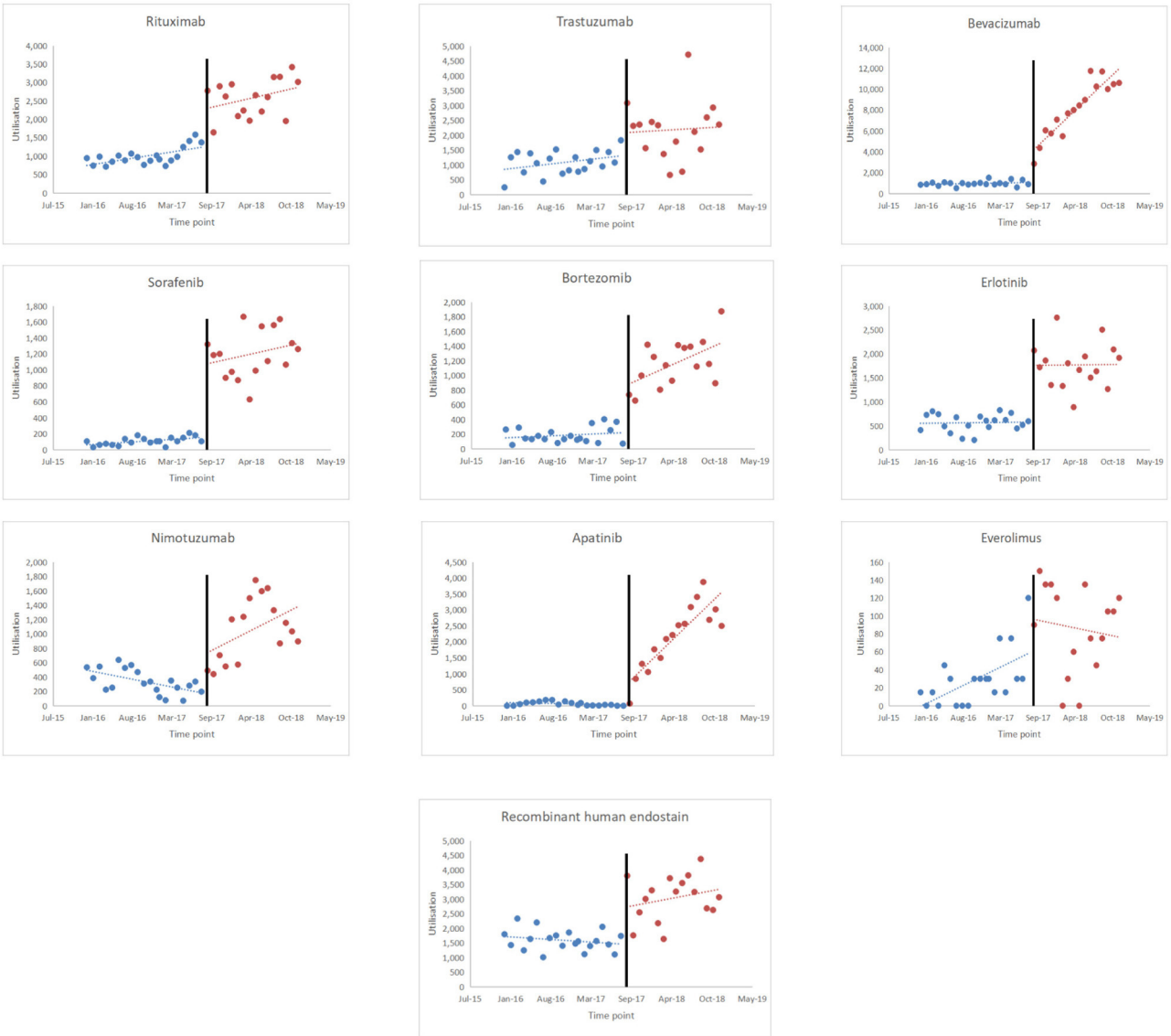


FIGURE 2 | Results of the regression analysis of the utilisation of study drugs before and after policy implementation shown in a scatter plot.

TABLE 5 | Changes in the trend and level of utilisation estimated by ITS regression analysis.

No.	Name	β_0(p)	β_1(p)	β_2(p)	β_3(p)	D-W
1	Rituximab	529.49 (0.000)	19.94 (0.032)	737.89 (0.000)	8.35 (0.587)	1.95
2	Trastuzumab	838.27 (0.010)	23.36 (0.371)	760.11 (0.104)	−10.29 (0.817)	2.00
3	Bevacizumab	854.03 (0.024)	11.06 (0.715)	2,628.39 (0.000)	503.69 (0.000)	1.93
4	Sorafenib	49.81 (0.492)	5.68 (0.351)	879.97 (0.000)	12.94 (0.215)	2.10
5	Bortezomib	139.72 (0.089)	4.15 (0.538)	632.05 (0.000)	31.57 (0.009)	1.93
6	Erlotinib	548.36 (0.000)	2.05 (0.829)	1,162.27 (0.000)	−0.55 (0.973)	1.95
7	Nimotuzumab	486.04 (0.026)	−12.32 (0.466)	425.78 (0.091)	52.56 (0.094)	2.14
8	Apatinib	23.0 (0.928)	7.19 (0.728)	334.31 (0.289)	175.76 (0.000)	1.97
9	Everolimus	−4.04 (0.838)	3.23 (0.057)	33.19 (0.247)	−4.16 (0.152)	2.00
10	Recombinant human endostatin	1,718.39 (0.000)	−12.11 (0.550)	1,191.47 (0.002)	54.76 (0.121)	2.04

TABLE 6 | The change of patient affordability for mPFS treatment course before and after the NHIC policy.

Name	Indication	Treatment course base on mPFS	Before				After	
			OOP (patient without PAP, CNY)	Affordability	OOP (patient with PAP, CNY)	Affordability	OOP (CNY)	Affordability
Rituximab	Lymphoma	6.7 M	873,596	U:16.02,R:37.76	—	—	112,659	U:1.90, R:4.46
Trastuzumab	Breast cancer	1 Y	364,989	U:6.69, R:15.78	156,424	U:2.87,R:6.76	25,218	U:0.43, R:1.00
Bevacizumab	Colorectal cancer	6.1M	237,900	U:4.36, R:10.28	156,000	U:2.86,R:6.74	18,282	U:0.31, R:0.72
Sorafenib	Kidney cancer	5.7 M	285,001	U:5.23, R:12.32	150,000	U:2.75,R:6.48	27,770	U:0.47, R:1.10
Bortezomib	Mantle cell lymphoma	14.9 M	645,213	U:11.83,R:27.89	215,071	U:3.94,R:9.30	62,488	U:1.58, R:3.71
Erlotinib	Non-small cell lung cancer	7.5 M	103,500	U:1.90, R:4.47	55,200	U:1.01,R:2.39	8,775	U:0.15, R:0.35
Nimotuzumab	Nasopharynx cancer	7 M	204,204	U:3.74, R:8.83	—	—	20,420	U:0.52, R:1,21
Apatinib	Gastric adenocarcinoma	2.6 M	57,045	U:1.05, R:2.47	—	—	7,213	U:0.06, R:0.14
Fulvestrant	Breast cancer	4.6 M	34,798	U:0.64, R:1.50	16,312	U:0.30,R:0.71	2,199	U:0.06, R:0.13
Everolimus	Kidney cancer	4.9 M	72,765	U:1.33, R:3.15	—	—	8,702	U:0.22, R:0.52
Lenalidomide	Multiple myeloma	10M	631,338	U:11.58,R:27.29	—	—	49,589	U:1.25, R:2.94
Recombinant human endostatin	Non-small cell lung cancer	6 M	97,949	U:1.80, R:4.23	—	—	12,852	U:0.33, R:0.76

Before the NHIC policy intervention, the per capita annual disposable income was CNY 54,538 in urban area and CNY 21,333 in rural area; after the NHIC policy intervention, the per capita annual disposable income was CNY 59,308 in urban area and CNY 25,263 in rural area.
U, Urban; R, Rural.
M, Months; Y, Year.

by evidence from Health Technology Assessment (HTA) panels were drawn from a pool of pharmacoeconomists and health insurance auditors to guarantee corporate innovation profits. Pharmaceutical companies that take part in price negotiations could then obtain benefits, such as bulk sales, after their drugs were included in the medical insurance catalogue list. The government vigorously supported the development and production of innovative medicines under the guidance of the Health China Strategy and the policy established by an innovative country. Thus, enterprises should break through technical problems and continue to promote the research and development of innovative drugs under the guidance of the spirit of innovation. The NHIC policy benefits people, and pharmaceutical companies have received widespread attention from society because of this. Entering the medical insurance catalogue is a positive incentive for pharmaceutical manufacturers to speed up research and development. The price drop of innovative anti-cancer medicines is also conducive to relieving pressure on medical insurance funds.

The government has implemented a "zero-tariff" policy to ensure accessibility and promote the price reduction of imported innovative anti-cancer medicines. However, the number of anti-cancer medicines in China is relatively lower than that in other countries, with most anti-cancer medicines in the country being generic drugs, because of patent protection and technology monopolies. Hence, the government should increase the subsidy for domestic pharmaceutical companies, cultivate pharmaceutical talents, and speed up the approval process of innovative drugs to embrace the innovative enthusiasm of enterprise in China.

Positive Effects of the NHIC Policy on the Availability of the Studied Drugs

The availability of innovative anti-cancer medicines is an important index to evaluate whether patients could access medical treatment. This study found that patients had more chances to access the studied anti-cancer medicines in tertiary hospitals than in secondary hospitals throughout the study period. This could be due to the fact that patients in China are more inclined to seek medical treatment in tertiary hospitals when they have serious illnesses, such as cancer. However, an increase in the number of patients with cancer will greatly increase the resource demand. The mean availability of the studied anti-cancer medicines was 27.44%, implying that these drugs were hardly available in the surveyed hospitals before the NHIC policy was implemented, and this low availability may be caused by various factors. One factor is the medication expenditures related to the availability of these drugs in hospitals

in LMICs (50). The 15 negotiated innovative anti-cancer medicines were all originator brands, and the prices of these drugs were higher than those of other common medicines even after the price negotiation. The high cost might be related to the low availability of these medicines in hospitals. According to the study of Zhu et al. in Jiangsu province, health service providers make higher profits from more costly pharmaceuticals because of the markup ratio prescribed by the government. The "zero-tariff" policy achieved full promotion in the public hospitals in Jiangsu province by the end of 2015. However, for hospitals, capital occupation costs, management costs, and damage costs are expensive, which are likely to reduce the revenue of hospitals without the mark-up ratio for high-value drugs. Therefore, due to financial constraints, secondary hospitals were unable to supply the innovative anti-cancer medicines (18). Furthermore, a study conducted in Pakistan showed that government hospitals experienced medicine shortage or medicine unavailability more frequently compared to private hospitals (17). In addition, some of the negotiated drugs lack real-world data, and similar alternative medicines are being sold in hospitals; thus, the purchase enthusiasm was not high.

After policy implementation, the mean availability increased to 43.33%, which means that the 15 innovative anti-cancer medicines became available in a few of the surveyed hospitals. Thus, the NHIC policy had a positive impact on the availability of medications in the hospital. However, drug availability is still low, which might be associated with the control of medical insurance cost. The control of medical insurance cost is an effective way to control the growth of medical expenses by allocating the medical insurance budget to all medical institutions and covering all medical services. Once the medical insurance costs of the hospital exceed the budget, however, the hospital needs to pay the excess cost. As the price of innovative anti-cancer medicines remained high, the hospitals were not motivated to pay the bill.

Hospitals should insist on the rational use of innovative anti-cancer medicines to avoid unnecessary medical expenses. Moreover, the government should release a supporting policy to separate the cost of innovative anti-cancer medicines and innovate the health insurance payment of negotiated drugs to facilitate the availability of innovative anti-cancer medicines in hospitals.

Factors Associated With Changes in Utilisation

The epidemic characteristics of cancer affect the utilisation of drugs. Lung cancer and breast cancer have a high incidence in China; the baseline levels of anti-cancer treatment drugs such as trastuzumab, bevacizumab, and recombinant human endostatin were high. The monthly utilisation of 10 of the study medicines suddenly increased in September 2017. One possible explanation is that new patients and their doctors waited for the implementation of the policy to use much cheaper drugs. The utilisation of innovative anti-cancer medicines increased at different levels after the policy was implemented. The most important reason was the price reduction, which may have affected the purchasing behaviour of patients. Many factors were associated with the changes in utilisation. For example, the remarkable increase in the utilisation of bevacizumab and bortezomib may be related to the cancellation of the PAP, which possibly led patients to buy more drugs at their own expense. The utilisation of apatinib for gastric adenocarcinoma significantly also increased, mainly because gastric adenocarcinoma had a high incidence in China. Furthermore, there was no obvious upward trend in the utilisation of other innovative anti-cancer medicines, which may be associated with the limitation of indications by the insurance program. For example, only eight treatment courses of rituximab, which is used to treat relapsed or drug-resistant follicular central lymphoma and non-Hodgkin's lymphoma, are covered by medical insurance. In Nanjing, patients with cancer can purchase innovative anti-cancer medicines with a prescription from a physician at the specialty pharmacy.

This study analysed the utilisation of innovative anti-cancer medicines in hospitals but not in retail pharmacies. Therefore, this study cannot completely reflect the utilisation of innovative anti-cancer medicines in Nanjing. In addition, the off-label drug use of innovative anti-cancer medicines has been previously reported. Standardised rational medication in hospitals has improved with the development of guidelines for the clinical diagnosis and treatment of cancers. This improvement may affect the utilisation of innovative anti-cancer medicines.

Including innovative anti-cancer medicines in the medical insurance implies an increase in insurance expenditures in the future and calls for a more careful monitoring of drug use. The government should improve the dynamic adjustment mechanism of the medical insurance catalogue to guarantee the accessibility of patients to innovative drugs and reduce the burden of medical insurance funds.

Improvement in the Affordability of Innovative Anti-cancer Medicines

Before the implementation of the NHIC policy, the OOP expenditures on the 12 innovative anti-cancer medicines for the mPFS treatment course were much higher than the per capita annual disposable income per capita. Even when the PAP relieved the economic burden of six innovative anti-cancer medicines to some degree, the high cost of innovative anti-cancer medicines may impoverish more households and lead to more premature cancer deaths (51). Therefore, the drug price reduction is closely related to winning the battle against poverty. Drug price reduction and reimbursement effectively alleviated most of the financial burden on patients. With these, patients can purchase innovative anti-cancer medicines, which can effectively improve the quality and length of life.

However, although the NHIC policy improved drug affordability, the supporting policies that help reduce the financial burden of innovative anti-cancer medicines were inadequate. For example, the PAP was cancelled after the NHIC policy was implemented. However, the affordability problem was even more serious for rural patients than for urban patients, especially low-income patients, during the study period. Hence, the government should increase tax incentives for medicines and

encourage companies to implement more assistance projects to promote the PAP and improve the medical security system of China. Moreover, patients need to undergo a number of medical examinations and standard tests for cancer before being diagnosed. They also need to use adjuvant chemotherapy drugs for treatment. However, the costs of medical examinations and adjuvant chemotherapy are a tremendous financial burden.

Policies should focus on addressing the inequity in the affordability of innovative anti-cancer medicines between urban and rural areas. The government should also consider including medical examinations and adjuvant chemotherapy in the medical insurance coverage and reducing the ratio of individual payments. Setting the reimbursement ratio based on the actual conditions of patients is a better measure; the reimbursement ratio of rural patients should be higher than that of urban patients. Moreover, the government should speed up the progress of medical insurance negotiations to include more innovative anti-cancer medicines in medical insurance to reduce the financial burden of more patients with cancer. With the increase in the incidence of cancer, the government should increase investment in health. Early screening, detection, diagnosis, and treatment are of great importance to protect the health of the people.

Our study has several strengths. This study is one of the few quantitative studies that provide evidence on the accessibility of the 15 negotiated innovative anti-cancer medicines. The study findings will serve as a basis for policymakers in the government to optimise and improve supporting policies. This study selected 36 months of data before and after the policy was implemented to comprehensively evaluate the long-term effects of the NHIC policy. The ITS model was used to better reflect the impact of policy interventions and the later stages of intervention. Nevertheless, this study has some limitations. First, we underestimated the availability and utilisation of anti-cancer medicines because private hospitals and pharmacies were not included in this study. Second, this study lacked a control group to explore other factors besides policy implementation that resulted in changes in drug utilisation. Third, this study was only conducted in Nanjing, Jiangsu province. More municipalities and provinces should be included to increase the representativeness of the findings. Medication equity is one of the purposes of the NHIC policy. Changes in medication equity after policy implementation may need to be analysed in future studies.

CONCLUSION

This study revealed that the NHIC policy effectively reduced the price and improved the availability and utilisation of 15 negotiated innovative anti-cancer medicines. The NHIC policy reduced the economic burden of patients with cancer. However, the availability of these innovative anti-cancer medicines remains low. The utilisation rate of innovative anti-cancer medicines is affected by many factors, which include the incidence of cancer, limitation of indications within the insurance program, and the rational use of innovative anti-cancer medicines. Improving supporting policies is necessary to promote the use of innovative anti-cancer medicines, and reducing the financial burden of patients is closely related to winning the battle against poverty. The government should introduce more policies to reduce the financial burden of patients and improve the health level of people. In addition, more innovative anti-cancer medicines should be included in the national price negotiation. The government should consider including medical examinations and adjuvant chemotherapy in the medical insurance and increase investment in health.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

WF, XX, and XL initiated the study concept. WF conducted data analysis and wrote the first draft of the manuscript. XX and YZ collected the drugs clinical trials data. HD led the data collection. XL and LS contributed to the data analysis and interpretation of the data and revised the draft of the manuscript. All authors read and approved the final manuscript.

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Efficacy of High-Intensity Focused Ultrasound Combined With GnRH-a for Adenomyosis: A Systematic Review and Meta-Analysis

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Objective: High-intensity focused ultrasound (HIFU) is an innovative non-invasive technology used for adenomyosis. Gonadotropin-releasing hormone agonist (GnRH-a) is a hormone commonly used for adenomyosis. We investigated and assessed the efficacy of HIFU combined with GnRH-a for adenomyosis.

Methods: For this systematic review and meta-analysis, we searched Pubmed, Cochrane Library, Web of Science, Embase, CNKI, WanFang, and VIP databases for relevant articles published in Chinese or English that compared HIFU combined with GnRH-a vs. HIFU alone in patients with adenomyosis. The last literature search was completed on January 31, 2021. Two reviewers independently assessed study eligibility and assessed risk of bias. Another two reviewers extracted the data. The RevMan5.3 software was used for the data analysis. Changes in volume of the uterine and adenomyotic lesion were defined as the primary outcomes. The secondary outcomes were visual analog scale (VAS) scores for dysmenorrhea, menstrual volume scores, serum CA125 levels, and recurrence rate. This study is registered with PROSPERO (CRD42021234301).

Results: Three hundred and ninety potentially relevant articles were screened. Nine studies with data for 766 patients were finally included. Compared with the HIFU alone group, the HIFU combined with GnRH-a group had a higher rate of uterine volume reduction (MD 7.51, 95% CI 5.84–9.17, $p < 0.00001$), smaller adenomyotic lesion volume (MD 4.11, 95% CI 2.93–5.30, $p < 0.00001$), lower VAS score for dysmenorrhea (MD 1.27, 95% CI 0.54–2.01, $p = 0.0007$) and menstrual volume score (MD 0.88, 95% CI 0.73–1.04, $p < 0.00001$), and lower CA125 level (SMD 0.31, 95% CI 0.05–0.56, $p = 0.02$) after the procedure. The recurrence rate in the HIFU combined with GnRH-a group was lower than that in the HIFU alone group (RR 0.28, 95% CI 0.10–0.82, $p = 0.02$).

Conclusions: Compared with HIFU treatment alone, HIFU combined with GnRH-a for the treatment of adenomyosis has greater efficacy in decreasing the volumes of the uterine and adenomyotic lesions and alleviating symptoms. However, since the number

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of the included studies was too small and most of them were written in Chinese, this conclusion needs to be referenced with caution. And the long-term evidence of its efficacy is still insufficient.

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Keywords: high-intensity focused ultrasound, gonadotropin-releasing hormone agonist, GnRH-a, adenomyosis, meta-analysis

INTRODUCTION

Adenomyosis is a gynecological disease characterized by ectopic endometrial tissue in the myometrium (1). It often occurs in women aged 30−40 years. The current prevalence of adenomyosis ranges from 20 to 35% (2, 3). The main clinical symptoms of the patients include abnormal uterine bleeding, dysmenorrhea, and infertility. Sex steroid hormone aberrations, inflammation, changes in cell proliferation, and neuroangiogenesis may be the key pathogenic mechanisms (4).

The treatment of adenomyosis includes medication and minimally invasive/surgical treatment (5). Medications include gonadotropin-releasing hormone (GnRH) analogs, progesterone, combined oral contraceptives, and non-steroidal anti-inflammatory drugs. Traditional minimally invasive/surgical treatments include hysterectomy and uterine artery embolization (UAE). However, hysterectomy is not a good choice for women who want to remain fertile. Although UAE treatment can improve patient symptoms, its effects on ovarian function and pregnancy are still uncertain (2).

High-intensity focused ultrasound (HIFU), as an emerging non-invasive technique for the treatment of benign tumors, has been used for adenomyosis since 2008 (6). Under ultrasonography or magnetic resonance (MRI) inspection, HIFU can cause high-intensity ultrasound energy to act on abnormal target tissues and eliminate the lesion through thermal and cavitation effects, and allows for the preservation of normal tissue around the lesion (7). In recent years, HIFU therapy has become a good alternative surgery for patients who want to preserve their uterus (8). However, adenomyosis is an estrogen-dependent disease, and HIFU treatment will not change the hormone status in the body. The risk of recurrence still exists. Gonadotropin-releasing hormone agonist (GnRH-a) is a hormone commonly used for adenomyosis. It can decrease the estrogen level to the menopausal level and promote the atrophy of adenomyotic lesions (9).

We did a systematic review and meta-analysis to investigate and evaluate the efficacy of HIFU combined with GnRH-a for adenomyosis and provide evidence-based medical evidence for the clinical application.

METHODS

Search Strategy

This meta-analysis is conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and was registered in PROSPERO (CRD42021234301). Two reviewers (LLP and JM) searched relevant studies published in Chinese or English using PubMed, Cochrane Library, Web of Science, Embase, CNKI (China National Knowledge Infrastructure), WanFang, and VIP (China Science and Technology Journal Database) databases from their inception dates to January 31, 2021. The following terms were used to search for all possible publications: "Adenomyosis," "High-intensity focused ultrasound," and "Gonadotropin-releasing hormone agonist." The English search formula is ((Adenomyos*) AND (("Gonadotropin-Releasing Hormone"[Mesh]) OR (GnRH agonist))) OR ((Adenomyos*) AND (("High-intensity focused ultrasound ablation" [Mesh]) OR (HIFU))).

Selection Criteria

The studies included in this meta-analysis met the following criteria: Vannuccini and Petraglia. (1) studies comparing HIFU combined with GnRH-a vs. HIFU alone in patients with adenomyosis. The HIFU combined with GnRH-a group was defined as experimental group, HIFU alone group was defined as control group. Struble et al. (2) Studies object: (1) women aged 18–50 years; (2) women with focal or diffuse adenomyosis diagnosed using ultrasonography, MRI, or computed tomography (CT); (3) patients who had not received any treatment for adenomyosis within 3 months before the study. Abbott (3) Outcome indicator: main outcome indicators are changes in volume of the uterine and adenomyotic lesions were defined as the primary outcome. Secondary outcomes were visual analog scale (VAS) scores for dysmenorrhea, menstrual volume scores, serum CA125 levels, and recurrence rate.

The exclusion criteria are as follows: (1) Reviews, animal experiments, case reports, conference abstracts, conference proceedings, editorial letters, guidance or comments; (2) repeated studies; (3) studies where full text is not available; (4) patients with uterine fibroids or other gynecological diseases, whose clinical symptoms are similar with those of adenomyosis, were also excluded; (5) studies reporting clinical outcomes at a follow-up shorter than 3 months were excluded because it takes some time for the lesions to absorb themselves after HIFU ablation.

Quality Assessment

Two investigators (LL P and J M) independently screened titles and abstracts for eligibility as well as the full text of each eligible study, to confirm the inclusion criteria. The quality evaluation criteria of individual studies was assessed using the

risk bias assessment tool in the Cochrane Evaluation Manual (10). This assessment tool include selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias.

Data Extraction

Two authors (RN L and TT Z) were responsible for data extraction, and another two authors (LL P and J M) verified the accuracy of data. Disagreements were solved by consensus. If it cannot be resolved, it was resolved through consultation with experts (Y W). The following data were obtained from the studies: first author, publication year, study design, sample size, average age, imaging tools for the diagnosis of adenomyosis, last follow-up time, total energy and average power during HIFU treatment. The primary efficacy endpoints were changes in volume of uterine and adenomyotic lesions. The secondary outcome indicators were VAS score for dysmenorrhea, menstrual volume scores, serum CA125 levels, and recurrence. Pregnancy outcomes, when available, were also extracted.

Statistical Analysis

The RevMan5.3 software was used for the data analysis by LX F. Binary variables are expressed as risk ratios (RR), and continuous variables are expressed as mean difference (MD). When the count units are inconsistent, the combined effect size is expressed as a standard mean difference (SMD). The 95% confidence interval (CI) is also expressed. We used the Chi-squared tests and Higgins' I^2 statistics to estimate heterogeneity among studies, with $I^2 < 30\%$ indicating low heterogeneity, more than 30% indicating high heterogeneity. The random-effects model was used for high heterogeneity, whereas the fixed-effect model was used for low heterogeneity. $P < 0.05$ were considered significant. If there is a high heterogeneity in studies, a sensitivity analysis will be performed by sequentially removing each single study. Descriptive analyses were used if the data cannot be combined.

RESULTS

Selected Study Characteristics

Of the 390 articles collected, 237 articles with duplicate or irrelevant data were excluded. After browsing the title and abstract, 84 were excluded for different reasons (46 articles were lack of important data, 16 full-texts were not available, nine articles were case reports, two articles were published in Italian, and 19 articles were excluded with other reasons). Sixty-nine full-text were assessed eligible, however, 60 were excluded for different reasons (11 articles' follow-up time were shorter than 3 months, 13 articles did not report recurrence, 17 articles were lack of other outcome indicators, and 19 articles had no control group). Nine studies with data for 766 patients were finally included in the present meta-analysis (11–19). The literature screening process is shown in **Figure 1**.

The experimental group included 346 cases, and the control group included 420 cases. Three were randomized controlled trials (12, 17, 19) and six were clinical controlled trials (11, 13–16, 18). Last follow-up time was 3 months in one study, 6 months in two studies, 12 months in six studies. Three studies mentioned the method of random sequence generation (12, 17, 19). Of the nine studies, one used MRI for the imaging diagnosis of adenomyosis, six used transvaginal ultrasonography or MRI, and three did not report specific imaging diagnostic methods. Although these studies provided information on the imaging diagnostic methods used, they did not provide the specific imaging criteria for the diagnosis of adenomyosis. The baseline characteristics of the included articles is shown in **Table 1**.

Quality Assessment

The quality assessment of the studies is shown in **Figure 2**. Among the nine included studies, only three (13, 18, 20) reported the method of generating the random allocation sequence, which was the random number table method. All the studies did not mention the random allocation hiding and blinding methods. The specific risk bias analysis is shown in **Figure 3**.

Outcome Measures

Changes in Uterine Volume

In the three studies included (14, 18, 19), the uterine volume reduction rate after HIFU was evaluated in 232 patients. The meta-analysis results showed that the uterine volume reduction rate in the HIFU with GnRH-a group was higher than that in the HIFU alone group at 12 months after the procedure (MD 7.51, 95% CI 5.84–9.17, $p < 0.00001$, $I^2 = 0\%$; **Figure 4**).

Changes in Adenomyotic Lesion Volume

Three studies (11, 12, 17) (239 cases) reported changes in lesion size before and after treatment. The meta-analysis results showed that the lesion volume in the experimental group was smaller than that in the control group (MD 4.11, 95% CI 2.93–5.30, $p < 0.00001$, $I^2 = 0\%$; **Figure 5**) at 3 and 6 months after the procedure. According to the follow-up time, we divided the articles into two subgroups with a follow-up of 3 months (MD 3.85, 95% CI 2.09–5.61, $p < 0.00001$, $I^2 = 0\%$) and a follow-up of 6 months (MD 4.33, 95% CI 2.73–5.93, $p < 0.00001$, $I^2 = 0\%$), and conducted a subgroup analysis. The results showed that there was no significant difference in the two groups ($p > 0.05$).

VAS Scores for Dysmenorrhea

A total of five studies (11, 13, 14, 17, 18) (367 cases) used the VAS to assess the dysmenorrhea of patients. The meta-analysis results showed that the VAS scores for dysmenorrhea in the HIFU with GnRH-a group was lower than that in the HIFU alone group after the procedure (MD 1.27, 95% CI 0.54–2.01, $p = 0.0007$, $I^2 = 83\%$; **Figure 6**). However, the heterogeneity analysis shows an high heterogeneity. Therefore, we performed a sensitivity analysis by sequentially removing each single study. When the TAN 2019 study was removed, the heterogeneity is reduced (MD 1.59, 95% CI 0.98–2.20, $p < 0.00001$, $I^2 = 65\%$; **Figure 7**).

Menstrual Volume Scores

Three studies (14, 16, 19) (243 cases) used the menstrual volume scores to assess menstrual bleeding. The meta-analysis results showed that the menstrual volume score of the HIFU with the GnRH-a group was lower than that of the HIFU alone group after the procedure (MD 0.88, 95% CI 0.73–1.04, $p < 0.00001$, $I^2 = 30\%$; **Figure 8**).

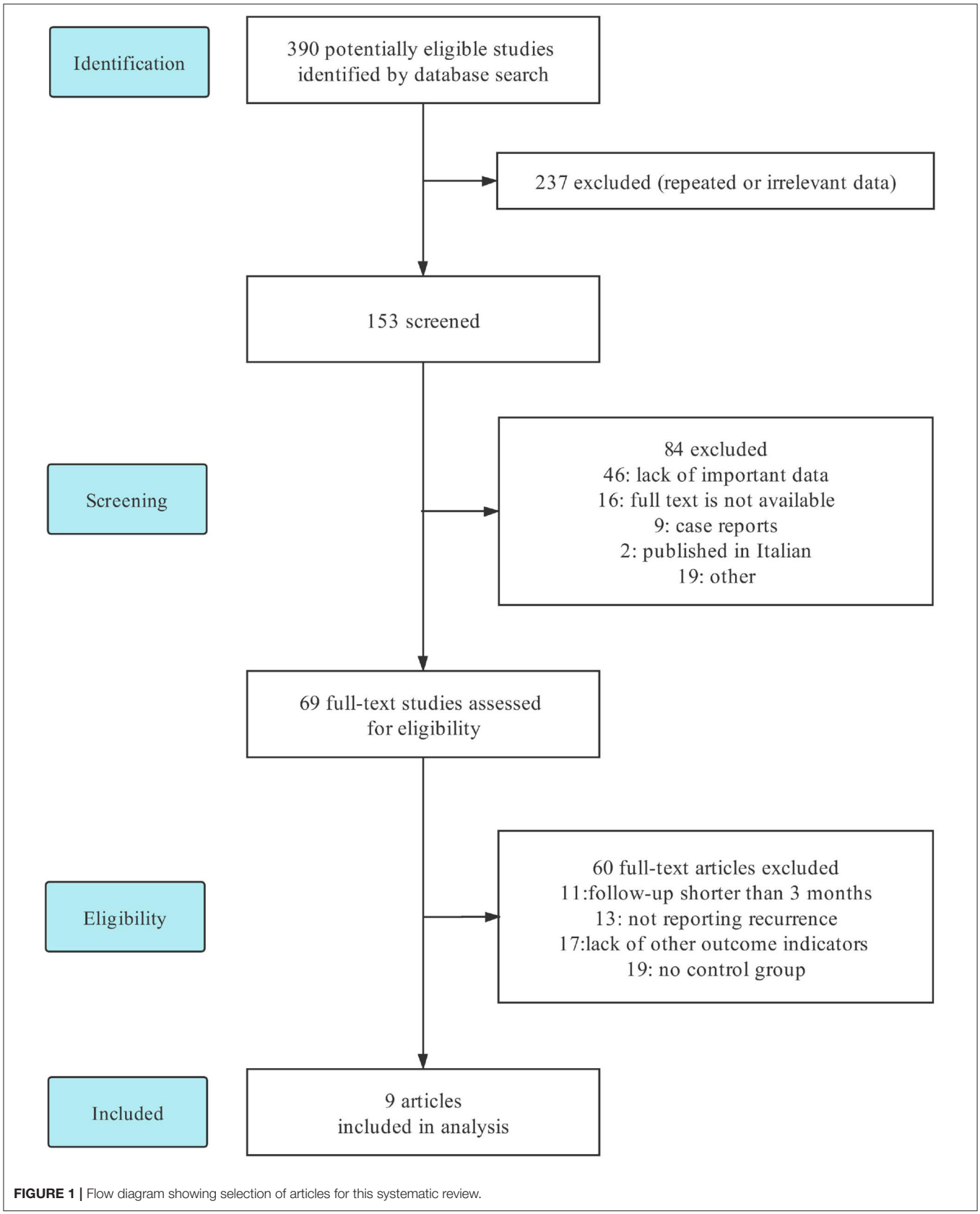


FIGURE 1 | Flow diagram showing selection of articles for this systematic review.

TABLE 1 | Characteristics of included studies.

References	Study design	Random sequence generation	Study group	Control group	Sample size (n)	Age (yeas)	Last follow-up time (months)	Diagnostic imaging	Total energy (J)	Average power (W)
Guo et al. (11)	Prospective	NA	HIFU+GnRH-a	HIFU	24/55	41.00 ± 4.74/ 39.6 ± 5.3	6	MRI	NA	350∼400
Yang and Xie (12)	Retrospective	random number table	HIFU+GnRH-a	HIFU	38/38	41.63 ± 6.36/ 41.73 ± 6.24	12	NA	NA	NA
Xiao-Ying et al. (13)	Retrospective	NA	HIFU+GnRH-a	HIFU	23/38	41 ± 3.53/ 41.24 ± 7.07	12	TVUS/MRI	398.26 ± 0/399.08 ± 0.71	392.73 ± 63.64/412.22 ± 315.23
Guo et al. (14)	Retrospective	NA	HIFU+GnRH-a	HIFU	18/45	41.44 ± 4.74/42.42 ± 5.09	12	TVUS/MRI	327793.89 ± 26690.71/303510.29 ± 18634.14	308.11 ± 12.41/272.07 ± 7.34
Li et al. (15)	Retrospective	NA	HIFU+GnRH-a	HIFU	70/64	26-53	12	NA	36900∼596200	293∼400
Jiang et al. (16)	Prospective	NA	HIFU+GnRH-a	HIFU	45/46	40.96 ± 4.42/39.98 ± 4.22	3	TVUS/MRI	298905.24 ± 24784.77/301886.68 ± 25323.4	294.32 ± 19.07/286.54 ± 13.66
Tan and Li (17)	Retrospective	random number table	HIFU+GnRH-a	HIFU	42/42	38.03 ± 7.21/37.85 ± 7.14	6	TVUS/MRI	NA	NA
Xu et al. (18)	Retrospective	NA	HIFU+GnRH-a	HIFU	41/48	41.9 ± 4.3/43.6 ± 5.1	12	TVUS/MRI	NA	50∼400
Yang et al. (19)	Retrospective	random number table	HIFU+GnRH-a	HIFU	40/40	40.23 ± 5.42/40.11 ± 5.52	12	NA	NA	NA

HIFU, High-Intensity Focused Ultrasound; GnRH-a, Gonadotropin-Releasing Hormone; TVUS, Transvaginal Ultrasound; MRI, Magnetic Resonance Imaging; NA, Not applicable.

Serum CA125 Levels

Three studies (11, 17, 18) (252 cases) evaluated the serum CA125 levels of the patients. The meta-analysis results showed that the serum CA125 level of the HIFU with GnRH-a group was lower than that of the HIFU alone group after the procedure (SMD 0.31, 95% CI 0.05–0.56, $p = 0.02$, $I^2 = 0\%$; **Figure 9**).

Recurrence Rate

Three studies (15, 16, 19) (314 cases) compared the recurrence rates of the experimental and control groups. The meta-analysis results showed that the recurrence rate in the HIFU with GnRH-a group was lower than that in the HIFU alone group (RR 0.28, 95% CI 0.10–0.82, $p = 0.02$, $I^2 = 0\%$; **Figure 10**).

Pregnancy Outcomes

One study reported pregnancy outcomes of the patients at 6 months after treatment. There were five pregnancies reported after intervention in HIFU combined with GnRH-a ($n = 45$), of which three resulted in natural childbirth and two ended in an abortion. In HIFU alone group ($n = 46$), there were four pregnancies reported after HIFU ablation, of which one resulted in natural childbirth, one resulted in miscarriage and two ended in abortion.

DISCUSSION

The present study is the first systematic review and meta-analysis investigating HIFU combined with GnRH-a for adenomyosis. The results of this meta-analysis of data from 766 patients showed that, compared with HIFU alone, HIFU combined with GnRH-a for the treatment of adenomyosis has greater efficacy in decreasing the volumes of the uterine and adenomyotic lesions and alleviating symptoms.

Adenomyosis is a common and difficult gynecological disease that seriously affects women's health and quality of life. Effective symptom relief, prevention of recurrence, and increasing the pregnancy rate are issues that should be solved. Compared to traditional treatment, HIFU is an non-invasive and innovative technology for adenomyosis (21). However, there is still at risk of recurrence. Therefore, HIFU combined with other therapies for adenomyosis has become the hotspot and trend in research in recent years. HIFU combined with GnRH-a is one of these methods, but no systematic review has been conducted.

The therapeutic mechanism of HIFU is to focus the ultrasound beams emitted outside the body on the targeted lesion. The thermal and cavitation effects converted by mechanical effect of ultrasound cause the temperature of the target tissue at the focal point raise above 60–100°C, in order to cause non-coagulable necrosis of the lesion. At the same time, the surrounding structures are not be damaged (22). Previous studies found that uterine smooth muscle tissue in adenomyotic lesions is sensitive to HIFU treatment (20). HIFU is an effective and ideal treatment for adenomyosis. A retrospective study by Lee et al. enrolled 889 patients with adenomyosis who underwent ultrasound-guided HIFU (USgHIFU). The results revealed that the reduction rates of uterine volume were 44.5, 50.7, and 60.1% at 3, 6, and 12 months after procedure, respectively (23). This is consistent with the results of a recent systematic and meta-analysis which showed a great effect in reducing the uterine volume after HIFU treatment for adenomyosis at 12 months (SMD: 0.85) (24).

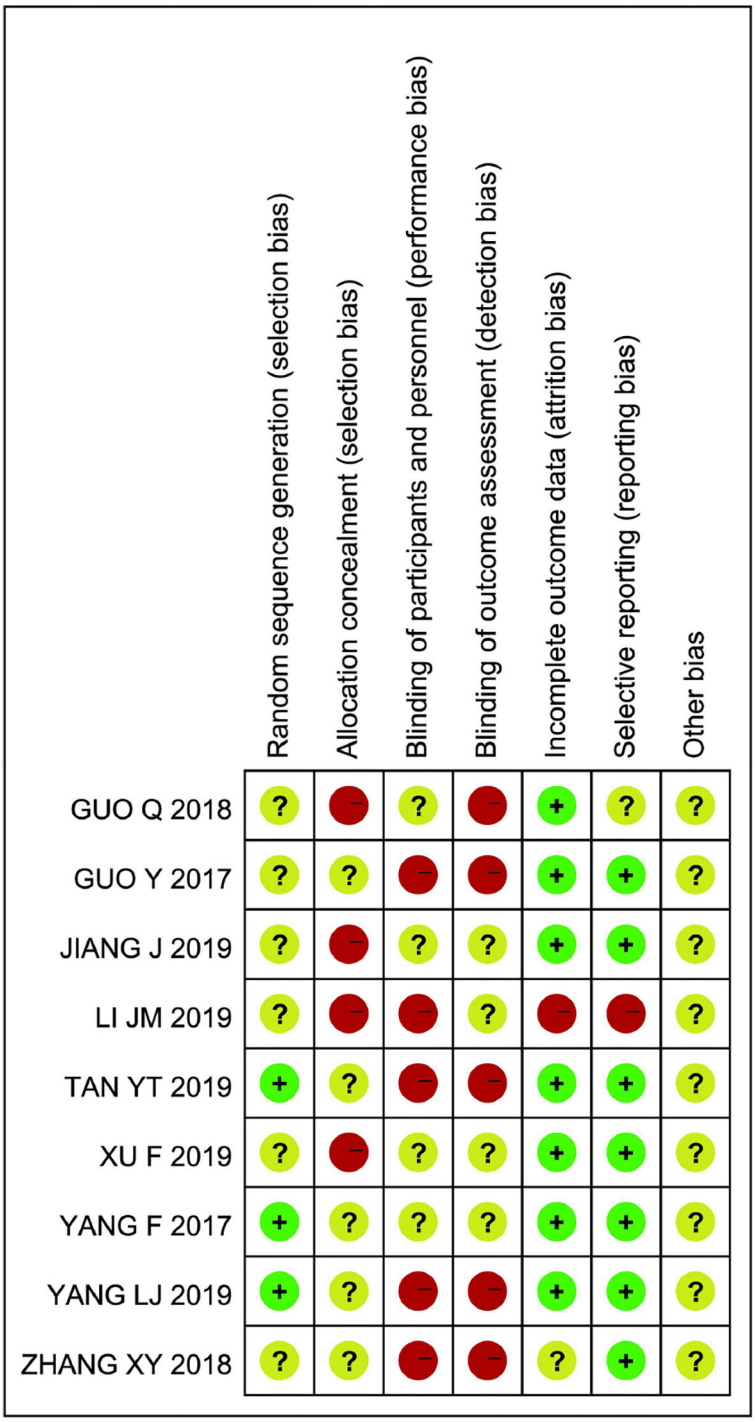


FIGURE 2 | Review authors' judgements about each risk of bias item for each of included study.

GnRH-a is a synthetic derivative of the gonadotropin-releasing hormone. It was first reported in 1991 for the treatment of adenomyosis and obtained good outcomes (25). GnRH-a can combine tightly with the GnRH receptors of the pituitary, so it can competitively downregulate the GnRH receptors in the body, thereby decreasing the level of gonadotropins secreted by the pituitary gland (26). The excitability of ovarian function is also decreased because of this, which inhibits the secretion of

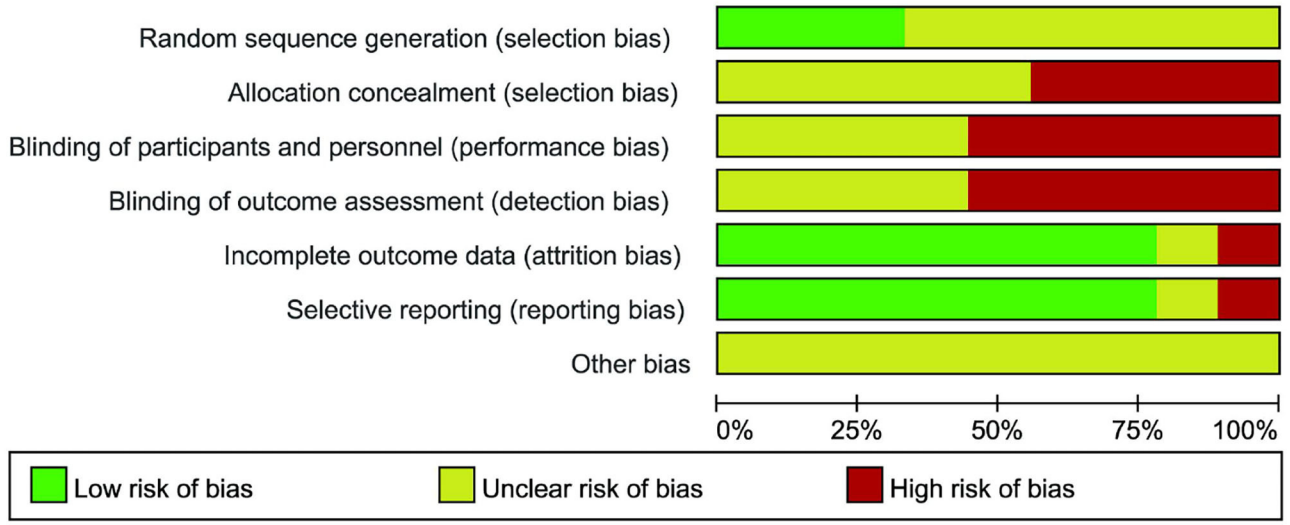


FIGURE 3 | Review authors' judgements about each risk of bias item presented as percentages across all included study.

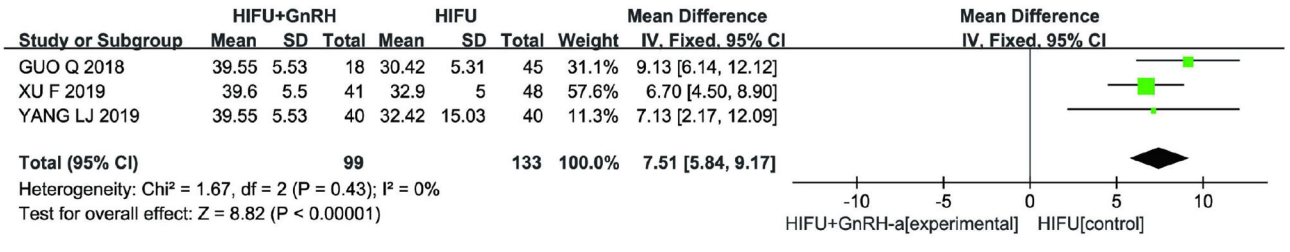


FIGURE 4 | Meta-analysis of uterine volume changes in two groups.

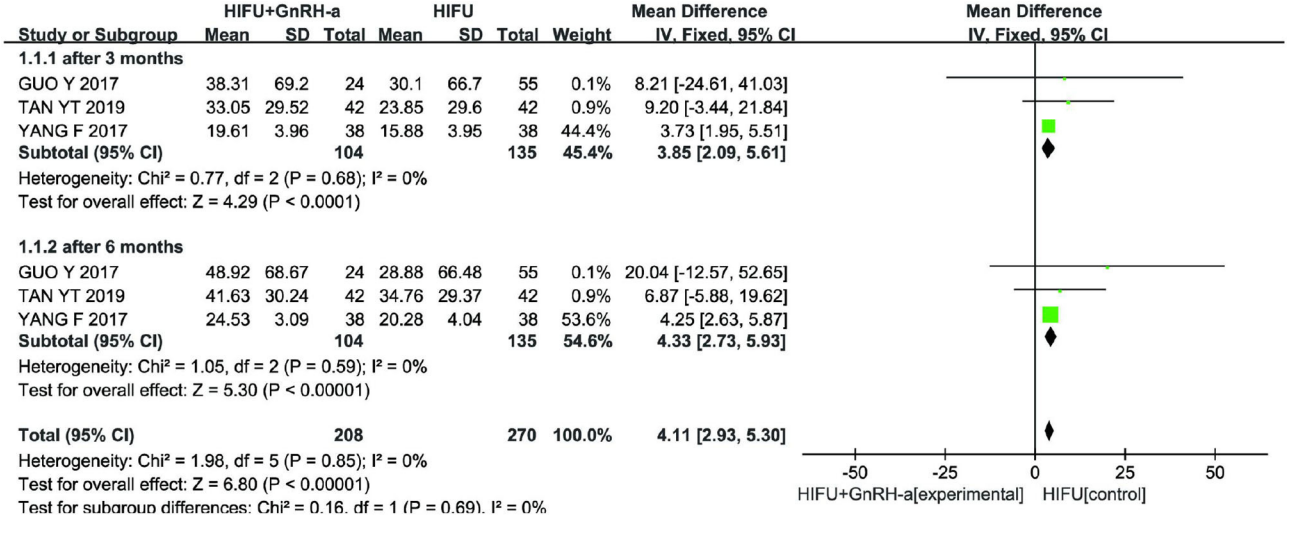


FIGURE 5 | Meta-analysis of lesion volume changes in two groups.

estrogen, promotes intimal atrophy, and prevents the continued expansion of the lesion. Up to now, many studies have confirmed the efficacy and safety of GnRH-a. Previous studies reported that GnRH-a can effectively decrease the uterine volume of patients with adenomyosis (27). To evaluate the improvement in chronic pelvic pain (CPP) after GnRH-a, Morelli et al.

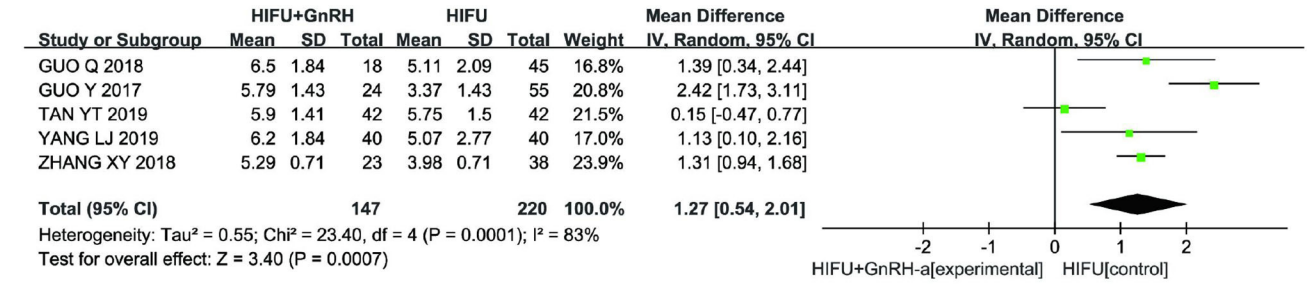


FIGURE 6 | Meta-analysis of visual analog scale (VAS) scores of dysmenorrhea in two groups.

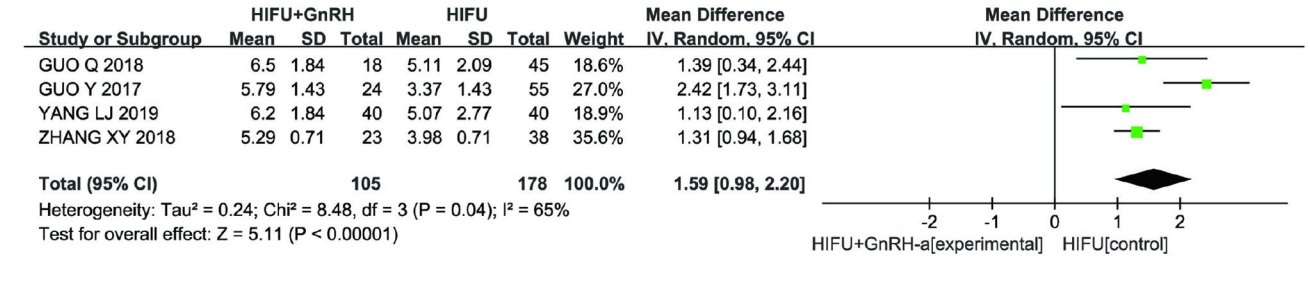


FIGURE 7 | Sensitivity analysis of visual analog scale (VAS) scores of dysmenorrhea in two groups.

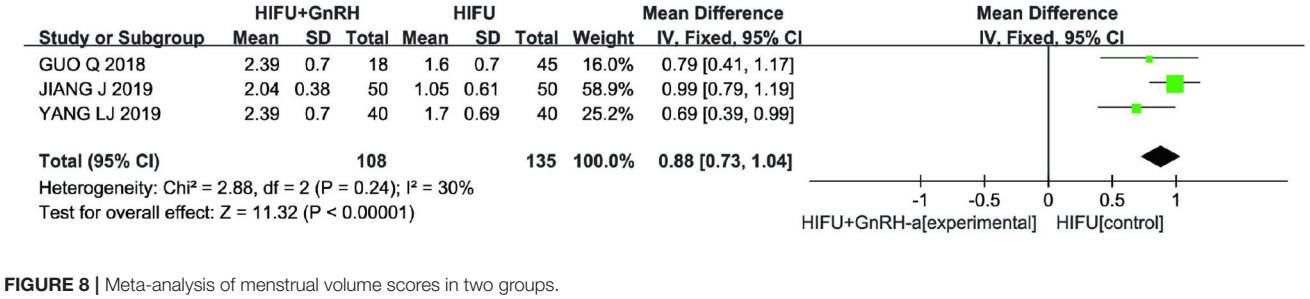


FIGURE 8 | Meta-analysis of menstrual volume scores in two groups.

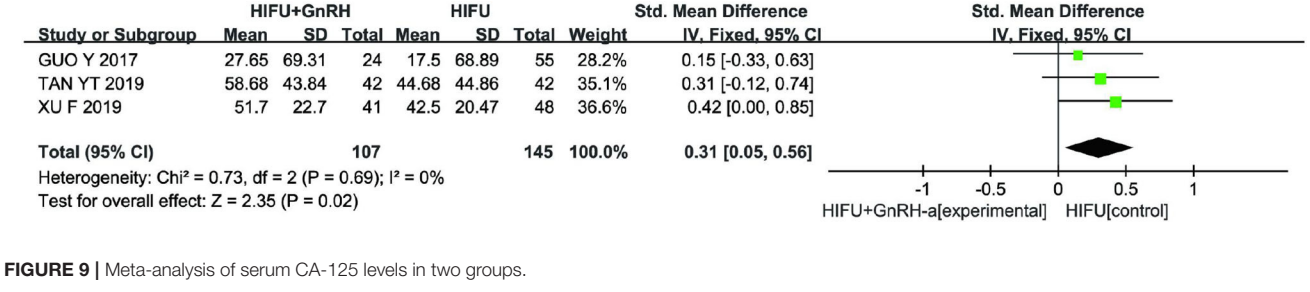


FIGURE 9 | Meta-analysis of serum CA-125 levels in two groups.

conducted a retrospective study on 63 premenopausal women with adenomyosis or endometriosis (28). The results showed that compared to baseline before treatment, a significant decrease in CPP intensity was observed in both adenomyosis group ($n = 15$) and endometriosis group ($n = 48$) ($p < 0.05$). This trend of reduction was more obvious in the adenomyosis group ($p < 0.001$). Meanwhile, a significant reduction was observed in days requiring analgesics ($p < 0.01$). GnRH-a can effectively relieve pain in patients with adenomyosis.

In fact, since adenomyosis is an estrogen-dependent disease, the hormonal environment of the patients will not be changed after HIFU treatment. Under estrogen stimulation, the lesions in the uterus may still recur or newly develop. HIFU combined with GnRH-a can help to maintain the efficacy of HIFU and

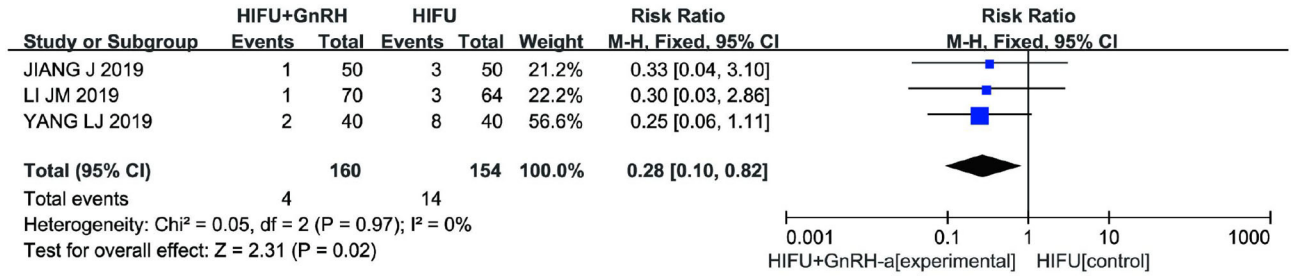


FIGURE 10 | Meta-analysis of recurrence rate in two groups.

TABLE 2 | Adverse reactions occurred in the patients after treatment.

	Complications	Total (*n*)	SIR grade
HIFU	Pain in treated region	62	A
	Low abdominal pain	15	A
	Sacral tail pain	37	A
	Radiating pain in the leg	10	A
	Neural response	4	A
	Skin burn	24	A
	Urinary retention	6	B
	Vaginal bleed discharge	26	A
	Thrombocytopenia	2	A
	Acute pelvic inflammatory disease	1	B
GnRH-a	Amenorrhea	58	A
	Mood change, Hot flashes, Night sweat, Insomnia	6	A

Data expressed as n. HIFU, High Intensity Focused Ultrasound. GnRH-a, Gonadotropin-releasing hormone agonist. SIR, Society of Interventional Radiology clinical practice guidelines.

reduce the recurrent rate. Our analysis showed that patients in the HIFU combined with GnRH-a group had a more pronounced decrease in uterine volume and lesion volume, and a lower recurrence rate. Most included studies suggested that patients should be injected GnRH-a three times after HIFU ablation. The first GnRH-a was administered on the first to third day of the first menstruation after HIFU treatment. Then, the interval between the two GnRH-a injections was 28 days.

Severe dysmenorrhea and excessive menstruation are the main symptoms that affect patients. Previous studies showed that the degree of adenomyosis infiltration of the uterus is related to the patient's pain (29). Gordts et al. proposed that hypermotility and increased expression levels of oxytocin receptors may be related to the degree of dysmenorrhea (30). Levgur et al. proposed that menorrhagia is related to the depth of adenomyotic lesion in the myometrium (31). A long-term results from single center proposed that HIFU had poor long-term efficacy for adenomyosis (32). The results of this retrospective analysis showed a significant effect in decreasing the dysmenorrhea score and the menorrhagia score at each follow-up time point. However, the effective rate of HIFU in alleviating dysmenorrhea and menorrhagia gradually decreased with the extension of follow-up time.

The results of our study showed that the symptoms of the two groups were all improved after the procedure, but the VAS scores for dysmenorrhea and menstrual volume scores of the HIFU combined with GnRH-a group were lower than those of the HIFU alone group. The serum CA125 levels was also decreased. Although the result of VAS scores for dysmenorrhea showed that HIFU combined with GnRH-a can better alleviate dysmenorrhea of patients, there still exists the excessive heterogeneity (I^2 = 83%) between studies. Therefore, we performed a sensitivity analysis by removing each single study sequentially. When the study of TAN 2019 was omitted, the heterogeneity is significantly reduced (I^2 = 65%). **Figure 6** displayed that there is no significance (MD 0.15, 95% CI −0.47–0.77) between the experimental group and the control group in the study of TAN 2019. However, there still exists the heterogeneity. The low quality of included studies may cause it. Most studies used scale of Uterine Symptom and Quality of Life (UFS-QoL) to evaluate the patients' severity of symptoms and health-related quality of life (HRQOL) (23, 33). The symptom severity scores higher, the symptoms of patients worse, whereas the HRQOL scores higher, the HRQOL of patients better. Regrettably, none of the included studies systematically assessed these specific symptoms, and were lack of investigations and evaluations on patients' health-related quality of life (34).

The relationship between adenomyosis and infertility is unclear, but adenomyosis can adversely affect female fertility (35, 36). This is mainly related to the disruption and thickening

of the myometrial junctional zone (JZ), and endometrial hypoacceptability (37). In recent years, owing to the continuous improvement of various ultrasound diagnostic methods and the increasing age of women seeking fertility treatment, the proportion of women with diagnosed adenomyosis among infertile women has increased. Traditionally, infertile patients with adenomyosis are treated by taking GnRH-a or surgically removing the adenomyotic lesion. Studies have pointed out that HIFU is a safe and effective procedure for infertile women and does not increase obstetric risks (38). Huang et al. performed a retrospective analysis on 93 patients with adenomyosis and infertility underwent USgHIFU ($n = 50$) or laparoscopic excision (LE) ($n = 43$) (39). They found that the pregnancy rate of the HIFU group (52%, 26/50) was significantly higher than that of the LE group (30.2%, 13/43). However, there is still a lack of high-quality randomized controlled trials comparing HIFU with other therapies. A meta-analysis revealed that infertile women receiving long-term GnRH-a treatment before receiving *in vitro* fertilization are associated with increased pregnancy rates (40). In this meta-analysis, only one study reported pregnancy outcomes. However, the sample size was too small, so we could not determine the group that could benefit more in terms of increased pregnancy rate. We look forward to more large-scale controlled clinical trials in the future.

Moreover, five studies reported adverse reactions after treatment (11, 13, 14, 17, 19), of which only two (17, 19) completely and uniformly reported specific data of the type and number of adverse reactions in the two groups. The results of the two articles indicated no statistically significant difference in the incidence of adverse reactions between the experimental and control groups ($P > 0.05$). In addition, three studies (11, 13, 14) also reported that no significant difference in the incidence of adverse reactions between the two groups. However, the three papers did not provide specific data. The combination of the number of adverse reactions in the two groups was not conducive for the comparison between the groups. In fact, owing to the working mechanism of the thermal effect of HIFU (41), patients in both the experimental and control groups had certain adverse reactions after HIFU ablation. We summarized and counted all the adverse reactions and the number of cases in the five articles (**Table 2**). Adverse reactions are mainly manifested as postoperative pain in the treatment area, sacral tail pain, and skin burning. According to the *Society of Interventional Radiology Clinical Practice Guidelines* (42) for the grade classification of adverse reactions, grades A and B are minor complications, and no serious complications occurred. The patients in the experimental group who took GnRH-a had symptoms such as amenorrhea and mood changes, hot flashes, night sweats, and insomnia. These symptoms will improve spontaneously at 2 months after discontinuation of the drug (14, 19), and no special treatment is required.

This systematic review and meta-analysis has some limitations. First, all the studies were conducted in China and most of them were written in Chinese, with a certain risk bias. In fact, China has the independent intellectual property rights (IPR) for HIFU technology. Therefore, many studies related to HIFU is conducted in China or written in Chinese. And the qualities of some included studies were generally low. Information on the main outcomes was incomplete, and the allocation concealment and blinding methods were not mentioned in detail. Second, the sample sizes of some articles were small. Third, most studies did not report the specific volumes of the uterine and adenomyotic lesion after treatment but, instead, replaced it with the reduction rates of the uterine and adenomyotic lesion volumes, so the outcome indicators must be carefully referenced. Forth, some articles were lacked of long-term follow-up results and assessment of patient quality of life.

At present, HIFU with GnRH-a therapy has not been reported in terms of its effect on the improvement of patient quality of life and the increase in pregnancy rate. This may become a new direction for future research. This systematic review did not discuss the classification of adenomyosis. Whether this therapy has a difference in efficacy between focal and diffuse adenomyosis is still unknown, so more randomized controlled trials must be conducted.

CONCLUSIONS

The results of this meta-analysis showed compared with HIFU treatment alone, HIFU with GnRH-a for the treatment of adenomyosis has greater efficacy in decreasing the volumes of the uterine and adenomyotic lesions and alleviating symptoms. However, since the number of the included studies was too small and most of them were written in Chinese, this conclusion needs to be referenced with caution. The long-term evidence of its efficacy is still insufficient.

DATA AVAILABILITY STATEMENT

The original contributions generated for the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

L-LP developed the search strategy and completed the manuscript writing. L-LP and JM completed the electronic search and selected appropriate literature. R-NL and T-TZ extracted the information of the selected studies. L-XF was responsible for data analysis using RevMan 5.3 software. YW advised on the data analysis and was responsible for correspondence. All authors carefully checked and approved the final manuscript.

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and Western medicine (2020KFA3006, State Key Laboratory of Ultrasound in Medicine and Engineering). The funding organization does not have any role in the design or conduct of this study.

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Clinical and Economic Evaluation of Acupuncture for Opioid-Dependent Patients Receiving Methadone Maintenance Treatment: The Integrative Clinical Trial and Evidence-Based Data

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Objective: From the health care and societal perspectives, this study aimed to evaluate the clinical and economic effects of acupuncture as an adjunctive therapy for patients receiving methadone maintenance treatment (MMT).

Methods: We conducted a parallel-arm RCT in China in 2019. Patients were included who met the diagnostic criteria and receive MMT for more than 30 days. Patients were randomly assigned to the exposed group (acupuncture plus MMT) or control group (MMT) at a 1:1 ratio. Daily methadone dosage, drug cravings using the VAS score, and insomnia using the Pittsburgh Sleep Quality Index (PSQI) were chosen as the effectiveness indexes, and the quality-adjusted life years (QALYs) was chosen as the utility index.

Results: Overall, 123 patients were included. The exposed group was significantly ($P < 0.05$) better than the control group in the improvement of daily methadone dosage (17.68 vs. 1.07), VAS (38.27 vs. 2.64), and PSQI (2.18 vs. 0.30). The QALY was 0.0784 (95%CI: 0.0761–0.0808) for the exposed group and 0.0762 (95%CI: 0.0738–0.0787) for the control group. The total cost of the exposed group (2869.50 CNY) was higher than the control group (2186.04 CNY). The ICER of daily methadone dosage (41.15), VAS (17.86), and PSQI (313.51) were shown to be economically efficient. While ICUR (310,663.64 CNY/QYLY) was higher than the cost suggested by WHO.

Conclusion: Acupuncture as an adjuvant therapy for MMT patients realizes its cost-effectiveness by reducing the dosage of methadone, improving drug cravings, and

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alleviating insomnia. It helps to improve quality of life, but since its cost exceeds what society is willing to pay, further study is needed.

Keywords: opioid dependence, acupuncture - therapy, methadone maintenance therapy, clinical evaluation, economic evaluation, randomized controlled trial

INTRODUCTION

Opioid use disorder (OUD) is a type of addictive disease that includes compulsive opioid use, increased tolerance to opioids, and obvious withdrawal reactions after stopping drug taking (1, 2). Evidence from The World Drug Report 2018 shows that approximately 31 million people worldwide suffer from OUD, which has caused the huge burden of serious disease and drug-related deaths (3). In the United States, approximately $1.02 trillion was spent on opioid use disorders and fatal opioid overdoses in 2017 (4). Incidence of fatal opioid overdose continue to surge in the United States (5). In China, about 1.8 million people use illicit drugs, of which 734,000 are opioid abusers, accounting for 40.8% of it (6). Opioid dependence have caused a heavy economic burden on patients and the health care systems worldwide.

Methadone maintenance treatment (MMT), an effective intervention for the treatment of opioid dependence, is by far the most widely used treatment (7, 8). MMT uses less dependency-inducing methadone to replace opioids, aiming to reduce opioid use through the principle of cross-tolerance. It is one of the current worldwide treatments for opioid dependents, reducing a range of social and public health problems caused by opioid abuse (9).

Though the widespread use of methadone in maintenance treatment for opioid dependence in many countries, MMT patients are often troubled by side effects, such as constipation, drowsiness, menstruation, decreased libido, and gastrointestinal symptoms (10). Besides, Lai's (11) study showed that there was still a high proportion, more than 30%, of patients who were caught re-taking drugs during MMT treatment. Despite this, it remains to be further studied whether the cause is drug addiction or methadone underdosing.

Acupuncture has been treating various diseases for thousands of years in China. As an alternative and complementary therapy, it is becoming increasingly popular in Western countries (12). Acupuncture has been recognized as an appropriate non-pharmacological therapy for the treatment of substance dependence by the World Health Organization (13). The existing studies have shown evidence that acupuncture might potentially reduce relapse through inhibiting attention bias to heroin (14), lowering the complications of drug dependence (15), and modifying morphine withdrawal syndrome (16). Compared with Western medicine, acupuncture has fewer side effects and limited adverse reactions. Several studies have found that acupuncture has potential effects in improving opioid dependence (17, 18). In the RCT of Chan 2014 (19), 60 patients treated with MMT were randomized to receive either true or sham acupuncture for a period of 4 weeks. Significant reductions in daily methadone consumption and improvements in sleep latency were observed in the true acupuncture group compared with the sham acupuncture group. A pilot RCT by Deng et al. (20) found that acupuncture helped reduce drug dose in patients who had already taken opioids and alleviate opioid cravings in patients who had not taken opioids. Another study by Crawford et al. (21) found that among 172 patients who had received at least four acupuncture treatments at the US Air Force Medical Center, the total prescription of morphine equivalent was reduced by 45%. A systematic review article by Baker et al. (22) concluded that auricular acupuncture may be effective as an adjuvant therapy to increase treatment retention and decrease methadone maintenance dosage. These studies proved the effectiveness of acupuncture for reducing drug use in different disease areas. Some have even suggested that it is better at pain relief than opioids (23–25). In addition, a randomized controlled trial we carried out proved that the effect of acupuncture as an adjunctive therapy of treating opioid dependence is better than methadone treatment alone (26).

Previous studies found that there is evidence that acupuncture improves opioid dependence. Whether this translates into better health outcomes for patients and fewer costs for the health care system needs to be investigated. And there is little known about the clinical and economic evaluations on acupuncture for opioid dependence patients, thus, this study aimed to conduct clinical and economic evaluation of acupuncture as an adjunctive therapy for patients receiving MMT in a randomized controlled trial. It is expected that the findings can provide references for clinicians to optimize treatment options.

METHODS

Study Design

We implemented a randomized controlled trial (RCT) in which 135 patients were randomly assigned to a routine group (control group) or an acupuncture plus routine group (exposed group) *via* a central randomization system (SAS 9.4) in a 1:1 ratio. After completing the clinical trial, we conducted the cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) on the collected data from the societal perspective. The protocol approved by the Ethics Committee of the First affiliated Hospital of Guangzhou University of Chinese Medicine (No. Y-2019-241) and registered in the Chinese Clinical Trial Registry (ChiCTR1900026357) has been published.

Participants

Participants were recruited with OUD from the methadone clinic of the Substance Dependence Department of Guangzhou Huiai Hospital from October 2019 to September 2020. OUD was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders [Fifth Edition (DSM-V)] of the American

TABLE 1 | The inclusion and exclusion criteria of subjects.

Inclusion criteria	Exclusion criteria
(1) Male or female. (2) 18–60 years old. (3) Had received MMT for not <30 days. (4) Were able to sign the informed consent. (5) Had not received any kind of acupuncture therapy during the previous 3 months.	(1) Serious heart, liver, lung, or kidney disease. (2) Venereal disease or AIDS. (3) The presence of severe digestive disease and athrepsia. (4) Major psychosis. (5) The receipt of other treatment that may affect the efficacy evaluation of the present intervention. (6) An infection, inflammation, scar, or injury close to the site of the selected acupoints. (7) Pregnant or planning to become pregnant.

Psychiatric Association. The specific inclusion and exclusion criteria are presented in **Table 1**.

Intervention

Exposed Group: Acupuncture Plus MMT

Participants received acupuncture plus MMT treatment in this group. Acupuncture was performed by a licensed acupuncturist. The selection of acupoint groups based on Jin's three-needle theory have specific names and contain three or four points. And three acupoints groups named Dingshen-zhen, Sishen-zhen, and Shouzhi-zhen were chosen in this study. The acupoints are described in detail in **Appendix 1**. Disposable stainless steel needles (Huatuo, Suzhou, China. Lengths and diameters 0.3 × 25 mm or 0.3 × 40 mm) were used in this group. Insertion was followed by manual stimulation, aiming to make patients feel the typical acupuncture sensation of de qi (considered to indicate effective needling, it is a sensation of soreness, numbness, distention, or radiating). Then the needles remained on the point for 30 min. Patients received a total of 18 sessions over a period of 6 weeks (3 times per week).

Control Group: MMT

Participants received MMT only. The dosage and reduction of methadone maintenance treatment are based on relevant national regulations (the details of the methadone instructions and reduction methods are in **Appendix 2**).

Clinical Outcome Measures

Effectiveness Indexes

Daily Dosage of Methadone

The daily consumption of methadone was recorded from baseline (0 week) to the 2nd, 4th, and 6th weeks. One primary outcome measure was the change in the daily consumption of methadone from baseline to the 6th week. Enrolled patients went to the clinic to take methadone every day, and the dosage was strictly administered by the doctor which was recorded in the clinic's computer system.

VAS

The severity of the opioid craving was assessed using a 100-mm visual analog scale (VAS) at baseline (0 week) and the 2nd, 4th, and 6th weeks. The amount of opioid craving that a participant felt ranged across a continuum from 0 (no craving) to 100 (strong craving). The opioid craving VAS score was determined by measuring in millimeters from the left-hand end of the line to the point that the participant marked (27). The other primary outcome measure was the change in VAS from baseline to the 6th week.

PSQI

Sleep quality was assessed using the Chinese version of the Pittsburgh Sleep Quality Index (PSQI) (28) at baseline and at the 6th week. The Chinese version of the PSQI has demonstrated reliability and validity similar to that of the original language version (29). The PSQI evaluates sleep disturbances through subjective sleep quality, sleep duration, sleep latency, habitual sleep efficiency, sleep disturbances, daytime dysfunction, and the use of sleeping medication. Each item is graded on a 4-point scale (0 points to 3 points), which is summed for a total score (0 points to 21 points). Higher scores show that patients suffer a higher severity of sleep disturbance, and a total score higher than 5 indicates "poor sleep."

Utility Index

The Quality adjusted life years (QALY) assessment was used as the utility index. The quality of life was assessed through the Chinese version of the SF-36 (30) at baseline and at the 6th week. The Chinese version of the SF-36 has demonstrated validity similar to that of the original language version (31). The quality of life was estimated by the SF-36 in eight domains: general health (GH), physical functioning (PF), role limitations due to physical problems (RP), role limitations due to emotional problems (RE), bodily pain (BP), social functioning (SF), vitality (VT), and general mental health (MH) (32). PF, RP, RE, BP, and SF assess the absence of limitations or disability, while GH, VT, and MH assess the positive state of well-being. Mid-range scores indicate no reported limitations or disabilities (33). In this study, higher scores indicate a better health status.

QALY was used to calculate the health utility value according to the corresponding coefficients of each dimension level in the SF-6D UK utility scoring model (health utility value = C + PF + RL + SF + PAIN + MH + VIT). Using the Area Under the Curve (AUC) method to calculate QALY (34–36), QALY is calculated as follows:

$$QALY = \frac{1}{2}\sum_{i=0}^{n-1}(t_{i-1} - t_i)(y_i + y_{i-1})$$

In the above formula, "y_i" represents the utility value of the health status of a survey object at time "t_i" ($i = 0, 1, 2\ldots\ldots, n$), and "$n$" represents the number of measurements taken by the survey object. This study is adjusted to be based on a time frame of 1 year.

Moreover, the subjects will be randomly asked to undergo a urine test to detect relapse of opioids.

Selection and Determination of Cost

All costs were calculated with CNY as the unit. Expense information was collected through questionnaires, which were filled out by the patient or accompanying family members based on their actual expenses.

Direct Costs

Direct costs consist of direct medical costs and direct non-medical costs. In this study, direct medical costs include the costs for acupuncture treatment, physical examination, and urine tests. Direct non-medical costs are related to transportation expenses incurred by the trial.

The standard of acupuncture treatment fee comes from the "Price Summary List of Basic Medical Services in Guangdong Province" published by the Guangzhou Municipal Development and Reform Commission in December 2018, the price of acupuncture treatment is 33 CNY per session. Since methadone is a controlled drug in China and there is no reference price, we investigated the material dependence clinic of methadone at Huiai Hospital in Guangzhou. The results of the investigation are as follows: Methadone is provided by China Pharmaceutical Group (Shenzhen) Pingshan Pharmaceutical Co., Ltd. The dosage of MMT for patients is determined by doctors and adjusted reasonably according to the patient's requirements. Regardless of the dosage, patients only need to pay 10 CNY per time.

Indirect Costs

Indirect costs were considered as a result of lost productivity caused by a reduction in the effective working hours or the ability to work of the patient and his/her family due to morbidity. The unit labor value was based on the per capita GDP of Guangzhou in 2019. The indirect costs were measured as follows:

$$\text{Indirect costs} = \text{Labor loss time} \times \text{Unit time labor value}$$

$$(\text{Unit time labor value} = \text{GDP per capita} \div 365 \text{ days} \div 8 \text{ h}).$$

Statistical Analysis

In this study, descriptive statistic analysis was conducted on the description of basic characteristics, comparative analysis of outcome, and cost. Measurement data were described by mean, and enumeration data were described by frequency and rate. CEA and CUA were conducted in the study. Further, incremental cost-effectiveness ratio (ICER) and incremental cost-utility ratio (ICUR) were adopted to determine which group would bring more economic benefit to patients.

In addition, only when ICER or ICUR is within the threshold standard range will it be applied. This study was classified according to the WHO's threshold level and China Guidelines for Pharmacoeconomic Evaluations (2020), taking 3-time per capita GDP as the threshold. According to China's per capita gross national product (GDP: 72,447 CNY) announced by the National Bureau of Statistics in 2020, the threshold for this study was determined to be 217,341 CNY.

Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC), including SAS PROC MIXED for linear mixed models. Two-sided $P < 0.05$ indicated statistical significance.

Sensitivity Analysis

Probabilistic sensitivity analysis was used to test the stability of the results. Probability sensitivity analysis was performed by the @RISK software, and its results are presented by the cost-effectiveness acceptability curves (CEAC).

RESULTS

From October 2019 to September 2020, 135 of the 326 patients screened were included at baseline and randomly assigned to the exposed group ($n = 68$) or the control group ($n = 67$). A total of 12 patients dropped out during the study period: 3 patients left the hospital, 1 patient fainted during acupuncture, 2 patients lost contact, and 6 patients had personal problems. Thus, we analyzed 123 patients who completed all treatments and after 6 weeks of follow-up. The flowchart of sampling and grouping is summarized in **Figure 1**.

Baseline Characteristics

Patient baseline characteristics are listed in **Table 2**. There was little difference in age, sex, weight, marital status, job, education, and other personal conditions between the two groups. In addition, there was no significant difference in specific situation of drug use, such as years of opioid use, route of previous opioid use, daily dosage of opioid used before MMT, and positive rate of urine test. And except the sex proportion, all scores of standardized differences were <0.2. According to standardized difference scores, most of the baseline variables were balanced between the two groups.

Outcomes

Outcomes of Effectiveness

As shown in **Table 3**, the outcomes of both groups included daily dosage of methadone, VAS score, and PSQI score.

Daily Dosage of Methadone

In the exposed group, the daily methadone dosage at the 6th week was reduced by an average of 17.68 mg compared to the 0 week and a $P < 0.001$ indicated a significant difference. While in the control group, the dosage was only reduced by 1.07 mg on average with no statistical significance ($P = 0.595$). Moreover, at the 6th week, it was statistically significant ($P < 0.001$) that the daily methadone dosage of the exposed group was 13.67 mg less than that of the control group.

VAS Score

In terms of VAS score, at the 6th week, the exposed group had a score of 11.39 ± 6.45 which compared to the baseline improved by 38.27 ± 2.97 ($P < 0.001$) after treatment, while the control group had a score of 48.93 ± 13.03 which had no improvement compared to the baseline (-2.64 ± 1.84, $P = 0.156$). Besides, the difference between the groups was significant at 37.54 ± 1.93 ($P < 0.001$).

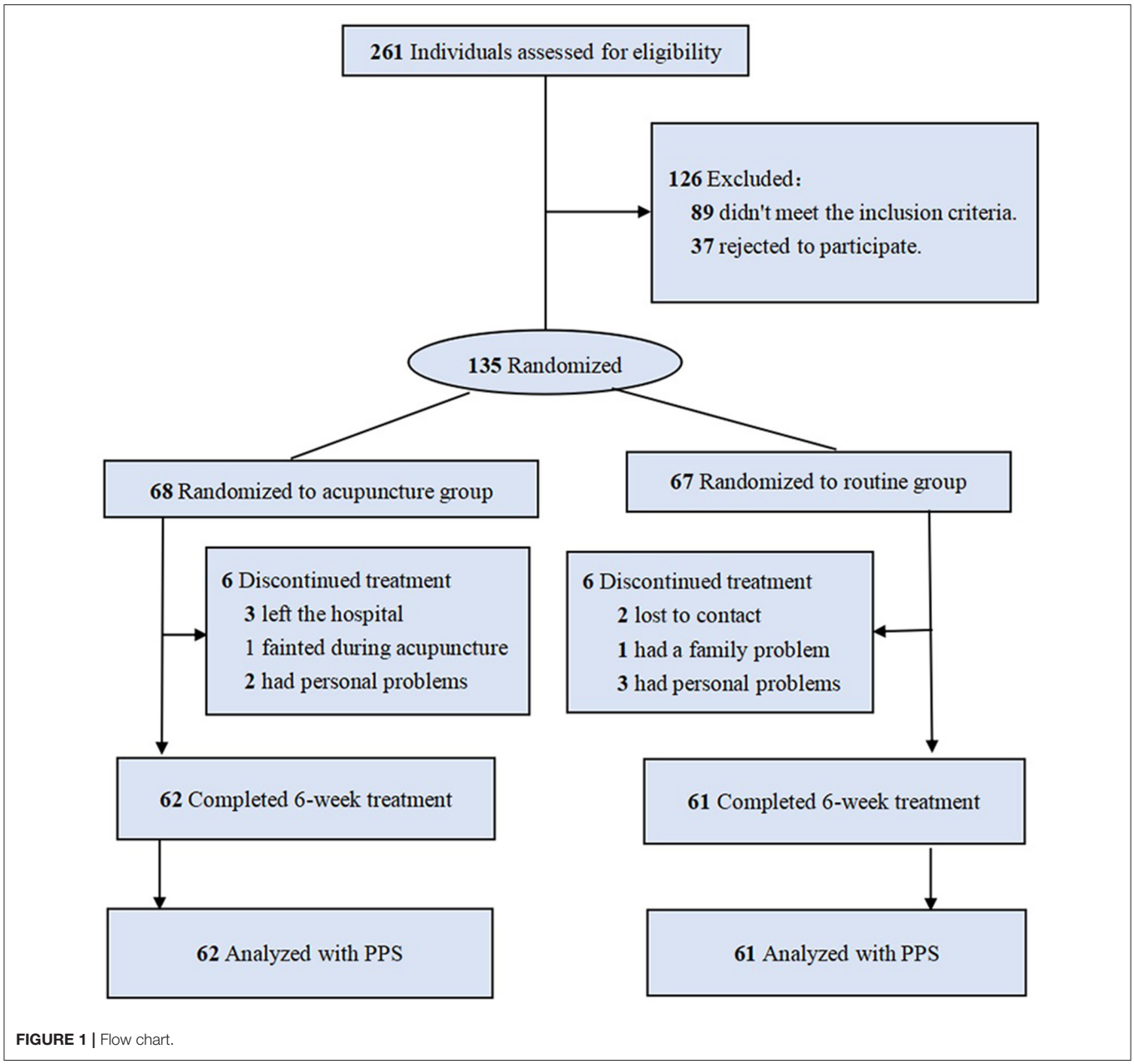


FIGURE 1 | Flow chart.

PSQI Score

As to the PSQI score, the mean score of the exposed group was 8.18 ± 4.55 and the control group was 9.06 ± 5.00 at the 6th week. Compared with the baseline, the exposed group improved by 2.18 ± 0.52 ($P < 0.001$), while the control group did not improve (-0.30 ± 0.42, $P = 0.477$). And difference between the groups was 0.93 ± 0.83 with no significance.

Outcome of Utility

No significant difference was observed in health utility values between the exposed group and control group ($P > 0.05$), though health utility values of the exposed group showed an increasing trend over time (see **Appendix 3**).

The QALY score was 0.0784 (95%CI: 0.0761–0.0808) for the exposed group and 0.0762 (95%CI: 0.0738–0.0787) for the control group. And the exposed group had more 0.0022 QALYs than the control group.

Costs

Details of the costs are shown in **Table 4**.

Total Costs

The mean total costs were 2,869.50 CNY and 2,186.04 CNY, respectively for the exposed group and control group. Total cost in the exposed group was higher

than the control group, and the difference of the mean total costs was statistically significant between the two groups ($P < 0.001$).

TABLE 2 | Characteristics at baseline (PPS).

Variable	Exposed group ($n = 62$)	Control group ($n = 61$)	Standardized difference
Age, mean (SD), y	51.79 (4.77)	51.08 (6.71)	0.02
Sex (male/female)	49/13	56/5	0.22
BMI, mean (SD), kg/m^2	21.76 (3.68)	22.54 (3.57)	0.06
Marital status (%)			
Married	20 (32.3)	21 (34.4)	0.03
Single	17 (27.4)	22 (36.1)	0.13
Divorced	25 (40.3)	18 (29.4)	0.16
Unemployed rate (%)	51 (82.3)	51 (83.6)	0.02
Education (%)			
Primary school	11 (17.7)	18 (29.5)	0.18
Middle school	25 (40.3)	22 (36.1)	0.06
High school or university	26 (41.9)	21 (34.4)	0.11
Years of opioid use, mean (SD)	16.76 (6.12)	16.44 (8.54)	0.01
Route of previous opioid use (%)			
Injection	49 (79)	41 (67.2)	0.13
Nasal	13 (21)	18 (29.5)	0.18
Oral	0 (0)	2 (3.3)	0.09
Daily dosage of opioid used before MMT (g/d)	1.08 (1.15)	0.90 (1.14)	0.14
Urine test positive (%)	5 (8.1)	11 (18)	0.17

PPS, per protocol set; SD, standard deviation; BMI, body mass index; MMT, methadone maintain treatment.
Standardized difference = difference in means or proportions divided by standard error. Imbalance was defined as an absolute value >0.20 (small effect size).

Direct Costs

In terms of direct medical costs, the mean was 1,303.94 CNY (exposed group) and 729.66 CNY (control group) with a $P \leq 0.05$ indicating a significant difference. The mean of direct non-medical costs was 112.35 CNY (exposed group) vs. 105.05 CNY (control group), and the $P = 0.766$ indicated that the difference was not significant.

Indirect Costs

The mean of indirect costs was 1,453.21 CNY and 1,351.33 CNY with the median of 958.50 CNY and 1,917.00 CNY for the exposed group and control group, respectively.

In sum, both groups showed a significant difference in direct medical costs ($P < 0.001$) and a non-significant difference in direct non-medical costs ($P = 0.766$) or indirect costs ($P = 0.690$). Overall, all types of costs were higher in the exposed group than in the control group.

Results of CEA

As shown in **Table 5**, regarding daily methadone dosage, the exposed group was associated with a more reduction of daily methadone dosage (16.61) compared with the control group, and with a higher cost (683.46 CNY). This means that increasing the effective rate by 1% cost an extra 41.15 CNY.

Regarding VAS score, compared with the control group, the exposed group was associated with a higher cost (683.46 CNY) and a higher effective rate (38.27). This means that increasing the effective rate by 1% cost an extra 17.86 CNY.

In terms of PSQI score, compared with the control group, the exposed group was associated with a higher cost (683.46 CNY) and a higher effective rate (2.18). This means that increasing the effective rate by 1% cost an extra 313.51 CNY.

TABLE 3 | Outcome comparison of the exposed group and control group (X ± SD).

Outcome	Follow-up	Exposed group	Control group	Difference between the groups	*P*-value
Daily dosage of methadone (Unit: mg)	Week 0	52.44 ± 9.03	49.41 ± 17.05	3.066 ± 2.65	0.250
	Week 4	37.05 ± 6.23	48.54 ± 16.71	−11.71 ± 2.01	<0.001
	Week 6	34.76 ± 7.9	48.34 ± 17.44	−13.67 ± 2.11	<0.001
	Effectiveness	17.68 ± 1.50	1.07 ± 2.24	/	/
	P-value	<0.001	0.635	/	/
VAS score	Week 0	49.39 ± 22.78	46.30 ± 19.63	3.10 ± 4.05	0.447
	Week 4	26.69 ± 15.17	50.92 ± 13.16	24.23 ± 2.55	<0.001
	Week 6	11.39 ± 6.45	48.93 ± 13.03	37.54 ± 1.93	<0.001
	Effectiveness	38.27 ± 2.97	−2.64 ± 1.84	/	/
	P-value	<0.001	0.156	/	/
PSQI score	Week 0	10.35 ± 4.81	8.76 ± 4.95	1.58 ± 0.88	0.077
	Week 4	8.75 ± 4.65	8.73 ± 4.80	0.02 ± 0.82	0.985
	Week 6	8.18 ± 4.55	9.06 ± 5.00	0.93 ± 0.83	0.271
	Effectiveness	2.18 ± 0.52	−0.30 ± 0.42	/	/
	P-value	<0.001	0.477	/	/

SD, standard deviation.
Repeated measures analysis of variance were used to analyze the individual effects of each factor due to interaction.

TABLE 4 | Description of different types of costs (Unit: CNY).

Cost type	Group	Mean	*SD*	P_{25}	*M*	P_{75}	*P value*
Total costs[a]	Exposed group	2,869.5	1,561.91	1,406	2,426	4,296.25	0.008
	Control group	2,186.04	1,247.36	899.5	2,422.5	2,844.5	—
Total direct costs[b]	Exposed group	1,416.29	172.75	1,369.5	1,409.5	1,470	<0.001
	Control group	834.71	113.39	795.5	819.5	903.5	—
Total direct medical costs[c]	Exposed group	1,303.94	98.72	1,317.5	1,337.5	1,341.5	<0.001
	Control group	729.66	64.03	723.5	733.5	747.5	—
Acupuncture fee	Exposed group	594	—	—	—	—	—
	Control group	—	—	—	—	—	—
Physical examination fee	Exposed group	286.44	98.72	300	320	324	0.192
	Control group	306.16	64.03	300	310	324	—
Urine test fee	Exposed group	3.5	—	—	—	—	—
	Control group	3.5	—	—	—	—	—
Medicine fee	Exposed group	420	—	—	—	—	—
	Control group	420	—	—	—	—	—
Direct non-medical cost[d]	Exposed group	112.35	165.70	72	72	144	0.766
	Control group	105.05	96.38	72	72	162	—
Indirect costs[e]	Exposed group	1,453.21	1,530.28	0	958.5	2,875.5	0.690
	Control group	1,351.33	1,278.52	0	1,917	1,917	—

SD, standard deviation.
[a] *Total costs are the sum of direct and indirect costs.*
[b] *Direct costs include direct medical expenses and direct non-medical expenses.*
[c] *Total direct medical costs include acupuncture fee, physical examination fee, urine examination fee, and drug fee.*
[d] *Direct non-medical cost is related to the transportation expenses incurred by the trial.*
[e] *Indirect cost is calculated by multiplying the labor lost time by 53.25 CNY per hour.*

TABLE 5 | Results of CEA.

	Cost (CNY)	Effectiveness	CER	ΔC (CNY)	ΔE	ICER
Daily methadone dosage						
Exposed group	2,869.50	17.68	162.30	683.46	16.61	41.15
Control group	2,186.04	1.07	2,043.03			
VAS score						
Exposed group	2,869.50	38.27	74.98	683.46	38.27	17.86
Control group	2,186.04	0	-			
PSQI						
Exposed group	2,869.50	2.18	1,316.28	683.46	2.18	313.51
Control group	2,186.04	0	-			

CEA, cost-effectiveness analysis; CNY, China Yuan; CER, cost-effectiveness ratio; C, cost; E, effectiveness; ICER, incremental cost-effectiveness ratio.
$\Delta C = Cost_{exposed\ Gourp} - Cost_{control\ group}$; $\Delta E = Effectiveness_{exposed\ Gourp} - Effectiveness_{control\ group}$; $ICER = \Delta C/\Delta E$.

Results of CUA

It was calculated that the incremental cost of the exposed group was 683.46 CNY with 0.0022 QALY as the incremental utility. The ICUR under the exposed group was 310,663.64 CNY/QALY, indicating that it may not be economical as an auxiliary treatment for patients in MMT given a willingness to pay 217,341 CNY per QALY (triple China's per capita GDP in 2020).

Sensitivity Analysis

The results of probability analysis are shown in **Figures 2–4**. The CEAC represents how the likelihood of a treatment regimen having a cost-effectiveness advantage changes as the threshold changes. The CEAC shows that for the MMT patients, the addition of acupuncture in MMT to reduce methadone dosage is cost-effective, with a 50% probability of being cost-effective at a willingness to pay <50 CNY. At the same time, to improve the VAS and PSQI, the willingness to pay is <20 CNY and 400 CNY, respectively. When triple China's per capita GDP (217,341 CNY) indicates a cost-effective threshold, all three CEAC reach a probability of 100%.

DISCUSSION

In this study, we focused on the clinical and economic evaluation of acupuncture plus MMT treatment, comparing with MMT only, which has been proved to be clinically

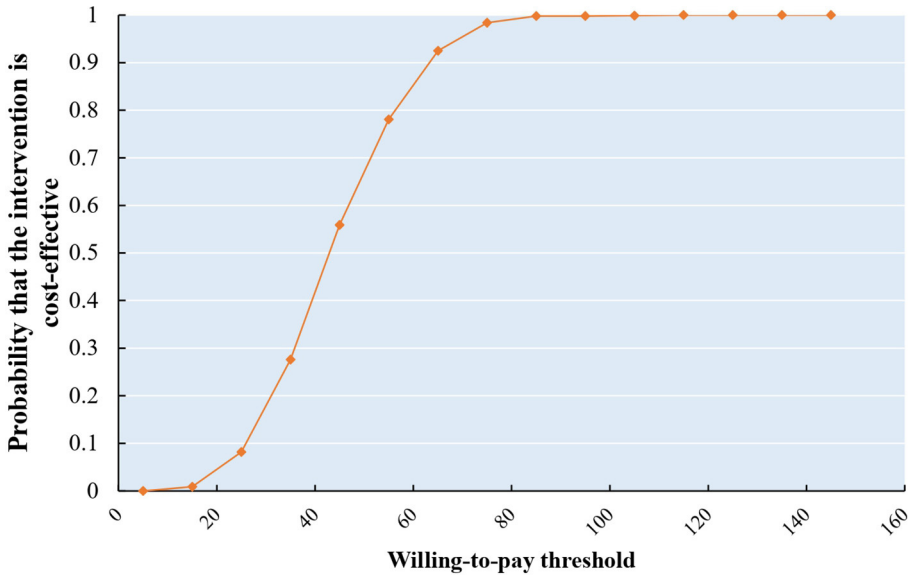


FIGURE 2 | CEAS of reduction in daily methadone dosage.

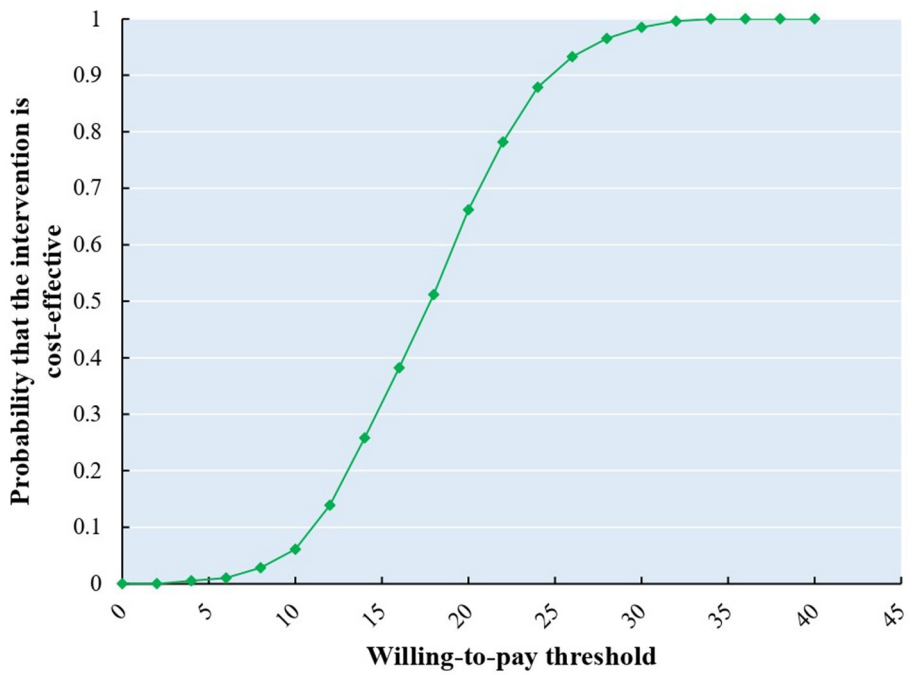


FIGURE 3 | CEAS of improvement of opioid craving (VAS).

effective in the treatment of opioid dependence. We compared the MMT with acupuncture plus MMT through clinical and economic evaluation outcome indicators including daily dosage of methadone, VAS score, PSQI score, and SF-36 score, to evaluate the treatment economy and effectiveness of acupuncture treatment in a randomized controlled trial.

By the end of 2020, China had about 1.80 million drug users (6). The United States has become the epicenter of the opioid epidemic and is experiencing an ongoing overdose crisis (4, 37). In 2017, the cost of opioid use disorders and fatal opioid overdoses was estimated at $1.02trillion (34). Methadone maintenance therapy is currently the most widely used and

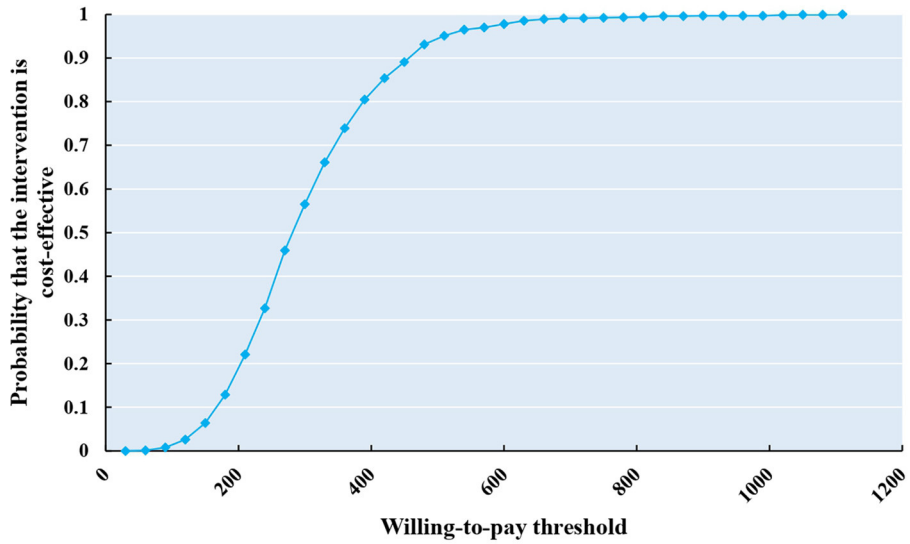


FIGURE 4 | CEAS of improvement of insomnia (PSQI).

effective treatment for opioid dependence worldwide (38–40). However, higher relapse rates persist during treatment (41, 42). But methadone itself also has many disadvantages. Long-term dependence on maintenance agents can cause insomnia, constipation, decreased libido, decreased sexual power, sweating, and other symptoms (40, 43, 44). Moreover, methadone is a synthetic opioid, and patients treated with MMT may become physically dependent and may experience methadone withdrawal symptoms (45). Methadone overdose has become a growing phenomenon in some countries (45). It has even led to a number of deaths from methadone overdoses (46). Therefore, in the treatment of OUD patients, methadone dependence and reduction of methadone dosage should also be paid attention to.

As a non-pharmacological method, acupuncture therapy is safe, has no side effects, and is not addictive. Its therapeutic effect on addictive diseases has been confirmed in animal and human studies (17, 47), and in addition, the therapeutic effects of acupuncture are also shown in various categories of diseases. A study of Eccleston et al. (48) showed that patients with chronic non-cancer pain after 6 weeks of acupuncture had lower consumption of opioids compared with the placebo group. Acupuncture may be an effective and safe pain-reducing treatment in palliative care for cancer patients that can help reduce the side effects of opioid use, including insomnia, constipation, and anxiety, according to a systematic review published in the BMJ (49). Chen et al. (50) conducted a meta-analysis which analyzed nine articles from the US, UK, and China involving 1,063 patients and concluded that acupuncture could be an effective treatment for OUD, among them, electroacupuncture could relieve opioid cravings and depression symptoms, and transcutaneous acupoint electrical stimulation is beneficial to the improvement of insomnia and anxiety. Following this, our research complements the effectiveness of manual acupuncture for OUD. Compared with methadone maintenance alone, the addition of acupuncture therapy could not only reduce the consumption of methadone, but also lowered cravings and improved insomnia. The therapeutic effect was better than methadone maintenance therapy alone (44, 51). These results are consistent with the results of our study. Our study outcome directly shows that in the group that was treated with acupuncture therapy, the daily dosage of methadone was significantly decreased, drug cravings based on the VAS score table were greatly lessened, and the insomnia score was also improved. Acupuncture therapy is also effective for other types of addictive diseases. Zeng et al. (52) observed that electroacupuncture helped improve psychiatric symptoms and anxiety and depression in methamphetamine addicts during abstinence in a 68-sample RCT using placebo needles as the control group. In a three-arm trial conducted at a German addiction center, Krause et al. (53) observed that ear acupuncture may improve autonomic cardiac function in alcohol addicts. We can say that acupuncture therapy as adjuvant treatment for addictive diseases has considerable potential and development prospects.

Furthermore, it should be noted that acupuncture treatment is cost-effective. In this study, after 6 weeks of treatment, we see that the CER value of reducing daily methadone dosage in the group that had been treated with acupuncture was dramatically lower than the MMT only group. In addition, as to the ICER, although the incremental cost-effectiveness ratio of acupuncture was not high, acupuncture's health value from the perspective of effectiveness deserves serious consideration, such as reduced drug usage, reduced drug cravings, and improvement of sleep. In other words, the extra cost it pays to get better results is in line with economic values. From the perspective of effectiveness, it is proven that acupuncture therapy has cost-effectiveness. But the cost-utility of acupuncture is not obvious. Its advantages are not positive either from a CUR or ICUR perspective. This may be due to the fact that acupuncture therapy mainly improves opioid dependence symptoms, while QALY is a comprehensive

indicator, including physical, psychological, and social aspects. Therefore, its effect on QALY improvement is not obvious. In all, these results suggest that the short-term economic benefits of acupuncture treatment in MMT patients are certain, and the long-term benefits can be further explored.

This research is meaningful. OUD imposes a significant economic burden on both individuals and society. It is of great significance to learn what method we choose to achieve better benefits with fewer costs to reduce the economic burden brought by OUD. We conducted this economic evaluation on acupuncture as an adjuvant therapy for MMT patients from a social perspective. The purpose was to provide decision-makers with an economic and effective reference for treatment strategies. Given that economic benefits of acupuncture are identified above, choosing acupuncture as an adjuvant treatment for MMT patients has the benefits of low expense, reliable effects, and security.

The strengths of this study are obvious. First, the pragmatic study design allowed the evaluation of clinical data of acupuncture for opioid-dependent patients receiving MMT in the RCT. Second, we collected both effectiveness indexes (daily dosage of methadone, VAS, and PSQI) and a utility index (SF-36) to evaluate clinical outcomes, whereas most evaluation studies only collected effectiveness indexes. Third, different types of costs were included in the evaluation. Fourth, it provides a new alternative treatment for opioid-dependent patients.

However, this study has some limitations which can be addressed in future studies. Firstly, the study had a relatively small sample size which may introduce uncertainty in the clinical results. Secondly, there was a gender difference between the two groups due to the absence of some participants. Though there is no evidence that gender difference would affect the efficacy of acupuncture on addictive diseases so far, it is an undeniable pity for us. And we may investigate this further through real-world studies. Thirdly, in the analysis of QALY, it is possible that a substantial QALY difference cannot be detected due to the short follow-up time. Until our study was conducted, no Chinese value set based on the mainland Chinese population was available and we used the UK population-based value set for the calculation of QALYs. So it is not clear whether our utility result is acceptable. We have planned to launch a new clinical trial next, which will have a larger sample size and a longer period of treatment and follow-up and use the Chinese-specific value set for the calculation of QALYs. Last, our country lacks authoritative data for reference, which leads to controversy over socially acceptable cost to raise a QALY cost. And taking foreign social willingness to pay standards as a reference may lead to misjudgment of the results (34). Hence, research on the treatment of MMT patients with acupuncture therapy still needs further development and improvement.

CONCLUSION

Acupuncture therapy showed advantages in reducing the daily dosage of methadone and improving VAS score and PSQI score for opioid-dependent patients receiving MMT when compared with routine treatment. The results of this study also showed the dominating cost-effectiveness advantage and potential cost-utility advantage for the exposed group. Therefore, this study can help to inform prescription practice for opioid-dependent patients receiving MMT, and the health care system can adjust or formulate policies to reduce the disease burden of opioid-dependent patients receiving MMT and improve their quality of life.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Ethics Committee of the First Affiliated Hospital of Guangzhou University of Chinese Medicine (No. Y-2019-241). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LL, YL, and SX contributed to the conception, design of the study, and contributed to the critical revision of the article for important intellectual content. HW and XW drafted the manuscript. HW, XW, JZ, and SG performed the acupuncture treatment for patients. HW, XW, and YL analyzed data. WL, RC, and YD collected and registered data. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.689753/full#supplementary-material

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Cost-Effectiveness Analysis of Vedolizumab Compared With Infliximab in Anti-TNF-α-Naïve Patients With Moderate-to-Severe Ulcerative Colitis in China

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Objective: To evaluate the cost effectiveness of vedolizumab vs. infliximab in the treatment of anti-tumor necrosis factor-alpha (TNF-α)-naïve patients with moderate-to-severe active ulcerative colitis (UC) in China.

Methods: The costs and effectiveness of vedolizumab and infliximab in the treatment of anti-TNF-α naïve patients with moderate-to-severe active UC were compared using a hybrid decision tree model and a Markov model. From the perspective of the Chinese healthcare system, this study simulated the lifetime health benefits [quality-adjusted life-years (QALYs)] and costs (USD) for patients with UC from the induction phase to the maintenance phase, with an annual discount rate of 5%. The clinical efficacy and transition probability data were based on a previously published network meta-analysis. The health utility, surgical risk, biologic drug discontinuation rate, and mortality were derived from previous literature and the Chinese statistical yearbook. The cost data were based on China's drug purchase and biding platform and the results of a survey sent to clinicians in 18 tertiary hospitals. One-way and probabilistic sensitivity analyses (PSAs) were performed to validate the robustness of the models' assumptions and specific parameter estimates.

Results: The results of the base-case analyses showed that compared with infliximab, vedolizumab led to a gain of 0.25 QALYs (9.56 vs. 9.31 QALYs) and was less expensive by $7,349 ($180,138 vs. 187,487), indicating that the use of vedolizumab was a dominant strategy. The results of one-way sensitivity analyses suggested that the annual discount rate and health-state costs had the greatest impact, but the results were otherwise consistent with those of the base-case analyses. The PSAs suggested that vedolizumab had a 98.6% probability of being effective at a threshold of 3 times the gross domestic product (GDP) per capita in China in 2020.

Conclusion: Compared with infliximab, vedolizumab appears to be a more cost-effective option in the treatment of anti-TNF-α naïve adult patients with moderate-to-severe, active UC in China.

Keywords: ulcerative colitis, vedolizumab, infliximab, cost-effectiveness analysis, China

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INTRODUCTION

Ulcerative colitis (UC) is an idiopathic, chronic inflammatory bowel disease (IBD), the cause of which is attributed to the interactions between genetic and epigenetic factors, including microbial factors (1). UC is a disease of the colonic mucosa caused by an inflammatory response mediated by T-helper 2 cells, presenting with typical symptoms of blood in the stool and diarrhea (2). It's reported that approximately 6.8 million patients living with IBD in 2017 (3). The prevalence of IBD increased from 79.5 per 100,000 persons in 1990 to 84.3 per 100,000 persons in 2017 globally (3). The highest reported annual incidence and prevalence of UC in Northern Europe were 24.3 per 100,000 person-years and 505 per 100,000 person-years, respectively (2, 4). The corresponding incidence and prevalence of UC reported in Asia and the Middle East were 6.3 per 100,000 person-years and 168.3 per 100,000 person-years, respectively (4). Among Asian countries, the annual incidence of UC is relatively high in China (5), with a mean of 1.18 per 100,000 person-years in China, and the disease primarily affects male patients (sex ratio: 1.29) (5). Among Chinese UC patients, 69.8% had moderate-to-severe disease (5).

Patients with UC have been reported to have a high disease burden, a poor quality of life, increased healthcare utilization, and decreased work productivity, leading to a high economic burden (6–9). It was estimated that the mean cost of IBD was $26,255 per patient in the first year after being diagnosed in 2007–2016 in United States (10). The estimated annual economic burden of UC between 2004 to 2016 in Canada has been reported to be risen from C$6,364 to C$49,327 in the first year after being treated with anti-TNF-α drugs, furthermore, it rose to C$245,260 for UC patients in the 5 years (11). In China, the per capita medical cost of patients with IBD in 2018–2019 has been reported to be $11,668 (12).

Currently, UC disease management strategies focus on the remission of clinical symptoms and endoscopic healing in the active stages (13). Therapeutic strategies mainly include treatment with conventional drugs and biologic agents (1). Conventional therapy consists of aminosalicylic acid, corticosteroids (i.e., budesonide, prednisolone), and immunosuppressants (14), whereas biologic agents mainly include anti-tumor necrosis factor-alpha (TNF-α) drugs, such as infliximab in China. Compared with conventional therapy, biologic agents can improve clinical remission and response and mucosal healing rates during induction and maintenance treatment in patients with moderate-to-severe active UC (typically defined as a Mayo score of 6–12. Mayo score is evaluated from four categories to assess the severity of UC: stool frequency, rectal bleeding, findings of flexible proctosigmoidoscopy or colonoscopy, and physician's global assessment. Each of category is scored on a scale from 0 to 3, therefore, the maximum of total score is 12 points) (14, 15). However, 10–30% of patients with IBD have reported no response to the initial anti-TNF-α treatment, and an additional 23–46% of patients with IBD may lose their response to the treatment (16). Patients with inadequate therapeutic response may require surgical intervention, which may further increase the economic burden (17, 18).

Another biologic agent, vedolizumab, is a gut selective biologic therapy that binds exclusively to the $\alpha_4\beta_7$ integrin and inhibits adhesion of lymphocytes to mucosal address in cell adhesion molecule-1 (MAdCAM-1), thereby preventing lymphocytic cells from entering the gut lamina propria and gut-associated lymphoid tissue (19). As vedolizumab exerts its effects gut selectively, the systemic anti-inflammatory effects observed with anti-TNF-α drugs are not observed after treatment with this agent (19). Previous clinical studies have reported the efficacy and adverse events of vedolizumab in anti-TNF-α-naïve and anti-TNF-α-failure patients (20, 21). In China, infliximab and vedolizumab have been approved by the Chinese National Medical Products Administration (NMPA) for the treatment of moderate-to-severe active UC. Infliximab has been used for UC for over 10 years in China, whereas vedolizumab was approved for use in March 2020. To be covered by China's national health insurance, the retail price of vedolizumab was reduced by 71% in 2020. Up to now, there's no biosimilar infliximab has been approved in China and it may have some impact on the price of infliximab in the future.

The aim of this study is to assess the cost effectiveness of vedolizumab vs. infliximab in patients with anti-TNF-α-naïve active UC from the perspective of the Chinese healthcare system and better inform healthcare decision-making in China.

METHODS

Model Structure

To assess the cost effectiveness of vedolizumab vs. infliximab in patients with moderate-to-severe active UC, a hybrid simulation model was used. The model consisted of a decision tree model component for assessing the induction therapy and a Markov model component with lifetime follow-up for assessing the maintenance therapy (22). In the decision tree model, patients with UC were treated with either infliximab or vedolizumab and evaluated for treatment efficacy after a 6-week induction period. subsequently, patients who responded to the biologic without discontinuation due to intolerability of adverse events were entered into the Markov model for assessing the maintenance therapy. Conversely, patients who did not respond were switched to conventional treatment (e.g., a combination of aminosalicylic acid preparations, glucocorticoids, and immunosuppressants) within the decision tree model. Patients with a clinical response to conventional therapy then entered the Markov model for assessing the maintenance treatment with conventional drugs, whereas those who did not respond to conventional drugs persisted in the moderate-to-severe disease health state until they required surgery (**Figure 1A**).

For the assessment of maintenance therapy, several health states were included in the Markov model to compare the cost effectiveness of vedolizumab and infliximab (**Figure 1B**): remission (Mayo score: 0–2), mild (Mayo score: 3–5), moderate-to-severe (Mayo score: 6–12), surgery, post-surgery remission,

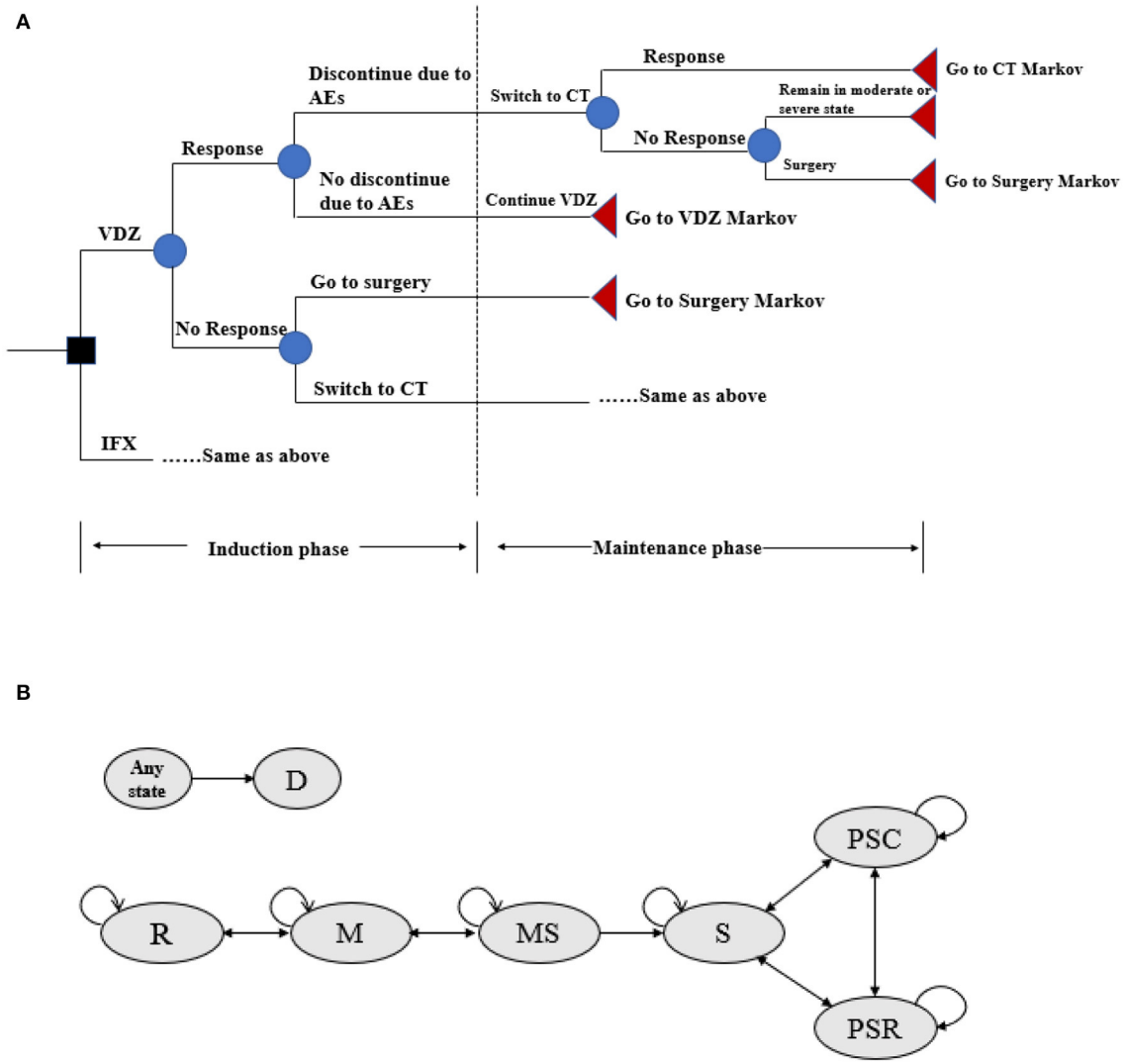


FIGURE 1 | (A) Decision tree model structure for VDZ and IFX. AEs, adverse events; CT, conventional therapy; IFX, infliximab; VDZ, vedolizumab. Response defined as reduction in Mayo score by ≥3 or a remission Mayo score < 3. **(B)** Markov model structure of maintenance therapy. R, remission; M, mild; MS, moderate-to-severe; S, surgery; PSR, post-surgery remission; PSC, post-surgery complications; D, death.

post-surgery complications, and death. The cycle length was set to 8 weeks (in accordance with the administration frequency of infliximab and vedolizumab in the maintenance period in clinical trials) (20, 21), and patients could transfer from one health state to another with a certain probability that depended on the patient's health status and treatment. Death could occur at any cycle, and patients can transfer to the death state from any other state. After 1 year of treatment with vedolizumab or infliximab, patients who were still in a moderate-to-severe health state were switched to conventional treatment or surgery due to a loss of response (22). Patients who transferred to surgery would discontinue their current treatment for the remainder of their lifetime. Following surgery, these patients could subsequently experience postsurgical complications (i.e., staple line ulcers, anastomotic strictures, pouchitis), require additional surgeries, or remain in postsurgical remission (22). Patients who responded to the biologic or were in remission but discontinued the drug due to adverse event intolerability were assumed to have switched to conventional therapy during the maintenance phase.

From the perspective of the Chinese healthcare system, this model simulated the development of lifetime disease in patients with moderate to severe active UC, and the cost was reported as US dollars in 2020. Quality-adjusted life-years (QALYs) and costs were discounted at an annual rate of 5% (23).

Model Inputs and Data Sources

Target Patient Population

The patient population in this study was Chinese adult patients with moderate-to-severe active UC, defined as a Mayo score of ≥6, who did not respond to conventional therapy and had

not previously received anti-TNF-α therapy. Based on interviews with Chinese clinical experts (**Supplementary File 1**) and data from the literature (24), a hypothetical cohort of 1,000 patients (48.6% male) with an average age of 36 years old and a weight of 60 kg was simulated in the model.

Treatment Comparators

Among biologics, only infliximab (Remicade®, intravenous injection, 100 mg/vial, Xian Janssen) and vedolizumab (Entyvio®, intravenous injection, 300 mg/vial, Takeda) have been approved for the treatment of UC in China. Hence, vedolizumab and infliximab were included for comparison in this study. Vedolizumab was given intravenously at weeks 0, 2, and 6 of the induction period and 300 mg once every 8 weeks in the maintenance period without dose escalation. Infliximab was injected 5 mg/kg at weeks 0, 2, and 6 of the induction period and every 8 weeks in the maintenance period without dose escalation.

Clinical Efficacy and Transition Probability

The clinical efficacy at the end of the induction and maintenance phases was measured based on the presence of a clinical response and remission. The effect was observed at the 6th week of the induction treatment and the 52nd week of the maintenance treatment, and the proportion of patients with a clinical response or remission was evaluated. The clinical efficacy and transition probability were presented in **Table 1** and **Supplementary Table 1** (25, 32–34).

Adverse Events and Discontinuation

The types and incidence of common adverse events in different comparator regimens, and discontinuation rates were based on published literature (**Table 1**) (26–31). The incidence of adverse events in each cycle was assumed to remain unchanged. In addition, infliximab and vedolizumab could be withdrawn due to a lack of response or adverse event. Therefore, patients needed to stop using the biologic agent and switch to traditional therapy.

TABLE 1 | Model inputs for clinical efficacy, adverse events, and discontinuation.

	VDZ	IFX	CT	References
Clinical efficacy				
At the end of induction phase				
6-week probability of response	62.35%	68.18%	34.29%	(25)
6-week probability of remission	30.25%	33.41%	8.93%	(25)
During the maintenance phase				
Annual probability of response	80.58%	56.71%	44.04%	(25)
Annual probability of remission	57.48%	31.65%	27.16%	(25)
Incidence of AEs				
Serious infection	0.48%	0.50%	3.47%	(26–29)
Tuberculosis	0.00%	0.00%	0.92%	(26–29)
Malignancy (including lymphoma)	0.04%	0.08%	0.06%	(26–29)
Acute hypersensitivity reactions	0.00%	0.00%	1.19%	(26–29)
Skin site reactions	0.29%	4.11%	4.93%	(26–29)
Probability of discontinuation				
Induction phase	3.08%	3.08%*	–	(27, 30, 31)
Maintenance phase per cycle	5.19%	5.19%*	–	(27, 30, 31)

**Due to limited data for infliximab, similar discontinuation rates were assumed as vedolizumab.*

VDZ, Vedolizumab; IFX, Infliximab; CT, conventional therapy.

Mortality

In the Markov model, age- and sex-specific all-cause mortality rates were used to estimate the probability of death over time. The relationship between age and mortality was fitted by an exponential function and adjusted each cycle based on the mortality of the Chinese general population (26, 35, 36).

Cost Estimation

In this study, the costs of biologic agents, injection management fees, costs of conventional drugs, health state costs, and costs related to the treatment of adverse events were included (**Table 2**). The cycle prices of vedolizumab and infliximab were based on the average price of China's provincial drug bidding for medical insurance reimbursement (37, 38). Other costs were derived from the expert interviews performed with 18 directors and deputy directors of tertiary hospitals in China (details in **Supplementary File 1**). The infusion management fee was $47.5 per cycle based on the clinical physician survey. For conventional treatment, the combination of different drugs and daily costs are presented in **Supplementary Table 2**. Among these drugs, mesalazine accounted for the highest proportion (70%), followed by prednisolone (42%), and the cost of each treatment cycle was $433.8.

According to the Mayo score, UC can be divided into three states: remission, mild disease, and moderate-to-severe disease. Patients in the moderate-to-severe state need to be hospitalized, and those with severe UC may require surgical intervention. After surgery, patients may experience remission or complications, which could increase the treatment costs. The health state costs and costs for the treatment of a single adverse event were based on the results of the expert interviews (**Supplementary File 1**).

Health Utilities

Health utility values were derived from published literature (**Table 2**) (39, 40). Utility decrements for adverse events were identified through a targeted review of the available published literature (41–45).

Cost-Effectiveness Analysis

The incremental cost-effectiveness ratio (ICER) was calculated based on the lifetime costs and QALYs (calculated by multiplying the health utility and the corresponding time living with this status and discounted at each cycle) for each intervention. Half-cycle correction was used to balance the Markov model, which changed only at the end of each cycle (46). To explore the main factors affecting the results, one-way sensitivity analysis was carried out by varying one parameter at a time while all others were held constant. The variations in these parameter values were based on a credible range of estimates (95% confidence interval, or ±20% when the data were not available). For instance, a lower price (a price reduction of 20%) for infliximab was applied in

TABLE 2 | Model inputs for costs and health utility.

	Costs ($)	Utility	References
Drug cost per cycle			
Vedolizumab induction phase	2,309.1	–	(37)
Infliximab induction phase	2,791.5	–	(38)
Vedolizumab maintenance phase	769.7	–	(37)
Infliximab maintenance phase	930.5	–	(38)
Conventional therapy*	433.8	–	Expert Survey
Administration cost per cycle*			
Vedolizumab	47.5	–	Expert Survey
Infliximab	47.5	–	Expert Survey
Health-state costs per cycle*		Health-state utility	
Remission	129.4	0.88	(39, 40)
Mild	162.5	0.76	(39, 40)
Moderate-severe	913.2	0.42	(39, 40)
Surgery	5,905.1	0.42	(39, 40)
Postsurgery remission	1,040.0	0.60	(39, 40)
Postsurgery complications	4,673.9	0.42	(39, 40)
Costs of AEs per event*		Decremental AE utility	
Serious infection	1,446.2	−0.47	(41)
Tuberculosis	660.7	−0.50	(42)
Malignancy (including lymphoma)	10,389.8	−0.18	(43)
Acute hypersensitivity reactions	208.8	−0.10	(44)
Skin site reactions	39.7	−0.03	(45)

**Cost information is based on a survey of 18 clinicians from 18 tertiary hospitals in China. AE, adverse event.*

the model to explore the impact on the results. A probabilistic sensitivity analysis (PSA) with 5,000 iterations was performed by varying all parameters at the same time according to pre-specified distributions. The cost parameter followed a gamma distribution, the utility and percentage parameters followed a beta distribution, and the transition probability followed a Dirichlet distribution (47). Utilizing 3 times the gross domestic product (GDP) per capita of China in 2020 ($31,500) as the upper limit of the threshold of willingness-to-pay (WTP), the economic burden of different intervention regimens was compared (23). The analysis was performed in Microsoft Excel 2019.

RESULTS

Base-Case Analysis

The results of the base-case analyses of vedolizumab and infliximab are presented in **Table 3**. The lifetime costs associated with vedolizumab treatment were lower than those associated with infliximab treatment ($180,138 vs. 187,487; mean difference: –$7,349). Similarly, the costs for biologic therapy ($4304 vs. 5,746; mean difference: –$1,442) and of the health state ($142,326 vs. 149,182; mean difference: –$6,856) were also lower for patients treated with vedolizumab. In terms of health outcomes, vedolizumab patients were expected to gain 0.25 QALYs (9.56 QALYs vs. 9.31 QALYs) over patients treated with infliximab, which mainly contributed by more patients living with remission (2.39 QALYs vs. 1.97 QALYs) and mild (1.53 QALYs vs. 1.39 QALYs) health states. Therefore, compared with infliximab, vedolizumab appears to be a dominant strategy (more QALYs gained and less cost incurred).

TABLE 3 | Base-case analysis results.

	VDZ	IFX	Difference
Costs	180,138	187,487	−7,349
quad Biologic therapy	4,304	5,746	−1,442
Conventional therapy	32,642	31,716	927
Health-state costs	142,326	149,182	−6,856
Adverse event costs	867	844	22
Outcomes			
QALYs	9.56	9.31	0.25
ICER ($ per QALY gained)			Dominant

ICER, incremental cost-effectiveness ratio; VDZ, vedolizumab; IFX, infliximab; QALY, quality-adjusted life-years.

One-Way Sensitivity Analysis

The results of the one-way sensitivity analyses are presented in **Figure 2**. The incremental cost per QALY gained was most sensitive to the change in annual discount rate, followed by health-state costs and the remission transition probability. However, the ICRE values were not over –$20,000. In addition, the reduction in the price of infliximab (20%) in the model did not have much impact on the results and the maximum value of ICER was still negative. With the variation in each factor, the results did not exceed the WTP threshold ($31,500), and compared with infliximab, vedolizumab remained cost-effective. The results of one-way sensitivity analyses suggested the robustness of the model and base-case analysis.

Probabilistic Sensitivity Analysis

After 5,000 iterations, the average lifetime costs of vedolizumab and infiximab strategies were $166,222 and 167,805 (mean difference: –$1,583), respectively. In addition, the average QALYs of vedolizumab and infiximab strategies were 9.70 QALYs and 9.40 QALYs (mean difference: 0.30 QALYs), respectively. The results of the PSA are illustrated in **Figure 3**. The PSA results were consistent with those of the base-case analysis, suggesting that compared with infliximab, vedolizumab had a 98.6% probability of being cost effective at a threshold of 3 times the GDP per capita in China in 2020 and that it was dominant (less costly and more effective) in 79.1% of simulations.

DISCUSSION

To our knowledge, this is the first study in China attempting to compare the cost effectiveness of vedolizumab and infliximab in adult patients with moderate-to-severe active UC who have had an inadequate response to, lost their response to, or were intolerant to conventional therapy using a hybrid decision tree

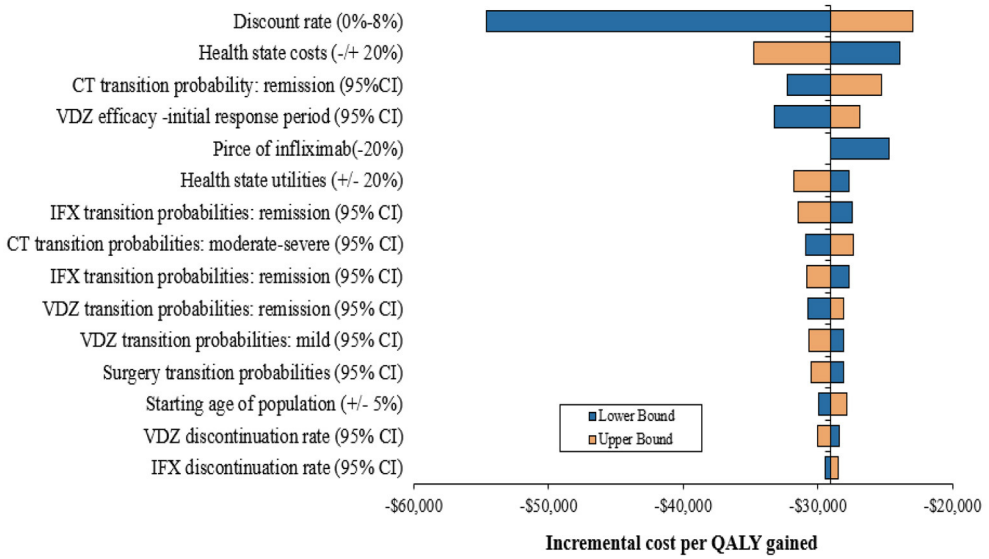


FIGURE 2 | One-way sensitivity analysis results. CT, conventional therapy, IFX, infliximab, VDZ, vedolizumab; CI, confidence interval.

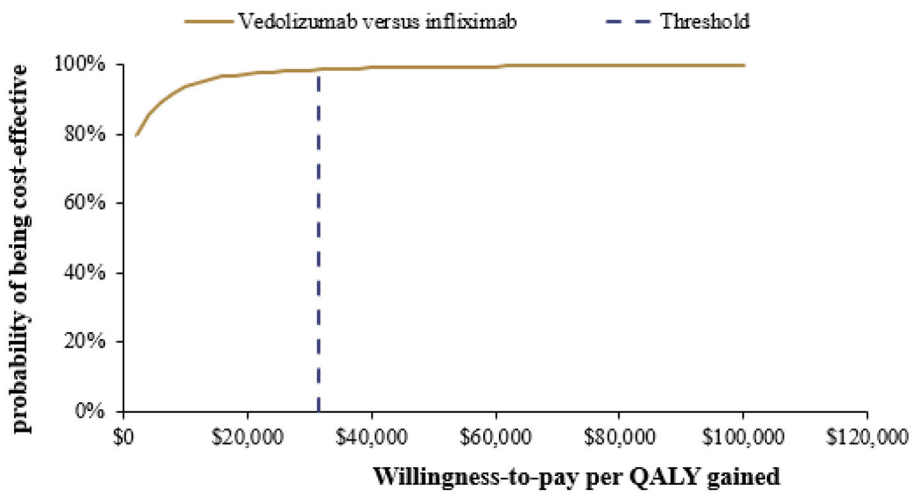


FIGURE 3 | Cost-effectiveness acceptability curve for vedolizumab vs. infliximab. QALY, Quality-adjusted life-year.

and Markov model. The base-case analysis results suggested that, compared with infliximab, vedolizumab incurred lower costs and was expected to gain more QALYs in Chinese patients with UC. In the one-way sensitivity analysis of vedolizumab vs. infliximab, the annual discount rate was the most significant influential factor, followed by health state costs. The results of the one-way sensitivity analysis and PSA were in line with those of the base-case analysis.

The results of this study are similar to those reported in Japan (48) and the United Kingdom (UK) (25). Compared with that of infliximab, the ICER of vedolizumab over a lifetime was JP¥ 4,687,692 (about US$42,300 in 2018) per QALY gained for adult anti-TNF-α-naïve patients with moderate-to-severe active UC in Japan, and the drug was considered cost effective (48). The probability of being cost effective strategy of vedolizumab was higher compared with infliximab at a threshold of JP¥ 5,000,000 in Japan (48). The study by Wilson et al. (25) suggested that compared with infliximab, vedolizumab incurred lower costs and gained more QALYs in the UK, which is in line with the base-case analysis in our study. Furthermore, the vedolizumab was a dominant strategy in 97.6% cases compared to infliximab in the PSA at a threshold of £30,000 in the UK (25).

Under the drug review and approval policy in China, vedolizumab was approved with exemption from a domestic clinical trial by the Chinese NMPA in 2020 to accelerate access to innovative drugs. Hence, the clinical efficacy data in this model

were generated from multicenter clinical trials. Since there are no head-to-head comparison studies between vedolizumab and infliximab, data from an indirect comparison network meta-analysis were used to calculate the probability of clinical response and remission (25). The response and remission probabilities for the anti-TNF-α-naïve UC population were derived from odds ratios (ORs) estimated in a mixed-treatment comparison in the meta-analysis (25). Given the clinical efficacies were not derive from direct comparison, some bias may be present in that study. However, the economic evaluation model and results were submitted to the National Institute for Health and Care Excellence (NICE) for Single Technology Appraisal in the UK, and the quality of the network meta-analysis was also assessed by NICE's Evidence Review Group (ERG) (49). In this study, the uncertainty of the data derived from that network meta-analysis was tested by performing sensitivity analysis.

Due to a lack of head-to-head comparative trials between vedolizumab and infliximab, the efficacy data of each treatment regimen were derived from a previous network meta-analysis (23). In addition, it was assumed that patients who needed surgery would stop using the biologic agent, while the probabilities of transferring to postsurgical complications, discontinuation, and death were derived from published studies (25, 32–34). The initial annual mortality rate was 0.00104 per 100,000 persons, the first cycle mortality rate was 0.00012 per 100,000 persons, and the coefficient of variation of mortality per cycle was 1.015 (35). As the disease progressed, the risk of death increased. It was assumed that the relative risks (RRs) of death in the remission and mild disease health states were the same, whereas those in the moderate-to-severe disease and surgery health states were 1.9 (36) and 1.3 (26), respectively.

For health state utility, utility weights as measured with the EQ-5D were mainly estimated based on a survey of patients with UC in Cardiff Hospital (39, 40). The study surveyed patients who had undergone surgery at least 6 weeks prior (39, 40), but the cycle length in the Markov model was 8 weeks. A survey response obtained at least 6 weeks later would not accurately reflect the quality of life for a patient who had undergone surgery during the model cycle in which the surgery occurred. Patients were expected to have a quality of life less than moderate to severe disease for the 2 weeks following the surgical procedure before progressively improving for the remainder of the cycle when they transitioned to post-surgical remission, postsurgical complications, or subsequent surgery. Therefore, patients undergoing surgery were assumed to have the same utility values as those with moderate-to-severe disease in this study.

To reduce the economic burden on patients, the coverage of high-value but high-price drugs by the national medical insurance has required negotiation with the National Healthcare Security Administration to reach an agreement after 2017 in China (50). At present, only vedolizumab and infliximab are approved for treating patients with UC and are listed in the National Reimbursement Drug List in China. Hence, these two drugs were compared in this study. To be covered by Chinese medical insurance, the retail price of vedolizumab was reduced by 71%, which mainly contributed to the cost-effective results (37). Vedolizumab and infliximab are reimbursed for anti-TNF-α Naïve patients with active UC and the co-payment varies across the provinces in China. At present, biosimilar infliximab is not available in China; the price of infliximab applied in this model was the average price of China's provincial drug bidding for medical insurance reimbursement in 2020, which is a relatively low but stable price (38). Nevertheless, the price of infliximab was reduced (20%) in the sensitivity analysis to explore the impact of price on the results, and we found that the drug remained cost effective.

This study also has some limitations. First, in the model analysis, only the direct medical cost of the treatment regimen was considered. Indirect costs and non-medical costs for the treatment of UC were not included. Therefore, the economic differences among patients receiving different treatments may have affected the results of the cost-effectiveness analysis. Second, as there are no head-to-head comparison studies for vedolizumab and infliximab, the data used in this study were derived from an indirect network meta-analysis, which may have led to bias in the economic evaluation. Third, although biologic drug discontinuation due to adverse event intolerability or loss of response was considered in this study, the data were mainly derived from randomized controlled trials, whose results may be different from those in real-world clinical practice. Fourth, due to the lack of data on the health utility value of the Chinese UC population, this study used data from published literature that reported utility values of patients in other countries. However, the sensitivity analysis results suggest that the variation in the utility values applied in the model had little impact on the cost-effectiveness analysis.

CONCLUSION

This study suggests that compared with infliximab, vedolizumab appears to be a more cost-effective first-line treatment option for anti-TNF-α-naïve adult patients with moderate-to-severe active UC in China.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

All the data included in this analysis were derived from published literature, public data and expert survey results. No patient-identifiable data were applied or used. Therefore, institutional review board approval was not required.

AUTHOR CONTRIBUTIONS

TZ and HG contributed to the design of this study. TZ, YS, HG, RM, and ZW collected the data. TZ and YS performed the analysis. TZ, HG, and YS prepared the manuscript. RM and ZW helped to revise the manuscript. All authors approved the final version of this study.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.704889/full#supplementary-material

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Cost-Effectiveness of Dronedarone and Amiodarone for the Treatment of Chinese Patients With Atrial Fibrillation

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Background: Atrial fibrillation (AF) is one of the most common arrhythmias in clinical practice, which brings great economic burden to patients. This study evaluated the economics of the new antiarrhythmic drug dronedarone and provides suggestions for allocation of health resources.

Methods: Amiodarone was selected as the control group, and the Markov model of AF was established using nine states. The total cost and quality-adjusted life year (QALY) of dronedarone and amiodarone groups were calculated and compared. The incremental cost effectiveness ratio (ICER) value was calculated and compared with the willingness to pay (WTP) and the sensitivity analyses was conducted.

Results: For China's healthcare system, the ICER of the dronedarone group compared with the amiodarone group was RMB 81,741 Yuan/QALY, which is lower than the current recommended WTP (3 times GDP per capita). Sensitivity analyses showed that the model was robust, and the drug price of dronedarone significantly impacted the results.

Conclusions: Compared with amiodarone, dronedarone is more economical in the Chinese healthcare system. However, due to the lack of data on the Chinese population for some parameters, the model needs further improvement and discussion. Real-world studies on the effects of dronedarone on Chinese patients with AF would be beneficial.

Keywords: atrial fibrillation, cost-effectiveness analysis, dronedarone, amiodarone, China

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INTRODUCTION

Atrial fibrillation (AF) is one of the most common arrhythmias in the clinic. As of 2017, there were an estimated 37.57 million patients with AF worldwide (1). The lifetime risk of AF in people over the age of 14 years is 26% for men and 23% for women (2). According to an epidemiological survey of 726,451 people in 31 provinces and regions in China in 2017, the standardized incidence of AF among people over 40 years old in China was 2.31%, and with increasing age, the prevalence in women (2.72%) was significantly higher than that in men (1.90%) (3).

The disease burden of AF is heavy, as it may lead to complications such as stroke, thromboembolism, heart failure (HF), myocardial infarction (MI), cognitive decline, dementia, and renal impairment, which can seriously affect patients' quality

of life (QoL) and increase their financial burden. The utility value of patients with AF (≥35 years old) measured by the European Five Dimension Health Scale (EQ-5D) scale is 0.53, and the total disability-adjusted life year (DALY) lost due to AF is 665,400 DALY (4).

Zhang et al. (5) found that stroke is the primary cause of the direct economic burden of AF in China, and the treatment cost of stroke caused by AF reaches 4.9 billion RMB every year, of which 89% is from patients with AF and stroke over 60 years old. Therefore, the QoL of patients with AF in China is low, and the economic burden is heavy. Current treatment of AF includes stroke prevention, ventricular rate control, rhythm control, and surgical and hybrid surgical treatment (6). Rhythm control is one of the important strategies for the treatment of AF, and the recovery and maintenance of sinus rhythm is also an indispensable part of the treatment. Currently, commonly used drugs for the maintenance of sinus rhythm include amiodarone, dronedarone, propafenone, sotalol, and flecainide. Among them, dronedarone is used for long-term rhythmic control of paroxysmal and persistent AF. Dronedarone is a new antiarrhythmic drug on the market, which went on the market in 2009. Its chemical structure is similar to amiodarone and clinical trials are numerous. ATHENA trial have shown that dronedarone can reduce the rate of first cardiovascular hospitalization and cardiovascular mortality in patients with non-permanent AF (7). The incidence of the main safety endpoint (MSE: the first occurrence of thyroid-, hepatic-, pulmonary-, neurologic-, skin-, eye-, or GI-specific events, or premature study drug discontinuation following an adverse event) was in the dronedarone group compared with amiodarone group (8).

In recent years, several economic evaluations in various countries have compared dronedarone with other antiarrhythmic drugs (9–13), and most of them have shown that dronedarone is more economical (9–12) than similar drugs for maintaining sinus rhythm. However, no studies on the economic evaluation of dronedarone have been based on the Chinese population; thus, it is unknown if the same conclusions can be applied to China. Therefore, the Markov model was used in this study to evaluate the economic performance of dronedarone in China. Amiodarone was selected as the control group based on the advice and guidelines of clinical experts, quality-adjusted life year (QALY) was used as output, and the incremental cost-effectiveness ratio (ICER) was calculated. The results may provide policy makers and health care providers with practical recommendations to help them make decisions and promote the rational and efficient allocation of health resources.

METHODS

Overview

We evaluated the cost-effectiveness of dronedarone. The Markov model was used in this study, which can simulate disease progression process through the transfer probability. The outputs in the model were QALY and ICER. The model was conducted from the perspective of the health care system in China. Therefore, only direct health care costs were included and expressed as 2020 values. Both costs and outcomes were discounted by 5% per year (14).

The study group was dronedarone, and the control group was amiodarone. The baseline characteristics of patients were determined based on a multicenter cross-sectional epidemiological survey from the Chinese Atrial Fibrillation Registry published by Sun et al. (15). The initial age was set at a mean age of 68.3 years old, and the female proportion was set at 46.9%.

The Markov model was established in Excel (Microsoft, Redmond, WA, USA) to simulate outcomes and costs. Based on the disease diagnosis and treatment guidelines and the opinions of clinical experts, the model was in a lifetime simulation and the cycle period was set at 1 year.

Model Structure and Assumptions

The model was based on a simulation of 1,000 individuals in the dronedarone and amiodarone groups. According to "The Understanding and Treatment of AF: Current Recommendations" (6), patients with AF could also face some complications such as HF, stroke, and MI. According to the opinions of clinical experts, the previous pharmacoeconomic evaluation model, the severity and frequency of the complications and the availability of data, other complications were not considered. Therefore, the above mentioned three complications were included in the model, and the additional complications were no longer considered. Most patients with paroxysmal or persistent AF are still at high risk of recurrence after restoration of sinus rhythm, so recurrence was included in the model as a separate state, and the risk of a patient's acute episode (recurrence) was considered in each cycle. Moreover, the adverse reactions of patients were taken into account in each cycle.

Based on the existing economic evaluation of AF, the 9-state Markov model was constructed: AF, off treatment, stroke, post-stroke, MI, post-MI, HF, post-HF, and death. The patient enters the model circulation from the state of "AF," In each cycle, patients with AF are likely to have adverse reactions related to antiarrhythmic drugs. Acute episodes of AF may occur during each cycle in patients with AF, patients in off treatment and patients with each complication. We assumed that only one recurrence of atrial fibrillation occurred per patient per cycle. The model structure and cycle events are shown in **Figures 1**, **2**.

In the process of maintaining sinus rhythm, the treatment plan will be adjusted due to adverse reactions, efficacy, and other reasons. However, according to the guidelines, amiodarone is a relatively backline option, so the model assumed that patients would enter the state of off treatment when they had poor efficacy or intolerance. In addition, the model's assumptions are as follows: (1) Patients will remain in the state of stroke, MI, and HF for one cycle, and then enter the state of post-stroke, post-MI, or post-HF. (2) All disutility and increased utility are calculated one time. (3) Since AF generally does not directly cause death, it is assumed that the mortality of atrial fibrillation is the same as the natural mortality. (4) The costs of rate control drugs were included in off treatment and complication status. Patients discontinued the use of the antiarrhythmic drugs in off treatment,

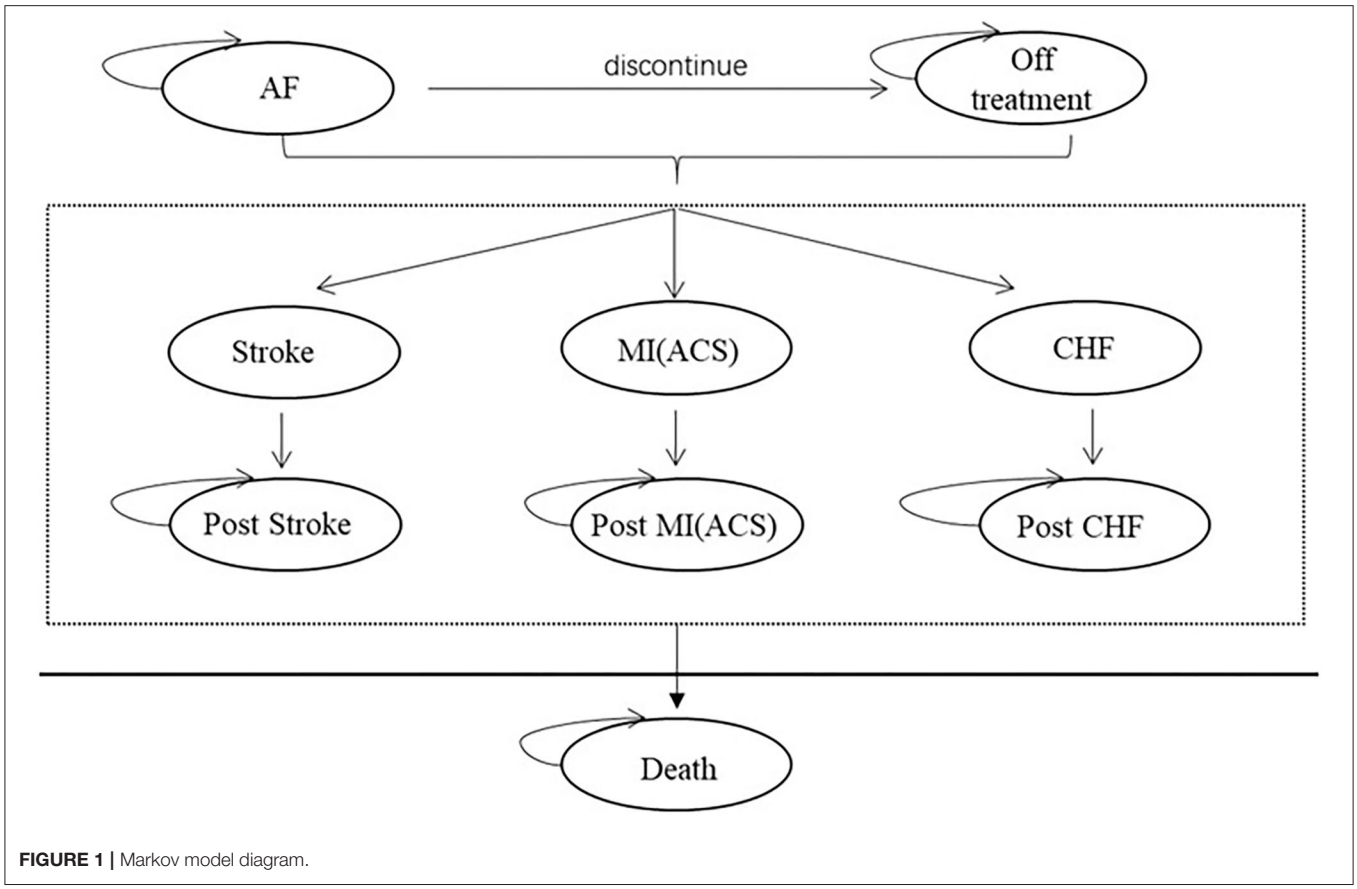


FIGURE 1 | Markov model diagram.

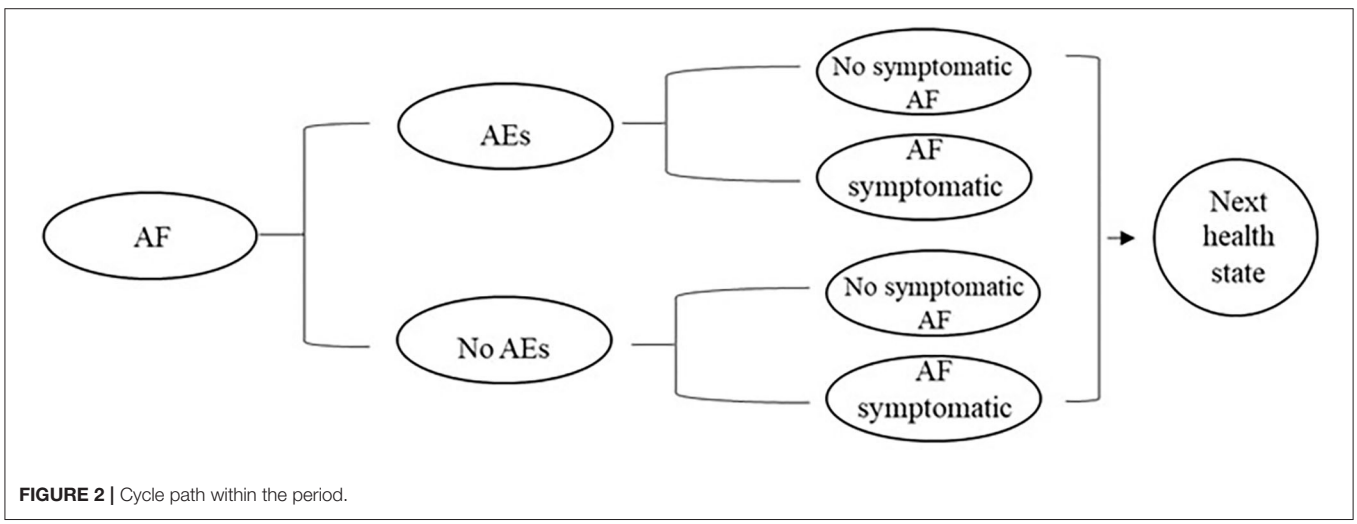


FIGURE 2 | Cycle path within the period.

then using rate control drugs. The patients were not taking the rate control drugs while taking the rate control drugs.

Model Inputs

Transition Probabilities

The transition probability between disease states in the model includes drug withdrawal rate related to drug treatment order, the incidence of various types of complications, and mortality. The transition probability parameters are shown in **Table 1**. The discontinuation rate in the study was based on the annual discontinuation rate of patients in the dronedarone group in the ATHENA study (7), and the discontinuation rate of amiodarone was calculated based on the odds ratio (OR) in an indirect comparative study by Freemantle et al. (16) that

TABLE 1 | Values and distribution of model parameters.

Parameter	Base analysis value	Lower limit	Upper limit	Distribution
Mortality				
Stroke vs. natural mortality (RR)	7.4000	6.5000	8.5000	Lognormal
Post-stroke vs. natural mortality (RR)	2.3000	2.0000	2.7000	Lognormal
MI-male vs. natural mortality (RR)	6.1700	5.9800	6.3600	Lognormal
MI-female vs. natural mortality (RR)	8.6700	8.4100	8.9400	Lognormal
Post-MI male vs. natural mortality (RR)	1.4700	1.3900	1.5500	Lognormal
Post-MI female vs. natural mortality (RR)	2.0200	1.9100	2.1500	Lognormal
HF 65–74	0.2200	——	——	Beta
HF male > 75	0.3500	——	——	Beta
HF female > 75	0.3000	——	——	Beta
Post-HF vs. natural mortality (RR)	1.7400	1.3900	2.0900	Lognormal
IPD vs. natural mortality (RR)	2.1000	1.6000	2.7000	Lognormal
ALI	0.0028	——	——	Beta
Complications				
AF to Stroke: dronedarone	0.0395	0.0237	0.0553	Beta
AF to Stroke: amiodarone vs. dronedarone (HR)	2.0000	1.3000	3.2000	Lognormal
AF to MI: dronedarone	0.0320	——	——	Beta
AF to MI: amiodarone	0.0420	——	——	Beta
AF to HF: dronedarone	0.1209	0.0895	0.1522	Beta
AF to HF: amiodarone vs. dronedarone (HR)	2.7000	2.0000	3.6000	Lognormal
Off treatment to Stroke vs. AF to Stroke (HR)	1.3514	1.0989	1.6667	Lognormal
Off treatment to MI vs. AF to MI (HR)	1.6949	−0.8621	3.3333	Lognormal
Off treatment to HF vs. AF to HF (HR)	1.2658	1.0417	1.5385	Lognormal
Off treatment				
Off treatment: dronedarone	0.1860	——	——	Beta
Off treatment: amiodarone vs. dronedarone (OR)	1.0000	0.6300	1.5800	Lognormal
Recurrence				
Recurrence: dronedarone	0.6345	——	——	Beta
Recurrence: amiodarone	0.4196	——	——	Lognormal
Off treatment Recurrence vs. dronedarone (OR)	1.6949	1.3158	2.2222	Lognormal
Incidence of adverse reactions				
IPD: dronedarone	0.0219	0.0105	0.0334	Beta
IPD: amiodarone vs. dronedarone (HR)	1.0000	0.5000	2.0000	Lognormal
ALI: dronedarone	0.0076	0.0009	0.0142	Beta
ALI: amiodarone vs. dronedarone (HR)	2.2000	0.8000	6.2000	Lognormal
Hyperthyroidism: dronedarone	0.0080	——	——	Beta
Hyperthyroidism: amiodarone	0.0588	——	——	lognormal
Cost (Yuan)				
Dronedarone	13140	10512	15768	Gamma
Amiodarone	1145	916	1134	Gamma
Examination: dronedarone	2992	2394	3590	Gamma
Examination: amiodarone	2300	1840	2760	Gamma
Anticoagulant	1620	1296	1944	Gamma
Rate control drugs	983	786	1179	Gamma
Stroke	25796	20637	30955	Gamma
Post-stroke	8696	6957	10435	Gamma
MI	65736	52589	78883	Gamma
Post-MI	8544	6835	10253	Gamma
HF	9189	7352	11027	Gamma
Post-HF	3038	2431	3646	Gamma

(Continued)

TABLE 1 | Continued

Parameter	Base analysis value	Lower limit	Upper limit	Distribution
Recurrence (per time)	213	171	256	Gamma
IPD	21380	17104	25656	Gamma
ALI	9735	3011	16459	Gamma
Hyperthyroidism	5837	4670	7005	Gamma
Utility				
AF	0.8100	0.6480	0.9720	Beta
Stroke	0.5600	——	——	Beta
Post-Stroke	0.7200	——	——	Beta
MI	0.6700	——	——	Beta
Post-MI	0.7300	——	——	Beta
HF	0.6850	——	——	Beta
Post-HF	0.741	——	——	Beta
Disutility: recurrence	0.0840	0.0672	0.1008	Beta
Disutility: IPD	0.1900	0.1520	0.2280	Beta
Disutility: ALI	0.1000	0.0800	0.1200	Beta
Disutility: Hyperthyroidism	0.1000	0.0800	0.1200	Beta

——, Indicates the missing data; IPD, Interstitial pulmonary disease; ALI, Acute liver injury.

included dronedarone, amiodarone, and placebo. When the drug is stopped, the patient will go into off treatment status.

Due to the lack of complication data in the head-to-head clinical studies of dronedarone and amiodarone, the incidence of stroke and HF was derived from a real-world study published by Gao et al. (17) in 2014 based on a United States healthcare database. The study reported the incidence of stroke, HF, and interstitial lung disease among patients taking antiarrhythmic drugs including dronedarone, amiodarone, and propafenone. The incidence of MI was based on real-world data from a Korean pharmacoeconomic evaluation (13). The incidence of the three complications in the discontinuation status was determined by amiodarone complication rate and was adjusted by rate-controlled versus rhythmically controlled hazard ratio (HR) (18) for complications.

The mortality rate of patients with AF is the same as the Chinese population natural mortality rate Stroke and post-stroke mortality rates were adjusted for the relative risk derived from a long-term survival study of stroke patients (19). MI and post-MI mortality were derived from a Danish study. Mortality in patients with new MI was based on mortality within 1 year of MI, and the mortality of post-MI was based on mortality after 1–3 years (20). The mortality rate of patients with HF was derived from a retrospective study of HF patients in Sweden, and the mortality rate of newly emerging patients with HF was based on the 1-year mortality. The mortality rate of post-HF was derived from a retrospective analysis of the SOLVD trial (21). The relative risk of interstitial pulmonary disease mortality was derived from an 11-year national patient-based study (22). The mortality rate of acute liver injury was derived from a retrospective study in China (23).

Recurrence

Relapse parameters are summarized in **Table 1**. The probability of AF recurrence during treatment was derived from the data of the DIONYSOS trial (8) and the probability of recurrence during off treatment was adjusted by OR from an indirect comparative study by Freemantle et al. (16).

Adverse Events

Adverse reaction parameters are shown in **Table 1**. Based on published economic evaluations, efficacy comparisons, and clinical trial data, the high-risk and clinically severe adverse reactions in the use of dronedarone and amiodarone were considered including interstitial pulmonary disease, acute liver injury, and thyroid dysfunction. The incidence of adverse reactions was derived from Hohnloser et al. (7), Le Heuzey et al. (8), and Gao et al. (17).

Cost

The cost parameters are shown in **Table 1**. Since the research perspective is China's healthcare system, the cost considered in the model was direct healthcare. Based on the clinical treatment needs of patients with AF and the opinions of clinical experts, the direct medical cost in this study included drug cost, cost of routine diagnosis and treatment, cost of treatment of complications, cost of adverse reactions, and cost of treatment for recurrent AF (acute AF episode).

The drugs included in the cost were dronedarone, amiodarone, rate-control drugs, and anticoagulants. The drug price is the median bidding price in the bidding database of Minet. It should be noted that since the original drug of dronedarone has not been used clinically in China, we used the price of the generic version of dronedarone (Daxinning, CSPC Ouyi Pharmaceutical Co., Ltd.). Because there are more amiodarone manufacturers, we weighted the cost of amiodarone according to the market share. Patients who stop treatment will use rate-control drugs whose drug cost is included in the total cost. In addition, a certain percentage of patients with AF

receive anticoagulant therapy including warfarin, dabigatran, and rivaroxaban. Based on expert advice, we assumed that 60% of patients received anticoagulant therapy and that warfarin, dabigatran, and rivaroxaban were used at 70, 20, and 10% rates.

The relevant medical items and frequency of use of medical items in the model were determined by "Atrial Fibrillation: Current Knowledge and Treatment Recommendations" (6) and expert consultation. The price of related medical services comes from the medical price documents formulated by the health departments of different cities. In the medical price documents, the median price was taken and weighted according to the proportion of medical institutions of different levels.

Among the costs of complications, stroke and post-stroke costs were derived from an economic evaluation by Ming et al. (24). MI and post-MI costs were derived from economic evaluations of interventional treatment and conservative treatment with drugs of acute non-ST-segment elevation MI based on a Markov model (25). The cost of HF was derived from China Health Statistics Yearbook 2020 (26). Post-HF cost was based on a pharmacoeconomic study published by Sun et al. (27).

Among the costs of adverse reactions, the cost of interstitial lung disease was derived from a study on the etiological classification and disease burden of interstitial lung disease in Fujian, China (28). The cost of acute liver injury was derived from a study measuring the cost associated with drug-induced liver injury, in which we used the cost data of patients hospitalized and whose treatment outcome was improved or cured (29). The cost of hyperthyroidism was derived from China Health Statistics Yearbook 2020 (26).

According to the treatment approach of cardioversion for patients with AF recurrence as stipulated in the guidelines (6), the median price from the medical price documents formulated by the health departments of different cities was taken to calculate the recurrent cost including cardioversion cost, amiodarone treatment cost, consultation fee, bed fee, nursing fee, and intravenous injection fee.

Utilities

The utility value parameters are shown in **Table 1** and were derived from existing health-related outcome studies of AF or other diseases. The utility value of AF status (without obvious symptoms or complications) was derived from a study of health-related QoL (HRQoL) in 743 patients with AF with an average age of 70.2 years in Taiwan, using the EQ-5D (30). The utility value of patients with AF in the model was 0.81 ± 0.25.

The stroke utility value was derived from a prospective multi-center study conducted by Yeoh et al. (31) in Singapore in 2018. In the study, the changes in health utility values at 3 and 12 months after stroke were −0.25 (−0.18, −0.32) and −0.09 (−0.03, −0.15), respectively. Therefore, the model assumes that the utility value will be reduced by 0.25 and maintained for 1 year after the occurrence of stroke, and the utility value will be reduced by 0.09 at 1 year after the occurrence of stroke (post-stroke state).

The value of MI was derived from a longitudinal study by Munyombwe et al. (32) based on data from the EMMACE-3 and EMMACE-4 trials, which measured the value of EQ-5D-3L scale in patients with AF in the United Kingdom at 1, 6, and 12 months of enrolment. The results showed that the mean utility value was 0.62 (standard deviation: 0.28) during hospitalization and 0.78 at 12 months. At the same time, the average utility value of the British population was 0.86. Based on this, it was calculated that the health utility value of the patients was decreased by 0.14 and 0.08, respectively, after MI and at 1 year after the occurrence of MI. Therefore, in the model, the utility value of patients after MI was decreased by 0.14 and maintained for 1 year, and the utility value after 1 year (post-MI) was decreased by 0.08.

The utility value of HF was derived from Jianwei et al. (33) in a study on the disease burden of Chinese patients with HF, in which EQ-5D-5L was used to measure the QoL of patients. The results showed that the average value of utility in patients with HF was 0.725. Since the utility of the normal population was not reported in the study, the QoL of the elderly (people over 60 years) measured by Yu et al. (34) served as the utility value of the healthy population (0.85 ± 0.20) and made a difference in obtaining the disutility value of HF. Therefore, the disutility value for patients with HF used in the study was 0.125. The value of utility after HF was derived from a study that used EQ-5D to measure the change in health utility value of Swedish patients with HF after 1 year, and the results showed that the health utility value of patients with HF after 1 year was increased by 0.06 compared to baseline (35).

The utility value of interstitial lung disease was derived from a study by Szentes et al. (36), and the utility value of patients with interstitial lung disease was reduced by 0.19. The utility value of thyroid dysfunction was from a health outcomes study based on the Korean population (37). Because utility values for acute liver injury have not yet been retrieved, it was assumed that adverse events would reduce them by 0.1 QALY in patients with AF, based on the study by Nilsson et al. (11).

Analytical Methods

First, a basic case analysis was performed, and a deterministic model was run. The values of all necessary parameters were input, the total cost and QALY of the dronedarone and amiodarone groups were calculated and compared, and the ICER value was calculated and compared to the willingness to pay (WTP). The model set WTP as 3 times per capita GDP. According to the statistical data released by the National Bureau of Statistics in 2021, 3 times per capita GDP in 2020 is RMB 217,341 Yuan.

Second, sensitivity analyses were carried out, a one-way sensitivity analyses model and probabilistic sensitivity analysis model were run. In one-way sensitivity analyses, the influence of uncertainty on ICER was tested by changing the value of the parameters. The upper limit or lower limit of the parameter was first determined according to the value and standard deviation in the literature. If neither of the two was determined, the upper limit was assumed to increase by 20%, and the lower limit was assumed to decrease by 20%. The range of the parameters for the one-way sensitivity analysis is shown in **Table 1**. To further verify the robustness of the model 1,000 Monte Carlo simulations were used to conduct probabilistic sensitivity analyses on the cost and utility, and a scatter plot and cost-effectiveness acceptability curve were drawn.

RESULTS

Base-Case Analyses

For the Chinese healthcare system, patients in the dronedarone group received an average of 5.41 QALYs per person during the study period, with a total direct medical cost of RMB 81,862 Yuan per person. Patients in the amiodarone group received an average of 5.14 QALYs per person over the study period, with a direct medical cost of RMB 59,492 Yuan per person.

Compared with amiodarone, the incremental utility of the dronedarone group was 0.27 QALY and the incremental cost was RMB 22,370 Yuan; Compared with amiodarone, patients in the dronedarone group received more health outcomes and spent more, with an incremental cost-effectiveness ratio of RMB 81,740 Yuan/QALY, which is lower than the current commonly recommended WTP (3 times per capita GDP: RMB 217,341 Yuan) in China.

Sensitivity Analyses

One-Way Sensitivity Analyses

The tornado diagram of one-way sensitivity analysis is shown in **Figure 3**. According to the results of one-way sensitivity analysis, the drug price of dronedarone, the discount of utility, the HR value of amiodarone vs. dronedarone in patients with stroke, the utility of AF, the discount of cost all greatly influenced the results. The decrease of the drug price of dronedarone and the discount of utility may cause the decrease of ICER. In the other hand, The decrease of the HR value of amiodarone vs. dronedarone in patients with stroke, the utility of AF and the discount of cost may cause the increase of ICER, making dronedarone an uneconomical regimen.

Probabilistic Sensitivity Analyses

Through 1,000 Monte Carlo simulations, we obtained the scatter in **Figure 4**. Most scatter points are in the first quadrant, which represents dronedarone having higher utility values but also higher costs. The red line in the figure represents the threshold of 3 times GDP per capita, and it can be seen that most of the points were below the threshold, verifying that dronedarone is more economical. The acceptable cost-effectiveness curve is shown in **Figure 5**, where the horizontal axis represents the range of the WTP threshold. The cost-effectiveness acceptability curve showed that when the WTP was 3 times GDP per capita, the dronedarone plan had an 92% probability of becoming more economical than the amiodarone plan. The stability of the basic analysis results was verified.

DISCUSSION

This study was the first to evaluate the economics of dronedarone and amiodarone in Chinese patients with AF, which is of significance for the selection of drugs for sinus rhythm maintenance in Chinese patients with AF and provides evidence of resource allocation for government departments. Based on the results of this study, the dronedarone treatment group had higher cost and utility than the amiodarone treatment group, with an incremental cost-effectiveness ratio lower than 3 times GDP per capita currently commonly used in China, and a higher probability of becoming a more economical regimen.

Many studies have been conducted on the economics of dronedarone in various countries using QALY as health outcome. Åkerborg et al. (9) analyzed the economics of adding dronedarone to the standard care of atrial fibrillation from the perspective of health care payers in Canada, Italy, Sweden and Switzerland. The results showed that dronedarone could increase QALYs by 0.10–0.11, and the incremental cost-effectiveness ratio (ICER) of dronedarone per QALY in Canada, Italy, Sweden and Switzerland were 5,828, 5,873, 14,970, and 8,554 euros respectively, which are less than the thresholds of these countries. Uncertainty analysis shows that the use of dronedarone for lifelong treatment and discount rates have a great impact on the research results. Reynolds et al. (12) and Berg et al. (10) conducted the same study from the perspective of health care payers in the United States and Canada, respectively, and obtained similar results. Nilson et al. (11) analyzed the economics of dronedarone and other antiarrhythmic drugs from the perspective of health insurance payers in Canada, Italy, Sweden and Switzerland. The results showed that compared with amiodarone, sotalol and flecainide, dronedarone can increase 0.68–1.90 QALYs, among which, compared with amiodarone, dronedarone can increase 0.86–1.02 QALYs, and ICER value is lower than the threshold of these countries, compared with other antiarrhythmic drugs, dronedarone may be economical. The results of uncertainty analysis showed that RR of mortalities for amiodarone, sotalol, flecainide to dronedarone, discount rates had a greater impact on the research results. Kim et al. (13) analyzed the economics of rhythm control drugs and rate control drugs from the perspective of Korean medical insurance payers, propranolol and pilsicainide were the most economical of rhythm control drugs and rate control drugs, respectively. Uncertainty analysis showed that the basic analysis results were robust. **Table 2** showed the detailed information. The basic analysis results of this study showed that, when the simulation time was lifetime, compared with amiodarone, dronedarone produced 0.27 more QALYs, and Similar to the results of other studies in which dronedarone could produce more QALYs. In these countries, changes in cost would make ICER significantly different, and more cost would determine whether dronedarone was relatively economical.

From the perspective of clinical efficacy, dronedarone has certain advantages in stroke, HF, myocardial infarction, and other complications as well as thyroid adverse reactions compared with amiodarone, but at the same time, clinical data showed that the RR of dronedarone was higher than that of amiodarone. The RR data were from the DYONISOS trial, but it is important to note that patients in the trial had persistent AF, and according to the applicable scope of the dronedarone, dronedarone was applied to patients with paroxysmal and persistent AF, especially paroxysmal AF. However, due to the uncomprehensive understanding of dronedarone, the trial was not reasonable for the group settings. This may have led to a higher relapse rate among patients in the DYONISOS trial. Due to inclusion of the DYONISOS trial in the meta-analysis of efficacy data and the relatively large sample size, the results of the meta-analysis may

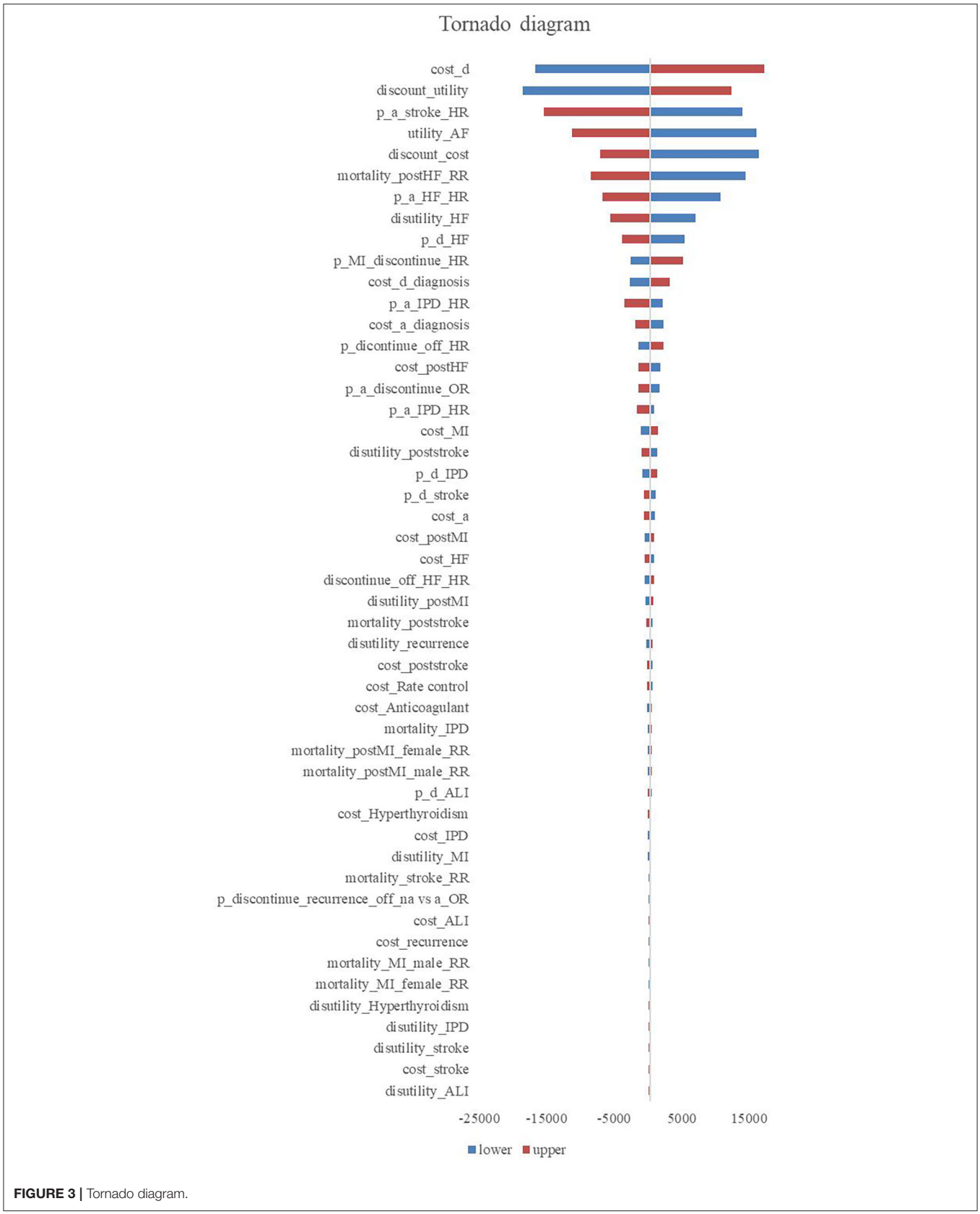


FIGURE 3 | Tornado diagram.

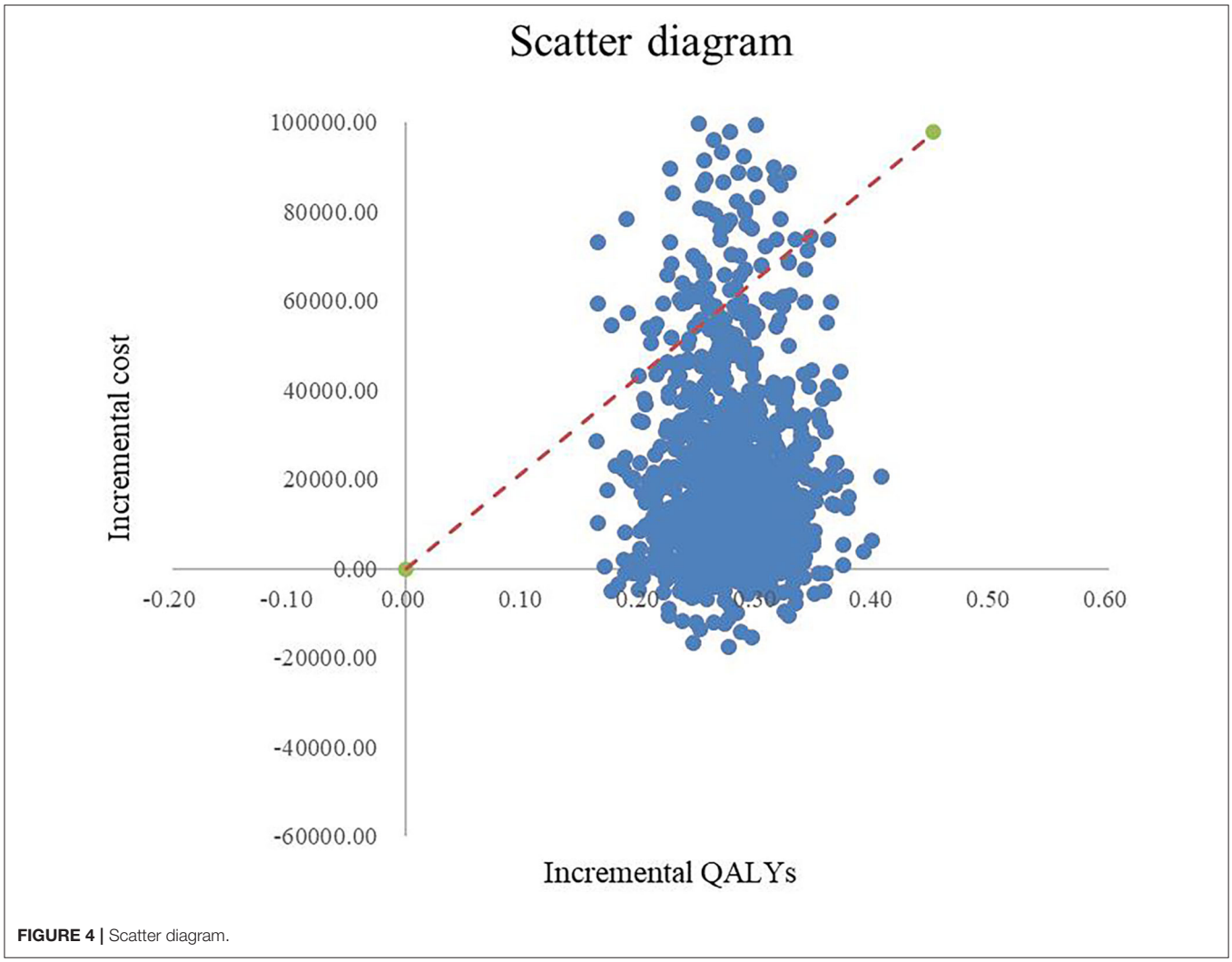


FIGURE 4 | Scatter diagram.

be influenced to some extent, which may also lead to a high RR of dronedarone and an underestimation of the health output of dronedarone.

In addition, according to the results of one-way sensitivity analysis, the HR value of stroke incidence in amiodarone patients compared with the dronedarone patients may have a greater influence on the results, which may be related to the higher incidence and mortality of stroke. Moreover, in the basic analysis, the difference of utility value between the two groups was small, making ICER more sensitive to the change of utility value. Similarly, the incidence and mortality of stroke were higher, so the HR of HF incidence in the amiodarone group compared to the dronedarone group may have also influenced the results.

In terms of cost, the annual drug price of dronedarone was much higher than amiodarone. It can also be seen from the results of the basic analysis that the drug cost in the dronedarone group was much higher than that in the amiodarone group, which became the decisive factor of the cost difference. Although the cost in the dronedarone group was reduced in terms of complications and adverse reactions, it was far from enough to offset the difference in drug costs. Based on the current results, a modest reduction in the price of dronedarone would benefit the health benefits of patients with AF and reduce their financial burden.

This study had some limitations. First, due to the lack of complication comparison in the head-to-head clinical studies of dronedarone and amiodarone, the incidence probability of complications included in the model was mainly derived from real-world studies based on the United States population. Therefore, our study had some population heterogeneity issues, which might result in overestimation or underestimation of results. Second, due to the limitation of data and simplifying the model, we assumed that if patients had intolerance or poor curative effect with the current treatment, they would enter a state of drug withdrawal; this setting may have certain differences in clinical practice. However, after two groups of patients are in the same stopped state, the setting for the effect on two groups of patients is the same; thus, when calculating the incremental

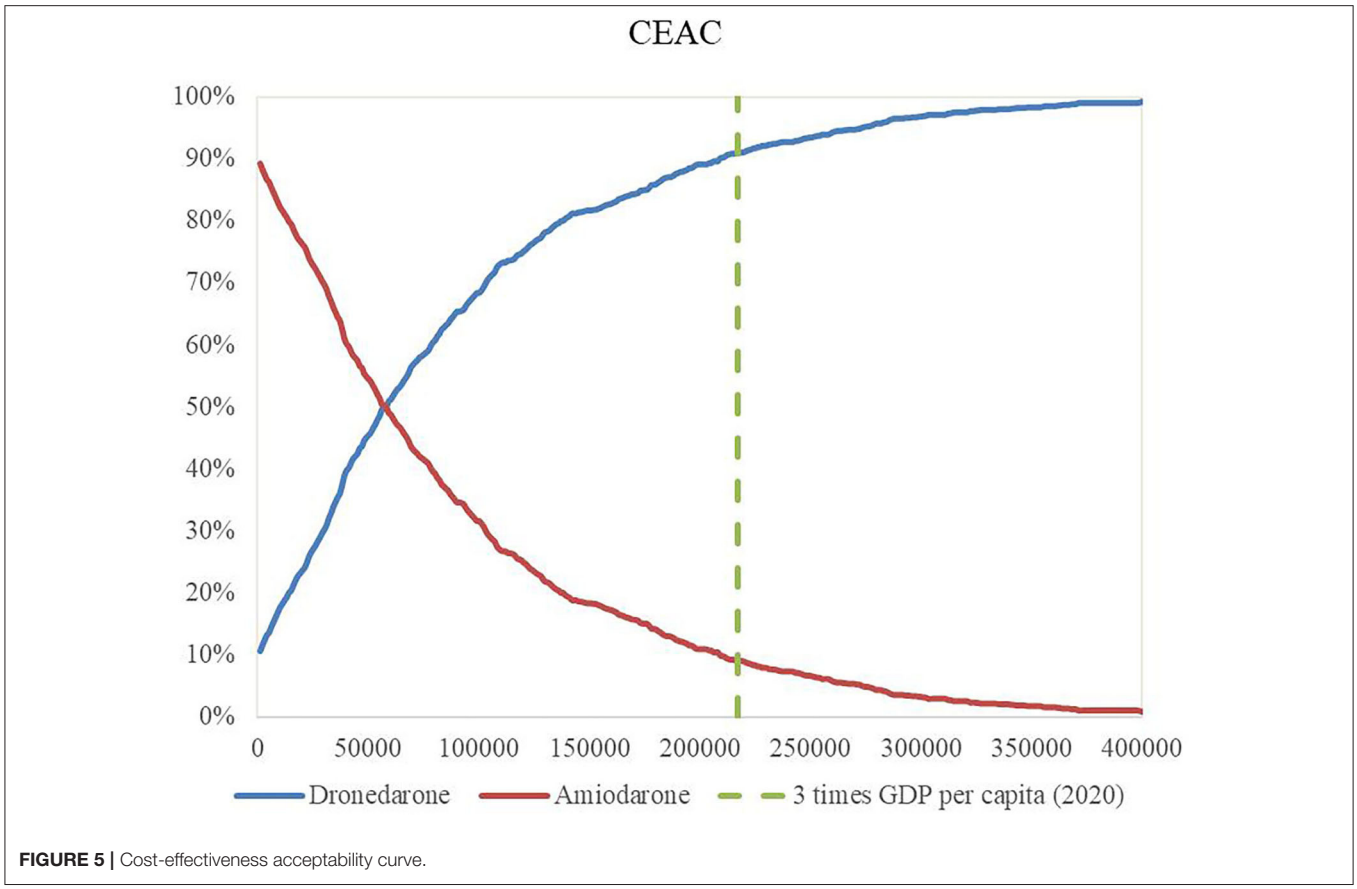


FIGURE 5 | Cost-effectiveness acceptability curve.

TABLE 2 | Information on the economic evaluations of dronedarone.

Study	Country	Comparators	Perspective	Patient population	Time horizon	Incremental QALYs	ICER	Major influence factors
Åkerborg et al. (9)	Canada, Italy, Sweden, Switzerland	Dronedarone + SOC vs. SOC	Health care payer	ATHENA patients	Lifetime	0.10–0.11	€5,828–€14,970	Lifetime therapy with dronedarone, discount rates.
Berg et al. (10)	Canada	Dronedarone +SOC vs. SOC	Health care payer	ATHENA patients	Lifetime	0.13	CAD$7560	Cost of cardiovascular hospitalization.
Nilsson et al. (11)	Canada, Italy, Sweden, Switzerland	Dronedarone vs. amiodarone, flecainide, sotalol	Health care payer	ATHENA patients	Lifetime	0.68–1.9	€2,290–€6,140	RR of mortalities for amiodarone, sotalol, flecainide to dronedarone, discount rates, cost of AF.
Reynolds et al. (12)	US	Dronedarone +SOC vs. SOC	Health care payer	ATHENA patients	Lifetime	0.11	$19,520	Lifetime therapy with dronedarone, no cost associated with AF recurrence on standard of care, discount rates.
Kim et al. (13)	Korea	Rate-control drugs vs. rhythm-control drugs	Health care payer	AF patients who were aged 18 years or older	20 years	2	$1,618	Discount rates, annual drug prices.

SOC, standard of care.

cost-effectiveness, the effect on the results was limited. At the same time, most of the utility data in the study came from the health output studies of foreign patients, and the situation of QoL in different states in the Chinese population needs to be explored. Finally, the treatment of complications such as stroke, HF, and myocardial infarction in the study was complex, and the cost data were derived from the literature and adjusted for the first year, second year, and beyond. However, this method was not derived from the burden of disease study in Chinese patients and needs to be further optimized in terms of accuracy.

In addition, our study will continue to conduct follow-ups, and the results will be updated according to the follow-up data.

CONCLUSIONS

According to the constructed Markov model, the economic evaluation of Chinese patients with AF receiving dronedarone or amiodarone to maintain sinus rhythm was conducted. The results showed that the incremental cost-effectiveness ratio of dronedarone compared to amiodarone was RMB 81,741 Yuan/QALY, lower than the WTP (3 times per capita GDP) commonly recommended in China at present, which was RMB 217,341 Yuan. The drug price of dronedarone, the HR value of HF in patients with amiodarone compared with dronedarone, and the HR value of stroke in patients with amiodarone compared with dronedarone were significant influencing factors of ICER. When the WTP was three times GDP per capita, the dronedarone plan had an 89% probability of being more economical than the amiodarone.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

LT, LW, and JJ designed this study, supervised the data collected, and proposed suggestions for revising the manuscript. Literature analysis were done by MZ, YR, and LW. MZ, YR, and LW built the model using software, collected the data for model, and operated model. MZ drafted the manuscript. All authors critically reviewed the manuscript and approved the final version of the manuscript. All authors agree to be accountable for the content of the work.

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Will the Inducing and Maintaining Remission of Non-biological Agents and Biological Agents Differ for Crohn's Disease? The Evidence From the Network Meta-Analysis

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Background: Several drugs currently are available for the treatment of Crohn's disease, including non-biological agents such as anti-inflammatory agents, steroids, immunosuppressive agents, and biologic agents such as anti-tumor necrosis factor (TNF), anti-α4β7 integrin, anti-alpha-4 integrin and anti-interleukin 12/23. However, the choice of treatments for induction and maintenance is still a challenge. The relevant comparison between non-biologic agents and biologic agents is few. In our research, we aimed to help making decisions, as well as providing clinicians and patients with medication references.

Methods: We searched MEDLINE, Embase, and the Cochrane Central Register of controlled trials for relevant randomized controlled trials published through to July 2020 and systematic reviews published from January 2011 to December 2020. Search results were screened by 2 independent reviewers first by title and abstract and then by full text. Disagreements were resolved through discussion with a third reviewer.

Results: 54 randomized controlled trials were included in our analysis. For induction of remission, azathioprine (OR, 3.5; 95% CrI, 1.4–8.9), infliximab (OR, 4.1; 95% CrI, 1.2–16.0), infliximab + azathioprine (OR, 7.0; 95% CrI, 1.2–41.0) and infliximab+ methotrexate (OR, 7.8; 95% CrI, 1.2–65.0) were more effective in first-line therapy than placebo. Adalimumab showed superiority to placebo in second-line therapy, but the range of SD was wide. For maintenance of remission, adalimumab (OR,2.24;95% CrI,1.17–4.76) and azathioprine (OR,2.05; 95% CrI,1.14–3.96) were more effective than placebo. Adalimumab (OR,0.56; 95%CrI,0.27–1.2), budesonide (OR,0.63; 95%CrI,0.26–1.6) and natalizumab (OR,0.65; 95%CrI,0.30–1.4) was associated with less risk of withdrawals when compared with placebo.

Conclusion: For induction of remission, azathioprine, infliximab, and infliximab + azathioprine were more effective in first-line therapy. In second-line therapy, adalimumab was more effective but should be interpreted carefully. For maintenance of remission, adalimumab and azathioprine were more effective. Besides, adalimumab, budesonide,

natalizumab had lower withdrawals. Therefore, biological agents were not always better than non-biological agents and they have their own advantages in different treatment methods of Crohn's disease.

Keywords: Crohn's disease, network meta-analysis, anti-inflammatory agents, immunosuppressive agents, anti-tumor necrosis factor, biologic agents, steroids

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal tract with symptoms evolving in a relapsing and remitting manner (1). It is also a progressive disease that leads to bowel damage and disability (1). Among adult CD patients, there is no particularly significant difference in the distribution of prevalence between men and women, and this disease usually occurs in young and middle-aged groups who are between 20 and 40 years old (2). The incidence of CD is always increasing in most parts of the world. The incidence and prevalence of CD is higher in developed countries than in developing countries, which is also higher in urban areas than in rural areas (2). It is reported that in addition to intestinal damage and disability, CD can also lead patients to experience symptoms of anxiety and/or depression, which will have a significant impact on quality of life (3). As the disease mechanism of CD remains unknown, a curative therapy is not yet available (4). The purpose of current treatment is to keep patients in remission. There are several drugs currently available for the treatment of CD, including non-biological agents: anti-inflammatory agents (such as mesalazine (5ASA), steroids [such as budesonide(BUD), prednisolone (PED)], immunosuppressive agents [such as azathioprine (AZA) and mercaptopurine (6MP), methotrexate (MTX)], and biologic therapies: anti-tumor necrosis factor (TNF) [such as infliximab (IFX), adalimumab (ADA), certolizumab pegol (CZP)], anti-α4β7 integrin [natalizumab (NTZ)], anti-alpha-4 integrin [vedolizumab(VDZ)] and anti-interleukin 12/23[ustekinumab (UST)] (5). However, the choice of treatments for induction and maintenance is still a challenge. Although there are currently many randomized clinical controlled trials (most of which are placebo-controlled) for traditional non-biological agents and those new biological agents (such as vedolizumab, ustekinumab), relevant head-to-head experiment comparison is few. The head-to-head comparison results can help making decisions, as well as providing clinicians and patients with medication reference.

Network Meta-analysis can help us conduct the integration of multiple clinical trials, especially in the absence of direct comparison evidence (6). Many previously published meta-analyses did not consider whether patients treated with biological agents had previously received treatment with anti-TNF agents, and the efficacy of patients treated with anti-TNF agents was significantly different from those who had not previously received treatment. Therefore, in our study, patients were divided into first-line treatment and second-line treatment according to whether they had received anti-TNF agents before. In addition, most of previously published researches (7–14) also focused on only biological agents, without considering the difference between the efficacy of traditional non-biological agents and biological agents. Some other researches (15, 16) only described the efficacy of immunosuppressants and didn't include some new biological agents. Therefore, based on the direct and indirect evidence in clinical trials, we conducted a network meta-analysis to compare the efficacy of therapies for induction and maintenance of remission including anti-inflammatory drugs, immunosuppressive agents, steroids, anti-TNF drugs, anti-α4β7 integrin, anti-alpha-4 integrin and anti-interleukin 12/23 or their combination in adult patients with CD.

METHODS

Eligibility Criteria

We included all randomized controlled trials that assessed treatments (mesalazine, budesonide, azathioprine, sulfasalazine (SSZ), everolimus (EVE), olsalazine (OLS), mercaptopurine, methotrexate, infliximab, adalimumab, certolizumab pegol, vedolizumab, ustekinumab, natalizumab) alone or in combination in adult patients with CD. We included trials assessing the induction of remission of non-biological and biological agents between 2 and 18 weeks. We include trials assessing the maintenance of remission of remission with at least 24 weeks in duration.

Trials studying only pediatric or postoperative patients and those trials without fixed treatments were excluded (such as standard of care). In addition, studies exclusively assessing fistulizing CD, and those didn't report the clear remission as the outcome were also excluded.

The primary outcome was remission, which was defined as Crohn's Disease Activity Index (CDAI)<=150 or HBI (Harvey-Bradshaw index)<5. We chose the remission criteria defined in the research if the CDAI was not reported. Secondary end point was total withdrawals which was defined as the total number of patients who were withdrawn from the research after randomization for any reason. Eligibility criteria were established using the PICOS (see in the **Supplementary Table 1**). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were also followed (see in the **Supplementary Table 2**).

Literature Search and Study Selection

We searched the relevant systematic reviews from January 2011 to July 2020, and selected the included trials that meet the eligibility criteria. Besides, we performed the database search through to December 2020 in MEDLINE by Ovid, Embase, and the Cochrane Library. The database and systematic reviews search strategies were reported in the **Supplementary Table 3**. Search results were screened by two independent reviewers first

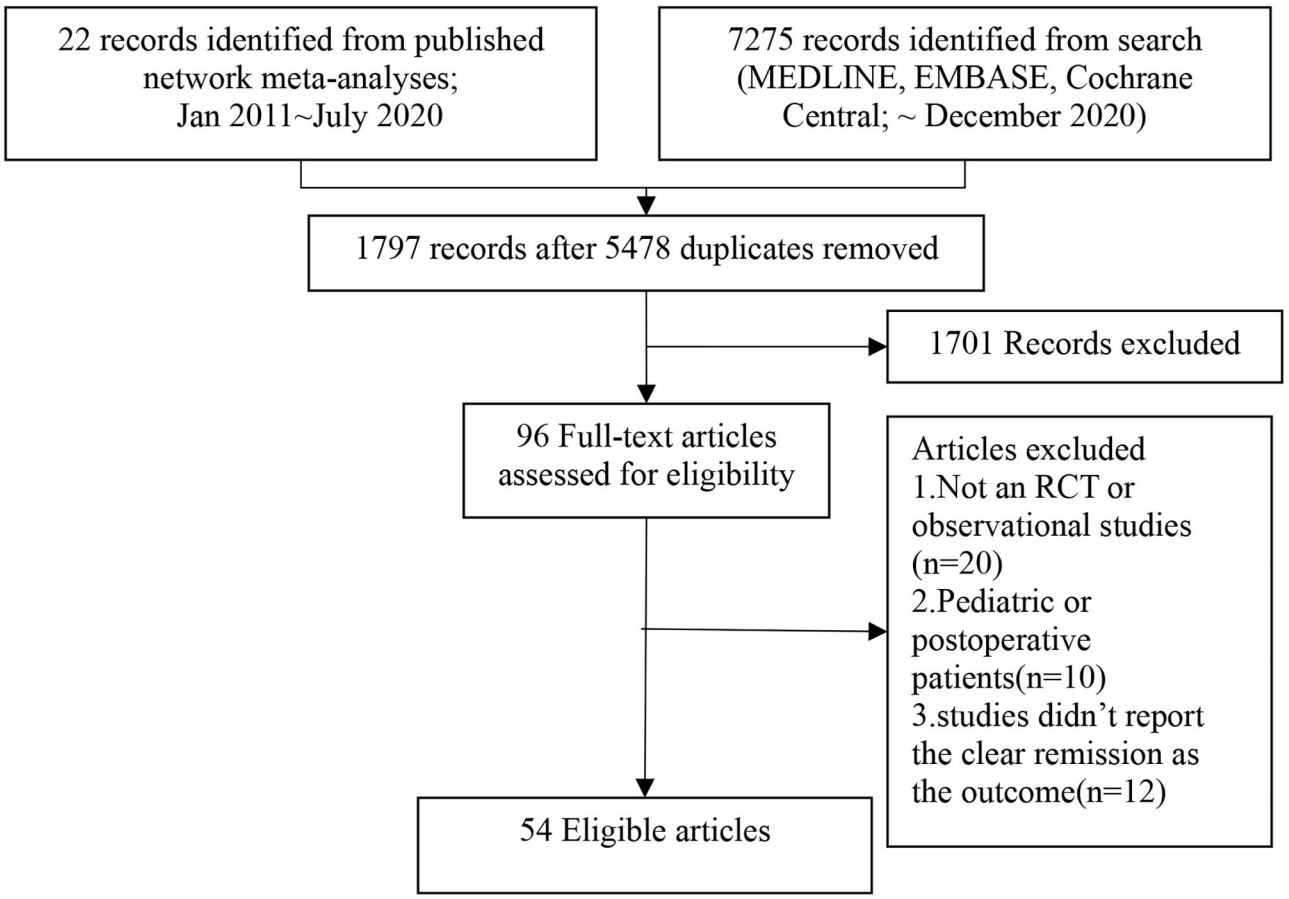


FIGURE 1 | Flow chat of eligible studies selection procedures.

by title and abstract and then by full text. Disagreements were resolved through discussion with a third reviewer.

Data Collection and Quality Appraisal

We extracted relevant characteristics from the relevant study. For induction, some articles reported results several time points, and we chose the result closest to 12 weeks as the primary outcome when the time point of the primary outcome was not specified or induction was not the primary goal of the study. For maintenance, we chose the time points closet to the end of the trial. Total withdrawals were extracted at the end of the trials for both induction and maintenance trials. Baseline disease severity was defined as CDAI (220-450) or HBI > 7.

We extracted the number of patients after randomization and those who experienced the outcome. If the outcomes were only reported in the graphic format, the software Engauge Digitizer 12.0 was used to get the percentages and the number would be calculated and rounded to the nearest whole number. The quality of trials was rated through the Cochrane Risk of Bias tool (17).

Synthesis of Results

We used a random-effects Bayesian network Meta-analysis to research treatment effects for remission and total withdrawals. For the clinical heterogeneity across trials, the random-effects model was more appropriate. R statistical software version 3.6.0 was used to do the statistical analyses with the gemtc package version 0.8-2 (www.r-project.org) and do the funnel plots with the netmeta package. The risk of bias graph was generated by Cochrane RevMan 5.3.

We chose uninformative prior probability distribution for all variables, each model uses 4 Markov chains to set the initial value, and the number of iterations is set to 20,000.

Sensitivity Analyses

In order to assess the robustness of the results, we did several sensitivity analyses for induction of remission, which was following: excluding trials with a high risk of bias; For maintenance of remission, the additional sensitivity analyses were following: including trials whose time points were 1 year or longer; For the withdrawal, the sensitivity analysis was following: including those withdrawal because of the adverse events.

RESULTS

Finally, we included 54 studies. PRISMA flow diagram could be found in **Figure 1**. Characteristics of included trials were

TABLE 1 | First-line therapy network meta-analysis results for induction of remission.

	5ASA	X6MP	ADA	ADAAZA	AZA	BUD	CZP	EVE	IFX	IFXAZA	IFXMTX	MTX	NTZ	OLS	P	SSZ	SSZ6MP	UST	VDZ
5ASA	5ASA	−0.13 (-1.59, 1.26)	−0.06 (-1.49, 1.41)	−0.8 (-3.08, 1.47)	0.65 (-0.58, 1.84)	−0.06 (-0.92, 0.79)	0.26 (-1.04, 1.58)	−0.59 (-2.5, 1.29)	0.80 (-0.66, 2.3)	1.32 (-0.59, 3.23)	1.43 (-0.63, 3.66)	0.44 (-1.6, 2.45)	0.04 (-1.15, 1.25)	**-2.17 (-4.28,−0.11)**	−0.61 (-1.41, 0.15)	−0.85 (-2.72, 0.92)	0.47 (-1.43, 2.29)	0.18 (-1.71, 2.02)	0.17 (-1.35, 1.63)
6MP	0.13 (-1.26, 1.59)	6MP	0.07 (-1.75, 1.99)	−0.67 (-3.2, 1.94)	0.79 (-0.88, 2.47)	0.07 (-1.41, 1.61)	0.39 (-1.32, 2.18)	−0.45 (-2.67, 1.78)	0.93 (-0.9, 2.87)	1.46 (-0.76, 3.71)	1.56 (-0.77, 4.11)	0.57 (-1.77, 2.93)	0.17 (-1.46, 1.9)	−2.04 (-4.42, 0.35)	−0.48 (-1.87, 0.93)	−0.72 (-2.49, 1.01)	0.6 (-1.2, 2.39)	0.31 (-1.88, 2.54)	0.3 (-1.59, 2.21)
ADA	0.06 (-1.41, 1.49)	−0.07 (-1.99, 1.75)	ADA	−0.74 (-2.52, 1.04)	0.72 (-0.75, 2.1)	0 (-1.42, 1.37)	0.32 (-1.31, 1.92)	−0.53 (-2.66, 1.52)	0.86 (-0.47, 2.2)	1.38 (-0.57, 3.31)	1.49 (-0.47, 3.6)	0.5 (-1.76, 2.7)	0.1 (-1.44, 1.63)	−2.11 (-4.43, 0.13)	−0.55 (-1.81, 0.65)	−0.79 (-2.98, 1.27)	0.52 (-1.67, 2.61)	0.23 (-1.88, 2.3)	0.23 (-1.57, 1.95)
ADAAZA	0.8 (-1.47, 3.08)	0.67 (-1.94, 3.2)	0.74 (-1.04, 2.52)	ADAAZA	1.45 (-0.84, 3.69)	0.74 (-1.52, 2.97)	1.06 (-1.34, 3.44)	0.22 (-2.54, 2.91)	1.59 (-0.6, 3.83)	2.12 (-0.51, 4.72)	2.23 (-0.4, 5.01)	1.24 (-1.62, 4.05)	0.85 (-1.5, 3.16)	−1.37 (-4.29, 1.49)	0.19 (-1.98, 2.32)	−0.06 (-2.88, 2.64)	1.27 (-1.57, 4)	0.97 (-1.79, 3.7)	0.96 (-1.57, 3.43)
AZA	−0.65 (-1.84, 0.58)	−0.79 (-2.47, 0.88)	−0.72 (-2.1, 0.75)	−1.45 (-3.69, 0.84)	AZA	−0.71 (-1.85, 0.44)	−0.4 (-1.78, 1.04)	−1.24 (-2.96, 0.48)	0.14 (-1.1, 1.48)	0.67 (-0.92, 2.31)	0.78 (-1.15, 2.89)	−0.21 (-2.29, 1.88)	−0.61 (-1.9, 0.72)	**-2.82 (-4.97,−0.69)**	**-1.26 (-2.19,−0.33)**	−1.51 (-3.47, 0.42)	−0.19 (-2.18, 1.78)	−0.48 (-2.39, 1.46)	−0.49 (-2.05, 1.09)
BUD	0.06 (-0.79, 0.92)	−0.07 (-1.61, 1.41)	0 (-1.37, 1.42)	−0.74 (-2.97, 1.52)	0.71 (-0.44, 1.85)	BUD	0.31 (-0.92, 1.57)	−0.53 (-2.41, 1.32)	0.85 (-0.54, 2.32)	1.38 (-0.46, 3.25)	1.49 (-0.52, 3.69)	0.5 (-1.49, 2.48)	0.1 (-1.02, 1.25)	**-2.11 (-4.17,−0.1)**	−0.55 (-1.23, 0.11)	−0.8 (-2.66, 0.98)	0.52 (-1.37, 2.37)	0.24 (-1.59, 2.05)	0.22 (-1.23, 1.65)
CZP	−0.26 (-1.58, 1.04)	−0.39 (-2.18, 1.32)	−0.32 (-1.92, 1.31)	−1.06 (-3.44, 1.34)	0.4 (-1.04, 1.78)	−0.31 (-1.57, 0.92)	CZP	−0.84 (-2.9, 1.16)	0.54 (-1.08, 2.2)	1.07 (-0.98, 3.09)	1.17 (-1, 3.51)	0.18 (-1.97, 2.29)	−0.21 (-1.61, 1.19)	**-2.43 (-4.64,−0.27)**	−0.86 (-1.93, 0.16)	−1.12 (-3.18, 0.84)	0.21 (-1.88, 2.24)	−0.08 (-2.1, 1.9)	−0.09 (-1.75, 1.54)
EVE	0.59 (-1.29, 2.5)	0.45 (-1.78, 2.67)	0.53 (-1.52, 2.66)	−0.22 (-2.91, 2.54)	1.24 (-0.48, 2.96)	0.53 (-1.32, 2.41)	0.84 (-1.16, 2.9)	EVE	1.38 (-0.62, 3.47)	1.91 (-0.39, 4.26)	2.02 (-0.47, 4.67)	1.03 (-1.51, 3.58)	0.63 (-1.3, 2.64)	−1.58 (-4.19, 1)	−0.02 (-1.75, 1.72)	−0.28 (-2.74, 2.17)	1.06 (-1.46, 3.52)	0.76 (-1.65, 3.21)	0.75 (-1.4, 2.91)
IFX	−0.8 (-2.3, 0.66)	−0.93 (-2.87, 0.9)	−0.86 (-2.2, 0.47)	−1.59 (-3.83, 0.6)	−0.14 (-1.48, 1.1)	−0.85 (-2.32, 0.54)	−0.54 (-2.2, 1.08)	−1.38 (-3.47, 0.62)	IFX	0.53 (-1.12, 2.12)	0.63 (-0.85, 2.25)	−0.36 (-2.64, 1.85)	−0.75 (-2.32, 0.79)	**-2.97 (-5.31,−0.71)**	**-1.4 (-2.72,−0.18)**	−1.65 (-3.86, 0.42)	−0.33 (-2.56, 1.78)	−0.62 (-2.75, 1.45)	−0.63 (-2.47, 1.11)
IFXAZA	−1.32 (-3.23, 0.59)	−1.46 (-3.71, 0.76)	−1.38 (-3.31, 0.57)	−2.12 (-4.72, 0.51)	−0.67 (-2.31, 0.92)	−1.38 (-3.25, 0.46)	−1.07 (-3.09, 0.98)	−1.91 (-4.26, 0.39)	−0.53 (-2.12, 1.12)	IFXAZA	0.1 (-2.07, 2.45)	−0.88 (-3.45, 1.65)	−1.28 (-3.25, 0.7)	**-3.49 (-6.1,−0.92)**	**-1.93 (-3.68,−0.21)**	−2.19 (-4.67, 0.23)	−0.86 (-3.38, 1.57)	−1.15 (-3.6, 1.27)	−1.16 (-3.34, 0.96)
IFXMTX	−1.43 (-3.66, 0.63)	−1.56 (-4.11, 0.77)	−1.49 (-3.6, 0.47)	−2.23 (-5.01, 0.4)	−0.78 (-2.89, 1.15)	−1.49 (-3.69, 0.52)	−1.17 (-3.51, 1)	−2.02 (-4.67, 0.47)	−0.63 (-2.25, 0.85)	−0.1 (-2.45, 2.07)	IFXMTX	−0.99 (-3.8, 1.66)	−1.38 (-3.66, 0.74)	**-3.6 (-6.46,−0.95)**	**-2.04 (-4.15,−0.13)**	−2.29 (-5.06, 0.23)	−0.97 (-3.75, 1.59)	−1.25 (-3.99, 1.27)	−1.26 (-3.76, 1)
MTX	−0.44 (-2.45, 1.6)	−0.57 (-2.93, 1.77)	−0.5 (-2.7, 1.76)	−1.24 (-4.05, 1.62)	0.21 (-1.88, 2.29)	−0.5 (-2.48, 1.49)	−0.18 (-2.29, 1.97)	−1.03 (-3.58, 1.51)	0.36 (-1.85, 2.64)	0.88 (-1.65, 3.45)	0.99 (-1.66, 3.8)	MTX	−0.4 (-2.46, 1.71)	−2.61 (-5.3, 0.06)	−1.05 (-2.92, 0.81)	−1.3 (-3.88, 1.21)	0.03 (-2.57, 2.58)	−0.26 (-2.8, 2.25)	−0.28 (-2.52, 1.98)
NTZ	−0.04 (-1.25, 1.15)	−0.17 (-1.9, 1.46)	−0.1 (-1.63, 1.44)	−0.85 (-3.16, 1.5)	0.61 (-0.72, 1.9)	−0.1 (-1.25, 1.02)	0.21 (-1.19, 1.61)	−0.63 (-2.64, 1.3)	0.75 (-0.79, 2.32)	1.28 (-0.7, 3.25)	1.38 (-0.74, 3.66)	0.4 (-1.71, 2.46)	NTZ	**-2.21 (-4.38,−0.12)**	−0.65 (-1.6, 0.23)	−0.9 (-2.9, 1)	0.42 (-1.6, 2.37)	0.14 (-1.83, 2.04)	0.12 (-1.47, 1.67)

(Continued)

TABLE 1 | Continued

	5ASA	X6MP	ADA	ADAAZA	AZA	BUD	CZP	EVE	IFX	IFXAZA	IFXMTX	MTX	NTZ	OLS	P	SSZ	SSZ6MP	UST	VDZ
OLS	**2.17 (0.11, 4.28)**	2.04 (-0.35, 4.42)	2.11 (-0.13, 4.43)	1.37 (-1.49, 4.29)	**2.82 (0.69, 4.97)**	**2.11 (0.1, 4.17)**	**2.43 (0.27, 4.64)**	1.58 (-1, 4.19)	**2.97 (0.71, 5.31)**	**3.49 (0.92, 6.1)**	**3.6 (0.95, 6.46)**	2.61 (-0.06, 5.3)	**2.21 (0.12, 4.38)**	OLS	1.56 (-0.35, 3.5)	1.32 (-1.31, 3.89)	2.64 (0.02, 5.23)	2.35 (-0.2, 4.92)	2.34 (0.03, 4.63)
P	0.61 (-0.15, 1.41)	0.48 (-0.93, 1.87)	0.55 (-0.65, 1.81)	−0.19 (-2.32, 1.98)	**1.26 (0.33, 2.19)**	0.55 (-0.11, 1.23)	0.86 (-0.16, 1.93)	0.02 (-1.72, 1.75)	**1.4 (0.18, 2.72)**	**1.93 (0.21, 3.68)**	**2.04 (0.13, 4.15)**	1.05 (-0.81, 2.92)	0.65 (-0.23, 1.6)	−1.56 (-3.5, 0.35)	P	−0.25 (-1.99, 1.44)	1.07 (-0.71, 2.82)	0.79 (-0.91, 2.48)	0.77 (-0.5, 2.05)
SSZ	0.85 (-0.92, 2.72)	0.72 (-1.01, 2.49)	0.79 (-1.27, 2.98)	0.06 (-2.64, 2.88)	1.51 (-0.42, 3.47)	0.8 (-0.98, 2.66)	1.12 (-0.84, 3.18)	0.28 (-2.17, 2.74)	1.65 (-0.42, 3.86)	2.19 (-0.23, 4.67)	2.29 (-0.23, 5.06)	1.3 (-1.21, 3.88)	0.9 (-1, 2.9)	−1.32 (-3.89, 1.31)	0.25 (-1.44, 1.99)	SSZ	1.32 (-0.51, 3.18)	1.03 (-1.36, 3.47)	1.03 (-1.09, 3.2)
SSZ6MP	−0.47 (-2.29, 1.43)	−0.6 (-2.39, 1.2)	−0.52 (-2.61, 1.67)	−1.27 (-4, 1.57)	0.19 (-1.78, 2.18)	−0.52 (-2.37, 1.37)	−0.21 (-2.24, 1.88)	−1.06 (-3.52, 1.46)	0.33 (-1.78, 2.56)	0.86 (-1.57, 3.38)	0.97 (-1.59, 3.75)	−0.03 (-2.58, 2.57)	−0.42 (-2.37, 1.6)	−2.64 (-5.23, −0.02)	−1.07 (-2.82, 0.71)	−1.32 (-3.18, 0.51)	SSZ6MP	**-0.29 (-2.73, 2.19)**	−0.3 (-2.45, 1.9)
UST	−0.18 (-2.02, 1.71)	−0.31 (-2.54, 1.88)	−0.23 (-2.3, 1.88)	−0.97 (-3.7, 1.79)	0.48 (-1.46, 2.39)	−0.24 (-2.05, 1.59)	0.08 (-1.9, 2.1)	−0.76 (-3.21, 1.65)	0.62 (-1.45, 2.75)	1.15 (-1.27, 3.6)	1.25 (-1.27, 3.99)	0.26 (-2.25, 2.8)	−0.14 (-2.04, 1.83)	−2.35 (-4.92, 0.2)	−0.79 (-2.48, 0.91)	−1.03 (-3.47, 1.36)	**0.29 (-2.19, 2.73)**	UST	−0.01 (-2.15, 2.12)
VDZ	−0.17 (-1.63, 1.35)	−0.3 (-2.21, 1.59)	−0.23 (-1.95, 1.57)	−0.96 (-3.43, 1.57)	0.49 (-1.09, 2.05)	−0.22 (-1.65, 1.23)	0.09 (-1.54, 1.75)	−0.75 (-2.91, 1.4)	0.63 (-1.11, 2.47)	1.16 (-0.96, 3.34)	1.26 (-1, 3.76)	0.28 (-1.98, 2.52)	−0.12 (-1.67, 1.47)	−2.34 (-4.63, −0.03)	−0.77 (-2.05, 0.5)	−1.03 (-3.2, 1.09)	0.3 (-1.9, 2.45)	0.01 (-2.12, 2.15)	VDZ

5ASA, mesalazine; BUD, budesonide; AZA, azathioprine; 6MP, mercaptopurine; MTX, methotrexate; IFX, infliximab; ADA, adalimumab; CZP, certolizumab pegol; NTZ, natalizumab; VDZ, vedolizumab; UST, ustekinumab; SSZ, sulfasalazine; EVE, everolimus; OLS, olsalazine; P, Placebo. The bold values meant that they were significantly different from the placebo.

shown in **Supplementary Data Sheet 1**. There were 6 trials (18–23) evaluated adalimumab, 4 trials (24–27) evaluated infliximab, 4 trials (28–31) evaluated certolizumab, 3 trials (32–34) evaluated vedolizumab, 1 trial (35) evaluated ustekinumab, 5 trials (36–40) evaluated natalizumab, 9 trials (41–49) evaluated immunosuppressants, 7 trials (50–56) evaluated anti-inflammatory drugs, 9 trials (57–65) evaluated glucocorticoid, 6 trials (66–71) evaluated combination therapy. Forty three trials provided data on induction of remission and 19 trials provided data on maintenance of remission. 46 trials provided the information about the concomitant therapy, which was reported in the **Supplementary Data Sheet 1**. CDAI was used to define remission in most trials except 1 trial (25) which used HBI. The risk of bias was judged to be high in the 7 trials (37, 38, 45, 46, 50, 53, 66). All these 7 trials evaluated the induction of remission and they were excluded in the sensitivity analyses. Model structures were shown in the **Supplementary Table 4**. A detailed assessment of the risk of bias was presented in **Supplementary Table 5** and **Supplementary Data Sheet 2**.

To assess the consistency of the evidence, we used the node-splitting analysis to study whether the results could be jointly summarized and plotted (72). The node-splitting analysis would produce the results by the direct comparison and indirect comparison. If there was no difference between their results, they were consistency. This function could be available by the mtc.nodesplit command in the gemtc package.

Synthesis of Results

Induction of Remission

First-Line Therapy for CD

For the patients who did not receive anti-TNF agents, AZA, IFX, IFX+AZA, IFX+MTX were different from placebo for inducing remission, which could be seen in the **Table 1**. AZA, IFX, IFX+AZA, IFX+MTX had a 1.6, 1.8, 30.8, and 39.3% cumulative probability of ranking highest for induction of remission (**Supplementary Table 6**). The funnel plot showed no significant asymmetry in the **Figure 2**.

In the sensitivity analyses, when we excluded those trials with high bias risk, we could find that AZA, IFX, IFX + AZA were different from placebo for inducing remission, which was reported in the **Supplementary Table 7**.

The node-splitting analysis of inconsistency for induction of remission was reported in the **Supplementary Table 8**.

Second-Line Therapy for CD

For the patients who received anti-TNF agents, ADA, NTZ, UST, VDZ were not different form placebo for inducing remission, which could be found in the **Table 2**, but we could find that the ranges of SD were large, so the reliability of point estimates were low. Instead, the probability of ranking was more credible. We could find that ADA (60%) and UST (21%) might have a higher probability of ranking highest for induction of remission (**Supplementary Table 9**).

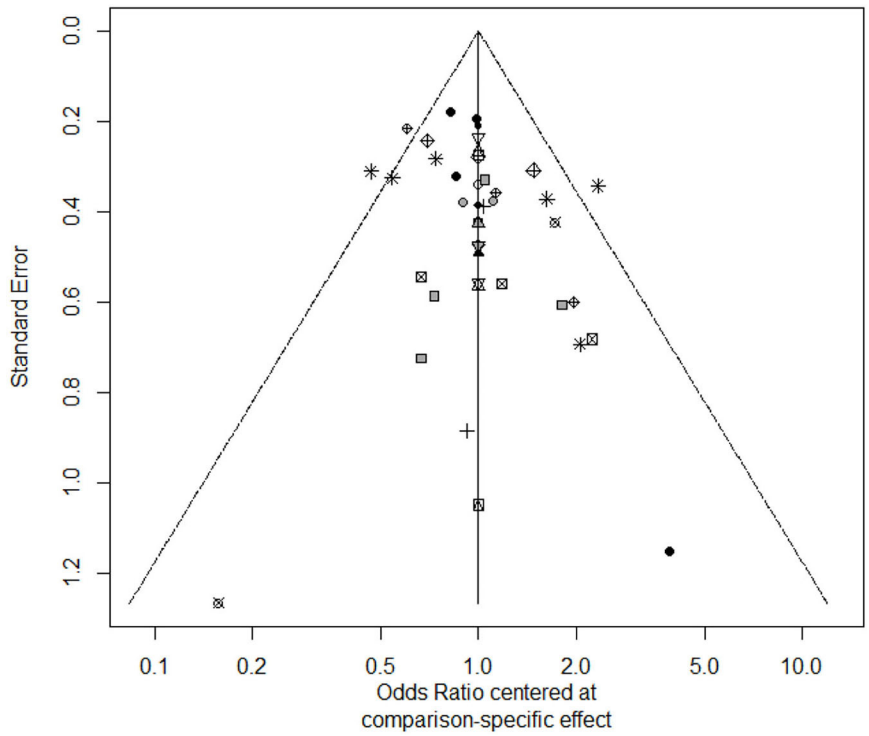


FIGURE 2 | The funnel plot of first-line therapy for induction of remission.

TABLE 2 | Second-line therapy network meta-analysis results for induction of remission.

	ADA	NTZ	P	UST	VDZ
ADA	ADA	−0.84 (−2.69, 0.96)	−1.12 (−2.34, −0.01)	−0.47 (−2.24, 1.23)	−0.94 (−2.73, 0.79)
NTZ	0.84 (−0.96, 2.69)	NTZ	−0.28 (−1.7, 1.1)	0.37 (−1.55, 2.29)	−0.1 (−2.02, 1.81)
P	1.12 (0.01, 2.34)	0.28 (−1.1, 1.7)	P	0.64 (−0.65, 1.95)	0.18 (−1.14, 1.51)
UST	0.47 (−1.23, 2.24)	−0.37 (−2.29, 1.55)	−0.64 (−1.95, 0.65)	UST	−0.46 (−2.32, 1.37)
VDZ	0.94 (−0.79, 2.73)	0.10 (−1.81, 2.02)	−0.18 (−1.51, 1.14)	0.46 (−1.37, 2.32)	VDZ

ADA, adalimumab; NTZ, natalizumab; VDZ, vedolizumab; UST, ustekinumab; P, placebo.

Maintenance of Remission

ADA and AZA were different form placebo for maintenance of remission, and other treatments were not different from placebo, which could be found in the **Table 3**. Rank probability for maintenance of remission was shown in the **Supplementary Table 10**. The funnel plot showed no significant asymmetry in the **Figure 3**.

The node-splitting analysis of inconsistency for maintenance of remission was reported in the **Supplementary Table 11**.

In the sensitivity analyses, when we included those trials whose time points were 1 year or longer, we could find that ADA and AZA were different form placebo for maintenance of remission, which was reported in the **Supplementary Table 12**.

Withdrawals

For total withdrawals, ADA, BUD and NTZ were not different form placebo, because their 95% confidence intervals were wide, which could be seen in the **Table 4**. 6-MP and MTX were associated with more WDAEs than placebo, which could be seen in the **Supplementary Table 13**. The funnel plot showed no significant asymmetry in the **Figure 4**.

The node-splitting analysis of inconsistency for withdrawals was reported in the **Supplementary Table 14**.

DISCUSSION

We conducted a systematic review and network meta-analysis of non-biological agents and biological agents for induction and maintenance of remission in adults with CD. Only head-to-head trials was identified in our network meta-analysis, and the node-splitting analysis was used to assess the consistency of the evidence. The purpose of this research is to help making decisions, as well as providing clinicians and patients with medication reference. For patients with prior exposure

TABLE 3 | Network meta-analysis results for maintenance of remission.

	ADA	AZA	CZP	IFX	IFXAZA	IFXMTX	MTX	NTZ	P	UST	VDZ
ADA	ADA	−0.09 (−1.01, 0.81)	−0.28 (−1.9, 1.23)	−0.43 (−1.35, 0.45)	0.18 (−1.29, 1.61)	−0.41 (−2.1, 1.23)	−0.26 (−1.56, 0.99)	0.16 (−1.48, 1.73)	**−0.81 (−1.56, −0.15)**	−0.46 (−2.08, 1.06)	−0.26 (−1.89, 1.26)
AZA	0.09 (−0.81, 1.01)	AZA	−0.19 (−1.77, 1.3)	−0.34 (−1.22, 0.52)	0.27 (−1.03, 1.55)	−0.33 (−1.99, 1.33)	−0.17 (−1.27, 0.89)	0.25 (−1.35, 1.81)	**−0.72 (−1.38, −0.14)**	−0.37 (−1.94, 1.11)	−0.17 (−1.75, 1.33)
CZP	0.28 (−1.23, 1.9)	0.19 (−1.3, 1.77)	CZP	−0.15 (−1.7, 1.48)	0.46 (−1.43, 2.42)	−0.13 (−2.24, 2.05)	0.02 (−1.71, 1.81)	0.45 (−1.55, 2.45)	−0.53 (−1.91, 0.88)	−0.18 (−2.15, 1.8)	0.02 (−1.95, 2.01)
IFX	0.43 (−0.45, 1.35)	0.34 (−0.52, 1.22)	0.15 (−1.48, 1.7)	IFX	0.61 (−0.68, 1.9)	0.01 (−1.39, 1.43)	0.18 (−1.12, 1.44)	0.6 (−1.08, 2.2)	−0.38 (−1.17, 0.36)	−0.03 (−1.66, 1.54)	0.17 (−1.47, 1.74)
IFXAZA	−0.18 (−1.61, 1.29)	−0.27 (−1.55, 1.03)	−0.46 (−2.42, 1.43)	−0.61 (−1.9, 0.68)	IFXAZA	−0.59 (−2.49, 1.32)	−0.43 (−2.08, 1.19)	−0.01 (−2.01, 1.93)	−0.98 (−2.34, 0.31)	−0.64 (−2.6, 1.26)	−0.44 (−2.42, 1.46)
IFXMTX	0.41 (−1.23, 2.1)	0.33 (−1.33, 1.99)	0.13 (−2.05, 2.24)	−0.01 (−1.43, 1.39)	0.59 (−1.32, 2.49)	IFXMTX	0.16 (−1.77, 2.04)	0.58 (−1.6, 2.71)	−0.39 (−2.02, 1.18)	−0.04 (−2.22, 2.05)	0.15 (−2.03, 2.27)
MTX	0.26 (−0.99, 1.56)	0.17 (−0.89, 1.27)	−0.02 (−1.81, 1.71)	−0.18 (−1.44, 1.12)	0.43 (−1.19, 2.08)	−0.16 (−2.04, 1.77)	MTX	0.42 (−1.39, 2.21)	−0.55 (−1.64, 0.52)	−0.21 (−1.99, 1.55)	−0.01 (−1.79, 1.76)
NTZ	−0.16 (−1.73, 1.48)	−0.25 (−1.81, 1.35)	−0.45 (−2.45, 1.55)	−0.6 (−2.2, 1.08)	0.01 (−1.93, 2.01)	−0.58 (−2.71, 1.6)	−0.42 (−2.21, 1.39)	NTZ	−0.97 (−2.43, 0.47)	−0.63 (−2.64, 1.38)	−0.43 (−2.45, 1.59)
P	**0.81 (0.15, 1.56)**	**0.72 (0.14, 1.38)**	0.53 (−0.88, 1.91)	0.38 (−0.36, 1.17)	0.98 (−0.31, 2.34)	0.39 (−1.18, 2.02)	0.55 (−0.52, 1.64)	0.97 (−0.47, 2.43)	P	0.35 (−1.06, 1.74)	0.55 (−0.87, 1.95)
UST	0.46 (−1.06, 2.08)	0.37 (−1.11, 1.94)	0.18 (−1.8, 2.15)	0.03 (−1.54, 1.66)	0.64 (−1.26, 2.6)	0.04 (−2.05, 2.22)	0.21 (−1.55, 1.99)	0.63 (−1.38, 2.64)	−0.35 (−1.74, 1.06)	UST	0.2 (−1.78, 2.2)
VDZ	0.26 (−1.26, 1.89)	0.17 (−1.33, 1.75)	−0.02 (−2.01, 1.95)	−0.17 (−1.74, 1.47)	0.44 (−1.46, 2.42)	−0.15 (−2.27, 2.03)	0.01 (−1.76, 1.79)	0.43 (−1.59, 2.45)	−0.55 (−1.95, 0.87)	−0.2 (−2.2, 1.78)	VDZ

AZA, azathioprine; MTX, methotrexate; IFX, infliximab; ADA, adalimumab; CZP, certolizumab pegol; NTZ, natalizumab; VDZ, vedolizumab; UST, ustekinumab; P, Placebo. The bold values meant that they were significantly different from the placebo.

to anti-TNF agents would have a great impact on the follow-up treatment effect, we divided the treatments into first-line therapy subgroup (with prior exposure to anti-TNF agents) and second-line therapy subgroup (without prior exposure to anti-TNF agents).

From the results in the first-line therapy for induction of remission, we could find that AZA, IFX, IFX+AZA, IFX+MTX were different from placebo for inducing remission. This finding was inconsistent with the results in the previous study (15), where AZA was not different from placebo for induction of remission in Crohn's disease. This might be because there were more clinical trials included in this study which led to different results. Moreover, although first-line therapy IFX+MTX had a higher-ranking probability, it was based on high bias risk studies. The sensitivity analysis which excluded 6 trials with high bias risk found that there was no significant difference between IFX + MTX and placebo. Therefore, only the combination medication (IFX + AZA) performed better than biologic agent monotherapy or non-biologic agent monotherapy. From the results in the second-line therapy for induction of remission, we could find that ADA might be a more efficacious treatment option, which should be interpreted cautiously because the credible interval was wide. Besides, for the time point in defining remission for included induction trials varied, induction studies should be compared carefully. We suggest that future induction trials use the same definition of remission to reduce intrinsic differences in study designs.

Non-biological agents such as AZA have always been common medicines for maintenance of remission in CD, and they also showed superiority in our research, which was consistent with clinical practice. Besides, in this network meta-analysis, ADA were superior to placebo for maintenance of remission, and there was no difference between AZA and ADA. In the sensitivity analysis, when we included those trials whose time points were 1 year or longer, the results were the same as the primary one. Therefore, it could be found that the biological agents were not always better than non-biologic agents for maintenance of remission in CD.

Patients with CD were less likely to have trial withdrawal with ADA, BUD, and NTZ relative to placebo. Besides, we also find this result was consistent with the result when we only included the withdrawals due to the adverse events. In contrast, we observed that the 6-MP and MTX were associated with higher WDAEs compared with placebo. However, these data should be analyzed carefully because randomized controlled trials have insufficient power to detect small but important rare adverse events.

Rational drug use for CD can significantly improve the quality of life of patients and reduce hospitalizations and operations. The appearance of biological agents provides more drugs are available for patients, but it also increases the difficulty of choice. In recent years, various biological agents have been paid more attention. However, according to our research, we have found that non-biological agents also had very good effects in the treatment of CD. Even the combination use of biological agent and non-biological agent was better than biological agent monotherapy. One network meta-regression published previously by Singh et

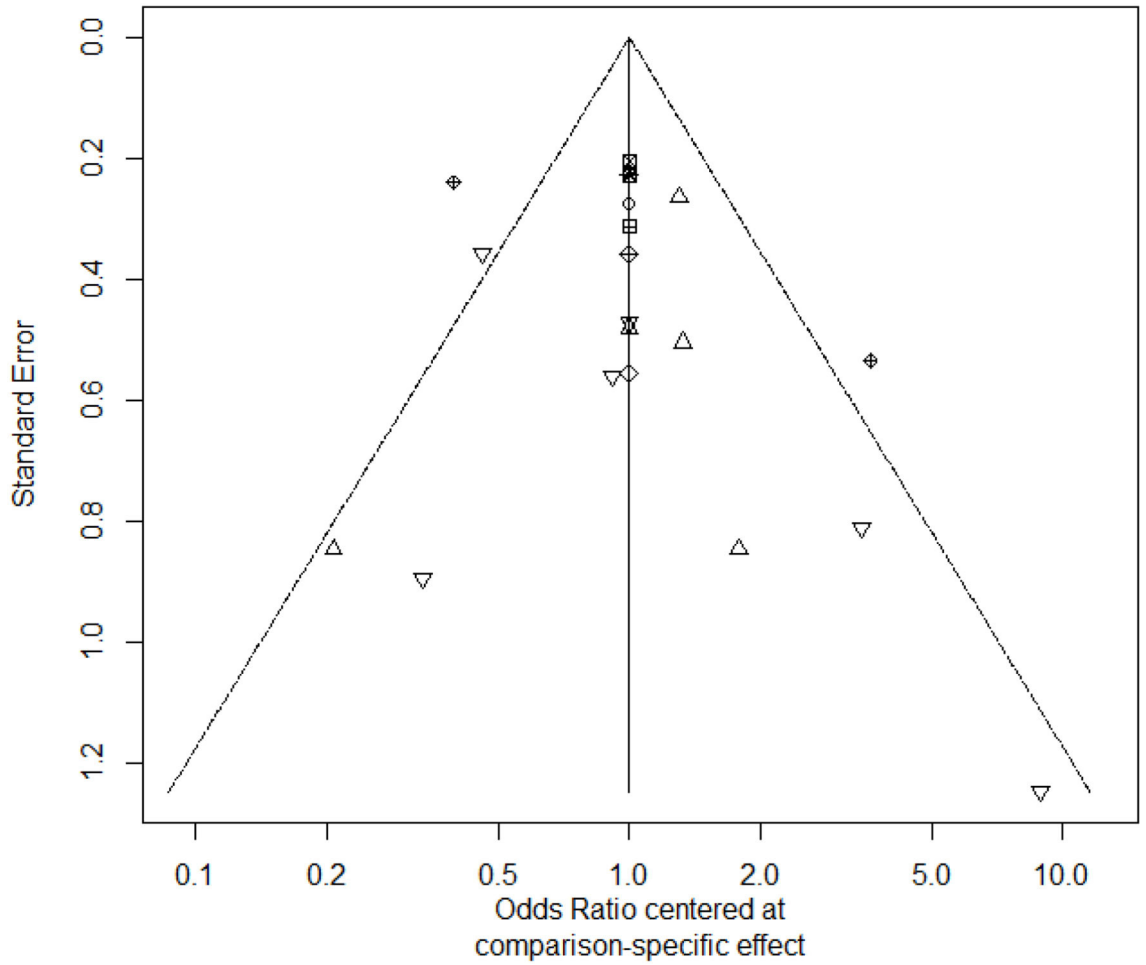


FIGURE 3 | The funnel plot of maintenance of remission.

al. (73) compared some biological agents for the induction and maintenance of remission, the results from their paper were consistent with our research.

For VDZ and UST, which have been approved for the treatment of CD recent years, we approved that they had significant efficacy compared with placebo in the induction and maintenance of remission, but due to insufficient sample size, their efficacy should be treated carefully. The highlight was that for patients who previously failed anti-TNF agents, these two drugs provided a new choice for patients because their mechanism was different from that of anti-TNF agents.

There also existed some limits in our research. Due to the lack of head-to-head trials and reliance on only indirect evidence (such as NTZ and ADA) resulted in wide 95% confidence intervals. In addition, in the node-splitting analysis of inconsistency, direct and indirect comparison results of 5ASA-6MP and 6MP-placebo were significantly different (**Supplementary Table 8**), which showed that for the induction of remission, the result about 6MP was questionable. Another concern with network meta-analysis was heterogeneity between trials, such as the inclusion criteria of patients, risk of bias, the severity of disease. Although we have divided the most important factors into subgroups, we could only perform descriptive analysis in the characteristics table for other heterogeneities. Finally, as our research was based on head-to-head clinical trials, both dosage and compliance were different from the real-world environment to a certain extent. For example, the different strategies of treating CD such as top-down approach and step-up approach could not be compared in our research.

CONCLUSION

For induction of remission, azathioprine, infliximab, infliximab + azathioprine were more effective in first-line therapy. In second-line therapy, adalimumab was more effective but should be interpreted carefully. For maintenance of remission adalimumab and azathioprine were more effective. Besides, adalimumab, budesonide, natalizumab had lower withdrawals.

TABLE 4 | Network meta-analysis results for withdrawals.

	5ASA	6MP	ADA	ADAAZA	AZA	BUD	CZP	EVE	IFX	IFXAZA	MTX	NTZ	NTZIFX	P	PED	SSZ	SSZ6MP	UST	VDZ
5ASA	5ASA	0.59 (−0.63, 1.81)	−0.84 (−1.89, 0.23)	−0.54 (−2.42, 1.37)	−0.21 (−1.3, 0.88)	−0.73 (−1.56, 0.15)	−0.06 (−1.19, 1.11)	0.44 (−1.3, 2.2)	0.95 (−0.25, 2.31)	0.45 (−1.2, 2.2)	0.81 (−0.68, 2.37)	−0.68 (−1.78, 0.38)	0.88 (−1.39, 3.32)	−0.25 (−1.04, 0.52)	−0.47 (−1.88, 1.03)	0.2 (−1.38, 1.75)	0.6 (−0.97, 2.16)	−0.5 (−1.74, 0.73)	−0.32 (−2.3, 1.71)
6MP	−0.59 (−1.81, 0.63)	6MP	−1.43 (−2.82, −0.02)	−1.13 (−3.23, 1)	−0.8 (−2.22, 0.62)	−1.32 (−2.7, 0.1)	−0.65 (−2.11, 0.84)	−0.15 (−2.11, 1.82)	0.36 (−1.13, 2)	−0.14 (−2.02, 1.82)	0.22 (−1.52, 2.02)	−1.27 (−2.71, 0.12)	0.29 (−2.17, 2.88)	−0.85 (−2.05, 0.34)	−1.07 (−2.87, 0.85)	−0.39 (−1.86, 1.05)	0.01 (−1.45, 1.45)	−1.09 (−2.63, 0.42)	−0.9 (−3.08, 1.29)
ADA	0.84 (−0.23, 1.89)	1.43 (0.02, 2.82)	ADA	0.3 (−1.29, 1.88)	0.63 (−0.42, 1.65)	0.11 (−1.07, 1.29)	0.78 (−0.34, 1.9)	1.29 (−0.44, 2.99)	1.79 (0.72, 2.98)	1.29 (−0.3, 2.94)	1.65 (0.19, 3.15)	0.16 (−0.92, 1.18)	1.72 (−0.5, 4.08)	0.58 (−0.17, 1.3)	0.37 (−1.31, 2.11)	1.04 (−0.62, 2.63)	1.44 (−0.21, 3.05)	0.34 (−0.89, 1.53)	0.53 (−1.45, 2.52)
ADAAZA	0.54 (−1.37, 2.42)	1.13 (−1, 3.23)	−0.3 (−1.88, 1.29)	ADAAZA	0.33 (−1.57, 2.2)	−0.18 (−2.17, 1.78)	0.48 (−1.46, 2.41)	0.98 (−1.35, 3.29)	1.48 (−0.4, 3.5)	0.99 (−1.25, 3.27)	1.35 (−0.78, 3.53)	−0.14 (−2.07, 1.71)	1.41 (−1.3, 4.25)	0.28 (−1.48, 2)	0.07 (−2.23, 2.4)	0.75 (−1.56, 2.98)	1.14 (−1.17, 3.4)	0.04 (−1.98, 2)	0.22 (−2.3, 2.75)
AZA	0.21 (−0.88, 1.3)	0.8 (−0.62, 2.22)	−0.63 (−1.65, 0.42)	−0.33 (−2.2, 1.57)	AZA	−0.52 (−1.71, 0.7)	0.15 (−0.98, 1.32)	0.65 (−0.9, 2.21)	1.15 (0.18, 2.3)	0.66 (−0.72, 2.14)	1.02 (−0.29, 2.41)	−0.47 (−1.57, 0.59)	1.08 (−1.09, 3.43)	−0.05 (−0.82, 0.72)	−0.27 (−1.93, 1.52)	0.41 (−1.24, 2.04)	0.8 (−0.84, 2.46)	−0.29 (−1.54, 0.93)	−0.11 (−2.09, 1.92)
BUD	0.73 (−0.15, 1.56)	1.32 (−0.1, 2.7)	−0.11 (−1.29, 1.07)	0.18 (−1.78, 2.17)	0.52 (−0.7, 1.71)	BUD	0.67 (−0.58, 1.91)	1.17 (−0.66, 2.97)	1.67 (0.37, 3.1)	1.18 (−0.56, 2.97)	1.54 (−0.05, 3.16)	0.05 (−1.19, 1.19)	1.61 (−0.74, 4.08)	0.47 (−0.48, 1.37)	0.25 (−1.06, 1.65)	0.93 (−0.79, 2.56)	1.33 (−0.37, 2.98)	0.23 (−1.13, 1.54)	0.41 (−1.64, 2.48)
CZP	0.06 (−1.11, 1.19)	0.65 (−0.84, 2.11)	−0.78 (−1.9, 0.34)	−0.48 (−2.41, 1.46)	−0.15 (−1.32, 0.98)	−0.67 (−1.91, 0.58)	CZP	0.5 (−1.3, 2.28)	1.01 (−0.26, 2.38)	0.51 (−1.19, 2.27)	0.87 (−0.67, 2.45)	−0.62 (−1.8, 0.48)	0.94 (−1.38, 3.39)	−0.19 (−1.07, 0.63)	−0.41 (−2.13, 1.38)	0.26 (−1.45, 1.9)	0.66 (−1.04, 2.32)	−0.44 (−1.74, 0.82)	−0.26 (−2.28, 1.8)
EVE	−0.44 (−2.2, 1.3)	0.15 (−1.82, 2.11)	−1.29 (−2.99, 0.44)	−0.98 (−3.29, 1.35)	−0.65 (−2.21, 0.9)	−1.17 (−2.97, 0.66)	−0.5 (−2.28, 1.3)	EVE	0.5 (−1.22, 2.36)	0.01 (−2.01, 2.11)	0.37 (−1.58, 2.4)	−1.13 (−2.88, 0.6)	0.43 (−2.17, 3.19)	−0.7 (−2.28, 0.86)	−0.92 (−3.07, 1.33)	−0.24 (−2.4, 1.88)	0.16 (−2, 2.3)	−0.95 (−2.79, 0.88)	−0.76 (−3.18, 1.66)
IFX	−0.95 (−2.31, 0.25)	−0.36 (−2, 1.13)	−1.79 (−2.98, −0.72)	−1.48 (−3.5, 0.4)	−1.15 (−2.3, −0.18)	−1.67 (−3.1, −0.37)	−1.01 (−2.38, 0.26)	−0.5 (−2.36, 1.22)	IFX	−0.49 (−1.96, 0.88)	−0.14 (−1.58, 1.24)	−1.63 (−3, −0.45)	−0.08 (−2.03, 1.96)	−1.2 (−2.3, −0.27)	−1.42 (−3.28, 0.4)	−0.74 (−2.62, 0.94)	−0.35 (−2.21, 1.36)	−1.45 (−2.93, −0.13)	−1.27 (−3.43, 0.8)
IFXAZA	−0.45 (−2.2, 1.2)	0.14 (−1.82, 2.02)	−1.29 (−2.94, 0.3)	−0.99 (−3.27, 1.25)	−0.66 (−2.14, 0.72)	−1.18 (−2.97, 0.56)	−0.51 (−2.27, 1.19)	−0.01 (−2.11, 2.01)	0.49 (−0.88, 1.96)	IFXAZA	0.36 (−1.49, 2.18)	−1.13 (−2.88, 0.49)	0.42 (−1.97, 2.94)	−0.7 (−2.26, 0.75)	−0.93 (−3.07, 1.25)	−0.26 (−2.39, 1.81)	0.15 (−1.99, 2.2)	−0.95 (−2.8, 0.78)	−0.77 (−3.17, 1.61)
MTX	−0.81 (−2.37, 0.68)	−0.22 (−2.02, 1.52)	−1.65 (−3.15, −0.19)	−1.35 (−3.53, 0.78)	−1.02 (−2.41, 0.29)	−1.54 (−3.16, 0.05)	−0.87 (−2.45, 0.67)	−0.37 (−2.4, 1.58)	0.14 (−1.24, 1.58)	−0.36 (−2.18, 1.49)	MTX	−1.5 (−3.06, −0.01)	0.07 (−2.34, 2.54)	−1.06 (−2.42, 0.21)	−1.28 (−3.31, 0.76)	−0.61 (−2.61, 1.31)	−0.21 (−2.21, 1.72)	−1.31 (−2.99, 0.29)	−1.12 (−3.42, 1.14)
NTZ	0.68 (−0.38, 1.78)	1.27 (−0.12, 2.71)	−0.16 (−1.18, 0.92)	0.14 (−1.71, 2.07)	0.47 (−0.59, 1.57)	−0.05 (−1.19, 1.19)	0.62 (−0.48, 1.8)	1.13 (−0.6, 2.88)	1.63 (0.45, 3)	1.13 (−0.49, 2.88)	1.5 (0.01, 3.06)	NTZ	1.56 (−0.7, 4.01)	0.43 (−0.31, 1.2)	0.21 (−1.42, 2)	0.88 (−0.73, 2.52)	1.28 (−0.33, 2.95)	0.18 (−1.03, 1.41)	0.37 (−1.59, 2.41)
NTZIFX	−0.88 (−3.32, 1.39)	−0.29 (−2.88, 2.17)	−1.72 (−4.08, 0.5)	−1.41 (−4.25, 1.3)	−1.08 (−3.43, 1.09)	−1.61 (−4.08, 0.74)	−0.94 (−3.39, 1.38)	−0.43 (−3.19, 2.17)	0.08 (−1.96, 2.03)	−0.42 (−2.94, 1.97)	−0.07 (−2.54, 2.34)	−1.56 (−4.01, 0.7)	NTZIFX	−1.13 (−3.44, 1.02)	−1.35 (−4.08, 1.33)	−0.68 (−3.44, 1.9)	−0.28 (−3.01, 2.3)	−1.38 (−3.9, 0.97)	−1.19 (−4.14, 1.66)
P	0.25 (−0.52, 1.04)	0.85 (−0.34, 2.05)	−0.58 (−1.3, 0.17)	−0.28 (−2, 1.48)	0.05 (−0.72, 0.82)	−0.47 (−1.37, 0.48)	0.19 (−0.63, 1.07)	0.7 (−0.86, 2.28)	1.2 (0.27, 2.3)	0.7 (−0.75, 2.26)	1.06 (−0.21, 2.42)	−0.43 (−1.2, 0.31)	1.13 (−1.02, 3.44)	P	−0.22 (−1.71, 1.38)	0.46 (−1.01, 1.9)	0.85 (−0.59, 2.33)	−0.25 (−1.21, 0.72)	−0.06 (−1.88, 1.82)
PED	0.47 (−1.03, 1.88)	1.07 (−0.85, 2.87)	−0.37 (−2.11, 1.31)	−0.07 (−2.4, 2.23)	0.27 (−1.52, 1.93)	−0.25 (−1.65, 1.06)	0.41 (−1.38, 2.13)	0.92 (−1.33, 3.07)	1.42 (−0.4, 3.28)	0.93 (−1.25, 3.07)	1.28 (−0.76, 3.31)	−0.21 (−2, 1.42)	1.35 (−1.33, 4.08)	0.22 (−1.38, 1.71)	PED	0.67 (−1.47, 2.68)	1.07 (−1.05, 3.08)	−0.03 (−1.91, 1.74)	0.16 (−2.27, 2.53)
SSZ	−0.2 (−1.75, 1.38)	0.39 (−1.05, 1.86)	−1.04 (−2.63, 0.62)	−0.75 (−2.98, 1.56)	−0.41 (−2.04, 1.24)	−0.93 (−2.56, 0.79)	−0.26 (−1.9, 1.45)	0.24 (−1.88, 2.4)	0.74 (−0.94, 2.62)	0.26 (−1.81, 2.39)	0.61 (−1.31, 2.61)	−0.88 (−2.52, 0.73)	0.68 (−1.9, 3.44)	−0.46 (−1.9, 1.01)	−0.67 (−2.68, 1.47)	SSZ	0.4 (−1.13, 1.94)	−0.7 (−2.43, 1.03)	−0.51 (−2.83, 1.86)
SSZ6MP	−0.6 (−2.16, 0.97)	−0.01 (−1.45, 1.45)	−1.44 (−3.05, 0.21)	−1.14 (−3.4, 1.17)	−0.8 (−2.46, 0.84)	−1.33 (−2.98, 0.37)	−0.66 (−2.32, 1.04)	−0.16 (−2.3, 2)	0.35 (−1.36, 2.21)	−0.15 (−2.2, 1.99)	0.21 (−1.72, 2.21)	−1.28 (−2.95, 0.33)	0.28 (−2.3, 3.01)	−0.85 (−2.33, 0.59)	−1.07 (−3.08, 1.05)	−0.4 (−1.94, 1.13)	SSZ6MP	−1.1 (−2.85, 0.63)	−0.91 (−3.25, 1.44)
UST	0.5 (−0.73, 1.74)	1.09 (−0.42, 2.63)	−0.34 (−1.53, 0.89)	−0.04 (−2, 1.98)	0.29 (−0.93, 1.54)	−0.23 (−1.54, 1.13)	0.44 (−0.82, 1.74)	0.95 (−0.88, 2.79)	1.45 (0.13, 2.93)	0.95 (−0.78, 2.8)	1.31 (−0.29, 2.99)	−0.18 (−1.41, 1.03)	1.38 (−0.97, 3.9)	0.25 (−0.72, 1.21)	0.03 (−1.74, 1.91)	0.7 (−1.03, 2.43)	1.1 (−0.63, 2.85)	UST	0.19 (−1.87, 2.29)
VDZ	0.32 (−1.71, 2.3)	0.9 (−1.29, 3.08)	−0.53 (−2.52, 1.45)	−0.22 (−2.75, 2.3)	0.11 (−1.92, 2.09)	−0.41 (−2.48, 1.64)	0.26 (−1.8, 2.28)	0.76 (−1.66, 3.18)	1.27 (−0.8, 3.43)	0.77 (−1.61, 3.17)	1.12 (−1.14, 3.42)	−0.37 (−2.41, 1.59)	1.19 (−1.66, 4.14)	0.06 (−1.82, 1.88)	−0.16 (−2.53, 2.27)	0.51 (−1.86, 2.83)	0.91 (−1.44, 3.25)	−0.19 (−2.29, 1.87)	VDZ

5ASA, mesalazine; BUD, budesonide; AZA, azathioprine; 6MP, mercaptopurine; MTX, methotrexate; IFX, infliximab; ADA, adalimumab; CZP, certolizumab pegol; NTZ, natalizumab; VDZ, vedolizumab; UST, ustekinumab; SSZ, sulfasalazine; EVE, everolimus; PED, prednisolone; P, placebo.

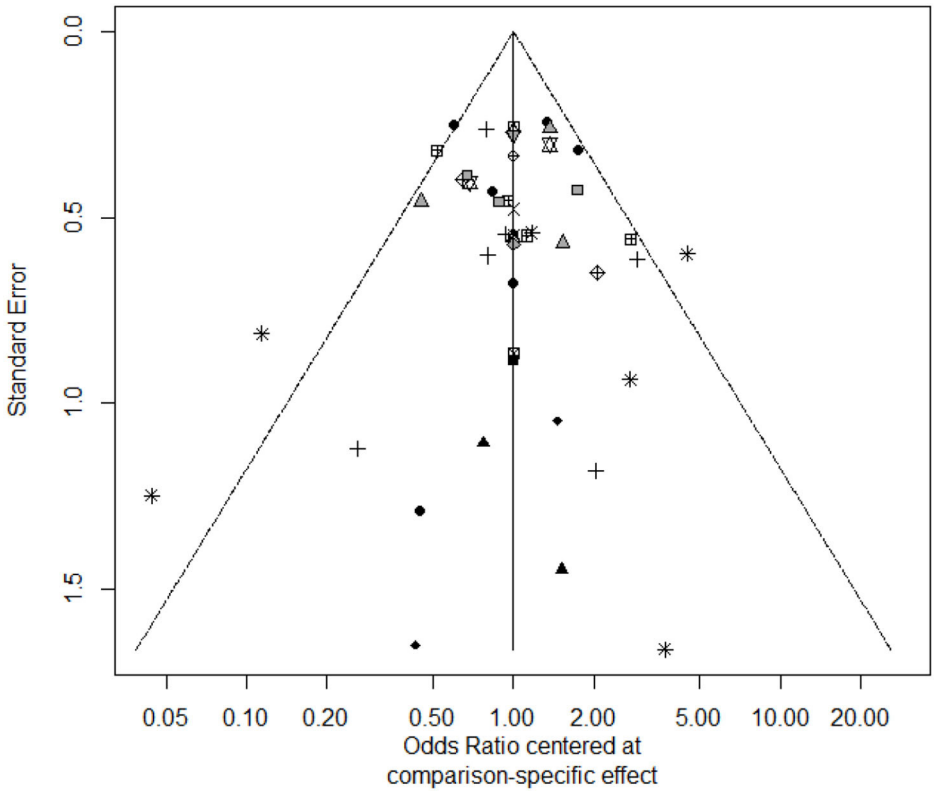


FIGURE 4 | The funnel plot of withdrawals.

Therefore, biological agents were not always better than non-biological agents and they have their own advantages in different treatment methods of Crohn's disease.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

MR, AM, and HL: conception of the study. MR, ZF, and YW: literature search and data extraction. FS and RM: statistical analysis. MR and YS: drafting the manuscript. AM and HL: revising and completion of final work. All authors reviewed and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.679258/full#supplementary-material

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Association of Circulating ANGPTL8 Levels With Renal Dysfunction: A Case-Control Study

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Background: Chronic kidney disease (CKD) is recognized as a major public health problem with high morbidity and mortality worldwide. Recently, angiopoietin-like protein 8 (ANGPTL8) was found to regulate lipid metabolism. Previous studies suggested that serum ANGPTL8 levels increased in patients with diabetes, especially in diabetic patients with albuminuria. This study aimed to investigate the association between circulating levels of ANGPTL8 and kidney function in the general population.

Methods: The subjects were patients with renal dysfunction [estimated glomerular filtration rate (eGFR) $<$ 60/min/1.73 m^2] from Risk Evaluation of cAncers in Chinese diabeTic Individuals: a lONgitudinal study (the REACTION study). Each case was matched by age, sex, and body mass index (BMI) with one control whose eGFR was $\geq$ 90 ml/min/1.73 m^2. The case and control groups were compared using a paired *t*-test. Binary logistic regression analysis was used to calculate the odds ratio (OR) of renal dysfunction (RD).

Results: Among 135 case-control pairs, circulating ANGPTL8 levels were elevated in patients with RD compared to control subjects [799.96 (410.12-1086.44) vs. 609.58 (365.13-740.06) pg/ml, $p < 0.05$]. Partial correlations showed that ANGPTL8 levels were negatively correlated with eGFR ($r = -0.26$, $p < 0.05$). Multivariable-adjusted binary logistic regression analysis showed that elevated ANGPTL8 levels were associated with an increased risk of RD (OR in quartile 4 vs. 1, 3.80; 95% CI, 1.71-8.41). Interestingly, the association between ANGPTL8 levels and RD was consistent with the overall findings in both nondiabetic individuals (OR, 1.44; 95% CI, 1.09 to 1.91) and diabetic patients (OR, 2.71; 95% CI, 1.13-6.49) in the subgroup analyses. Furthermore, the estimates for this association were also significant in females (OR, 2.12; 95% CI, 1.33-3.37), individuals aged $>$ 60 years (OR, 1.55; 95% CI, 1.16-2.07), individuals with a BMI $<$ 24 (OR, 1.66; 95% CI, 1.16-2.39), and individuals without hyperlipidaemia (OR, 1.61; 95% CI, 1.16-2.23) (all *p*-values $<$ 0.05).

Conclusion: Elevated circulating ANGPTL8 levels were associated with increased risk of RD in the general population, especially among females, individuals aged > 60 years, individuals with a BMI < 24, individuals without diabetes mellitus, individuals with diabetes mellitus (DM), and individuals without hyperlipidaemia. This finding implies that ANGPTL8 may play a role in the pathological process of RD.

Keywords: ANGPTL8, eGFR, renal dysfunction, creatinine, chronic kidney disease, case-control study

INTRODUCTION

Chronic kidney disease (CKD) is defined as kidney damage caused by a variety of factors, including diabetes, hypertension, autoimmune diseases, lipid dysregulation, and urinary tract infections (1, 2). CKD is recognized as a major public health problem with high morbidity and mortality worldwide, and it requires substantial financial and social resources (3–5). Recently, the global morbidity of CKD has been as high as 11-13% (6). According to the 2010 Global Burden of Disease study, CKD was ranked 27th in the list of causes of total global deaths in 1990 but rose to 18th in 2010, and the ranking of chronic kidney disease has also risen in recent years (7, 8). CKD is characterized by a decrease in renal function, as indicated by the estimated glomerular filtration rate (eGFR); unfortunately, there are no obvious clinical symptoms in the early stage until severe damage occurs. Early identification, diagnosis, and treatment are important to prevent disease progression because progressive CKD is associated with many adverse outcomes, including end-stage kidney disease, cardiovascular disease, and increased mortality (7, 8). There is a lack of sensitive and specific biomarkers to diagnosing and treating CKD and novel biomarkers urgently need to be identified.

Angiopoietin-like protein 8 (ANGPTL8), which is also called betatrophin, "refeeding induced in fat and liver" (RIFL), lipasin, TD26, and C19orf80, is an atypical member of the angiopoietin-like protein family. ANGPTL8 is secreted mainly from the liver in humans and from adipose tissue and the liver in mice (9–12). ANGPTL8 participates in the regulation of triglyceride (TG) metabolism by inhibiting the activity of lipoprotein lipase (LPL) (13).

Previous studies found that ANGPTL8 levels were increased in diabetic patients, especially in patients with diabetic nephropathy (14–17). Yang et al. found that circulating ANGPTL8 levels were significantly increased in type 2 diabetic patients with albuminuria and that ANGPTL8 was positively correlated with the urine albumin-to-creatinine ratio (ACR) in this population (17). A negative correlation between ANGPTL8 levels and the eGFR was also reported in a study by Maurer et al. (14). The present study aims to explore the association between ANGPTL8 levels and RD in the general population as well as diabetic patients.

SUBJECTS AND METHODS

Study Participants

The participants in the present study were recruited from Hubei Province in China during 2011–2012 as part of Risk Evaluation of cAncer in Chinese diabeTic Individuals: a lONgitudinal study (the REACTION study), which was conducted among 259,657 adults aged 40 years and older in 25 communities across mainland China during 2011–2012 (baseline) and which invited participants to attend follow-up visits during 2014–2016 (18–20). At baseline, a comprehensive set of questionnaires, clinical measurements, oral glucose tolerance tests (OGTTs), and laboratory examinations were conducted following standardized protocols for all of the participants. RD was defined as an eGFR of <60 ml/min/per 1.73 m^2 and/or the presence of markers of renal injury for more than one trimester (6). The eGFR was calculated based on Modification of Diet in Renal Disease for Chinese, as follows: eGFR ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$) = 175 × Serum $creatinine^{-1.234}$ × $Age^{-0.179}$ (×0.79, if female) (21). Each case was matched by age, sex, and body mass index (BMI) with one control whose eGFR was ≥90 ml/min/1.73 m^2.

The Committee on Human Research at Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, approved the study protocol, and all of the participants provided written informed consent. All of the methods were performed in accordance with the relevant guidelines and regulations.

Clinical and Biochemical Evaluation

Data were collected from local community clinics at baseline and follow-up visits. As previously described in the REACTION study (20), information on sociodemographic characteristics, lifestyle factors, medical history, and family history were collected by trained staff using a standard questionnaire.

Measurement of ANGPTL8 Levels

Blood samples were collected after overnight fasting. Serum was obtained after centrifugation, aliquoted, and then stored at −80°C. ANGPTL8 levels in the fasting serum were quantified using commercially available ELISA kits (Eiaab Science, Wuhan, China; Catalog No. E11644h) with an intra-assay coefficient of variation (CV) of ≤6.5% and an inter-assay CV of ≤9.2% (provided by the manufacturer). The procedures were performed according to the manufacturer's instructions. All of the samples were analyzed in duplicate.

Statistical Analysis

The baseline characteristics of the participants are presented as medians (interquartile ranges, IQRs) for asymmetrically distributed data, as percentages and frequencies for continuous variables, and as numbers (proportions) for categorical variables. The highest and lowest 0.5% of data points for ANGPTL8 levels were trimmed. The data were tested for a normal distribution

using the Kolmogorov-Smirnov test. We obtained *p*-values for differences between groups using a paired *t*-test or a non-parametric test for continuous variables that were normally distributed or abnormally distributed, respectively, and using the $\chi 2$ test for categorical variables. The correlations between variables were assessed using Spearman correlation analysis and partial correlation analyses by controlling for covariates, including age, sex, BMI, lipid profiles, and glucose profiles. Binary logistic regression analysis was conducted to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for renal dysfunction in quartiles of ANGPTL8 levels. We adjusted multivariable models for age, sex, BMI, glycated hemoglobin A1c (HbA1c), high-density lipoproteins (HDL), low-density lipoproteins (LDL), TG, cholesterol, fasting plasma glucose (FPG), 2 h postprandial blood glucose (2hPG), alanine transaminase (ALT), aspartate aminotransferase (AST), DM and hyperlipidaemia. Subgroup analyses were conducted based on sex, age, BMI, history of DM, or hyperlipidaemia. A two-tailed *p*-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software (version 26.0) and Stata software (version 11.0).

RESULTS

Characteristics of the Study Population

The baseline characteristics of the study participants are shown in **Table 1**. Among 135 case-control pairs, no significant differences in age, sex, BMI, HbA1c, HDL, LDL, total cholesterol, TG, FPG, 2hPG, ALT, and AST data were detected between the case and control groups. The eGFR values in the case group were lower than those in the control group [45.91 (38.29-55.89) vs. 112.24 (101.13-123.45) ml/min/1.73 m^2; $p < 0.001$], and creatinine levels were higher in the case group [142.81 (105.30-154.00) vs. 63.96 (56.20-69.30) μmol/L; $p < 0.001$].

Association Between ANGPTL8 Levels and Renal Function

The circulating ANGPTL8 levels were significantly increased in the case group compared to the control group [799.96 (410.12-1086.44) vs. 609.58 (365.13-740.06) pg/ml, $p < 0.05$; **Table 1**]. Furthermore, the serum ANGPTL8 levels were inversely associated with the eGFR ($r = -0.26$, $p < 0.05$; **Figure 1**). Binary logistic regression analysis showed that compared with individuals in the first quartile of ANGPTL8, patients in the fourth quartile of ANGPTL8 levels had a 3.27-fold increased risk of RD (OR = 3.27, 95% CI = 1.60-6.68) in the unadjusted model. Notably, the relationship between ANGPTL8 levels and RD still existed after adjusting for covariables (OR = 3.80, 95% CI = 1.71-8.41; **Table 2**). After Z-transform standardization, the OR for RD was 1.68 (95% CI = 1.24-2.28) per unit increase in the Z score of ANGPTL8 levels.

Association Between ANGPTL8 Levels and Metabolic Variables

The correlations between the ANGPTL8 levels and metabolic variables in all participants were analyzed by Spearman correlation analysis. As shown in **Table 3**, after controlling for multiple variables, ANGPTL8 levels were positively correlated with age ($r = 0.20$, $p < 0.05$), BMI ($r = 0.15$, $p < 0.05$), creatinine ($r = 0.30$, $p < 0.001$), and AST ($r = 0.25$, $p < 0.001$) but negatively correlated with the eGFR ($r = -0.27$, $p < 0.001$) and LDL ($r = -0.13$, $p < 0.05$). There were no associations between ANGPTL8 levels and HbA1c, HDL, total cholesterol, TG, FPG, or ALT (all *p*-values > 0.05).

TABLE 1 | Clinical and biochemical parameters for non-renal dysfunction subjects and renal dysfunction patients.

Characteristics	Non-renal dysfunction	Renal dysfunction	All	*P*-value
N (%)	135 (50)	135 (50)	270 (100)	
Age (years)	66.24 (61.00-74.00)	66.30 (60.00-74.00)	66.27 (61.00-74.00)	0.934
Male sex *n* (%)	58 (43)	58 (43)	116 (43)	1.000
BMI (kg/m^2)	23.25 (20.88-24.90)	23.15 (20.60-25.14)	23.20 (20.79-25.07)	0.926
ANGPTL8 (pg/ml)	609.58 (365.13-740.06)	799.96 (410.12-1086.44)	704.77 (381.99-924.50)	0.002
eGFR (ml/min/1.73 m^2)	112.24 (101.13-123.45)	45.91 (38.29-55.89)	79.08 (50.49-111.63)	0.000
Creatinine (μmol/L)	63.96 (56.20-69.30)	142.81 (105.30-154.00)	103.38 (61.28-120.28)	0.000
HbA1c (%)	5.96 (5.50-6.00)	6.00 (5.50-6.10)	5.98 (5.50-6.10)	0.319
HDL (mmol/L)	1.50 (1.23-1.71)	1.42 (1.16-1.59)	1.46 (1.19-1.67)	0.072
LDL (mmol/L)	2.83 (2.26-3.36)	2.91 (2.22-3.48)	2.87 (2.23-3.42)	0.987
Total cholesterol (mmol/L)	4.99 (4.38-5.49)	5.09 (4.25-5.72)	5.04 (4.26-5.57)	0.979
TG (mmol/L)	1.47 (0.84-1.63)	1.58 (0.99-1.88)	1.53 (0.92-1.74)	0.069
FPG (mmol/L)	5.66 (4.89-5.68)	5.97 (4.98-5.87)	5.82 (4.94-5.77)	0.121
2h PG (mmol/L)	7.54 (5.80-7.93)	7.93 (5.86-8.36)	7.73 (5.84-8.21)	0.450
ALT (U/L)	13.70 (9.00-17.00)	13.87 (8.00-18.00)	13.79 (9.00-17.25)	0.946
AST (U/L)	23.55 (18.00-26.00)	25.54 (19.00-27.00)	24.54 (18.00-26.00)	0.206

BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobinA1c; HDL, high-density lipoproteins; LDL, low-density lipoproteins; TG, triglycerides; FPG, fasting plasma glucose; 2h PG, 2h postprandial blood glucose; ALT, alanine transaminase; AST, aspartate aminotransferase.

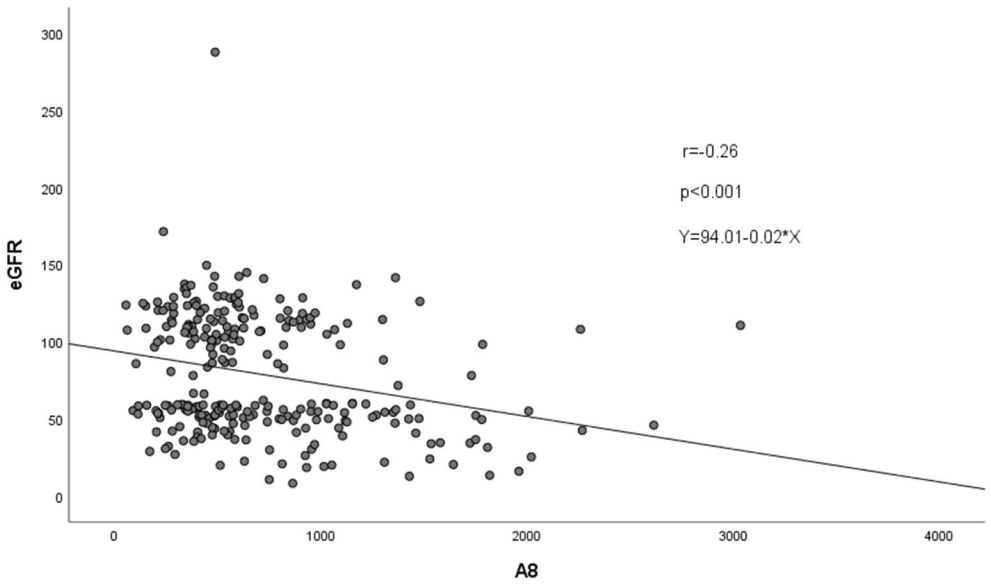


FIGURE 1 | Scatter and linear plots of ANGPTL8 levels and renal function.

TABLE 2 | Risk ratios for clinical outcomes according to quartiles of ANGPTL8.

Outcome		Model1	Model2	Model3
RD	Q1 (Reference)	1	1	1
	Q2 (OR, 95% CI)	1.10 (0.56-2.17)	1.11 (0.55-2.23)	0.99 (0.47-2.07)
	Q3 (OR, 95% CI)	1.10 (0.56-2.17)	1.19 (0.59-2.38)	1.22 (0.59-2.52)
	Q4 (OR, 95% CI)	3.27 (1.60-6.68)	3.59 (1.69-7.61)	3.80 (1.71-8.41)
	Per unit increase in Z score	1.55 (1.18-2.03)	1.59 (1.20-2.11)	1.68 (1.24-2.28)

Model 1 was unadjusted.
Model 2 was adjusted for age, sex and BMI.
Model 3 was adjusted for all variables in model 2 plus HbA1c, HDL, LDL, TG, cholesterol, FPG, 2h PG, ALT, AST, DM, and hyperlipidaemia.

Subgroup Analyses

As shown in **Figure 2**, the association between ANGPTL8 levels and RD was consistent with the overall findings in both non-diabetic individuals (OR, 1.44; 95% CI, 1.09-1.91) and diabetic patients (OR, 2.71; 95% CI, 1.13-6.49). Furthermore, the estimates for this association were also significant in females (OR, 2.12; 95% CI, 1.33-3.37), individuals aged > 60 (OR, 1.55; 95% CI, 1.16-2.07), individuals with a BMI < 24 (OR, 1.66; 95% CI, 1.16-2.39), and individuals without hyperlipidaemia (OR, 1.61; 95% CI, 1.16-2.23) (all p-values < 0.05). However, no significant association was found between ANGPTL8 levels and RD in male subjects, individuals aged ≤ 60, individuals with a BMI ≥ 24, or individuals with hyperlipidaemia (all p-values > 0.05).

DISCUSSION

In our study, we found that circulating ANGPTL8 levels were higher in patients with RD and negatively correlated with RD in the general population. Furthermore, multivariable-adjusted binary logistic regression analysis showed that patients in the highest quartile of ANGPTL8 levels had a 3.8-fold higher risk of RD than those in the lowest quartile. Moreover, subgroup analyses revealed significant differences among subgroups divided according to female sex, age > 60 years, BMI < 24, non-DM status, DM status, and non-hyperlipidaemia status.

The accumulating data on ANGPTL8 levels imply a complex role in metabolic function, potentially involving cross talk between lipid and glucose regulation (22). Previous studies found that circulating ANGPTL8 levels increased in diabetic patients (23). Furthermore, other studies demonstrated that circulating ANGPTL8 levels were much higher in patients with diabetic nephropathy than in diabetic patients without RD (14–16). Issa et al. proposed that ANGPTL8 could be used to predict the incidence of DM, and they also concluded that changes in renal function significantly decreased DM risk (24). Interestingly, the present study found that the association between ANGPTL8 levels and CKD existed not only in diabetic patients but also in non-diabetic individuals, indicating that ANGPTL8 may play a role in kidney disease, not just high glucose-mediated damage in diabetic nephropathy.

TABLE 3 | Partial correlations between ANGPTL8 levels and clinical variables.

	Model 1		Model 2*		Model 3*	
	R	***P*-value**	**Partial r**	***P*-value**	**Partial r**	***P*-value**
Age	0.24	0.000	0.19	0.002	0.20	0.001
BMI	0.02	0.710	0.06	0.323	0.15	0.022
eGFR	−0.26	0.000	−0.26	0.000	−0.27	0.000
Creatinine	0.28	0.000	0.29	0.000	0.30	0.000
HbA1c	0.03	0.621	−0.05	0.424	−0.06	0.381
HDL	−0.01	0.887	−0.02	0.711	−0.07	0.309
LDL	−0.09	0.154	−0.15	0.014	−0.13	0.037
Total cholesterol	−0.07	0.246	−0.10	0.099	0.09	0.159
TG	−0.03	0.684	0.05	0.397	−0.03	0.624
FPG	0.04	0.496	−0.04	0.477	−0.04	0.586
2h PG	0.12	0.048	0.01	0.901	0.09	0.167
ALT	0.04	0.534	0.08	0.223	−0.09	0.141
AST	0.10	0.091	0.24	0.000	0.25	0.000

**When a variable was calculated in the Partial correlation, it would not be included in adjustment model.*
Model 1 was unadjusted.
Model 2 was adjusted for age, sex and BMI.
Model 3 was adjusted for all variables in model 2 plus, HbA1c, HDL, LDL, TG, cholesterol, FPG, 2h PG, ALT, AST, DM, and hyperlipidaemia.

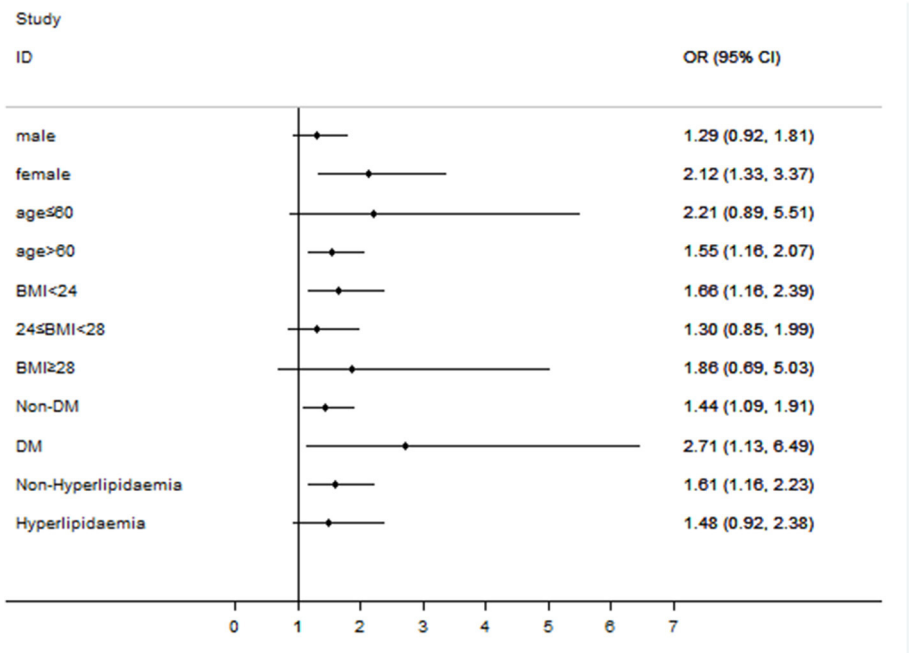


FIGURE 2 | Subgroup analyses: the relationship between ANGPTL8 levels and renal dysfunction varied among subgroups divided according to sex, age, BMI, and underlying disease status. Subgroup analyses of the OR of RD according to a 1-SD increase in ANGPTL8 levels. The final model was adjusted for age, sex, BMI, diabetes, and hyperlipidaemia, except for the stratifying variable.

However, our case-control study could not identify the causal mechanisms driving the observed associations between ANGPTL8 levels and RD. A possible explanation for the involvement of increased circulating ANGPTL8 levels in impaired renal functions is that RD impairs the excretion of ANGPTL8. In this case, the elevated ANGPTL8 levels in individuals with RD may be a consequence of—not the cause of—CKD. However, this theory was challenged by the study of Chen et al. (25). They found that there were increased urinary ANGPTL8 levels in type 2 diabetic patients compared with healthy subjects, but there were no differences among the normoalbuminuria, microalbuminuria, and macroalbuminuria

groups. This finding ruled out the possibility that reduced clearance of ANGPTL8 resulted from decreased glomerular filtration in the different groups.

Another possible mechanism is that the high serum levels of ANGPTL8 impair renal function, but the biological mechanism remains unclear. First, we found that ANGPTL8 levels were positively correlated with age, which was also reported in several previous studies (11, 15, 23, 26–28). Furthermore, subgroup analyses also suggested that the association between ANGPTL8 levels and RD was more significant in older participants. With increasing age, proinflammatory cytokine levels in the body increase (29, 30). Abu-Farha et al. also found that ANGPTL8 levels positively correlated with high sensitivity C-reactive protein (HsCRP) levels in humans (27). Moreover, chronic inflammation is a common feature in RD due to multiple factors, such as the induction of proinflammatory cytokines, oxidative stress, uraemia, and high rates of infection (2, 31). Therefore, age-related inflammation may mediate the association between ANGPTL8 levels and RD. Second, ANGPTL8 plays a critical role in lipoprotein and triglyceride regulation (16, 26, 28, 32, 33). Lipid accumulation in the renal parenchyma is detrimental to renal function (34). The study of Yang et al. suggested that triglycerides might partially mediate the correlation between ANGPTL8 levels and the ACR (17). Moreover, elevated plasma levels of ANGPTL8 are associated with atherosclerosis (28, 35). Recently, it has been appreciated that severe occlusive disease of the renal artery results in chronic renal ischaemia and can lead to the development of chronic renal insufficiency (36, 37). Therefore, ANGPTL8 may cause RD by damaging the renal artery.

Limitations

Some limitations of this study need to be acknowledged. First, all of the participants in our study were Chinese, limiting the generalizability of the findings, which must be confirmed in other ethnic groups. Second, the cross-sectional study design used here limits our interpretation of the causal relationship driving the observed associations between ANGPTL8 levels and RD events. Further prospective cohort studies are needed to answer this question. Finally, the sample size of our study was relatively small, and further physiological studies are needed to determine the causal links and underlying mechanisms.

CONCLUSION

In conclusion, increased circulating ANGPTL8 levels were associated with an increased risk of RD in the general population. Furthermore, subgroup analyses indicated that the relationship between ANGPTL8 levels and RD was significant in females, individuals aged > 60, individuals with a BMI < 24, individuals without DM, individuals with DM, and individuals without hyperlipidaemia. ANGPTL8, a newly discovered protein involved in a variety of pathological and physiological processes, may be closely related to CKD. This implies that ANGPTL8 may play a role in the pathological process of RD and provides a foundation for further exploration of the causes of chronic kidney dysfunction. Nevertheless, future longitudinal studies with longer follow-ups are warranted to explain the causal relationship between ANGPTL8 levels and RD; moreover, research should continue to explore the relevant mechanisms.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XY and XM designed the study. XM, HZ, DL, PY, and LH collected the data. XM and HZ performed the serum ANGPTL8 measurements and the statistical analysis. XY and XM wrote the paper. DL, PY, LH, JZ, and WL reviewed the paper and provided suggestions. XY is the guarantor of this work, had full access to all the data in the study, and takes responsibility for the integrity of the data. All authors reviewed the manuscript.

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Trends of Antibiotic Use and Expenditure After an Intensified Antimicrobial Stewardship Policy at a 2,200-Bed Teaching Hospital in China

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Objective: This study aimed to evaluate the effects of intensified Chinese special rectification activity on clinical antibiotic use (CSRA) policy on a tertiary-care teaching hospital.

Methods: A 48-month longitudinal dataset involving inpatients, outpatients, and emergency patients were collected. Study period included pre-intervention stage (adopting soft measures like systemic training) and post-intervention stage (applying antibiotic control system to intensify CSRA policy). Antibiotic use was evaluated by antibiotic use rate (AUR) or antibiotic use density (AUD). Economic indicator was evaluated by antibiotic cost in prescription or antibiotic expenditure in hospitalization. Data was analyzed by interrupted time series (ITS) analysis.

Results: The medical quality indicators remained stable or improved during the study period. AUR of inpatients (AURI) declined 0.553% per month ($P = 0.025$) before the intervention and declined 0.354% per month ($P = 0.471$) after the intensified CSRA policy was implemented. AUD, expressed as defined daily doses per 100 patients per day (DDDs/100PD), decreased by 1.102 DDDs/100PD per month ($P = 0.021$) before and decreased by 0.597 DDDs/100PD per month ($P = 0.323$) thereafter. The ratio of antibiotic expenditure to medication expenditure (AE/ME) decreased by 0.510% per month ($P = 0.000$) before and fell by 0.096% ($P = 0.000$) per month thereafter. AE per patient decreased by 25.309 yuan per month ($P = 0.002$) before and decreased by 7.987 yuan per month ($P = 0.053$) thereafter. AUR of outpatient (AURO) decreased by 0.065% per month before ($P = 0.550$) and decreased by 0.066% per month ($P = 0.994$) thereafter. The ratio of antibiotic cost to prescription cost in outpatient (ACO/PCO) decreased by 0.182% per month ($P = 0.506$) before and decreased by 0.216% per month ($P = 0.906$) thereafter. AUR of emergency patient (AURE) decreased by 0.400% per month ($P = 0.044$) before and decreased by 0.092% per month ($P = 0.164$) thereafter. The ratio of antibiotic cost to prescription cost in emergency patient (ACE/PCE) decreased by 0.616% per month ($P < 0.001$) before and decreased by 0.151% per month ($P < 0.001$) thereafter.

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Conclusions: Implementation of CSRA policy was associated with declining antibiotic use and antibiotic expenditure in inpatients, outpatients, and emergency patients. However, it is also important to note that the declining trend of antibiotic consumption slowed due to the limited capacity for decline in the later stages of CSRA intervention.

Keywords: antimicrobial stewardship, intensified intervention, antibiotic consumption, interrupted time series analysis, China

BACKGROUND

Antibiotics have been widely used for more than 70 years. During this time, inappropriate or excessive use of antibiotics has accelerated antibiotic resistance. Substantial reports have demonstrated the causal relationships between antibiotic consumption and selective pressure in resistant organisms (1–4). Hence, strengthening antimicrobial stewardship (AMS) has become a global healthcare concern. In 2007, the Infectious Diseases Society of America published the Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship. These guidelines were the first to conceptualize AMS as a set of interventions targeted toward addressing the rapid development of antibiotic resistance in hospital settings. Thereafter, many countries joined the AMS program and achieved positive outcomes (5–8).

The overuse of antibiotics is also a serious problem in China (9). The percentage of antibiotic prescriptions for inpatients reached 70% (10), although the target recommended by the World Health Organization is below 30% (11). A high rate of antibiotic prescription also occurs in outpatient cases (12, 13). The antibiotic use density (AUD), expressed as defined daily doses per 100 patients per day (DDDs/100PD), increased to 80.1 DDD/100 patient days before 2011 in China, which is much higher than the average AUD worldwide of >40 DDDs/100PD (14). Given these facts, focused strategies are necessary to reduce antibiotic use in China. Since 2009, the government has reissued a series of policies and regulations to address this issue. The most stringent intervention was the Chinese Special Rectification Activity on Clinical Antibiotic Use (CSRA), which was initiated in 2011. Thirteen detail-oriented measures concerning management, procurement, and usage of antibiotics were proposed. CSRA guidelines were implemented nationwide for three consecutive years from 2011 to 2014.

Many Chinese studies have evaluated the impact of CSRA guidelines on antibiotic use in hospitals and affirmed the positive outcomes yielded by this policy (15–18). However, most prior studies were cross-sectional analyses or pre- post-comparisons at two time points that could not reveal the dynamics of particular variables over time. Such studies may not be able to fully examine the potential effects of CSRA. Moreover, most of these studies were published in Chinese journals, reducing the dissemination of their contents to a global audience. Only two studies about CSRA were retrieved from databases in a foreign language, and each had a different slant to it. For example, Zou et al. (2) reported a correlation between antibacterial usage and bacterial resistance after CSRA, while another study showed the impact of CSRA guidelines on reducing multidrug-resistant organism isolates in critically ill patients (19). Overall, more empirical research is needed to deepen our understanding of the impacts of CSRA guidelines and effectively communicate these findings with the global community.

Changzhou No. 2 People's Hospital, a 2,200-bed tertiary general hospital affiliated with a medical university in Jiangsu, began to implement CSRA guidelines in 2011. First, the implementation of the policy consisted of soft measures such as founding an AMS team, implementing systemic training, and strengthening the education of healthcare providers. By April 2012, an antibiotic control system (ACS) was constructed in this hospital which integrated specific targets of the CSRA policy into the original Hospital Information System (HIS). Rigid measures have been deployed over the entire hospital to intensify the AMS since April 2012.

Here, we conducted an interventional study in this hospital from 2011 to 2014, with a focus on how antibiotic use and economic indicators differed before and after the intensified intervention. Combined with interrupted time series (ITS) analysis, the strongest and quasi-experimental approach for evaluating longitudinal effects of intervention (20), we aimed to obtain a robust estimation of the effects of an intervention to offer constructive policy suggestions to improve managerial decisions regarding antibiotics.

METHODS

Setting and Study Design

The study was conducted in Changzhou No. 2 People's Hospital, a 2,200-bed general tertiary-care teaching hospital in Jiangsu, China. The annual number of outpatient and emergency visits to the hospital is more than 2.39 million, and the annual number of discharged patients is 102.4 thousand. As a result, this hospital has a significant impact on Changzhou. Changzhou lies to the south of Jiangsu province. It is located in the affluent Yangtze Delta region of China, halfway between Shanghai and Nanjing. The city covers an area of 4,385 square kilometers and has a permanent resident population of 5.27 million people. In 2020, the GDP of this city reached 780.53 billion yuan.

As described in the introduction, Changzhou No. 2 People's Hospital began to implement the CSRA policy in 2011. First, the implementation of the policy only consisted of soft measures. By April 2012, the ACS was constructed, and rigid measures

have been deployed over the entire hospital to intensify CSRA policy. To evaluate the impacts of intensified CSRA policy on this hospital and even on local patients, we conducted a 48-month, retrospective time series analysis study in this hospital. Data related to outpatients, emergency patients, and inpatients were retrieved from the HIS between January 2011 and December 2014 in hospital-wide population-level monthly. The pre-intervention period was defined as from January 2011 to March 2012 (15 months in total), and the post-intervention period was defined as from April 2012 to December 2014 (33 months in total).

Intensified CSRA Policy

First, we briefly introduce the Chinese special rectification activity on clinical antibiotic use (CSRA) initiated by the Chinese government in 2011. This policy strengthens the clinical antibiotic management in thirteen detailed ways. The five most important ones are as follows: (1) antibiotics are categorized into three classifications, namely, unrestricted, restricted, and special level. For each level of antibiotics, they can only be prescribed by clinicians who have been authorized according to their technical titles; (2) limit the number of antibiotics used in hospitals. In a general tertiary hospital, the total number of unique antibiotic cannot exceed 50; (3) set a specific target for antibiotic use. Antibiotic use rate (AUR) of inpatients, emergency patients, and outpatient cannot exceed 60, 40, 20%, respectively. AUD should be controlled under 40 DDDs/100PD in a general tertiary hospital; (4) microbial specimen detection is required before antibiotic use and detection rate of inpatients must exceed 30%; (5) vetting exercises should be carried out periodically by infectious disease experts or clinical pharmacists. In response to the policy of the government, Changzhou No. 2 People's Hospital began to implement the CSRA policy in 2011. At first, soft measures such as founding an AMS team (including infectious disease professionals, clinical microbiologists, pharmacists, and nurses), systemic training, and education were only adopted. Thus, we defined the period from January 2011 to March 2012 as pre-intensified policy stage.

Here, we emphatically introduced the intensified CSRA policy. In April 2012, rigid measures were deployed over the entire hospital to intensify AMS. We developed an ACS and integrated it into HIS. In ACS, the classification of antibiotics and prescription authorization are computerized. Data related to AUR, AUD, and microbial specimen detection rates of each ward can be easily retrieved from the ACS. Clinicians in each ward would receive bonuses if they met the quota, or penalties if the quota was not met. In addition, for each inappropriate prescription, there was a penalty of 50 yuan, and for each inappropriate medical record, the penalty increased to 500 yuan. In short, ACS, along with awards and penalties, offered better opportunities and incentives to optimize antibiotic use. Thus, we called it intensified CSRA policy. We defined the period from April 2012 to December 2014 as post-intensified policy stage.

Study Outcomes

In this study, four items, namely, antibiotic use rate of inpatients (AURI), AUD, the ratio of antibiotic expenditure to medication expenditure (AE/PE), and antibiotic expenditure per patient (AE per patient) were selected as indicators of inpatient antibiotic use. AUD is defined as the number of defined daily doses/100 patient-days (DDDs/100PD) according to the anatomical therapeutic chemical (ATC)/DDD classification stated by WHO. DDD is the average daily dose in grams of a specific agent given to an average adult patient.

We selected three indicators to evaluate antibiotic use of outpatients, namely, antibiotic use rate of outpatients (AURO), antibiotic cost of outpatient/total prescription cost of outpatient

TABLE 1 | Study outcome variables.

Classification	Indicators	Measurement	Units of measurement
Inpatient	antibiotic use rate of inpatients (AURI)	the number of discharged patients who used antibiotics/the total number of discharged patients	Percentage
	antibiotic use density (AUD)	the usage of all kind of antibiotics calculated by defined daily dose (DDD)[a] × 100/(number of patients × length of stay per patient)	DDDs/100PD
	AE/ME	antibiotic expenditure (AE)/total medication expenditure(ME)	Percentage
	AE per patient	total antibiotic expenditure/the number of discharged patients	RMB[b]
Outpatient patient	antibiotic use rate of outpatients (AURO)	the number of outpatients who used antibiotics/the total number of outpatients	Percentage
	ACO/PCO	antibiotic cost of outpatients (ACO)/prescription cost of outpatients (PCO)	Percentage
	ACO per patient	antibiotic cost of outpatients (ACO)/the total number of outpatients	RMB
Emergency patient	antibiotic use rate of emergency patients (AURE)	the number of emergency patients who used antibiotics/the total number of emergency patients	Percentage
	ACE/PCE	antibiotic cost of emergency patients (ACE)/prescription cost of emergency patients (PCE)	Percentage
	ACE per patient	antibiotic cost of emergency patients (ACE)/the total number of emergency patients	RMB

[a] *DDD is stated by the WHO.*
[b] *RMB is the abbreviation of renminbi, a Chinese currency.*

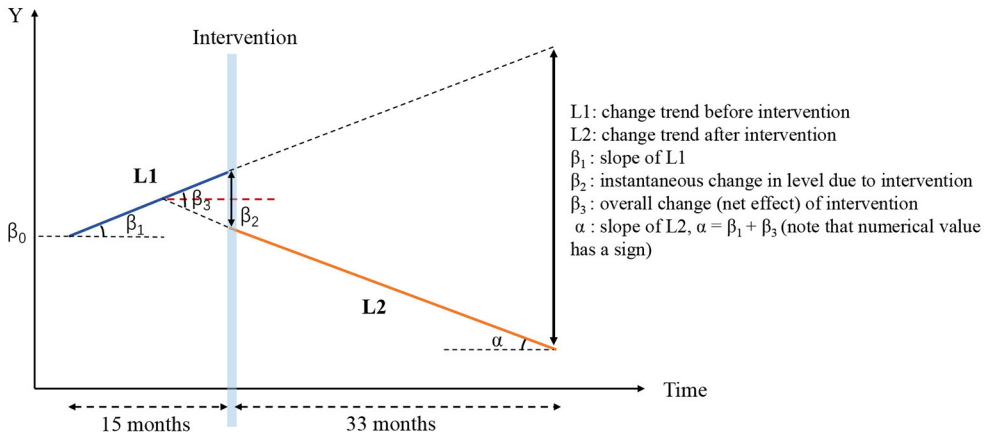


FIGURE 1 | Graphical illustration of interrupted time series analysis model in this study.

TABLE 2 | Annual medical quality indicators in the Changzhou No. 2 People's Hospital, 2011–2015.

Medical quality indicators	2011	2012	2013	2014	2015	Time series analysis model		
						β	*P*	Trend
Number of hospitalizations (1,000 patients)	30.89	50.35	58.91	67.78	71.36	9.838	0.011	Increasing
Average length of stay (Days)	11.3	11.1	10.3	10.1	10.0	−0.36	0.013	Decreasing
Recovery rate (%)	34.62	30.00	28.10	28.36	25.74	−1.94	0.023	Decreasing
Improvement rate (%)	63.21	67.29	69.85	69.81	72.51	2.112	0.012	Increasing
Invalid rate (%)	1.92	2.44	1.87	1.67	1.63	−0.135	0.226	Stable
Mortality rate (%)	0.26	0.27	0.18	0.16	0.11	−0.041	0.012	Decreasing
Nosocomial infection rate (%)	1.62	2.99	2.10	1.88	1.64	−0.107	0.623	Stable

(ACO/PCO), and antibiotic cost per patient in outpatient (ACO per patient).

Similarly, we selected three indicators to evaluate antibiotic use of emergency patient which include antibiotic use rate of emergency patients (AURE), antibiotic cost of emergency patient/total prescription cost of emergency patient (ACE/PCE), and antibiotic cost per patient in emergency patient (ACE per patient).

The values of outcome variables were calculated at the hospital level every month, and the measurement is explained in detail in **Table 1**.

During the study period, medical quality indicators were also captured in hospital-wide population level every year. They were the number of hospitalizations, patient-days, recovery rate, improvement rate, invalid rate, mortality rate, and nosocomial infection rate.

Statistical Analysis

We briefly describe ITS analysis, the strongest quasi-experimental approach, for evaluating the longitudinal effects of intervention when a control group is unavailable or unethical (20). This type of study design can reduce threats to internal validity and obtain richer information from the data.

In this model, the results of each variable are presented in three parts as described in our previous study (21). They are as follows: (1) slope for the pre-intervention period, (2) instantaneous change in level for the post-intervention period based on pre-intervention trend, and (3) change in slope from pre-intervention to post-intervention. The formula of the model is as follows:

$$Y_t = \beta_0 + \beta_1 T + \beta_2 D + \beta_3 P + \varepsilon$$

where Y is the main outcome indicator, such as the AURI; T is a continuous time variable, assigning 1–48 in this study; D is a dummy variable assigned a value of 0 before intervention and 1 after the intervention; P is a time variable counting the number of months after the intervention—for the time before the intervention, $P = 0$, and after the intervention, P is assigned a value from 1 to 34 in this study; ε is a random variable which cannot be explained in the linear model, which we designate the "error term"; β_0 is the baseline level of the outcomes when $T = 0$; β_1 is an estimate of changing trends during the pre-intervention period; β_2 is the level of changes in the policy intervention; β_3 is the trend change of the outcome caused by the policy intervention. Here, $\beta_1 + \beta_3$ represents the final trend of the outcome variable after policy intervention, which we call

the net effect. A graphical illustration of the ITS model is shown in **Figure 1**.

Linear regression was carried out in order to assess the changes in trends of medical quality indicators during the study period. The linear trend by year is defined as the slope of the response over time, expressed by a coefficient (β).

The Durbin–Watson test is the most commonly used method for testing first-order autocorrelation of data (22). Generally, autocorrelation exists if the Durbin–Watson statistic approaches 0 or 4. Conversely, data are independent if the Durbin–Watson statistic is close to 2. The feasible generalized least square (FLGS) method can be used to adjust the first-order autocorrelation errors if needed (23–25). Statistical analysis was performed using STATA v.14 software (STATA Corporation, College Station, TX, USA). Continuous variables are summarized as means and standard deviations. Statistical significance was confirmed at a p-value of $\leq$0.05.

RESULTS

Medical Quality Indicators

As shown in **Table 2**, medical quality indicators were captured regarding the number of hospitalizations, patient-days, recovery rate, improvement rate, invalid rate, mortality rate, and nosocomial infection rate. During and after the study period, the number of hospitalizations and improvement rate significantly increased annually (β = 9.838 and 2.112, P = 0.011 and 0.012, respectively). Simultaneously, the average length of stay and recovery rate both significantly decreased (β = −0.36 and −1.94, P = 0.013 and 0.023, respectively), and the incidence of mortality mildly decreased (β = −0.041, P = 0.012). There was no significant change in the invalid rate (β = −0.135, P = 0.226). Meanwhile, the nosocomial infection rate appeared to be declining, however, the results was not statistically significant (β = −0.107, P = 0.623). In summary, medical quality indicators remained stable or improved during and after the implementation of CSRA policy.

Overall Changes in Antibiotic Use Due to Intensified CSRA Policy

Overall Changes in Antibiotic Use in Inpatients Before and After Intervention

Table 3 shows the overall change in the four indicators with respect to inpatient antibiotic use before and after the intervention. AURI decreased from 70.23% to 58.05% ($P < 0.001$) after the implementation of the intensified CSRA policy. AUD dropped from 87.02 to 58.26 DDDs/100PD ($P < 0.001$) after intervention. AE/ME was significantly decreased, from 24.04 to 17.49% ($P < 0.001$). Moreover, AE per patient decreased, resulting in a savings of 322.56 yuan per patient after intervention ($P < 0.001$). Overall, the intensified CSRA policy had a positive effect on reducing antibiotic use in inpatients.

Overall Changes in Antibiotic Use in Outpatients Before and After Intervention

The overall changes in the three indicators with regard to antibiotic use in outpatient are displayed in **Table 4**. AURO decreased from 24.95 to 21.87% after intensified CSRA policy was implemented ($P < 0.001$). ACO contributed to 42.68% of PCO before intervention, and decreased to 39.06% after intervention (P = 0.006). Unexpectedly, ACO per patient increased by 36.05 yuan when compared with the pre-intervention period, and this difference was statistically significant ($P < 0.001$). In summary, the intensified CSRA policy reduced AURO, but increased antibiotic cost per patient when using a two-time points comparison.

TABLE 3 | Overall changes of four indicators representing inpatient antibiotic use.

Indicators*	Before intervention	After intervention	*P*-Value
AURI (%)	70.23	58.05	<0.001
AUD (DDDs/100PD)	87.02	58.26	<0.001
AE/ME (%)	24.04	17.49	<0.001
AE per patient (yuan)	1238.72	916.16	<0.001

**The indicators in this table were calculated on the average of the monthly data.*
AURI, antibiotic use rate of inpatients; AUD, antibiotic use density, expressed as defined daily doses per 100 patients per day (DDDs/100PD); AE, antibiotic expenditure; ME, medication expenditure.

TABLE 4 | Overall changes of three indicators representing antibiotic use in outpatient.

Indicators*	Before intervention	After intervention	*P*-Value
AURO (%)	24.95	21.87	<0.001
ACO/PCO (%)	42.68	39.06	0.006
ACO per patient (yuan)	158.71	194.76	<0.001

**The indicators in this table were calculated on the average of the monthly data.*
AURO, antibiotic use rate of outpatients; ACO, antibiotic cost of outpatients; PCO, prescription cost of outpatients.

TABLE 5 | Overall changes of three indicators representing antibiotic use in emergency patient.

Indicators*	Before intervention	After intervention	*P*-Value
AURE (%)	64.71	55.10	<0.001
ACE/PCE (%)	67.80	58.44	< 0.001
ACE per patient (yuan)	117.23	122.74	0.006

**The indicators in this table were calculated on the average of the monthly data.*
AURE, antibiotic use rate of emergency patients; ACE, antibiotic cost of emergency patients; PCE, prescription cost of emergency patients.

Overall Changes in Antibiotic Use in Emergency Patients Before and After Intervention

The overall changes in the three indicators with regard to antibiotic use in emergency patients are displayed in **Table 5**. There was a significant decline in AURE after intensified CSRA policy intervention, from 64.71 to 55.10% ($P < 0.001$). ACE/PCE dropped from 67.80 to 58.44% ($P < 0.001$). ACE per patient is as much of a surprise as ACO per patient, because it increased by 5.51 yuan when compared to the pre-intervention period (P = 0.006). In summary, the intensified CSRA policy reduced AURE, but

increased antibiotic cost per patient when using a two-time points comparison.

ITS Analysis of Inpatient Antibiotic Use

The ITS analysis and the changing trend of four indicators with regard to inpatient antibiotic use are displayed in **Table 6** and **Figure 2**, respectively. (1) AURI: AURI declined at a rate of 0.553% ($P = 0.025$) per month before the intensified policy was implemented. At the beginning of the intervention, the AURI dropped by 1.647% instantly ($P = 0.426$). However, the trend of AURI slowed down after the intensified policy was executed, decreasing at 0.354% ($P = 0.471$) per month. (2) AUD: AUD decreased by 1.102 DDDs/100PD ($P = 0.021$) per month before the intensified CSRA policy was implemented. At the beginning of the intervention, the AUD fell quite dramatically to a level of 9.419 DDDs/100PD ($P = 0.037$). However, after that, the downward trend gradually slowed down, decreasing at 0.597 DDDs/100PD ($P = 0.323$) per month. (3) AE/ME: AE/ME decreased before the intensified CSRA policy was implemented, and the rate of decrease was 0.510% per month ($P = 0.000$). The ratio dropped by 1.344% ($P = 0.123$) in the first month of intervention. Subsequently, AE/ME fell at a rate of 0.096% ($P = 0.000$) per month, which was significantly lower than that in the previous period. (4) AE per patient: AE per patient decreased at the rate of 25.309 yuan ($P = 0.002$) per month during the pre-intervention period. After the intensified CSRA policy was executed, no significant decline was noted immediately. In the post-intervention period, AE per patient decreased by 7.987 yuan ($P = 0.053$) per month, and the rate was significantly lower than before. In general, antibiotic use and expenditure in inpatients notably decreased during the pre-intervention period and the declining

TABLE 6 | ITS analysis of inpatient antibiotic use.

Indicators	β_1(SE)	*P*-value	β_2(SE)	*P*-value	β_3(SE)	*P*-value	$\beta_1 + \beta 3$	Parameters of model fit		
								Dw	Root MSE	R^2
AURI (%)	−0.553 (0.237)	**0.025**	−1.647 (2.049)	0.426	0.199 (0.274)	0.471	−0.354	1.861	2.079	0.875
AUD (DDDs/100PD)	−1.102 (0.459)	**0.021**	−9.419 (4.390)	**0.037**	0.505 (0.505)	0.323	−0.597	2.085	4.944	0.799
AE/ME (%)	−0.510 (0.088)	**0.000**	−1.344 (0.855)	0.123	0.414 (0.096)	**0.000**	−0.096	1.888	0.996	0.881
AE per patient (yuan)	−25.309 (7.691)	**0.002**	−18.600 (69.727)	0.791	17.322 (8.707)	0.053	−7.987	1.976	73.177	0.771

AURI, antibiotic use rate of inpatients; AUD, antibiotic use intensity, expressed as defined daily doses per 100 patients per day (DDDs/100PD); AE, antibiotic expenditure; ME, medication expenditure; Dw, Durbin-Watson. Bold values mean P<0.05 and they are statistically significant.

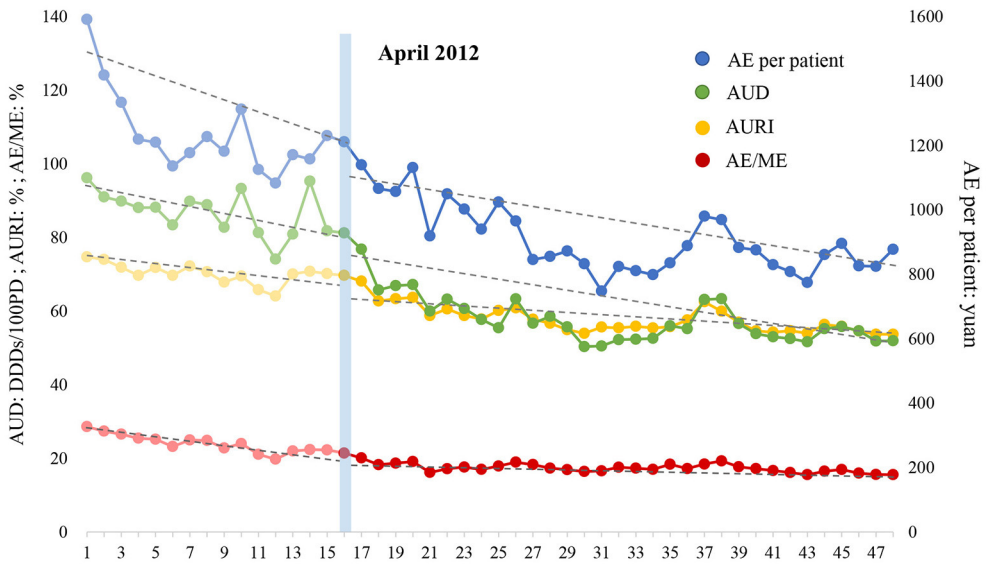


FIGURE 2 | Effect of intensified CSRA policy on four indicators representing inpatient antibiotic use. AURI, antibiotic use rate of inpatients; AUD, antibiotic use intensity, expressed as defined daily doses per 100 patients per day (DDDs/100PD); AE, antibiotic expenditure; ME, medication expenditure.

trend gradually tapered after the intensified CSRA policy was implemented.

ITS Analysis of Antibiotic Use in Outpatient

Table 7 shows the results of three indicators with regard to outpatient antibiotic use estimated by the ITS model, and **Figure 3** illustrates the overall trend of these three indicators. (1) AURO: AURO decreased at the rate of 0.065% ($P = 0.550$) per month before the intervention. An immediate drop of 1.731% ($P = 0.097$) was observed at the beginning month of intervention. After the intervention, the decreasing trend seemed to become slightly sharper at a rate of 0.066% ($P = 0.994$) per month, although this decrease was not statistically significant. (2) ACO/PCO: ACO/PCO declined at a rate of 0.182% ($P = 0.506$) per month before the intensified policy was implemented. The ratio instantly increased by 0.892% ($P = 0.744$) in the first month of intervention. After the intervention, the declining trend accelerated to a rate of 0.216% ($P = 0.906$) per month. (3) ACO per patient: Surprisingly, ACO per patient increased at a rate of 1.965 yuan per month ($P = 0.003$) before the intervention. At the beginning of the intervention, this indicator increased to a level of 14.623 yuan (P = 0.021) immediately. After that, the increasing trend of ACO per patient slowed down, increased by 0.320 yuan (P = 0.021) per month. In general, AURO and ACO/PCO gradually decreased before the intervention and the intensified CSRA policy accelerated the downward trend. Although ACO per patient significantly increased during the pre-intervention period, the intensified CSRA policy curbed the rapid increase of this indicator.

ITS Analysis of Antibiotic Use in Emergency Patient

The ITS analysis results and the changing trend of antibiotic use with regard to emergency patients are shown in **Table 8** and **Figure 4**, respectively. (1) AURE: Before the intensified CRSA policy was implemented, AURE was reduced by 0.400% ($P =$

TABLE 7 | ITS analysis of antibiotic use in outpatient patient.

Indicators	β_1(SE)	*P*-value	β_2(SE)	*P*-value	β_3(SE)	*P*-value	$\beta_1+\beta_3$	Parameters of model fit		
								Dw	Root MSE	R^2
AURO (%)	−0.065 (0.108)	0.550	−1.731 (1.022)	0.097	−0.001 (0.120)	0.994	−0.066	1.805	1.122	0.761
ACO/PCO (%)	−0.182 (0.272)	0.506	0.892 (2.714)	0.744	−0.034 (0.291)	0.906	−0.216	1.834	3.489	0.468
ACO per patient (yuan)	1.965 (0.630)	**0.003**	14.623 (6.118)	**0.021**	−1.645 (0.687)	**0.021**	0.320	1.826	7.131	0.723

AURO, antibiotic use rate of outpatients; ACO, antibiotic cost of outpatients; PCO, prescription cost of outpatients; Dw, Durbin-Watson. Bold values mean P<0.05 and they are statistically significant.

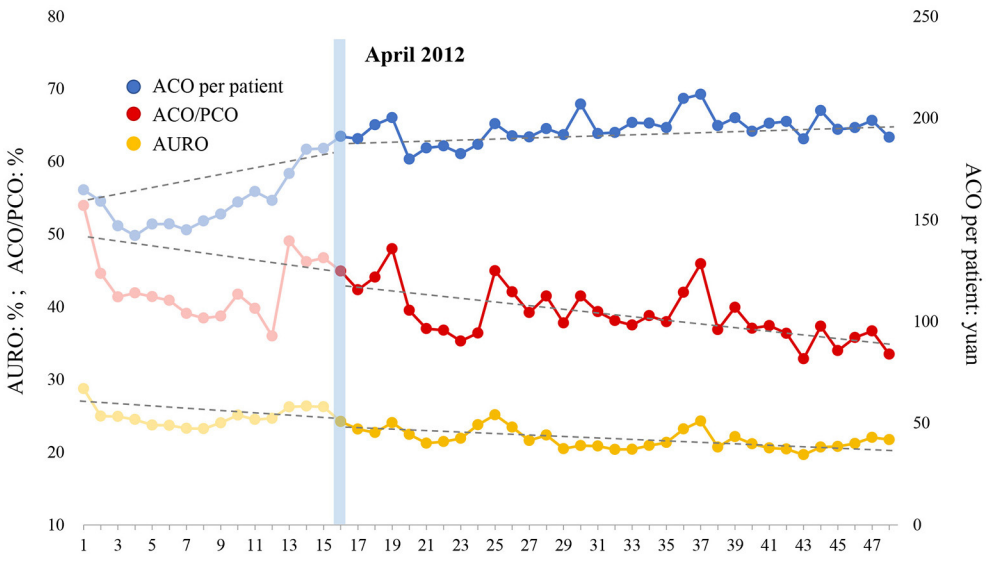


FIGURE 3 | Effect of intensified CSRA policy on three indicators representing antibiotic use of outpatient patient. AURO, antibiotic use rate of outpatients; ACO, antibiotic cost of outpatients; PCO, prescription cost of outpatients.

TABLE 8 | ITS analysis of antibiotic use in emergency patient.

Indicators	β_1(SE)	*P*-value	β_2(SE)	*P*-value	β_3(SE)	*P*-value	$\beta_1+\beta_3$	Parameters of model fit		
								Dw	Root MSE	R^2
AURE (%)	−0.400 (0.193)	**0.044**	−4.817 (1.762)	**0.009**	0.308 (0.218)	0.164	−0.092	2.055	1.860	0.873
ACE/PCE (%)	−0.616 (0.102)	**0.000**	−2.492 (1.030)	**0.020**	0.465 (0.107)	**0.000**	−0.151	1.947	1.531	0.903
ACE per patient (yuan)	0.208 (0.385)	0.591	11.398 (3.841)	**0.005**	−0.630 (0.412)	0.133	−0.422	1.918	4.974	0.426

AURE, antibiotic use rate of emergency patients; ACE, antibiotic cost of emergency patients; PCE, prescription cost of emergency patients; Dw, Durbin-Watson. Bold values mean P<0.05 and they are statistically significant.

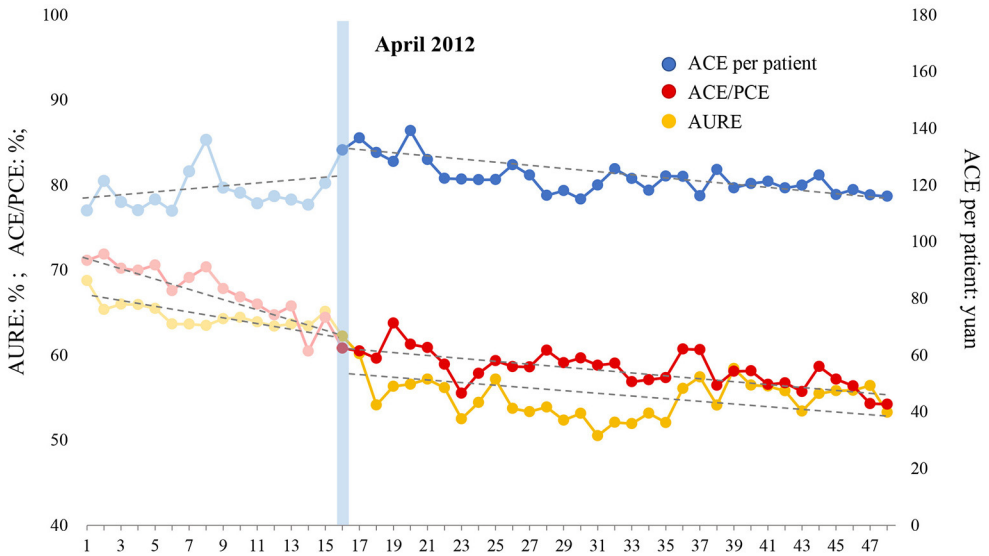


FIGURE 4 | Effect of intensified CSRA policy on three indicators representing antibiotic use of emergency patient. AURE, antibiotic use rate of emergency patients; ACE, antibiotic cost of emergency patients; PCE, prescription cost of emergency patients.

0.044) per month. At the beginning month of the intervention, there was a notable decrease in the level of 4.817% (P = 0.009). After the intervention, the declining trend gradually slowed down, decreasing by 0.092% (P = 0.164) per month. (2) ACE/PCE: ACE/PCE decreased before the intervention, and the rate of decrease was 0.616% (P < 0.001) per month. At the beginning of the intervention, the ratio dropped greatly by 2.492% instantly (P = 0.020). However, the downward trend slowed down after the intervention, and decreased at a rate of 0.151% (P<0.001) per month. (3) ACE per patient: ACE per patient increased at a rate of 0.208 yuan (P = 0.591) per month before the intervention. At the beginning month of the intervention, this indicator increased to a level of 11.398 yuan (P = 0.005) immediately. After that, ACE per patient began to decrease at a rate of 0.422 yuan (P = 0.133) per month. In general, AURE and ACE/PCE notably decreased before the intervention, and the declining trend gradually tapered after the intensified CSRA policy was implemented. Although ACE per patient increased during the pre-intervention period, intensified CSRA policy stopped this increasing trend and showed a positive effect on reducing the antibiotic cost in the emergency patient.

DISCUSSION

During and after the study period, the rate of nosocomial infection remained stable, and the rate of mortality mildly decreased, which indicates that the continued decline in antibiotic use is unlikely to negatively impact the quality of medical care provided.

The findings of this study demonstrate that antibiotic use of inpatients (AURI and AUD), outpatient (AURO), and emergency patients (AURE) notably decreased in the pre-intervention period from January 2011 to March 2012. Thus, it was apparent that soft measures such as systemic training and education play an important role in reducing antibiotic use. Similarly, a study by Onorato et al. (6) also confirmed the positive impact of a persuasive and educational AMS program on antibiotic use in ICUs in Italy. Although an intensified intervention led to an

instant reduction in antibiotic use in April 2012 as expected, an accelerated downward trend was not observed from April 2012 to December 2014. Instead, the declining trend gradually tapered during the post-intervention period. To our knowledge, this may be primarily attributed to the capacity for reduction at different stages. In the beginning, a high rate of prescription at baseline provides sufficient room for reduction. When a lower level of antibiotic use is achieved, there is little room for further reduction. Similar findings were also observed in other AMS reports. For instance, two studies found no significant change in antibiotic use in the hospitals of women and children following AMS because of the low base levels of antibiotic use in these institutions (26, 27).

The impact of intensified CSRA policy on antibiotic expenditure (AE/ME, AE per patient, and ACE/PCE) is almost the same as that of antibiotic use. The growth trajectories of the cost indicators changed from a steep descending trend to a softened descending trend. As stated above, there is little room for a further decline in the later stages of intervention. We were even delighted to see that the downward trend of ACO/PCO sharpened after the intensified CSRA policy was implemented. But to our surprise, ACO per patient increased by 36.05 yuan and ACE per patient increased by 5.51 yuan in pre- post-comparisons. In the ITS analysis, ACO per patient also greatly increased prior to the full implementation of the intensified CSRA policy, which is inconsistent with other indicators. Maybe we can interpret this phenomenon from the policy itself. The CSRA policy only imposed quotas of AUR and AUD, but no claims were made about the cost of antibiotics. Thus, physicians might prescribe expensive antibiotics to ease the impact of the policy in the short term. Additionally, drug price inflation may also contribute to the increase of antibiotic cost during the whole study period. Similar findings have been reported in other studies where antibiotic expenditure fluctuated before reaching a stable status over a prolonged period (28, 29). Encouragingly, the upward trend of ACO per patient greatly softened from $\beta = 1.965$ to $\beta = 0.320$ after the intensified intervention, and the upward trend of ACE per patient reversed from $\beta = 0.208$ to $\beta = -0.442$ after the intensified intervention. They all demonstrated that intensified CSRA policy showed a positive effect on reducing antibiotic expenditure.

After 4 years of CSRA implementation in this hospital, AURO decreased from 25 to 22%, and AURI decreased from 65 to 54% in the last month of the study period. These two indicators are quite close to the goals set by the CSRA policy. However, AURE gradually approached 55% and AUD approached 52 DDDs/100PD in the last month of the study period, which far exceeded target values (AURE of 40% and AUD of 40DDDs/100PD). This begs several questions: are the goals of AURE and AUD set by the CSRA policy reasonable? To what extent is further reduction achievable without endangering the quality of care in this hospital? In China, data from 114 general tertiary-care hospitals in 30 provinces showed that the rate of antibiotic prescription was 27.82% in emergency departments in 2016 (30). One study showed that the level of AUD decreased to 49.5 DDDs/100 PD after CSRA in a general tertiary hospital, which is similar to our finding (31). Another study showed an excellent outcome of decreased antibiotic consumption (28.08 DDDs/100PD) following the implementation of CSRA policy, far below the target (2). These initial results were quite promising, and motivated us to continue working on reducing AURE and AUD.

LIMITATIONS

We acknowledge that there are some limitations to our study. First, this study was a single-center study without a control group. Although ITS analysis was applied to minimize the threats to internal validity, we still could not ensure that CSRA policy implementation was the only reason for the changes we report in our findings. A concurrent control hospital can be implemented in future studies to account for simultaneous secular trends in antibiotic use (32). Second, the indicators in this study do not fully encompass the possible impacts of CSRA policy. Reducing antibiotic use and expenditure may reflect reductions in overuse, but we cannot be certain that these observed changes reflect better quality antibiotic prescription. Third, we did not examine disease-specific antibiotic use or expenditure. However, different disease-specific factors might have different effects on these outcomes. For different specific diseases, there are differences in treatment modality, infection prevention, and antibiotic usage. These findings should be interpreted with caution due to these limitations.

CONCLUSION

In summary, this study provides detailed ITS analysis of the impact of CSRA policy (soft measures and intensified rigid measures) on antibiotic use in a single teaching hospital. Implementation of CSRA policy was associated with declining antibiotic use and antibiotic expenditure in inpatients, outpatients, and emergency patients. However, it is also important to note that the declining trend of antibiotic consumption slowed down due to the limited capacity for a decline in the later stages of CSRA intervention.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Institutional Ethics Committee approval was obtained from the Nanjing Medical University Ethics Committee (Grant number: ethical review 201236). Due to this being a retrospective study, the patient data were aggregated and the individual patients' information was not reported in this study. Therefore, the study was approved with a waiver for informed consent.

AUTHOR CONTRIBUTIONS

XQ and XL initiated the study concept. XQ conducted data analysis and wrote the first draft of the manuscript. YP and JG collected the data of inpatients. SX and YL led the data collection of outpatients and emergency patients. XL and DS contributed to the data analysis and interpretation of the data and also revised the draft of the manuscript. All the authors read and approved the final manuscript.

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Cost-Effectiveness Analysis of Ultrasound Screening for Thyroid Cancer in Asymptomatic Adults

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Objectives: This study evaluated the long-term cost-effectiveness of ultrasound screening for thyroid cancer compared with non-screening in asymptomatic adults.

Methods: Applying a Markov decision-tree model with effectiveness and cost data from literature, we compared the long-term cost-effectiveness of the two strategies: ultrasound screening and non-screening for thyroid cancer. A one-way sensitivity analysis and a probabilistic sensitivity analysis were performed to verify the stability of model results.

Results: The cumulative cost of screening for thyroid cancer was $18,819.24, with 18.74 quality-adjusted life years (QALYs), whereas the cumulative cost of non-screening was $15,864.28, with 18.71 QALYs. The incremental cost-effectiveness ratio of $106,947.50/QALY greatly exceeded the threshold of $50,000. The result of the one-way sensitivity analysis showed that the utility values of benign nodules and utility of health after thyroid cancer surgery would affect the results.

Conclusions: Ultrasound screening for thyroid cancer has no obvious advantage in terms of cost-effectiveness compared with non-screening. The optimized thyroid screening strategy for a specific population is essential.

Keywords: ultrasound screening, thyroid cancer, Markov model, cost-effectiveness, asymptomatic adults

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INTRODUCTION

Thyroid cancer is one of the most common malignancies, which accounts for 1 to 1.5% of all malignant tumors in the United States (1). With the rapid development of the ultrasound technique in the primary care, the incidence of thyroid cancer exploded in the past few decades including in Korea and many other countries (2–4). However, the increase of incidence and prevalence does not company with increasing disease-specific fatality (5–7). The International Agency for Research on Cancer under the World Health Organization and other relevant expert organizations agree that the rising incidence of thyroid cancer in many countries, especially in high-income countries, is largely caused by over-diagnosis and numerous false-positive cases (8), with ultrasound screening being the most widely used method of diagnosing thyroid cancer.

Relevant studies and recommendations were issued to reduce and prevent this phenomenon. In 2017, the United States Preventive Services Task Force on thyroid cancer screening online, did not endorse thyroid cancer ultrasound screening for asymptomatic adults because of the lack of evidence (9). In addition, Korean studies demonstrated that thyroid cancer screening did not reduce the thyroid cancer-related fatality (10). Although active surveillance of thyroid cancer is call in low-risk people with incidental thyroid neoplasm, most individuals go with surgical removal given inadequate evidence confirmed their lifelong safety without surgery. Over-diagnosis put people at the unnecessary risk of thyroid surgery such as hoarseness and primary hypoparathyroidism without a balanced benefit, leading to unnecessary labeling of lifelong diagnosis and unnecessary treatments (11).

Further, thyroid cancer ultrasound screening overdrew the finance of healthcare system with accumulated diagnosed cases. There are some studies reported the economic burden and value of thyroid cancer ultrasound screening (12, 13). A study in 2013 showed ultrasound screening for thyroid cancer was cost-effective in selected obese patients (14). However, it is not clear whether screening for all asymptomatic individuals has the advantage of cost-effectiveness compared with the cost in the long run. This study aimed to evaluate the long-term effectiveness of ultrasound screening for thyroid cancer in asymptomatic adults taking the United States as example through decision-tree Markov models, facilitating the decision making for clinicians and policy makers.

MATERIALS AND METHODS

Model Design

We established a Markov decision-tree model using the decision analysis software (TreeAge Pro 2011; TreeAge Software, Williamstown, MA, USA) and developed two different strategies: thyroid cancer ultrasound screening and non-screening according to the disease progression and treatment prognosis. For the screening strategy, all asymptomatic populations aged ≥20 years (15, 16), underwent neck ultrasound screening which revealed healthy status (no nodules), benign nodules (follow-up with no treatment), or malignant nodules (follow-up and treatment). For the non-screening strategy, individuals underwent routine physical examinations (palpation), which also showed healthy status (no nodules), benign nodules (follow-up with no treatment), or malignant nodules (follow-up and treatment).

There were some assumptions underlying the use of these two strategies. First, considering that all Koreans underwent thyroid cancer screening in 2008, we used the Korean thyroid cancer epidemiological data for 1990 and 2010 to determine the transition probabilities for the screening group and the non-screening group, respectively, assuming that the natural incidence of thyroid cancer had remained unchanged between these years (17–19). Second, we assumed that the cost of routine physical examinations for the non-screening group was lower than that of ultrasound examinations for the screening group. Third, we assumed that individuals in the two groups were initially aged 20 years because thyroid disease in children differs from that in adults (16). Accordingly, we used the average disease incidence because the mobility and mortality for different ages were difficult to obtain, but we considered age-wise differences in natural mortality. Fourth, we did not consider any treatments for postoperative complications.

We compared long-term cost-effectiveness of the screening group and non-screening strategies in this study. Because we were unable to obtain the relevant data on thyroid nodules and thyroid cancer in different disease statues, we simply divided thyroid nodules into benign and malignant (thyroid cancer) and established a basic model. The transition probabilities in the model were calculated on the basis of the results of published clinical trials and official data procured from the Korea Statistical Office (20–24). Follow-ups for the screening group and non-screening groups were both lifelong. The quality of life and financial burden of patients were closely related to the recurrence of thyroid cancer. Therefore, we used recurrence as an absorbing state to provide a more accurate description of differences in the effectiveness and costs of these two strategies. The model ran over a 55-year time horizon according to the disease characteristics and life expectancy of Koreans (21); healthy individuals could live as long as their projected life expectancy. **Figure 1** presents a simplified disease status model.

Effectiveness

We included six health statuses were included in the models: recurrence, thyroid cancer postoperative stability, thyroid cancer, benign thyroid nodules, health, and death. The effectiveness was reported in quality-adjusted life years (QALYs), which were calculated by multiplying the utility values for each health state by the duration of health state. Utilities were derived from studies on the quality of life of patients with thyroid cancer, and all future QALYs were discounted 5% annually. **Table 1** presents the specific utility values.

Costs

In our model, we calculated total costs from the perspective of the whole society, encompassing the costs of examination, surgery, drugs, follow-ups (once a year for life), and productivity losses. Hospitalization costs and labor losses caused by thyroid cancer were calculated on the basis of expert recommendations and guidelines for various countries, according to which 1 to 2 days of hospitalization are required for patients who undergo thyroid cancer surgery, followed by approximately 2 weeks for the recovery, the hospitalization costs, and labor losses of thyroid cancer were estimated (26). All costs, which are listed in **Table 2** were expressed in U.S. dollars, using the dollar value in 2017, and an inflation rate equal to the mean of the annual changes in the Consumer Price Index for Medical Care since the year of the reported cost was applied (26). All future costs were discounted 5% annually.

Abbreviations: QALYs, quality-adjusted life years; CER, cost-effectiveness ratio; ICER, incremental cost-effectiveness ratio.

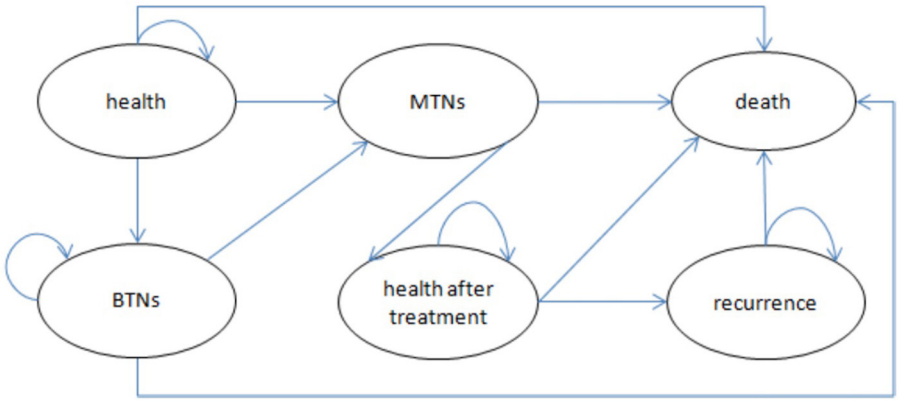


FIGURE 1 | Bubble chart of Markov model. BTNs, benign thyroid nodules (state); MTNs, malignant thyroid nodules (state).

TABLE 1 | Health utility values and associated model variables.

Variable	Base-case	Range	Distribution	Source
Thyroid cancer recurrence	0.54	0.49–0.59	Beta (α: 176, β: 150)	Selberherr et al. (25)
Thyroid cancer postoperative stability	0.99	0.74–1.00	Beta (α: 1, β: 0)	Selberherr et al. (25)
Thyroid cancer	0.60	0.54–0.66	Beta (α: 153, β: 102)	The United States Cancer Statistics (26)
Benign thyroid nodules	0.99	0.89–1.00	Beta (α: 100, β: 1)	Selberherr et al. (25)
Perfect health	1.00			
Death	0			

TABLE 2 | Cost variables for the modeling.

Cost component	Base-case	Range	Distribution	Source
c_t	20,174.5786	16,737.47–24,283.81	Gamma (α: 29, β: 706)	(26–29)
c_n	251.46	126.06–311.52	Gamma (α: 7, β: 34)	(26–29)
c_tf	1,264.9032	731.99–2309.31	Gamma (α: 3, β: 492)	(26–29)
c_nf	798.6	399.30–1597.20	Gamma (α: 2, β: 449)	(26–29)
c_recurrence	6,050.22	3,024.78–91.00	Gamma (α: 4, β: 1513)	(26–29)
c_o	50.16	25.08–75.24	Gamma (α: 4, β: 13)	(26–29)

c_t, thyroid cancer treatment costs; c_recurrence, thyroid cancer recurrence costs; c_tf, thyroid cancer postoperative follow-up costs; c_nf, thyroid benign nodules follow-up costs; c_n, thyroid ultrasound screening costs; c_o, general physical examination costs.

Outcomes

We calculated cumulative costs and effectiveness by performing Markov queue simulations, and simulation results of the model were expressed as cost-effectiveness ratio (CER) and incremental cost-effectiveness ratio (ICER). If the cost was lower and the effect was better, then a strategy entailing a smaller CER was the recommended. If the cost was low and the effect was also poor, then the ICER was calculated and compared with the set threshold value. If it exceeded the threshold, then the cost was lower, and if it was below the threshold, then the higher-cost solution was selected. Because the cost of this study was expressed in U.S. dollars, we set the threshold at $50,000/QALY in light of recommendations made in several medical decision analysis studies conducted in the United States (14).

Transition Probability

The transition probability between disease states in the model was obtained from clinical trials, standardized follow-up trials, and official data of the Korean Bureau of statistics (13). By using the incidence or transition probability of different disease states in 1990 and 2010, respectively, the event probability in 1-year period was calculated by using the formula 1 given below:

$$tp = 1 - (1 - tp_t)^{1/t} \quad (1)$$

where tp is the transition probability and t is the time.

The transition probability included the incidence rate of benign nodules, the incidence rate of malignant nodules, the probability of benign nodule developing into malignant

TABLE 3 | Probability variables used in the modeling.

Variable	Group	Base-case	Range	Distribution	Source
Health→ BTNs	SG	0.19	0.14–0.24	Beta (α: 50, β: 211)	
	NSG	0.68	0.51–0.85	Beta (α: 19, β: 9)	
Health→ MTNs	SG	0.000039	0.000029–0.000049	Beta (α: 62, β: 1575948)	Kwong et al. (15)
	NSG	0.000583	0.000437–0.000729	Beta (α: 61, β: 105337)	Kwong et al. (15)
BTNs→ MTNs	SG	0.00854478	0.00640859–0.01068098	Beta (α: 61, β: 7070)	Kwong et al. (15)
	NSG	0.00854478	0.00640859–0.01068098	Beta (α: 61, β: 7070)	Kwong et al. (15)
MTNs→ death	SG	0.000003	0.00000195–0.00000325	Beta (α: 62, β: 23640522)	Teng
	NSG	0.000005	0.000004–0.000007	Beta (α: 62, β: 11175470)	Teng
Health after treatment → Recurrence	SG	0.001029	0.000772–0.001286	Beta (α: 61, β: 59621)	Wang et al. (22)
	NSG	0.001029	0.000772–0.001286	Beta (α: 61, β: 59621)	Wang et al. (22)

BTNs, benign thyroid nodules (state); MTNs, malignant thyroid nodules (state); SG, screening group; NSG, non-screening group.

nodules, mortality of malignant nodules, recurrence rate of malignant nodules, and natural mortality rate. This study assumed that the natural incidence rate of thyroid cancer is comparable across ethnicities. The probability of benign nodules developing into malignant nodules was the same in the two groups, and the incidence of malignant nodules is different from the result of screening. So the incidence rate of malignant nodules was different in two groups due to screening. With the increase of the detection rate of thyroid cancer, the mortality also increased. In addition, it is found that the surgical treatment of thyroid cancer is the same, and the postoperative recurrence rate should be the same. Due to the increased number of cancers found, the cancer mortality had also increased.

In addition, the recurrence rates were the same in two groups after the same surgical treatment of thyroid cancer. The specific values and distribution of transition probability are listed in **Table 3**.

Sensitivity Analyses

A one-way sensitivity analysis was performed in relation to the probabilities of all costs, utility values, and transitions to determine the effects of different values of variables and uncertainties on the model results. The range of values for the variables was determined on the basis of those used for sensitivity analyses in previous studies, as shown in **Tables 1**–**3**.

A probabilistic sensitivity analysis entailing Monte Carlo simulations was set to simulate 1,000 times. We assumed that the transfer probability and utility value were beta distribution, and the cost was gamma distribution.

For the parameters with available value ranges, the values were assigned according to the upper and lower parameter limits. According to the previous literature and our own research experience, for the parameters whose value range was not available, a basic value is selected ±10% was selected. The specific parameters are shown in **Tables 1**–**3**.

RESULTS

Results of the Base-Case Analysis

The results of a long-run simulation of the status of thyroid cancer metastasis revealed that the cumulative cost of screening for thyroid cancer was $18,819.24, with 18.74 QALYs, whereas the cumulative cost of non-screening was $15,864.28 with 18.71 QALYs. The ICER of the two groups was $106,947.5/QALY, which greatly exceeded the set threshold value of $50,000/QALY (**Table 4**). Although both the cost and utility of thyroid cancer screening were higher than those for non-screening, they were unacceptable relative threshold values, and non-screening for thyroid cancer was determined to be a better cost-effective strategy. The difference between the cumulative utility values of the two strategies was evidently nominal, and the costs of screening were much higher, so the cost-effectiveness advantage of the screening group was not significant.

Sensitivity Analyses

As shown in **Figure 2**, one-way sensitivity analyses were performed for all costs, probabilities, and utility values. The utility values of health after thyroid cancer surgery, and benign nodules; follow-up costs of benign thyroid nodules; incidences of benign nodules; and some other parameters impacted on the model results. The lower utility value of benign nodules and the utility value of health after thyroid cancer surgery could have influenced the result, making a screening strategy more cost-effective.

The results obtained after performing 1,000 Monte Carlo simulations were consistent with those of the cohort simulation. **Figure 3**, which depicts a Monte Carlo simulation scatter plot, reveals most of the sites in the 1,000 simulation analyses fell within the first quadrant. In other words, both the cost and effectiveness of the screening group was exceeded those of the non-screening group. About 70% of the sites were located in the willingness to pay, indicating a 70% probability that non-screening for thyroid cancer was more cost-effective compared with screening. The acceptable cost-effectiveness curve is shown in **Figure 4**. The acceptability of the screening group was higher than that of non-screening group when the willingness to pay

TABLE 4 | Summary findings of a cost-effectiveness analysis of thyroid cancer screening data.

Strategy	Total Cost	Total QALY	Incremental Cost	Incremental QALY	ICER
Screening	$18,819.24	18.74	2,954.96	0.03	106,947.5
Non-screening	$15,864.28	18.71			

QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio.

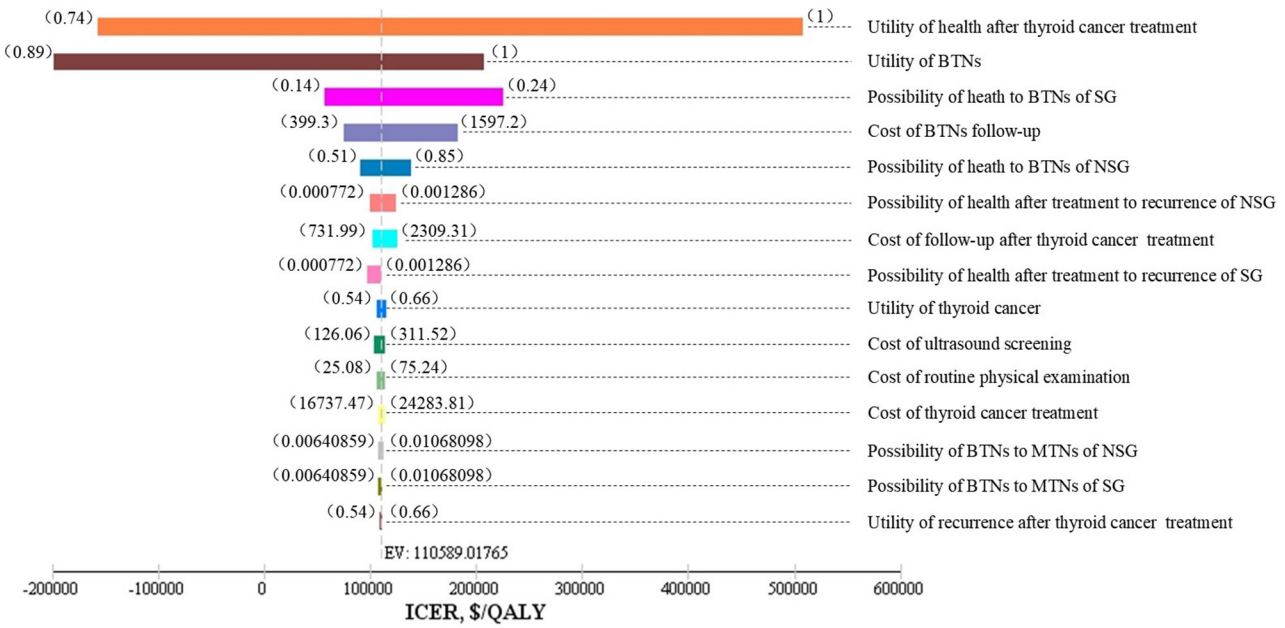


FIGURE 2 | Tornado diagram. SG, screening group; NSG, non-screening group; BTNs, benign thyroid nodules (state); MTNs, malignant thyroid nodules (state); EV, expected value.

was higher than $115,000. The results of the sensitivity analysis showed that a non-screening strategy was more cost-effective at a set threshold value and confirmed the reliability of our results.

DISCUSSION

This study showed that thyroid screening obtained 18.74 QALYs, and gained 0.03 QALYs more than the non-screening population, with an incremental cost of $2,954.96 incurred for screening. In the setting of this study, ultrasound screening of thyroid cancer is undoubted cost-effectiveness compared with non-screening in asymptomatic adults. Thyroid cancer identified by ultrasound screening in general population may not be that which impairs people's lives. Without such screening, many people may go peacefully with their thyroid nodules in their lifelong time. This quantitative result informed the policy maker to prevent such screening in the aspect of the society.

Although our study are against the thyroid cancer screening the whole asymptomatic population under the model background of this study, thyroid cancer screening may be useful in selected people. Thyroid cancer screening for specific populations, may be cost-effectiveness in selected conditions (14). In addition, ultrasound tests are necessary in people with suspected thyroid nodules or at higher risks of thyroid malignancy. The clinical practice guideline needs to consider both the values and preferences and local baseline characteristics of the population.

According to the results of our sensitivity analysis, follow-up costs associated with benign thyroid nodules impacted on the results of our model. In this model, patients were required to undergo regular lifelong follow-up with very low recurrent rate of thyroid cancer. The follow-up strategy for people with thyroid nodules may need proper exploration and investigation. In addition, postoperative monitoring may also be excessive and may generate unnecessary costs. Research conducted on the annual monitoring costs of papillary thyroid cancer indicates that annual postoperative surveillance of the patients is excessive and may contribute to unnecessary costs. One study evaluated the cost-effectiveness of tapering postoperative surveillance to 3-year intervals after 5 years of annual surveillance in place of perpetual annual follow-ups for patients with low-risk papillary thyroid cancer who demonstrated excellent therapeutic responses (29). The model and sensitivity analyses of our study are consistent with the results of this study, which also provide economic evidence for postoperative monitoring of thyroid cancer.

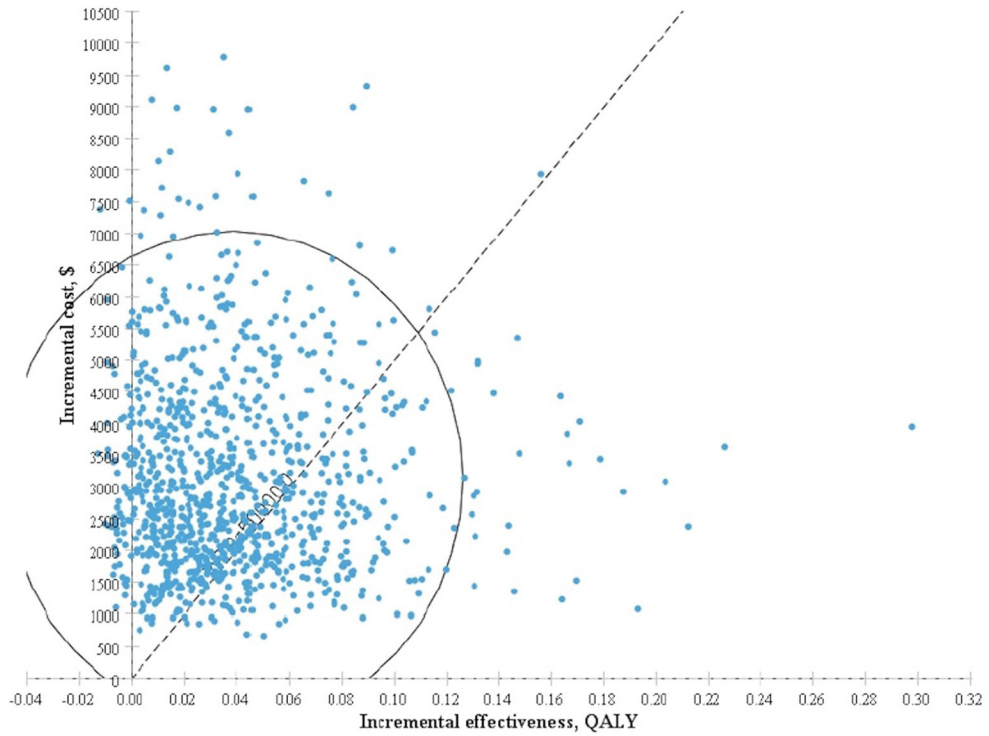


FIGURE 3 | Incremental cost-effectiveness scatter plot for screening group vs. non-screening group based on Monte Carlo simulation.

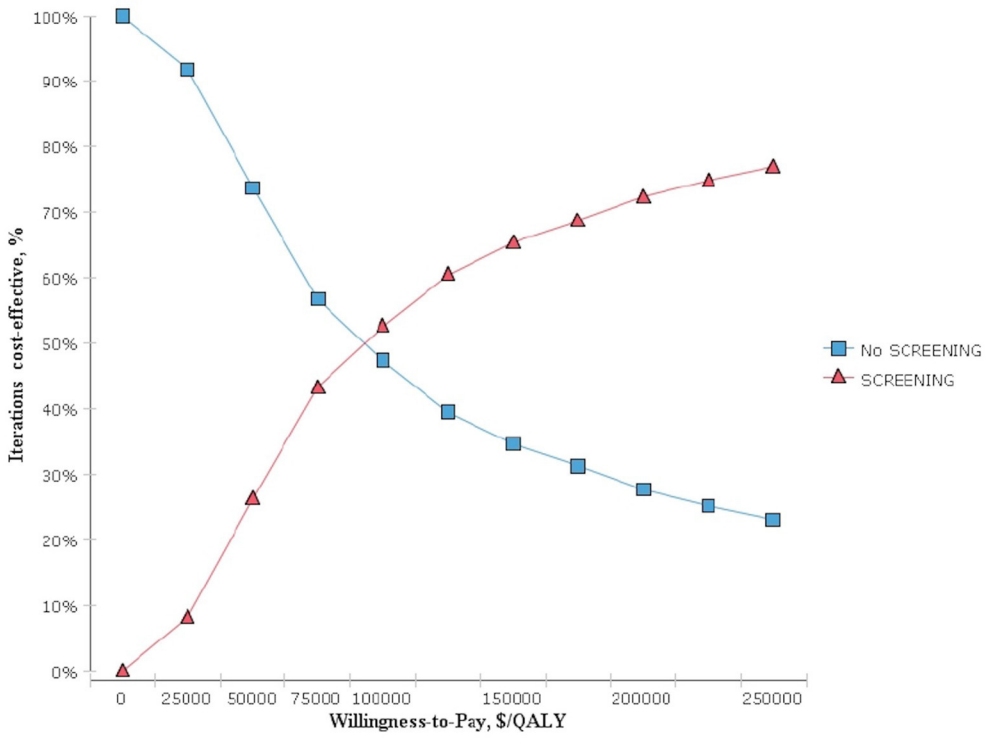


FIGURE 4 | Monte Carlo simulation cost-effectiveness acceptability curve.

There are several limitations to be acknowledged. First, because of the lack of studies on the health utility values for patients with benign thyroid nodules, we estimated the value for patients with benign thyroid nodules according to their disease status and life status when inputting model parameters, assigning the same health utility value to these patients and postoperative patients. However, patients with benign nodules may experience negative moods after identifying the nodule due to cancerophobia or other stresses. Although thyroid nodules do not compromise health of an individual, negative emotions, such as anxiety, can lead to diminished health benefits but unmeasurable in the current study. Second, all the costs in this study were derived from the literature, and can be out-of-date when our results are in used. However, our sensitivity analyses confirmed the robustness of the results within acceptable changes of the costs.

CONCLUSION

Ultrasound screening for thyroid cancer in an asymptomatic population is not cost-effective, and inappropriate in asymptomatic adults. Policy makers need to be cautious with unregulated thyroid cancer screening in avoidance of the waste of healthcare resource. Further studies are needed to keep the screening and follow-up strategy up to date.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

NY and HY developed the Markov model and analyzed the data collected from literature and wrote the manuscript. MH made substantial contributions to the conception and design of the study and reviewed and edited the manuscript. SL conceived the study, participated in the coordination and the acquisition of data, and helped to draft the manuscript. JG co-reviewed and co-edited the manuscript. All authors have read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.729684/full#supplementary-material

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Predictors of Quality of Life in Patients With Myocardial Infarction Combined With Dyslipidemia

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Background: Dyslipidemia is an important risk factor for myocardial infarction (MI). This study aimed to examine the health-related quality of life (HRQoL) and its predictors of patients with MI combined with dyslipidemia in China.

Methods: Information on patients' sociological characteristics, lifestyle, clinical characteristics, and quality of life were collected by electronic medical records and questionnaires. Tobit regression model was used to investigate the predictors of quality of life.

Results: There were 756 patients responded. The average EQ-5D score of all the patients was 0.95 (SD: 0.11). For all patients, factors such as age, high-fat and high-cholesterol diet, sports, family history of dyslipidemia, history of peripheral artery disease significantly affected HRQoL.

Conclusions: Post-discharge care of the elderly group should be paid more attention to and suggestions on the healthy lifestyle (fat control) of the patients should be encouraged to improve the quality of life of these population.

Keywords: myocardial infarction, dyslipidemia, health-related quality of life, predictors, real-world data, China

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INTRODUCTION

Coronary heart disease (CVD) is caused by coronary artery luminal stenosis or occlusion. A survey of the World Health Organization showed that 17.9 million people die each year from CVD (1). Myocardial infarction (MI) is the most serious type of coronary heart disease. The World Bank estimates that the number of people with MI in China will rise to 23 million in 2030 (2). The disease burden of MI is relatively heavy. The mortality rate of acute myocardial infarction (AMI) raised sharply from 14.04 per 100,000 people in 2004 to 64.25 in 2014 (3). Dyslipidemia is a strong predictor of MI (4, 5), Patients should strictly control their low-density lipoprotein-cholesterol levels (LDL-C) (6). In China, the prevalence of Dyslipidemia in Chinese people aged ≥18 years was 40.40% (7). Such a high prevalence of dyslipidemia may increase the risk of MI, and it is necessary to control blood lipids, especially in patients with MI.

Health-related quality of life (HRQoL) is generally considered as a multidimensional assessment of the patients' overall physiological and psychological function, which can reflect the influence of different stages of disease and treatment measures on the patients' health status (8). HRQoL can also be combined with time to calculate quality-adjusted life years (QALYs) to compare the economics of different interventions in pharmacoeconomic evaluation. In recent years, although the prognosis and survival rate of MI have been significantly improved, the motor ability of patients after acute MI is impaired (9), and quality of life is also negatively affected (mobility and anxiety) (9, 10). In addition, dyslipidemia may decrease the quality of life in patients with MI. Recently, more and more studies have reported HRQoL in patients with MI (11–14), even patients with MI subtypes were also involved (15), and some studies have also investigated the factors that influence the quality of life of patients with MI (16–18). However, most of them only involved sociodemographic and clinical related factors, and the measurement of quality of life in patients with MI combined with dyslipidemia and related factors study had not been observed.

Therefore, hospital case data and questionnaire data were used in this study to evaluate the quality of life based on health preferences of Chinese patients with MI combined with dyslipidemia and to explore factors associated with quality of life. The results of this study will fill in the data gaps, provide real-world evidence for the measurement of QALY of this disease, and help to conduct economic research on relevant interventions. In the meanwhile, the data on quality of life and its relationship with related factors will help healthcare professionals adjust and improve care strategies for patients with this disease and help policymakers evaluate the effectiveness of policies from the perspective of patient-centered care.

METHODS

Data Source and Collection

Data from this study were collected from a multi-center retrospective study of Chinese patients with MI combined with dyslipidemia. We divided mainland China into five geographical regions: East, West, South, North, and Central, and selected at least one sample hospital from each region. Therefore, six Grade-A tertiary hospitals in mainland China that have a sound electronic case data platform and agree to participate in this study were selected as sample centers. Patients who met inclusion-exclusion criteria in six sample centers were enrolled in the study.

The basic information and clinical characteristics of patients were obtained from electronic medical records. We also conducted a cross-sectional study to collect information on patients' quality of life and lifestyle. From May to July, 2019, patients meeting the requirements were invited to the sample centers for face-to-face questionnaire survey. The ethical evaluation of this study was conducted by the ethics committees of all the six participating hospitals.

Population

We screened patients according to the hospital's electronic medical record data and we did telephone interview to determine whether patients agreed to enter the study. The patients who met the inclusion and exclusion criteria were asked whether they could go to sample hospitals for a questionnaire survey and whether they were willing to participate in the study.

Inclusion criteria: (1) Patients who were admitted to the hospital for AMI between January 1, 2016, and December 31, 2016, and the earliest hospitalization of a patient with myocardial infarction is regarded as "index hospitalization." There were no restrictions on whether the patient had complications or had a first episode of myocardial infarction in "index hospitalization"; (2) Patients did not die before face-to-face questionnaire survey; (3) Patients were taking lipid-regulating drugs, or the first blood lipid test showed LDL-C $\geq$1.8 mmol/L during the "index hospitalization."

Exclusion criteria: (1) Patients participated in interventional clinical trials after "index hospitalization"; (2) There is a barrier to communication between investigators and the patient or family (if the patient has died).

Health-Related Quality of Life Measurement

HRQoL was measured using the EuroQoL three-dimensional scale (EQ-5D-3L). EQ-5D-3L is one of the most widely used universal scales to describe and evaluate health status, and its score can be used to calculate QALY. EQ-5D-3L has five dimensions: mobility (MO), self-care (SC), usual activities (UA), pain/discomfort (PD), and anxiety/depression. Each dimension is divided into three levels: unlimited, moderately limited, and completely limited, representing the three health states of each dimension, respectively (19). There are up to 243 combinations of all health states in the five dimensions, and each combination has a corresponding value. The Chinese tariff (20) was adopted in this study, with a value range of −0.149-1. −0.149 represents death and 1 represents complete health.

Statistical Analysis

Descriptive statistics were applied to baseline characteristics. The mean value and standard deviation of EQ-5D-3L utility value were reported and stratified by gender. Considering the non-normal distribution of EQ-5D index scores (Shapiro-Wilk test, $P < 0.05$), Kruskal-Wallis was used to test the significance of EQ-5D score among grouping variables.

To perform multivariate and correlation analysis, the variables expected to be related to HRQoL were divided into three categories: sociological characteristics (Gender, Age, BMI, Medical insurance, Education status, Marital status, Employment status, Income level), lifestyle (Smoking, Drinking, Diet: whole Grains, Diet: high-fat and high-cholesterol, Sports) and clinical characteristics (Family history of dyslipidemia, Medical history: MI, hypertension, type 2 diabetes, the disorder of lipid metabolism, post PCI, peripheral artery disease). A multivariate Tobit regression model was used to evaluate the relationship between MI combined with dyslipidemia and HRQoL. The model adjusted for patients' sociological characteristics, lifestyle, and clinical characteristics, and was grouped by gender. A Tobit regression model is a truncated model, which can be used for upper or lower truncated problems in cross-sectional studies. The

TABLE 1 | Baseline information and EQ-5D index score of all patients.

Variable	Overall (n = 756) [n(%)]	Male [n(%)]	Female [n(%)]	EQ-5D index score (SD)	P-value
Overall	756 (100.00)	613 (100.00)	143 (100.00)	0.95 (0.11)	
Gender					0.000***
Female	143 (18.92)		143 (100.00)	0.91 (0.17)	
Male	613 (81.08)	613 (100.00)		0.96 (0.10)	
Age#	60.45 (SD:10.88)	59.53 (SD:10.63)	64.39 (SD:11.09)		
Age classification (year)					0.000***
≤50	121 (16.01)	113 (18.43)	8 (5.59)	0.97 (0.09)	
>50, ≤60	238 (31.48)	194 (31.65)	44 (30.77)	0.96 (0.09)	
>60, ≤70	272 (35.98)	220 (35.89)	52 (36.36)	0.95 (0.10)	
>70	125 (16.53)	86 (14.03)	39 (27.27)	0.90 (0.18)	
BMI (kg/m2)					0.573
≤18.4	19 (2.51)	14 (2.28)	5 (3.50)	0.96 (0.08)	
>18.4, ≤23.9	252 (33.33)	202 (32.95)	50 (34.97)	0.95 (0.10)	
>23.9, ≤27.9	380 (50.26)	316 (51.55)	64 (44.76)	0.95 (0.12)	
>27.9	105 (13.89)	81 (13.21)	24 (16.78)	0.94 (0.14)	
Medical insurance					0.068
Basic medical insurance system[a]	676 (89.42)	546 (89.07)	130 (90.91)	0.95 (0.11)	
Other medical insurance system	45 (5.95)	38 (6.20)	7 (4.90)	0.96 (0.10)	
Uninsured	35 (4.63)	29 (4.73)	6 (4.20)	0.91 (0.15)	
Education status[b]					0.015*
Primary education	105 (13.89)	60 (9.79)	45 (31.47)	0.93 (0.11)	
Medium education	560 (74.07)	469 (76.51)	91 (63.64)	0.95 (0.12)	
High education	91 (12.04)	84 (13.70)	7 (4.90)	0.96 (0.09)	
Marital status					0.009**
Current single[c]	44 (5.82)	30 (4.89)	14 (9.79)	0.91 (0.12)	
Married	712 (94.18)	583 (95.11)	129 (90.21)	0.95 (0.11)	
Employment status[d]					0.076
Formal wage	144 (19.05)	137 (22.35)	7 (4.90)	0.97 (0.09)	
Non-formal wage	91 (12.04)	60 (9.79)	31 (21.68)	0.94 (0.12)	
Retired	503 (66.53)	400 (65.25)	103 (72.03)	0.96 (0.89)	
Other	18 (2.38)	16 (2.61)	2 (1.40)	0.95 (0.12)	
Income level (yuan)[e]					0.000***
<2,400	187 (24.74)	132 (21.53)	55 (38.46)	0.96 (0.08)	
≥2,400, <4,000	186 (24.60)	140 (22.84)	46 (32.17)	0.93 (0.12)	
≥4,000, <5,500	191 (25.26)	162 (26.43)	29 (20.28)	0.93 (0.16)	
≥5,500	192 (25.40)	179 (29.20)	13 (9.09)	0.97 (0.07)	
Smoking					0.037*
No smoking history/give up smoking	496 (65.61)	360 (58.73)	136 (95.10)	0.94 (0.13)	
Sometimes	88 (11.64)	87 (14.19)	1 (0.70)	0.96 (0.09)	
Often	172 (22.75)	166 (27.08)	6 (4.20)	0.97 (0.08)	
Drinking					0.006**
No drinking history/give up drinking	515 (68.12)	379 (61.83)	136 (95.10)	0.94 (0.13)	
Sometimes	186 (24.60)	179 (29.20)	7 (4.90)	0.96 (0.08)	
Often	55 (7.28)	55 (8.97)	0 (0.00)	0.97 (0.07)	
Diet (whole grains)					0.070
Often	534 (70.63)	423 (69.00)	111 (77.62)	0.95 (0.11)	
Sometimes	214 (28.31)	183 (29.85)	31 (21.68)	0.94 (0.12)	
Never	8 (1.06)	7 (1.14)	1 (0.70)	0.95 (0.07)	
Diet (high-fat and high-cholesterol)					0.000***
Often control	550 (72.75)	441 (71.94)	109 (76.22)	0.95 (0.11)	

(Continued)

TABLE 1 | Continued

Variable	Overall (n = 756) [n(%)]	Male [n(%)]	Female [n(%)]	EQ-5D index score (SD)	P-value
Sometimes control	170 (22.49)	142 (23.16)	28 (19.58)	0.93 (0.12)	
Never control	36 (4.76)	30 (4.89)	6 (4.20)	0.91 (0.13)	
Sports					0.000***
Often	467 (61.77)	377 (61.50)	90 (62.94)	0.96 (0.09)	
Sometimes	178 (23.54)	151 (24.63)	27 (18.88)	0.95 (0.09)	
Never	111 (14.68)	85 (13.87)	26 (18.18)	0.87 (0.19)	
Family history of dyslipidemia					0.075
No	479 (63.36)	388 (63.30)	91 (63.64)	0.95 (0.12)	
Yes	277 (36.64)	225 (36.70)	52 (36.36)	0.94 (0.11)	
Medical history					
Myocardial infarction (MI)[f]					0.374
No	718 (94.97)	581 (94.78)	137 (95.80)	0.95 (0.11)	
Yes	38 (5.03)	32 (5.22)	6 (4.20)	0.94 (0.11)	
Hypertension					0.327
No	315 (41.67)	259 (42.25)	56 (39.16)	0.95 (0.12)	
Yes	441 (58.33)	354 (57.75)	87 (60.84)	0.94 (0.11)	
Type 2 diabetes					0.258
No	533 (70.50)	437 (71.29)	96 (67.13)	0.95 (0.11)	
Yes	223 (29.50)	176 (28.71)	47 (32.87)	0.94 (0.13)	
Disorder of lipid metabolism					0.039*
No	520 (68.78)	426 (69.49)	94 (65.73)	0.95 (0.11)	
Yes	236 (31.22)	187 (30.51)	49 (34.27)	0.95 (0.13)	
Post PCI					0.524
No	222 (29.37)	172 (28.06)	50 (34.97)	0.95 (0.12)	
Yes	534 (70.63)	441 (71.94)	93 (65.03)	0.95 (0.11)	
Peripheral artery disease					0.115
No	656 (86.77)	538 (87.77)	118 (82.52)	0.95 (0.11)	
Yes	100 (13.23)	75 (12.23)	25 (17.48)	0.93 (0.13)	

PCI, percutaneous coronary intervention; BMI, Body mass index; In BMI, each category includes an upper limit and does not include a lower limit.

[#]Mean and standard deviation were reported.

[a]Basic medical insurance = BMISUE + BMISUR + NRCMS. BMISUE, basic medical insurance system for urban employees; BMISUR, basic medical insurance system for urban residents; NRCMS, the new rural cooperative medical system.

[b]Education status: primary education = not graduated from primary school + primary school; medium education = Junior high school + high school + technical secondary school/junior college graduate; high education = Bachelor + master + doctor.

[c]Current single = unmarried + divorce + death of a spouse.

[d]Employment status: formal wage = formal employees + individuals and freelancers; non-formal wage = Farming + unemployed.

[e]Income is grouped according to quartile.

[f]Patients who experienced MI before index hospitalization.

**P < 0.05; **P < 0.01; ***P < 0.001.*

correct Tobit model allows nursing researchers to improve the estimate of bias coefficients through review when measures of health status are limited by limited data (21).

All data were analyzed using Stata SE 15 (Stata Software, StataCorp), and $P \leq 0.05$ was considered a statistically significant level.

RESULTS

Baseline Characteristics

A total of 756 patients responded to the survey. All patients agreed to participate in the study and received informed consent. A total of 756 respondents (613 male and 143 female) completed the survey. **Table 1** presents the respondents' general characteristics and means EQ-5D index score. The average age of the 756 patients was 60.45 (SD: 10.88) years old, and most of the patients were >50 and ≤70. Nearly 50% of the patients' BMI was >23.9 and ≤27.9, and 89.42% of the patients had basic medical insurance. Additionally, 74.07% of the patients had medium education and 34.1% of the patients had retired. 58.33% of the patients had hypertension. The average EQ-5D score of all the patients was 0.95 (SD: 0.11). Respondents who were male, who were younger, who were highly educated, married, high income (≥5,500 yuan/month), who often smoke, often drink, often control High-fat and high-cholesterol, often do sport, who had a disorder of lipid metabolism, who had medium and great medication adherence obtained higher index scores.

Figure 1 presents the distribution of the EQ-5D index score. Overall, the distribution was extremely uneven, with a significant difference between 1 and 0.96.

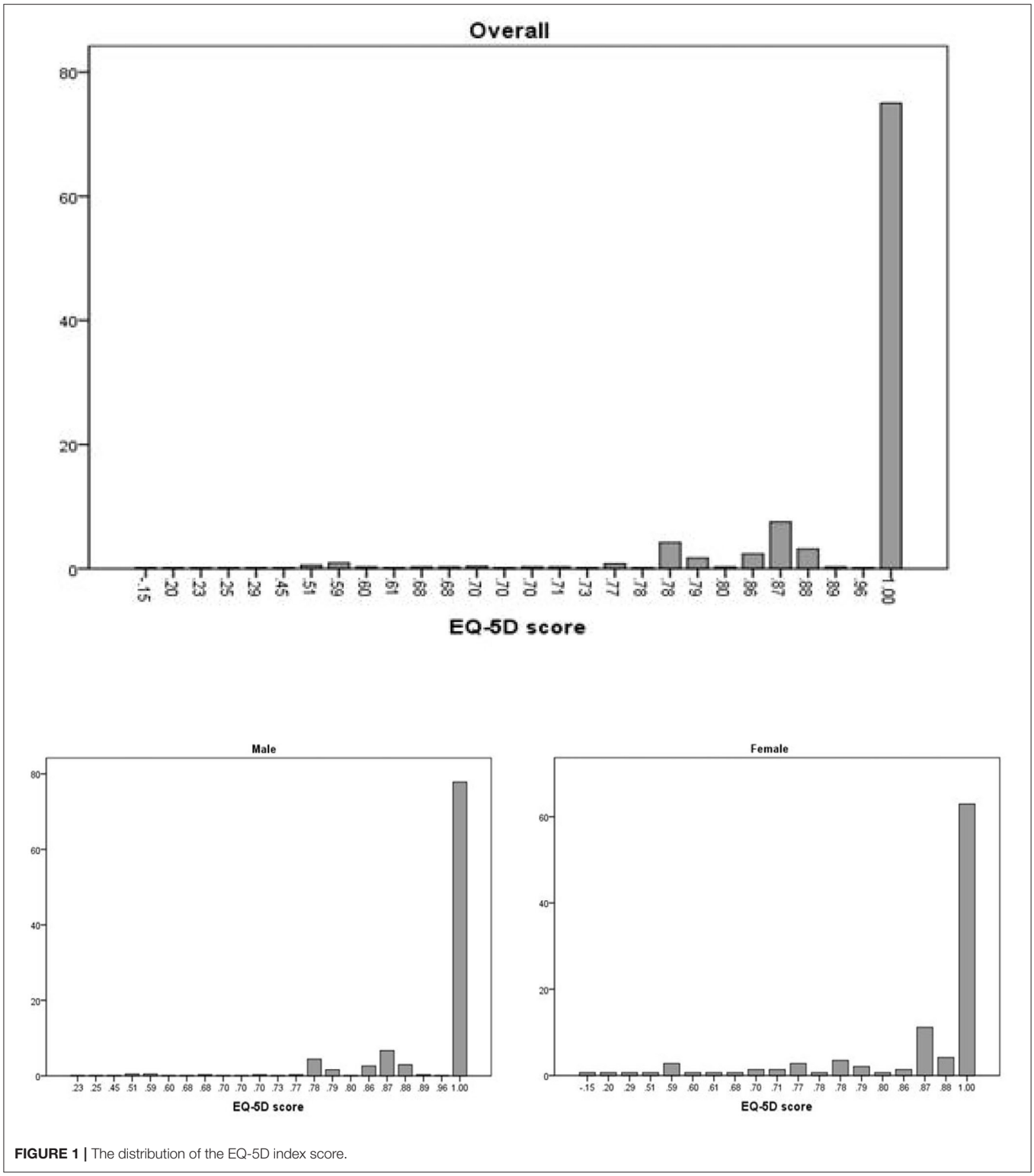


FIGURE 1 | The distribution of the EQ-5D index score.

The Associated Factors of HRQoL

The Results of the Tobit regression for the EQ-5D score are shown in **Table 2**. Tobit regression model shows that compared with patients aged >18 and ≤ 50 years old, patients aged >70 years old (coefficient = −0.17, $P < 0.01$) had poorer HRQoL; There was statistical significance between the increase in the frequency of high-fat and high-cholesterol food consumption and the decrease in the index score (sometimes control:

coefficient = −0.09, $P < 0.01$; Never control: coefficient = −0.17, $P < 0.01$); Patients who never exercise (coefficient = −0.22, $P < 0.001$) had worse HRQoL than those who often exercise. Compared with patients without a family history of dyslipidemia, patients with a family history of dyslipidemia (coefficient = −0.07, $P < 0.05$) had worse HRQoL. Compared with patients without peripheral artery disease, patients with this disease (coefficient = −0.08, $P < 0.05$) had poorer HRQoL.

For the male, different from all patients, the patients with a Disorder of lipid metabolism (coefficient = 0.09, $P < 0.05$) had better HRQoL than those without, and no significant change was observed in peripheral artery disease. In addition, male patients showed a significant difference in BMI. Compared with patients with BMI ≤ 18.4, patients with higher BMI (>18.4, ≤23.9: coefficient = −0.33, $P < 0.01$; >23.9, ≤27.9: coefficient = −0.33, $P < 0.01$; >27.9: coefficient = −0.32, $P < 0.01$) had poorer HRQoL.

For the female, patients with Hypertension have better HRQoL than those without (coefficient = 0.18, $P < 0.01$), and no significant change was observed in peripheral artery disease, family history, and never control high-fat and high-cholesterol food. In addition, patients with higher education (coefficient = 1.83, $P < 0.001$) had better HRQoL than patients with lower education; Patients with other employment types (coefficient = −0.99, $P < 0.01$) had worse HRQoL than those with formal jobs. Patients who smoked occasionally (coefficient = 1.29, $P < 0.001$) had better HRQoL than those who did not currently smoke. Patients who never ate Whole Grains Food (coefficient = 1.19, $P < 0.001$) had better HRQoL than those who often eat Whole Grains Food regularly.

DISCUSSION

This study first reported the quality of life and related factors of patients in MI combined with dyslipidemia. Our study used EQ-5D to determine the quality of life of patients with MI combined with dyslipidemia and used the Tobit model to evaluate the influencing factors of the index score. This study fills the gap of HRQoL and its influencing factors in these patients.

In our study, the mean EQ-5D-3L index score for all patients was 0.95. There are many studies on the quality of life of patients with MI, but most of them used scales that cannot obtain the utility value directly. Lee et al. adopted the Coronary Revascularization Outcome Questionnaire (CROQ) to measure the HRQoL of Korean patients with MI (22). Ul-Haq et al. used the General Health Questionnaire (GHQ), Self-rated Health (SRH), and one post-MI specific tool (MacNew QLMI) Celia to measure HRQoL of Pakistani with MI (23). Wlodarczyk et al. used the Nottingham Health Profile (NHP) to measure the HRQoL of Polish with MI (24). Munyombwe et al. used EQ-5D-3L to measure the HRQoL of British with MI. The mean index score was 0.78 (SD: 0.3) (25). In contrast, the Quality of life in our study was higher among patients with MI combined with dyslipidemia, which may be correlated with the year of measurement and individual differences and nursing differences. Since HRQoL is one of the key data points for cost-effectiveness approaches, more research should focus on determining the regional and global quality of life index scores for this population.

In our study, like the results of other Quality of life studies of MI patients, the female in our study had a lower HRQoL than the male (24, 25). Female and male had different predictors, unlike previous study (26), highly educated women had higher quality of life, but there were no significant differences in marital status. In addition, our study also included lifestyle variables. The results showed that there were significant differences in quality of life among females on factors such as smoking and dietary fiber diet. We observed that patients who sometimes smoke had a higher quality of life than current non-smokers, which may be related to the "smokers' paradox." Several studies have found that smokers had a lower mortality rate after AMI than non-smokers (27, 28). And patients who survived after MI were more likely to be smokers (29). The reduction of mortality may be related to the decrease of MI recurrence, and the reduction of recurrence may increase the patient's HRQoL. In terms of diet, patients may consume high-fat food while eating dietary fiber. Hyperlipidemia may increase the risk of MI recurrence and affect patients physically and mentally, thus reducing the quality of life.

For all patients, analysis of influencing factors showed that a healthy lifestyle (exercise, frequent control high-fat consumption) improved quality of life. Exercise and control of a high-fat diet have synergistic effects on fat consumption and fat intake, respectively. The reduction of fat may reduce the risk of hyperlipidemia and thus improve the quality of life. In addition, exercise boosts dopamine production, and physical activity is associated with the improvement of depression and anxiety (30, 31). Multiple studies have indicated that depression or anxiety was an overseen complication in MI patients (32–34). The above analysis showed that exercise helps improve the HRQoL of MI patients. These also suggest that in the treatment of patients with MI combined with dyslipidemia, the improvement of lifestyle should be strengthened, and the patient's compliance with a healthy lifestyle should be improved, as well as the control of fat level.

There are some limitations to this study. First, this study is a cross-sectional study of a retrospective analysis, so it is unable to explore the long-term changes in quality of life and the changes in related predictors of patients with MI combined with dyslipidemia, which is also the future direction of this study. Secondly, the EQ-5D-3L scale was adopted in this study to measure the quality of life of patients, which may be influenced by the ceiling effect compared with the EQ-5D-5L scale. Thirdly, patients in this study were from six tertiary hospitals, and patients in secondary and primary hospitals were not included, so there may be a certain selection bias.

CONCLUSION

Dyslipidemia is one of the risk factors of MI. Although there have been many studies on the quality of life of patients with MI, there is no study to measure the quality of life of patients with MI combined with dyslipidemia. This research adopts the EQ-5D-3L to measure the HRQoL of the patients with MI combined with

TABLE 2 | Tobit regression for EQ-5D score.

Variable		Overall		Male		Female	
		Coefficient (se)	***P*-value[#]**	**Coefficient (se)**	***P*-value[#]**	**Coefficient (se)**	***P*-value[#]**
Gender	Male	Ref					
	Female	−0.07 (0.04)	0.053				
Age classification (year)	>18, ≤50	Ref		Ref		Ref	
	>50, ≤60	−0.07 (0.05)	0.135	−0.09 (0.05)	0.080	−0.05 (0.20)	0.810
	>60, ≤70	−0.07 (0.06)	0.246	−0.05 (0.06)	0.371	−0.12 (0.19)	0.531
	>70	−0.17 (0.06)	0.008**	−0.13 (0.07)	0.046*	−0.20 (0.20)	0.320
BMI (kg/m^2)	≤18.4	Ref		Ref		Ref	
	>18.4, ≤23.9	−0.13 (0.08)	0.125	−0.33 (0.11)	0.002**	0.14 (0.13)	0.296
	>23.9, ≤27.9	−0.13 (0.08)	0.100	−0.33 (0.10)	0.001**	0.12 (0.13)	0.381
	>27.9	−0.15 (0.09)	0.088	−0.32 (0.11)	0.003**	0.12 (0.15)	0.420
Medical insurance	Basic medical insurance system[a]	Ref		Ref		Ref	
	Other medical insurance system	−0.01 (0.07)	0.918	0.04 (0.07)	0.584	−0.06 (0.15)	0.671
	Uninsured	−0.12 (0.07)	0.098	−0.14 (0.08)	0.084	−0.24 (0.14)	0.088
Education status[b]	Primary education	Ref		Ref		Ref	
	Medium education	0.03 (0.04)	0.535	0.03 (0.05)	0.501	−0.03 (0.09)	0.732
	High education	0.04 (0.06)	0.519	−0.00 (0.07)	0.983	1.83 (0.31)	0.000***
Marital status	Current single[c]	Ref		Ref		Ref	
	Married	0.08 (0.05)	0.068	0.10 (0.06)	0.066	0.06 (0.08)	0.496
Employment status[d]	Formal wage	Ref		Ref		Ref	
	Non-formal wage	0.04 (0.07)	0.580	0.04 (0.07)	0.617	−0.24 (0.26)	0.368
	Retired	0.05 (0.05)	0.332	0.05 (0.05)	0.283	−0.28 (0.24)	0.236
	Other	−0.01 (0.10)	0.915	0.03 (0.11)	0.804	−0.99 (0.30)	0.001**
Income level (yuan)[e]	<2,400	Ref		Ref		Ref	
	≥2,400, <4,000	−0.09 (0.05)	0.060	−0.07 (0.05)	0.203	−0.12 (0.09)	0.175
	≥4,000, <5,500	−0.08 (0.05)	0.105	−0.05 (0.05)	0.301	−0.15 (0.10)	0.147
	≥5,500	0.07 (0.05)	0.204	0.08 (0.06)	0.152	0.02 (0.17)	0.911
Smoking	No smoking history/give up smoking	Ref		Ref		Ref	
	Sometimes	0.02 (0.05)	0.742	0.01 (0.05)	0.842	1.29 (0.22)	0.000***
	Often	0.06 (0.04)	0.122	0.05 (0.04)	0.202	−0.15 (0.14)	0.295
Drinking	No drinking history/give up drinking	Ref		Ref		Ref	
	Sometimes	0.05 (0.04)	0.167	0.07 (0.04)	0.069	−0.02 (0.16)	0.908
	Often	0.08 (0.06)	0.163	0.09 (0.06)	0.141		
Diet (Whole Grains)	Often	Ref		Ref		Ref	
	Sometimes	−0.03 (0.03)	0.410	−0.02 (0.03)	0.578	−0.12 (0.08)	0.102
	Never	−0.01 (0.10)	0.940	−0.05 (0.10)	0.639	1.19 (0.27)	0.000***
Diet (High-fat and high-cholesterol)	Often control	Ref		Ref		Ref	
	Sometimes control	−0.09 (0.03)	0.005**	−0.07 (0.04)	0.044*	−0.17 (0.07)	0.018*
	Never control	−0.17 (0.05)	0.001**	−0.15 (0.06)	0.012*	−0.07 (0.12)	0.582
Sports	Often	Ref		Ref		Ref	
	Sometimes	−0.02 (0.04)	0.667	−0.02 (0.04)	0.633	−0.03 (0.09)	0.729
	Never	−0.22 (0.04)	0.000***	−0.19 (0.04)	0.000***	−0.30 (0.08)	0.001**
Family history of dyslipidemia	No	Ref		Ref		Ref	
	Yes	−0.07 (0.03)	0.015*	−0.08 (0.03)	0.011*	0.09 (0.08)	0.263
Medical history							
Myocardial infarction (MI)[f]	No	Ref		Ref		Ref	
	Yes	−0.07 (0.06)	0.256	−0.06 (0.07)	0.373	−0.09 (0.14)	0.514
Hypertension	No	Ref		Ref		Ref	
	Yes	0.01 (0.03)	0.821	−0.03 (0.03)	0.400	0.18 (0.07)	0.006**

(Continued)

TABLE 2 | Continued

Variable		Overall		Male		Female	
		Coefficient (se)	*P*-value[#]	Coefficient (se)	*P*-value[#]	Coefficient (se)	*P*-value[#]
Type 2 diabetes	No	Ref		Ref		Ref	
	Yes	−0.01 (0.03)	0.687	−0.03 (0.03)	0.323	0.02 (0.07)	0.726
Disorder of lipid metabolism	No	Ref		Ref		Ref	
	Yes	0.06 (0.03)	0.080	0.09 (0.04)	0.019*	−0.03 (0.06)	0.636
Post PCI	No	Ref		Ref		Ref	
	Yes	−0.03 (0.03)	0.272	−0.02 (0.03)	0.580	−0.11 (0.07)	0.114
Peripheral artery disease	No	Ref		Ref		Ref	
	Yes	−0.08 (0.04)	0.048*	−0.05 (0.04)	0.311	−0.12 (0.07)	0.087

Se, robust standard error; PCI, percutaneous coronary intervention; BMI, Body mass index; ln BMI, each category includes an upper limit and does not include a lower limit.
[#]P-value are numbers in robust standard error.
[a]Basic medical insurance = BMISUE + BMISUR + NRCMS. BMISUE, basic medical insurance system for urban employees; BMISUR, basic medical insurance system for urban residents; NRCMS, the new rural cooperative medical system.
[b]Education status: primary education = not graduated from primary school + primary school; medium education = Junior high school + high school + technical secondary school/junior college graduate; high education = Bachelor + master + doctor.
[c]Current single = unmarried + divorce + death of a spouse.
[d]Employment status: formal wage = formal employees + individuals and freelancers; non-formal wage = Farming + unemployed.
[e]Income is grouped according to quartile.
[f]Patients who experienced MI before index hospitalization.
**P < 0.05; **P < 0.01; ***P < 0.001.*

dyslipidemia, at the same time analyze the predictive factors of HRQoL from the sociology characteristics, lifestyle, and clinical characteristics. The results of this study fill in the data gaps in the field of related diseases and provide real-world data for cost-effectiveness analysis. The study found that the quality of life of female was lower than male, and female had more predictors; In addition, for all patients, we should pay more attention to the post-discharge care of the elderly group, increase the advocacy and suggestions on healthy lifestyle (fat control) of the patients to improve the quality of life of these patients.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because sharing of raw data would be contingent on approval from the research ethics office because of the ethics consideration. Requests to access the datasets should be directed to lihongchao@cpu.edu.cn.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Peking University First Hospital; Wuhan Asia Heart Hospital; Guangdong Provincial People's Hospital; Nanjing Drum Tower Hospital; Sichuan Provincial People's Hospital; Zhongshan Hospital, Fudan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AM, HL, and PC designed this study. Data were collected and managed by YZ, XS, JC, BX, JT, and ZW. MZ performed the statistics using software and drafted the manuscript. AM and HL supervised the data analysis and proposed suggestions for revising the manuscript. All authors critically reviewed the manuscript, approved the final version of the manuscript, and agree to be accountable for the content of the work.

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Analysis of the Status and Tendency of R&D Input in the Field of Rare Diseases Funded by the National Natural Science Foundation of China

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Background: Through collection and sorting of rare disease projects funded by the National Natural Science Foundation of China, an understanding was gained of the categories of projects funded by the foundation in the field of rare diseases, types of diseases, categories of disease systems, regional distribution, distribution of supporting institutions, and their dynamic changes, followed by an analysis of focuses and influences of relevant state policies. This will help improve the rare disease-relating policies of the state in supporting the key fields, thus promoting healthy and sustainable development in the field of rare diseases.

Method: Through the website of inquiry of projects funded by the National Natural Science Foundation of China, a retrieval was made concerning the projects funded by the foundation in the field of rare diseases during the period from 1986 to 2019, followed by descriptive analysis of fund input of rare disease projects, number of projects, temporal and regional distribution, and the analysis of the law of their dynamic changes.

Result: As of the end of 2019, there were 57 rare diseases and 678 related projects funded by the National Natural Science Foundation of China, with accumulated total funding of ¥ 253,525,000. Among the categories of projects, the most-funded projects were general (¥ 150,145,000, 59.22%), followed by Youth Foundation projects (¥ 53,719,000, 21.19%) and key projects (¥ 15,870,000, 6.26%); among the categories of disease systems, the most funded disease system was the nervous system (¥ 93,186,000, 37.76%), followed by the respiratory system (¥ 35,444,000, 13.98%); the most funded diseases were multiple sclerosis (¥ 34,870,000, 13.75%), idiopathic pulmonary fibrosis (¥ 29,854,000, 11.78%), and retinitis pigmentosa (¥ 27,005,000, 10.65%); the most funded regions were East China (¥ 106,987,000, 42.20%) and North China (¥ 71,844,000, 28.34%), while the least funded region was Northwest China (¥ 7,295,000, 2.88%); among the supporting institutions, the most funded institutions were Peking University (¥ 24,720,000, 9.75%), and Sun Yat-sen University (¥ 14,505,000, 5.72%).

Conclusion: With the promulgation of more policies on encouragement of innovation and accelerated approval procedures, etc., the National Natural Science Foundation of China has been increasing its funding to rare diseases, covering increasingly more

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categories of funded projects, more types of diseases, and wider regions. Nonetheless, the support for scientific research in China is still relatively weak. Therefore, it is proposed that the healthy and sustainable development in the course of rare diseases should be promoted through the improvement of relevant rare disease policies, encouragement of R&D of medicine for rare diseases, the establishment of special funds for rare diseases, acceleration of fund circulation, and combination of balanced development and preferential funding to key regions and major diseases.

Keywords: rare diseases, National Natural Science Foundation of China, R&D input, development tendency, funded

BACKGROUND

A rare disease refers to a disease with a low prevalence and its definition may vary in different countries. The WHO defines rare diseases as one with prevalence between 0.65‰ and 1‰ (1, 2). In China, there is no official definition of rare diseases. Some experts believe that rare diseases may be defined as diseases with neonatal morbidity of 0.1‰ or prevalence of 0.002‰ (3). Due to the smaller number of patients with rare diseases, the prices of orphan drugs have been high. Some countries are making a new exploration by the establishment of special funds for the treatment of rare diseases, to reduce the burden of patients. For instance, the U.S. National Institute of Health has invested over US$ 10 billion in research of rare diseases in recent 10 years, significantly improving the initiatives in research of rare diseases and R&D of orphan drugs. In China, there is still a lack of legal systems relating to rare diseases and orphan drugs. In addition, the support for scientific research is considerably weak. In China, scientific research funds are divided into national funds (such as the National Natural Science Foundation of China (NSFC), National Scientific and Technology Support Fund, and the Fund for Key Projects of the Ministry of Science and Technology), provincial and ministerial funds (such as the natural science funds of the Ministry of Education, provincial science and technology departments, and other provincial natural science funds), and other funds. Nonetheless, the funds for research of rare diseases are mainly from the NSFC, which grants certain subsidies for research of rare diseases every year (4–6) and established the discipline of rare diseases in its Department of Health Sciences in 2021. In recent years, China has promulgated a series of policies to support the R&D of orphan drugs and constantly strengthened R&D input in the field of rare diseases. At the same time, the state is also paying higher attention to rare diseases. In the "Two Sessions" in 2021, National People's Congress and Chinese People's Political Consultative Conference members submitted the proposals on rare diseases, namely, enhancement of mechanism of prevention, treatment, and screening of rare diseases; establishment of a unified rare disease patients registration system; establishment of state-level rare disease diagnosis and treatment center; improvement of the green channel for launch orphan drugs; and multiparty sharing of cost in medical insurance system and "1 + N" multilayer safeguard (7).

The research on R&D investment in rare diseases in China is blank at present. Chen Xin and other scholars (8) found that there were 3,132 projects funded by NSFC from 2008 to 2013, totaling about 1.29 billion yuan. Zhang Yang and other scholars (9) found that the funding status of basic research projects on rare diseases at home and abroad is based on the "Dimension" database. There were 2,887 scientific research funding projects on rare diseases and their drugs, from 1976 to August 2019, involving 57 countries. Among them, 988 projects were funded by the United States, with a cumulative amount of US$ 2.1 billion, with the largest support. Since 2008, China has funded a total of 56 projects with a funding amount of $ 21 million. However, there is no secondary analysis of single diseases funded by NSFC based on the catalog due to the different definitions and catalog of rare diseases in various countries. The research of Meilin (10) shows that the existing research on rare diseases in China is mainly supported by NSFC, and the research funds related to rare diseases, the proportion of research funds in the overall health expenditure and the number of research carried out have increased. However, the aforementioned studies have raised common problems that there is no clear definition of rare diseases, less R&D investment, and lack of a special funding system.

In 1986, the NSFC was established (11). At present, receipt of funds from NSFC has been an important indicator for measuring whether a unit has the qualification and capacity for high-level research and for assessing its academic research and position. The foundation has attracted a majority of scholars who make significant contributions to Chinese science and technology, providing support to and guidance on domestic innovation in key researches. In this paper, an analysis is made focusing on R&D input in the field of rare diseases by NSFC during the period from January 1, 1986, to December 31, 2019, and it analyzes the status and tendency of R&D input in the field of rare diseases funded by NSFC. The overall R&D inputs, types of projects, categories of disease systems, types of diseases, geographical regions, and supporting institutions of rare diseases by NSFC, and also their dynamic changes, followed by an analysis of focuses and influences of relevant state policies, thus providing references for optimization of funding orientation in the field and prevention and treatment of rare diseases.

METHOD

Based on the 121 types of rare diseases in the *Catalog of the First Batch of Rare Diseases* issued by the National Health Commission

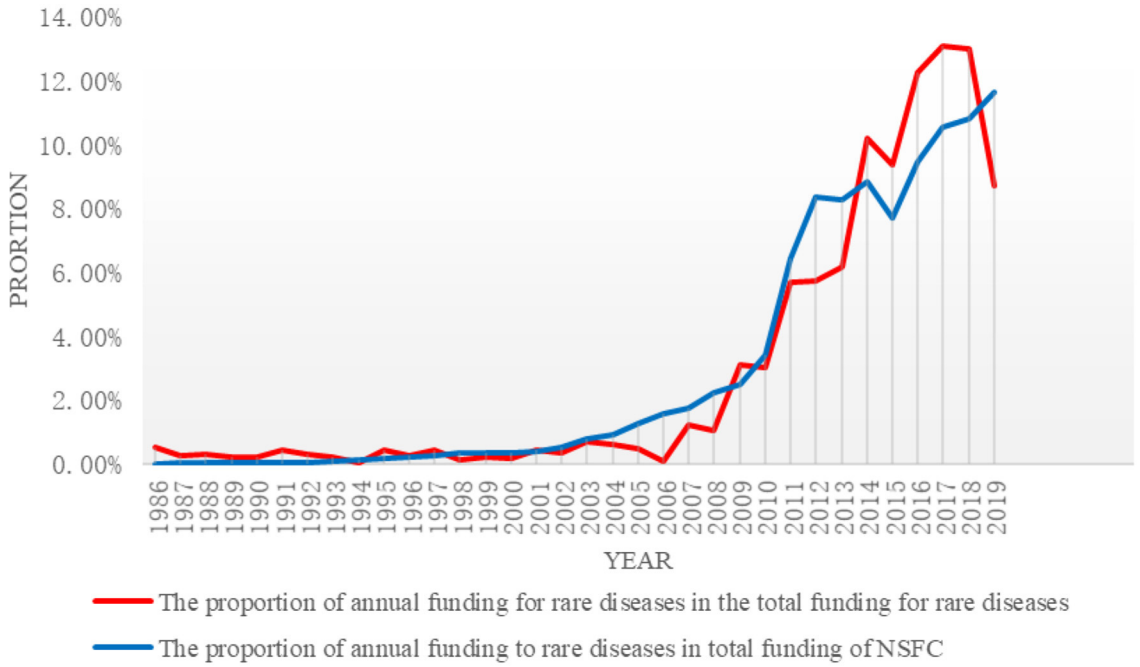


FIGURE 1 | The proportion of funding to rare diseases in the total funding of NSFC and the changes.

in May 2018, a retrieval was made by the type of diseases on the website of "inquiry of projects funded by the National Natural Science Foundation of China" (http://fund.zsci.com.cn/Index/index.html) for the period from January 1, 1986, to December 31, 2019. Then a descriptive analysis was made on the quantity and category of funded projects, category of disease systems, type of diseases, regional distributions, and supporting institutions, thus summarizing the characteristics and tendency of such funding.

RESULT

The Overall R&D Input in the Field of Rare Diseases by NSFC

As of the end of 2019, a total of 658 projects were founded by NSFC, with accumulated total funding of ¥ 253,525,000. The supported projects were increased from two projects in 1986 to 54 projects in 2019, an increase of 2,600%; the total funding was increased from ¥ 1,350,000 in 1986 to ¥ 22,090,000 in 2019, an increase of about 15.4 times. Please refer to **Figure 1** for details. The proportion of annual funding to rare diseases in the total annual funding of NSFC was relatively stable (<1% in all years). With increased total funding, the funding to rare diseases was increased accordingly, suggesting a gradual growth.

The proportion of annual funding to rare diseases in total funding of NSFC was almost unchanged. In this study, the annual funding to rare diseases by NSFC was divided into three stages by their proportion (<1, 1–5, and >5%) in the total funding: the initial stage (1986–2006); the slow growth stage (2007–2010); and the fast growth stage (2011–2019). Please refer to **Table 1** for details.

At the initial stage, there were the fewest projects funded by NSFC and the least amount of funding. The proportion of annual funding to rare diseases in the total funding of NSFC was relatively low, with a smooth trend and low growth rate. At the slow growth stage, there was a minor change in funding to rare diseases. The funding was increased from ¥ 3,110,000 in 2007 to ¥ 7,655,000 in 2010. During the 4 years, the total funding was ¥ 2,1297,000, which is two times the funding at the initial stage. On average, 19.75 projects were funded every year and the amount of funding was ¥ 5,324,300. During this period, the funding was the highest in 2009 (¥ 78,750,000) and the lowest in 2007 (¥ 3,110,000). The proportion of funding increased to 3.02% and the accumulative proportion increased by 8.40%. Although there is not much difference compared with the accumulated proportion at the initial stage, it can be seen that the increase was significant at the slow growth stage. At the fast growth stage, on average, 56 projects were funded every year and the amount of funding was ¥ 23,782,600. The highest funding was ¥ 33,270,000 in 2017 and the lowest funding was ¥ 14,470,000 in 2011, suggesting a significant growth on the whole. It can be seen that funding to the field of rare diseases in recent years has been enormous: the annual funding exceeded ¥ 30,000,000 in the 3 years from 2016 to 2018 and the accumulated proportion in the 9 years was 84.43%.

R&D Input in Rare Diseases Among the Projects Funded by NSFC

Among the projects funded by NSFC, the most funded projects were general projects (¥ 150,145,000) which accounted for

TABLE 1 | R&D input in rare diseases by NSFC and the changes.

Year	Total projects (each)	Total funding (00,000 yuan)	Average funded projects (projects/year)	Average annual fund (x ± s)	Maximum	Minimum	Accumulated proportion (%)
1986–2006	71	1,818.50	3.38	86.604 ± 1.82	182.50	18.50	7.17
2007–2010	79	2,129.70	19.75	532.432 ± 44.72	787.50	265.70	8.40
2011–2019	508	21,404.30	56.44	2,378.267 ± 25.14	3,327.00	1,447.00	84.43
Total	658	25,352.50	19.35	745.661 ± 061.36	3,327.00	18.50	100.00

TABLE 2 | R&D input in rare diseases among the projects funded by NSFC.

Categories of projects	Total projects (each)	Total funding (00,000 yuan)	Average funding per project (00,000/project)	Proportion (%)
General projects	309	15,014.50	48.59	59.22
Youth Foundation projects	267	5,371.90	20.12	21.19
Key projects	6	1,587.00	264.50	6.26
Regional science foundation projects	33	1,229.70	37.26	4.85
International (regional) cooperation and exchange projects	11	1,130.40	102.76	4.46
Major research plans	4	450.00	112.50	1.77
Outstanding Youth Foundation projects	2	220.00	110.00	0.87
Emergency management projects	11	185.00	16.82	0.73
Special fund projects	13	126.00	9.69	0.50
Cooperative research fund for overseas, Hong Kong and Macau scholars	2	38.00	19.00	0.15
Total	658	25,352.50	38.53	100.00

59.22% of the total funding. This suggested that over half of rare disease projects funded by NSFC were general projects, followed by Youth Science Foundation projects (¥ 53,719,000) which accounted for 21.19% of the total funding or, namely, about one-quarter; although the total funded key projects were relatively fewer, its total funding ranked the third (¥ 15,870,000), with an average funding per project of ¥ 2,645,000. Please refer to **Table 2** for details. At all three stages, there were funded general projects, Youth Science Foundation projects, and regional science foundation projects, with a sharp growth trend. At the initial stage and the slow growth stage, the funded key projects, major research plans, and other projects were relatively fewer and their funding was relatively greater at the fast growth stage.

R&D Input in Rare Diseases by NSFC by the Category of Disease Systems

Concerning the categories of rare disease systems, the top three disease systems with the highest funding were the nervous system (¥ 93,186,000, 36.76%), the respiratory system (¥ 35,444,000, 13.98%), and the blood and hematopoietic system (¥ 23,525,000, 9.28%). The average funding per project was the highest for the cardiovascular system, which accounted for 71.04% and the lowest for malignant tumors, which accounted for 27.64%. Please refer to **Table 3**. At the initial stage, the blood and hematopoietic system received the most funding. At the slow growth stage and the fast growth stage, the funding to blood and the hematopoietic system was increased significantly, with its total funding ranked the first. At the fast growth stage, the increase of funding to the respiratory system was second only to that of funding to the nervous system.

R&D Input in Rare Diseases by NSFC by the Type of Diseases

As of the end of 2019, there were 57 rare diseases funded by the NSFC. As can be seen from **Figure 2**, the types of rare diseases funded by NSFC in recent 20 years from 1986 to 2008 are <10. It suggests that the types of funds are limited and fixed. From 2008 to 2019, the number of rare diseases projects funded by NSFC varied from 14 to 27, which deserves mentions that it reached a maximum in 2017. For the sake of better describing the figure change over time clearly, the study divided every 5 years into one

TABLE 3 | R&D input in rare diseases by NSFC by the categories of disease systems.

Ranking	Category of disease systems (12)	Total projects (each)	Total funding (00,000 yuan)	Average funding per project (00,000 yuan)	Proportion (%)
1	Nervous system	244	9,318.60	38.19	36.76
2	Respiratory system	79	3,544.40	44.87	13.98
3	Blood and hematopoietic system	72	2,352.50	32.67	9.28
4	Cardiovascular system	28	1,989.00	71.04	7.85
5	Metabolic system	46	1,457.00	31.67	5.75
6	Malignant tumors	41	1,133.50	27.64	4.47
7	Muscles and bones	16	535.50	33.47	2.11
8	Endocrine system	5	261.00	52.20	1.03
9	Urogenital system and gonadal hormone	8	252.00	31.50	1.00
10	Digestive system	4	147.00	36.75	0.58
	Other	115	4,362.00	37.93	17.19
	Total	658	25,352.50	38.53	100.00

period for further analysis, and the changing trend is shown in **Figure 3**. It can be seen from the figure that the number of rare diseases funded by NSFC fluctuated between 5 and 15 every 5 years, and the fluctuation range was very small from 1986 to 2005. The types of rare diseases funded increased rapidly every 5 years after 2005.

The most funded rare disease by NSFC was multiple sclerosis (¥ 34,870,000, 13.75%), followed by idiopathic pulmonary fibrosis (¥ 29,854,000, 11.78%) and retinal pigment degeneration (¥ 27,005,000, 10.65%). The rare disease with the least funded projects and funding was systemic sclerosis (¥ 5,110,000, 2.02%). The average funding per project was the highest for homocystinemia and the amount was ¥ 717,600, indicating NSFC gave strong support to it; the average funding per project was the lowest for retinal pigment degeneration and the amount was ¥ 276,500. The maximum funding was about two times the minimum funding, indicating there was a priority in the provision of funding to diseases. Please refer to **Table 4**. At the initial stage, NSFC provided relatively more funding to multiple sclerosis, retinal pigment degeneration, Wilson disease, retinoblastoma, and hemophilia. At the following two stages, the funding to foregoing diseases was also gradually increased, accounting for a large proportion on the whole. Among the other diseases, nearly over half of them were not funded at the initial stage and the slow growth stage. At the fast growth stage, the funded types of diseases were the most with the highest funding.

R&D Input in Rare Diseases by NSFC by Seven Major Geographical Regions

The most funded regions by NSFC were East China (¥ 106,987,000) and North China (¥ 718,440,000), while the region least funded by NSFC was Northwest China (¥ 7,295,000). In East China, the most funded municipality was Shanghai, and the funding was ¥ 52,325,000 which was significantly higher than that in other provinces or municipalities; in North China, the most funded municipality was Beijing, and the funding was ¥ 624,840,000 which was significantly higher than that in Shanghai. However, other provinces and municipalities in this region received relatively less funding, suggesting the uneven distribution of funding. Please refer to **Table 5** for details. At the initial stage, Shanghai, Beijing, Sichuan, and Anhui received significantly higher funding than other areas. However, Guizhou, Heilongjiang, Shandong, and Shaanxi did not receive any funding until the slow growth stage. At all three periods, Beijing and Shanghai, etc. always received higher funding than other areas.

Supporting Institutions Funded by NSFC Concerning Rare Diseases

It can be learned from **Table 6** that, the top three supporting institutions that received the most funding were Peking University (¥ 24,720,000, 9.75%), Sun Yat-Sen University (¥ 14,505,000, 5.72%), and Shanghai Jiao Tong University (¥ 11,550,000, 4.56%), which was consistent with the funding received by the seven geographical regions. Among the top 10 supporting institutions, Tongji University ranked fourth concerning the amount of funding which reached ¥ 11,390,000, although its funded projects were the least. The average funding per project was ¥ 876,200/project, being the highest among all other supporting institutions. At the initial stage, a total of 34 supporting institutions received funding. Among them, the Sun Yat-Sen University, the Sichuan University, and the Anhui University of Chinese Medicine received more funding, which was consistent with the funding received by foregoing regions; at the slow growth stage, nearly one-third of supporting institutions received funding; at the fast growth stage, nearly all supporting institutions received funding. No matter at the slow growth stage or the fast growth stage, Peking University always ranked first concerning the amount of funding.

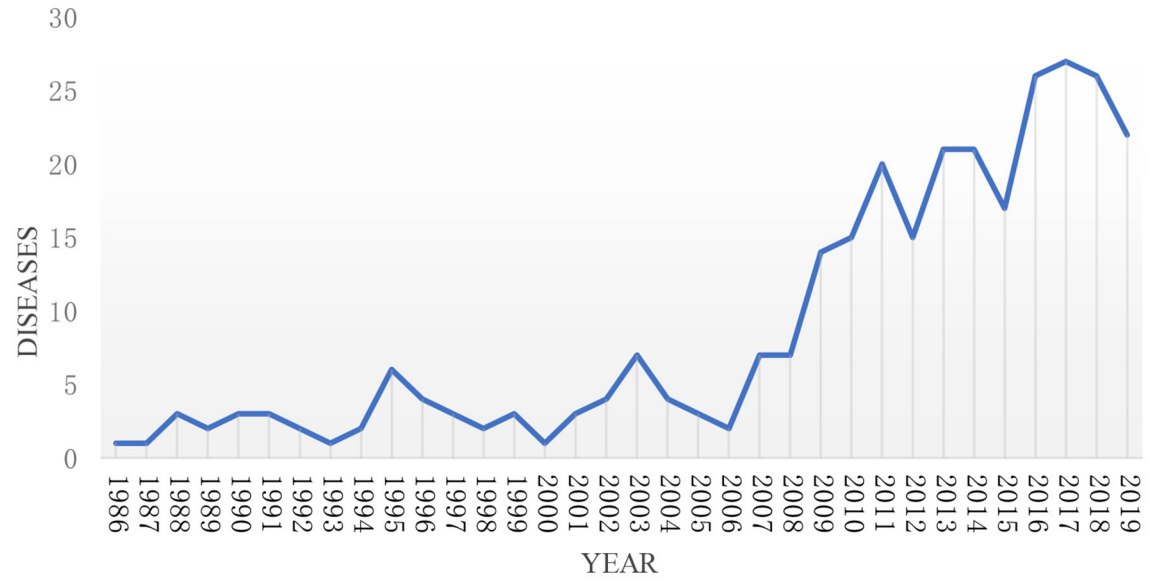


FIGURE 2 | The trend of the types of rare diseases funded by NSFC and its change every year from 1986 to 2019.

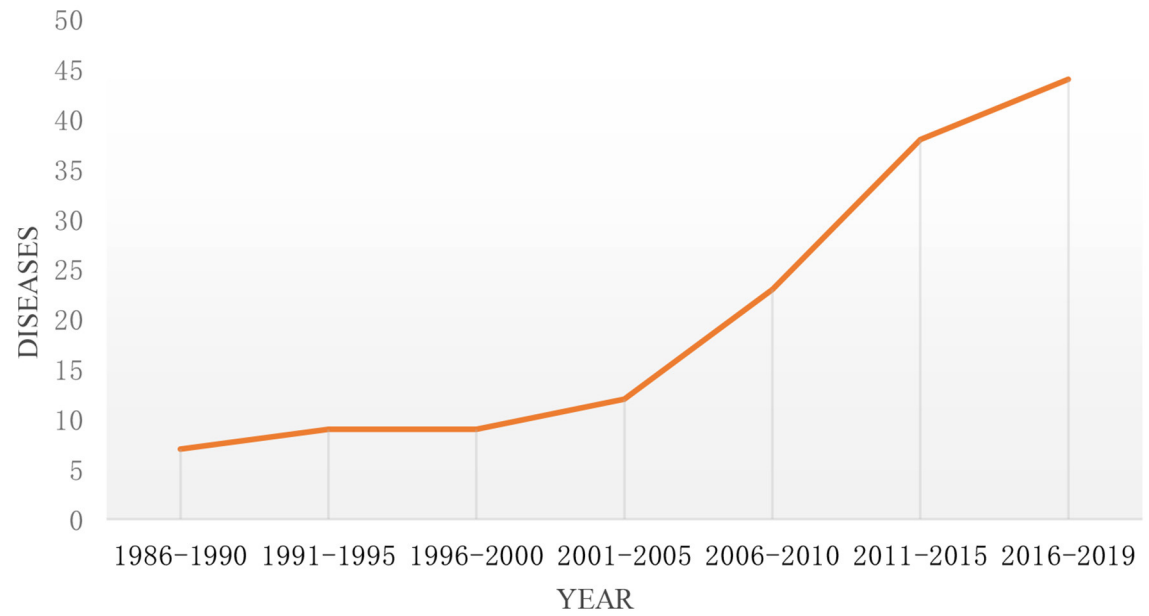


FIGURE 3 | The trend of the types of rare diseases funded by NSFC and its change every 5 years from 1986 to 2019.

DISCUSSION

On the whole, the support of NSFC to the field of rare diseases has witnessed gradual growth in terms of both the number of projects and the amount of funding. The input has been constantly increased. In recent years, in particular, the amount of funding has been increased significantly, which is closely contributable to the high attention to rare diseases paid by the state in recent years, the establishment of the Rare Diseases Society and Local Rare Diseases Society of Chinese Research Hospital Association and China Alliance of Rare Diseases, the construction of National Rare Diseases Registry System of China, and the work on clinical cohort study (9). In October 2017, the State Council issued the *Opinions on Deepening the Reform of the Examination and Approval System to Encourage the Innovation of Drugs and Medical Devices*, under which support to R&D of orphan drugs and medical devices was stressed; in January 2018, the former China Food and Drug Administration and

TABLE 4 | R&D input in the main types of rare diseases by NSFC.

Ranking	Type of diseases	Total projects (each)	Total funding (00,000 yuan)	Average funding per project (00,000 yuan)	Proportion (%)
1	Multiple sclerosis	96	3,487.00	36.32	13.75
2	Idiopathic pulmonary fibrosis	71	2,985.40	42.05	11.78
3	Retinal pigment degeneration	72	2,700.50	37.51	10.65
4	Amyotrophic lateral sclerosis	51	2,312.10	45.34	9.12
5	Homocystinemia	25	1,794.00	71.76	7.08
6	Hemophilia	55	1,750.50	31.83	6.90
7	Neuromyelitis optica	29	1,194.00	41.17	4.71
8	Retinoblastoma	41	1,133.50	27.65	4.47
9	Hereditary spastic paraplegia	16	532.00	33.25	2.10
10	Charcot-Marie-Tooth disease	17	512.50	30.15	2.02
11	Systemic sclerosis	14	511.00	36.50	2.02
	Other	171	6,440.00	37.66	25.40
	Total	658	25,352.50	38.53	100.00

TABLE 5 | R&D input in rare diseases by NSFC by seven major geographical regions.

Administrative regions	Total projects (each)	Total funding (00,000 yuan)	Average funding per project (00,000 yuan)	Maximum	Minimum
Northeast China	37	1,692.00	45.73	877.00	322.50
North China	180	7,184.40	39.91	6,248.40	35.00
East China	270	10,698.70	39.62	5,232.50	334.00
Central China	68	2,231.50	32.82	1,058.50	442.00
South China	27	1,203.00	44.56	999.00	50.00
Northwest China	21	729.50	34.74	317.50	89.00
Southwest China	55	1,613.40	29.33	891.40	79.00
Total	658	25,352.50	38.53	6,248.40	35.00

TABLE 6 | Supporting institutions funded by NSFC concerning rare diseases.

Ranking	Supporting institutions	Total projects (each)	Total funding (00,000 yuan)	Average funding per project (00,000 yuan)	Proportion (%)
1	Peking University	46	2,472.00	53.74	9.75
2	Sun Yat-Sen University	45	1,450.50	32.23	5.72
3	Shanghai Jiao Tong University	30	1,155.00	38.50	4.56
4	Tongji University	13	1,139.00	87.62	4.49
5	Capital Medical University	30	1,071.50	35.72	4.23
6	Central South University	33	1,021.5	30.95	4.03
7	Harbin Medical University	15	877.00	58.47	3.46
8	Fudan University	27	794.50	29.43	3.13
9	Peking Union Medical College Hospital	19	760.00	40.00	3.00
10	Zhejiang University	18	703.00	39.06	2.77
	Other	382	13,908.5	36.70	54.86
	Total	658	25,352.5	38.53	100.00

the Ministry of Science and Technology issued the *Guidance to Strengthening and Promotion of Scientific and Technological Innovation in Food and Drugs*, under which prior support to R&D of drugs and medical devices for treatment of rare diseases was also proposed; in March 2018, the State Council issued the *Opinions on Reform and Improvement of Supply Guarantee for Generic Drugs and the Usage Policies*, under which development of generic drugs for treatment and prevention of major infectious diseases and for treatment of rare diseases was encouraged; in May 2018, the National Health Commission published the

Catalog of the First Batch of Rare Diseases; in October 2019, the State Council issued the *Opinions on Promoting Inheritance, Innovation and Development of Traditional Chinese Medicine*, under which clinical researches of rare diseases were proposed. All these policies pointed out the R&D of orphan drugs, thus promoting the development of orphan drugs in China (13, 14).

As the most important part of the NSFC, the general projects were mostly funded in terms of both the number of funded projects and the amount of funding, accounting for the greatest portion in R&D input in rare diseases with over 50%. This indicates that general projects are the key field funded by NSFC. As to other projects, the number of funded projects and the amount of funding varied due to their different establishment time and application conditions.

East China and North China were mostly funded by NSFC. In these two regions, the funding received by Shanghai and Beijing was most outstanding. This is because first-tier cities possessed richer resources and more high-level talents, providing favorable conditions for experts to apply for funding from NSFC. However, the funding received by different regions varied due to limited research capacity. Taiwan, Hong Kong Special Administrative Region, Macau Special Administrative Region, Tibet Autonomous Region, and Qinghai Province had not received funding. In the future, R&D input in the foregoing five provinces should be increased.

National Natural Science Foundation of China makes the greatest R&D input in rare diseases relating to the nervous system. Among them, multiple sclerosis, amyotrophic lateral sclerosis, neuromyelitis optica, hereditary spastic paraplegia, and Charcot-Marie-Tooth disease accounted for nearly half of the top 10 diseases. Although the rare diseases relating to the nervous system did not rank top three at the initial stage concerning received funding, they were always mostly funded at the slow growth stage and the fast growth stage, indicating that the state gradually pays more attention to the diseases relating to the nervous system. In this category of diseases, multiple sclerosis was mostly funded. Multiple sclerosis is an autoimmune disease with the central nervous system which often occurred in young and middle-aged people. It was mostly funded by NSFC, probably because its incidence in China was higher than that in European and American countries and the drug price was also higher (15).

CONCLUSIONS

To sum up, currently, diagnosis and treatment of rare diseases and R&D of orphan drugs are still at the initial stage. The orphan drugs cannot satisfy the demand of patients due to high prices and low availability. Although NSFC has increased R&D input in rare diseases with the increased funds, the growth is insignificant and relatively smooth on the whole, accounting for about 0.02%. Therefore, the input in rare diseases should be still increased. The rights and interests of rare disease patients may be safeguarded concretely through the encouragement of innovation in R&D of orphan drugs by experts and scholars, optimization of approval procedures, the inclusion of rare disease into medical insurance, and preparation and improvement of relevant policies (16). Therefore, it is required that the special fund should be gradually increased for promulgation and improvement of policies relating to orphan drugs; that the definition of rare diseases in China should be facilitated; and that more funds should be provided to research teams for R&D of orphan drugs. At the same time, higher attentions should be paid to basic research of rare diseases; R&D input in rare diseases with lower prevalence should be increased; and the preparation of standards for diagnosis and rare diseases should be accelerated. In addition, the input in rare diseases in different administrative regions should be balanced, so that more funds may be used in regions and types of diseases in most urgent need. Finally, while balancing the input in other types of diseases, the priority of funding should be given to R&D of orphan drugs for diseases that are hardly curable with high treatment costs and greatly affect the quality of life of patients, thus, promoting fast and sustainable development in the treatment of rare diseases.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: http://fund.zsci.com.cn/Index/index.html.

AUTHOR CONTRIBUTIONS

HC was a major contributor in writing and reviewing the manuscript. WC contributed to methodology, statistics, and charting. XL and JM contributed to data collection. NY and DL contributed to the conception and design of the study. All the authors read and approved the submitted version.

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A Systematic Review of Methods and Study Quality of Economic Evaluations for the Treatment of Schizophrenia

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Background: Schizophrenia is a severe and complex disease with substantial economic and social burdens. Despite multiple treatment choices, adverse events, and impaired social functions are still challenges in clinical therapy. Pharmacoeconomic evaluations could provide evidence to help decision makers improve the utilization of scarce resources. However, there remains some challenges especially in modeling due to uncertainties in progression of schizophrenia. There are limited summaries about the overall methodologies of schizophrenia economic evaluations.

Objective: The aim of this study is to review the existing economic evaluations of antipsychotics for the treatment of schizophrenia and summarize the evidence and methods applied.

Methods: An electronic literature search was performed in PubMed, Web of Science, EBSCO host, The Cochrane Library and ScienceDirect from January 2014 to December 2020. Search terms included "schizophrenia," "schizophrenic," "pharmacoeconomic," "economic evaluation," "cost-effectiveness," and "cost-utility." The Literature was screened and extracted by two researchers independently and assessed with the Quality of Health Economic Studies (QHES) List and Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement.

Results: A total of 25 studies were included in the review. The regions included Europe, North America, Asia and Africa. Most of the studies chose second-generation antipsychotics as comparators and integrated treatment sequences. Time horizons varied from 1 year to lifetime. The healthcare sector was the most common perspective, accordingly, most of the evaluations considered only direct medical costs. The Markov model and decision tree model were the most common choices. Adverse events, compliance and persistence were considered important parameters. Quality-adjusted life-years were the major outcomes applied to the economic evaluations. All utilities for health states and adverse events were collected from published literature. All of the studies applied uncertainty analysis to explore the robustness of the results. The quality of the studies was generally satisfactory. However, improvements were needed in the choice of time horizons, the measurements of outcomes and the descriptions of assumptions.

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Conclusions: This study highlights the methodology of economic evaluation of schizophrenia. Recommendations for modeling method and future study are provided.

Keywords: schizophrenia, economic evaluation, systematic review, modeling, method review

INTRODUCTION

Schizophrenia is a severe and complex mental illness with early onset coupled with behavior or cognitive disorders that have a significant impact on patients' family and society. A systematic review reported that the global age-standardized prevalence of schizophrenia was 0.28% and the prevalence of cases rose from 13.1 million cases in 1990 to 20.9 million cases in 2016 (1). The average annual healthcare costs were estimated to be between $23,887 and $24,988 according to a real-world retrospective study in the US (2). Patients may incur higher expenditures due to comorbidities that are common among them (3). Furthermore, indirect medical costs related to productivity lost or caregiving were 8.5 times higher compared with direct medical costs according to a retrospective study based on medical insurance database in Guangzhou, China (4). Also, schizophrenia has significant impact on caregivers of the patients. The well-being of both patients and caregivers could be affected during their cognitive appraisal processes of the illness, help-seeking experience and the interaction within the families (5) and the burden of caregivers exists in physical and mental health, social relationship, and financial life (6).

Economic evaluations could generate evidence incorporating both costs and consequences for decision makers to clarify different uses for scarce resources (7). Despite the multiple choices of medications in schizophrenia treatment, there still exist substantial burdens and difficulties in clinical therapies due to low adherence and adverse events. Thus, pharmacoeconomic evidence is required to balance the clinical effects with the resources consumed. However, there remain some challenges especially in modeling due to uncertainties in the progression of the diseases, emphasizing the requirements for systematic reviews of the methods applied in the analysis.

Previous systematic reviews have evaluated studies published since 2000 (8–10). However, none of them fully discussed the treatment sequences or methods applied. Furthermore, most of them adopted an extensive range of years of publication, which may not characterize the studies in recent years. Therefore, this study was conducted to review the model-based economic evaluations published recently for antipsychotics and summarize the modeling techniques, including model structures, basic settings, integration and translation of the clinical events, and selection of utility values. In addition, the review also aimed to assess the quality of the studies.

METHODS

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement developed by Moher et al. (11).

Eligibility Criteria

The inclusion criteria were as follows: (a) economic evaluations adopting cost-effectiveness analysis (CEA) or cost-utility analysis (CUA) approach; (b) patients diagnosed with schizophrenia with no limitation on gender or age; (c) intervention including all antipsychotics; and (d) outcomes presented as incremental cost-effectiveness (ICER). Studies were excluded if they met the any of the following criteria: (a) not reported in English; (b) not related to economic evaluation; (c) cost of illness, health-related quality of life or budget impact analysis studies; (d) abstracts or studies with full-text unavailable; (e) not model-based studies; and (f) chose clinical effect as the only outcome.

Search Strategy

An electronic literature search was performed in PubMed, Web of Science, EBSCO host, The Cochrane Library, ScienceDirect from January 2014 to December 2020. Search items included "schizophrenia," "schizophrenic," "pharmacoeconomics," "economic evaluation," "cost-effectiveness," and "cost-utility." The detailed strategy is provided in **Supplementary Material**. In addition, references from retrieved studies were searched manually to avoid missing data.

Data Extraction and Analysis

The included studies were screened, extracted and double checked by two researchers independently. Disagreements were resolved by discussion or by consulting a third researcher. General information was collected including title, first author's surname, year of publication, country or region, intervention, and treatment sequences. To summarize the methods applied, characteristics such as perspectives, type of costs, outcomes, model structures, and necessary parameters were recorded. The results and conclusions of studies were included in the extracted form but were not reported as main outcomes due to the arguments regarding the extrapolation of evaluation results (12). All the information was recorded and compared using Microsoft Excel 2016.

Quality Assessment

According to the review of quality assessment tools conducted by Walker et al. (13) in 2012, the Quality of Health Economic Studies (QHES) List was recommended to discriminate the quality of studies as a quantitative measurement. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement (14) published in 2012 was recommended by the International Society for Pharmacoeconomics and Outcomes research (ISPOR) as a report checklist and for guidance to optimize the quality of reporting. Both QHES and CHEERS were applied to quantitatively and qualitatively assess the quality of studies.

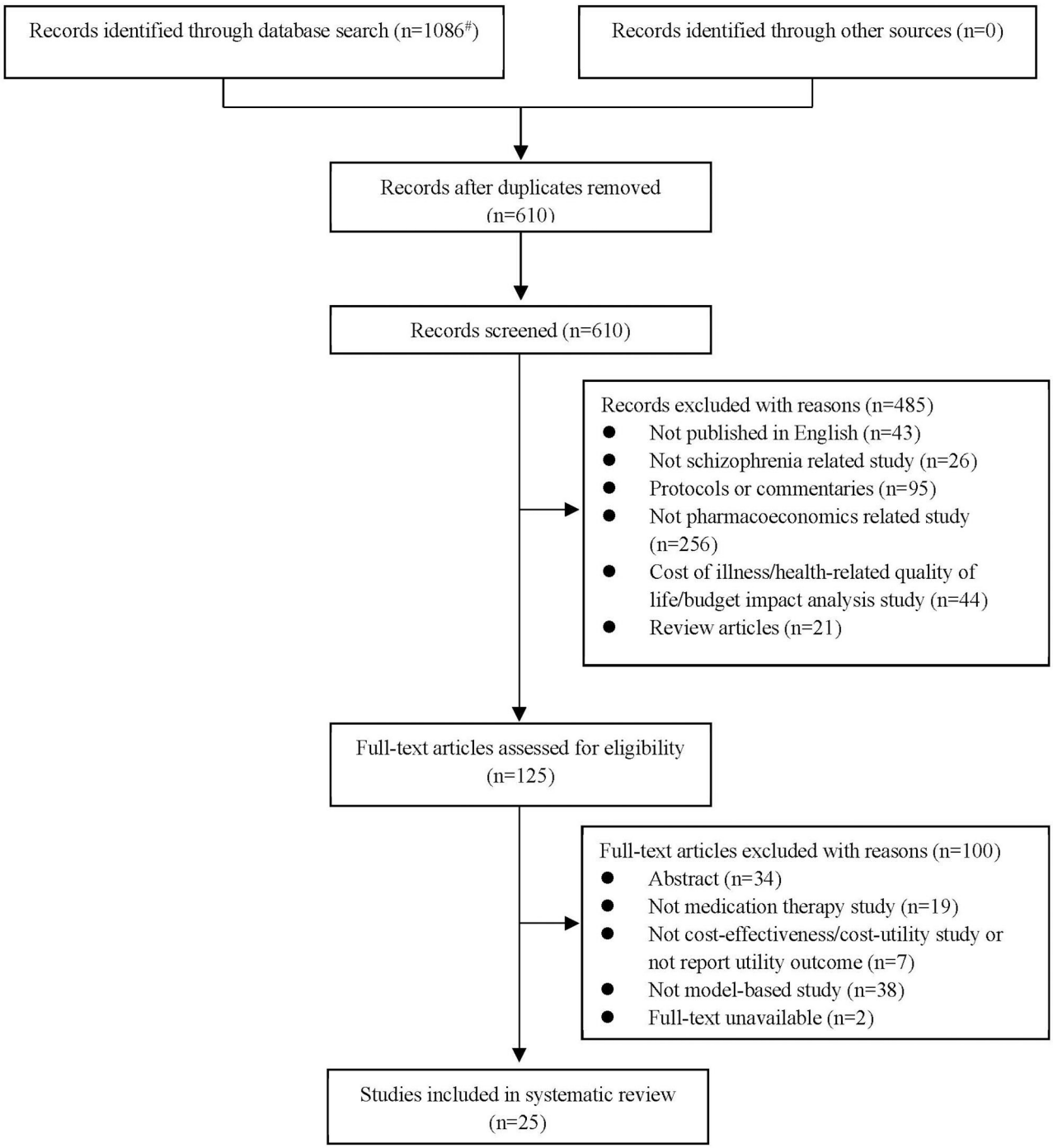


FIGURE 1 | Flow of information through different phases of the systematic review according to the PRISMA statement [#Detailed search results: PubMed Database (n = 202), Web of Science Database (n = 377), EBSCO host Database (n = 113), The Cochrane Library Database (n = 286), ScienceDirect Database (n = 108)].

RESULTS

A total of 1,086 citations were retrieved from five electronic databases. After removing duplicates, 610 studies were eligible to enter the screening process and judgements were generated according to the titles and abstracts. Finally, 25 articles published in English were identified and included in the systematic review. A flow of the literature screening was provided in **Figure 1** according to the PRISMA statement (11).

Basic Characteristics of Included Studies

The characteristics of the included studies were summarized in **Table 1**. The studies covered the regions of Europe (15, 18, 21, 23–28, 32, 34–36, 39), North America (16, 17, 31), Asia (19, 22, 29, 30, 33, 37, 38), and Africa (20). Eleven (44%) (16, 17, 19–22, 29, 32, 36, 37, 39) of the 25 studies specified the onset or averaged ages of patients and four studies (16%) (15, 18, 23, 24) focused on patients in acute or relapsed states. Second-generation antipsychotics (SGAs) also known as atypical antipsychotics were the most common interventions chosen in the analyses, where seven studies (28%) (15, 18, 21, 24, 25, 27, 30) compared the cost-effectiveness of long-acting-injections (LAIs). Eight studies (32%) (18–22, 25, 28, 39) included both first-generation and second-generation antipsychotics as compared interventions where haloperidol was the commonest ($n = 7$, 87.5%). Most of the studies measured the outcomes using quality-adjusted life-years (QALYs) ($n = 23$, 92%), while only 2 studies (8%) (19, 20) applied disability-adjusted life-years (DALYs).In addition, nine studies (18, 21, 24, 25, 27, 28, 30, 31, 33) reported both utility and clinical effects, where yearly relapse or relapse avoidance was the most frequent choice.

Due to the diverse efficacy and low compliance rate, therapeutic changes are common among schizophrenia patients, which makes treatment sequences worth consideration. Nineteen studies (76%) (15–18, 20–25, 27–31, 33, 35, 36, 38) specified treatment sequences in the models (**Table 2**). The methods of setting second-line medications were flexible, including changing to drugs that differed from the first-line or applying mixed therapies based on market share (22, 30, 36) or simple averaging (22, 31). Clozapine was the most common last-line therapy.

Results of Methodology Review

Perspectives and Related Costs

Various terms were used to define the study perspectives of the reviewed articles. Therefore, the terms were classified into three categories in this review, which were defined as health care sector perspective (including healthcare system, ministry of health, national health service, and government), payer perspective (including payer, third-party payer, and health insurance), and societal perspective (including societal, modified societal, and broadly societal perspective) based on the report recommended by ISPOR (40). Notably, studies of single-payer health system countries using both the healthcare system and payer were classified into the payer perspective. The perspectives determine the types of costs considered in the analysis (7, 40). Direct medical costs, both direct and indirect costs, and costs paid by payers are most relevant to the health care sector perspective, the societal perspective, and the payer perspective, respectively (7, 41).

Among the eight studies (32%) choosing the health care sector perspective (15, 17–19, 22, 24, 25, 27), seven studies adapted direct medical costs, while one study (15) included indirect costs which is inconsistent with the perspective. The payer perspective was chosen by 13 studies (52%) (21, 23, 28, 30–39) where six studies specified costs paid by payers and seven studies (28, 31, 33, 35–38) merely included direct medical costs. Among the 3 (14.3%) societal perspective-studies (20, 26, 29), only 1 study (20) took both direct and indirect costs into account, indicating that some confusion existed in distinguishing perspectives. One study chose both the healthcare sector and the societal perspective with direct and indirect costs (16).

Types of Models and Health States

The characteristics of the models and related health states are summarized in **Table 3**. The Markov model (17, 19, 20, 22, 23, 26, 29, 32, 35–37) and the decision tree model (15, 24, 25, 27, 28, 30, 34) were the most common choices. One study (16) combined the decision tree model with the Markov model to better reflect complication-related treatment switches within the first year of treatment and long-term metabolic complications. Most of the Markov models consisted of a series of health states, which represent treatment sequences, disease progression or related adverse events and were connected by probabilities based on the averaged cohort level (27). Microsimulation models (18, 33, 38, 39) are more flexible and natural for simulating clinical reality by incorporating patient-level characteristics. Due to the differentiation in the choice of therapy and the treatment effect among patients, a patient-level simulation model as well as a Markov model incorporating treatment sequences, relapse, remission, adherence and adverse events could be more suitable for clinical practice.

Time Horizon and Cycle Length

As summarized in **Tables 3**, **6** (24%) studies (19, 20, 22, 29, 37, 39) chose the lifetime horizon in the model. However, considering the low adherence and frequent changes of medication, a certain number of studies (15, 16, 18, 21, 24–27, 30–33, 35) chose a relatively short time horizon. Among these, most Markov model-based studies explored uncertainty by extending the time horizon as a complementary analysis, while most decision tree model-based or microsimulation model-based studies conducted mere 1-year analyses (15, 24, 25, 27, 30, 31, 33, 34). As a chronic mental disease, schizophrenia should be simulated for a long time period or even lifetime in the model. However, due to the uncertainty in therapy and disease progression, it might be challenging to simulate further into the future as it becomes more unpredictable. Therefore, selecting the appropriate time frame covering events in the near future and then exploring time horizon uncertainty may be a reasonable method for economic evaluations for schizophrenia.

The cycle lengths of Markov models in the included studies varied from 4 weeks to 1 year, where 3 months (21, 26, 30, 32, 33, 35) and 1 year (16, 19, 20, 22, 37) were the most frequently used. The reasons for 3-month cycle selection included appropriate capture the both clinical practice and associated events according to clinical opinion (21, 30), consistent with clinical trials (26), while explanation for 1-year cycle selection was consideration of the realistic treatment management of schizophrenia (37). The length of cycle selection should be depend on both disease and intervention (7), and should be short enough to avoid multiple changes within a single cycle (42). Therefore, a 1-year cycle length may be less preferable compared to a 3-month cycle length.

TABLE 1 | Basic characteristics.

References	Country/region	Patients	Interventions	Perspectives	Type of Costs	Outcome measurement	Discount rate
Einarson et al. (15)	Sweden	Schizophrenia patients with relapse	Paliperidone LAI, olanzapine LAI, risperidone LAI, haloperidol LAI, oral olanzapine	Health care sector perspective	Direct and indirect costs	QALYs	NA
Lachaine et al. (16)	Canada	Moderate to severe schizophrenia patients above 40	Asenapine, olanzapine	Health care sector perspective, societal perspective	Direct and indirect costs	QALYs	5%
Park et al. (17)	United States	Schizophrenia patients above 40	Olanzapine, risperidone, quetiapine, ziprasidone	Health care sector perspective	Direct costs	QALYs	3%
Dilla et al. (18)	Spain	Schizophrenia patients in relapse due to low compliance	Olanzapine LAI, risperidone LAI	Health care sector perspective	Direct costs	QALYs, relapse averted, life years	3%
Anh et al. (19)	Vietnam	Schizophrenia patients above 15	Chlorpromazine, haloperidol, levopromazine, risperidone, clozapine, olanzapine	Health care sector perspective	Direct costs	DALYs	3%
Lubinga et al. (20)	Uganda	Schizophrenia patients with average age of 25	Chlorpromazine, haloperidol, risperidone, olanzapine, quetiapine	Societal perspective	Direct and indirect costs	DALYs	3%
Druais et al. (21)	France	Stable schizophrenia patients with average age of 38	Paliperidone LAI, risperidone LAI, aripiprazole LAI, olanzapine LAI, haloperidol LAI, oral olanzapine	Payer perspective	Direct costs	QALYs, relapse averted	4%
Lin et al. (22)	Singapore	Schizophrenia patients with average age of 37	Amisulpride, aripiprazole, chlorpromazine, olanzapine, paliperidone, quetiapine, risperidone, sulpiride, trifluoperazine, ziprasidone	Health care sector perspective	Direct costs	QALYs	3%
Rajagopalan et al. (23)	Scotland and Wales	Schizophrenia patients in relapse	Lurasidone, aripiprazole	Payer perspective	Direct costs	QALYs	3.50%
Einarson et al. (24)	Finland	Schizophrenia patients in relapse	Aripiprazole LAI, paliperidone LAI, olanzapine LAI, risperidone LAI	Health care sector perspective	Direct costs	QALYs, relapse averted	NA
Einarson et al. (25)	Portugal	Schizophrenia patients	Paliperidone LAI, risperidone LAI, haloperidol LAI, oral olanzapine	Health care sector perspective	Direct costs	QALYs, relapse averted	NA
Barnes et al. (26)	United Kingdom	Patients unresponsive to clozapine	Olanzapine, amisulpride	Societal perspective	Direct costs	QALYs	Not specified
Einarson et al. (27)	Spain	Schizophrenia patients	PP3M, PP1M	Health care sector perspective	Direct costs	QALYs, relapse averted, hospitalization averted	NA

(Continued)

TABLE 1 | Continued

References	Country/region	Patients	Interventions	Perspectives	Type of Costs	Outcome measurement	Discount rate
Einarson et al. (28)	Netherlands	Schizophrenia patients	PP3M, PP1M, haloperidol LAI, risperidone microspheres, oral olanzapine	Payer perspective	Direct costs	QALYs, relapse (hospitalization treated or out-patient treated)	NA
Wiwat et al. (29)	Thailand	Stable schizophrenia patients above 15	Aripiprazole, risperidone	Societal perspective	Direct costs	QALYs	3%
Nuhoho et al. (30)	United Arab Emirates	Stable schizophrenia patients	Paliperidone LAI, other oral antipsychotics	Payer perspective	Direct costs	QALYs, rate of hospitalization, relapse, emergency	NA
Aigbogun et al. (31)	United States	Stable schizophrenia patients	Brexpiprazole, cariprazine, lurasidone	Payer perspective	Direct costs	QALYs, relapse averted, hospitalization averted	NA
Németh et al. (32)	Hungary	Patients with negative symptoms of schizophrenia with average age of 40	Cariprazine, risperidone	Payer perspective	Direct costs	QALYs	4%
Zhao et al. (33)	China	Schizophrenia patients	Olanzapine ODT, olanzapine SOT, aripiprazole SOT	Payer perspective	Direct costs	QALYs, averaged annual relapse	NA
Abdall-Razak et al. (34)	United Kingdom	Not specified	Paliperidone, amisulpride	Payer perspective	Direct costs	QALYs	NA
Dutina et al. (35)	Serbian	Adult patients about to receive for the second-line treatment	Aripiprazole, olanzapine	Payer perspective	Direct costs	QALYs	3%
Arteaga et al. (36)	France	Adult chronic schizophrenic patients stabilized on PP1M with baseline age of 38.75	PP3M, PP1M	Payer perspective	Direct costs	QALYs	4%
Yi et al. (37)	China	Schizophrenia patients with starting age of 35	Amisulpride, olanzapine	Payer perspective	Direct costs	QALYs	3%
Lin et al. (38)	China	Not specify	Aripiprazole ODT, aripiprazole SOT, olanzapine SOT	Payer perspective	Direct costs	QALY	NA
Jin et al. (39)	United Kingdom	Individuals referred to secondary care mental health services with mean age of 23.5	Amisulpride, aripiprazole, haloperidol, olanzapine, quetiapine, risperidone, placebo, clozapine	Payer perspective	Direct costs	QALYs	3.5%

LAI, long-acting-injection; ODT, orally disintegrating antipsychotic tablets; SOT, standard oral tablets; PP3M, paliperidone administered every 3 months; PP1M, paliperidone administered every month; QALY, quality-adjusted life year; DALY, disability-adjusted life year; NA, not applicable.

Adverse Events

Adverse events (AEs) could impact adherence, efficacy and therapy changes as well as health-related quality of life, especially for schizophrenia. Thus, it is meaningful to take relevant AEs into account in the models. The AEs selected in the evaluations are listed in **Table 4**. The effect of the extrapyramidal system (EPS), weight gain, and diabetes were the most common adverse events considered. A few studies built separate health states for possible AEs to reflect the influence by applying transition probabilities, costs and utility of the health states (16, 22, 26). The majority of studies incorporated the prevalence, costs and disutility of AEs in each cycle to reflect the impact on disease progression. Both methods were acceptable as long as the choice was made based on proper consideration of the disease progression and available evidence (42).

However, some studies did not fully describe the consideration of AEs (27, 30) or even did not include AEs (15, 24, 25, 28) due to the similar incidence rates, small expenditures or short

TABLE 2 | Treatment sequences[#] in the included studies.

References	Consideration of the treatment sequence	First-line treatment	Second-line treatment	Third-line treatment
Einarson et al. (15)	Yes	Paliperidone LAI or olanzapine LAI or risperidone LAI or oral olanzapine or haloperidol LAI	Olanzapine LAI or paliperidone LAI or haloperidol LAI or oral olanzapine*	Clozapine
Lachaine et al. (16)	Yes	Asenapine or olanzapine	Aripiprazole or ziprazidone or risperidone or quetiapine	NA
Park et al. (17)	Yes	Olanzapine or risperidone or quetiapine or ziprasidone	Olanzapine or risperidone or quetiapine or ziprazidone*	Clozapine
Dilla et al. (18)	Yes	Olanzapine LAI or risperidone LAI	Other antipsychotics	NA
Anh et al. (19)	No	Chlorpromazine or haloperidol or levopromazine or risperidone or clozapine or olanzapine	NA	NA
Lubinga et al. (20)	Yes	Chlorpromazine or haloperidol or risperidone or olanzapine or quetiapine	Risperidone or haloperidol*	Perphenazine
Druais et al. (21)	Yes	Paliperidone LAI or risperidone LAI or aripiprazole LAI or olanzapine LAI or haloperidol LAI or oral olanzapine	25%paliperidoneLAI+25%risperidone LAI+25%aripiprazoleLAI+25%olanzapine LAI**	NA
Lin et al. (22)	Yes	Amisulpride or aripiprazole or chlorpromazine or haloperidol or olanzapine or paliperidone or quetiapine or risperidone or sulpiride or trifluoperazineor ziprazidone	The other drugs excluded the first-line drugs***	Clozapine
Rajagopalan et al. (23)	Yes	Lurasidone or aripiprazole	Amisulpride	Clozapine
Einarson et al. (24)	Yes	Aripiprazole or paliperidone or olanzapine or risperidone	Olanzapine or risperidone*	Clozapine
Einarson et al. (25)	Yes	Paliperidone or risperidone or haloperidol or olanzapine	Haloperidol or olanzapine*	Clozapine
Barnes et al. (26)	No	Olanzapine or amisulpride	NA	NA
Einarson et al. (27)	Yes	PP3M or PP1M	Aripiprazole	Clozapine
Einarson et al. (28)	Yes	PP3M or PP1M or haloperidol or risperidone or olanzapine	Haloperidol or oral olanzapine	Clozapine
Wiwat et al. (29)	Yes	Aripiprazole or risperidone	Clozapine	NA
Nuhoho et al. (30)	Yes	Paliperidone LAI or paliperidone LAI plus oral antipsychotics	Risperidone or paliperidone or aripiprazole or olanzapine or quetiapine***	Risperidone or paliperidone or aripiprazole or olanzapine or quetiapine*
Aigbogun et al. (31)	Yes	Brexpiprazole or cariprazine or lurasidone	Olanzapine or risperidone or quetiapine or ziprazidone or aripiprazole**	NA
Németh et al. (32)	No	Cariprazine or risperidone	NA	NA
Zhao et al. (33)	Yes	Olanzapine ODT or olanzapine SOT or aripiprazole SOT	Aripiprazole or amisulpride or ziprazidone or clozapine	NA
Abdall-Razak et al. (34)	No	Paliperidone or amisulpride	NANA	
Dutina et al. (35)	Yes	Aripiprazole or olanzapine	Clozapine	NA
Arteaga et al. (36)	Yes	PP3M or PP1M	Paliperidone, olanzapine, aripiprazole, risperidone***	NA
Yi et al. (37)	No	Amisulpride or olanzapine	NA	NA
Lin et al. (38)	Yes	Aripiprazole ODT or aripiprazole SOT or olanzapine SOT	Not specify	NA
Jin et al. (39)	No	Amisulpride, aripiprazole, haloperidol, olanzapine, quetiapine, risperidone, placebo, clozapine	NA	NA

LAI, long-acting-injection; ODT, orally disintegrating antipsychotic tablets; SOT, standard oral tablets; PP3M, paliperidone administered every 3 months; PP1M, paliperidone administered every month; NA, not applicable.

[#]If patients show no response to the therapies or relapse during the current treatment, they will change to the next-line treatment.

**A single drug different from the previous treatment line was chosen as the current treatment line.*

***Clinical and economic inputs were determined by a weighted average with equal proportions of data for the drugs.*

****Clinical and economic inputs were determined by market share of the drugs.*

TABLE 3 | Basic characteristics of the models in the included economic evaluations.

References	Types of model	Model states	Time horizon	Cycle length
Einarson et al. (15)	Decision tree, cohort	Incorporating clinical events including discontinuation, exacerbation, compliance, hospitalization	1 year	NA
Lachaine et al. (16)	Decision tree combined with 9-state Markov model, cohort	Diabetes, stroke, CHDs, hypertension, no comorbidity, 2/3/4 comorbidities, death	5–10 years	1 year
Park et al. (17)	9-state Markov model, cohort	First line treatment with/without irreversible SE, 2nd line treatment with/without irreversible SE, clozapine treatment with/without irreversible SE, uncontrolled state with/without SE, death	10 years	18 weeks
Dilla et al. (18)	Discrete event simulation, microsimulation	Treatment, treatment emergent adverse events, relapse, doctor-initiated treatment re-evaluation, patient-initiated treatment discontinuation	5 years	NA
Anh et al. (19)	3-state Markov model, cohort	Schizophrenia patients, recovery patients, schizophrenia-specific and other causes of deaths	Lifetime	1 year
Lubinga et al. (20)	10-state Markov model, cohort	Residual on/off 1st line AP, acute on/off 1st line AP, residual on/off 2nd line AP, acute on/off 2nd line AP, residual on 3rd line	Lifetime	1 year
Druais et al. (21)	4-state Markov model, cohort	Stable treated, stable non-treated, relapse, death	5 years	3 months
Lin et al. (22)	4-state Markov model, cohort	Stable treated, stable non-treated, relapse, death	Lifetime	1 year
Rajagopalan et al. (23)	5-state Markov model, cohort	Non-stable/relapse trial of antipsychotic agents, stable/adherent, stable/non-adherent, relapse, death	10 years	6 weeks
Einarson et al. (24)	decision tree, cohort	Incorporating clinical events including discontinuation, exacerbation, compliance, hospitalization	1 year	NA
Einarson et al. (25)	decision tree, cohort	Incorporating clinical events including discontinuation, exacerbation, compliance, hospitalization	1 year	NA
Barnes et al. (26)	3-state Markov model, cohort	Symptom response, SEs, death	1–10 years	3 months
Einarson et al. (27)	decision tree, cohort	Incorporating clinical events including discontinuation, exacerbation, compliance, hospitalization	1 year	NA
Einarson et al. (28)	decision tree, cohort	Incorporating clinical events including stable, intolerant, relapse treated as out-patient, relapse requiring hospitalization and dropout	1 year	NA
Wiwat et al. (29)	4-state Markov model, cohort model	Remission with 1st antipsychotics, relapse, remission with clozapine, death	Lifetime	4 weeks
Nuhoho et al. (30)	Decision tree, cohort	Incorporating clinical events including adherence, exacerbation, hospitalization	1 year	3 months
Aigbogun et al. (31)	Decision-analytic model, cohort	Incorporating clinical events including treatment discontinuation, relapse/impending relapse, AEs	1 year	NA
Németh et al. (32)	8-state Markov model, cohort	Constructed according to both severity of symptoms and disease types	1–10 years	1/12 weeks
Zhao et al. (33)	Decision-analytic model, microsimulation	Incorporating adherence levels, relapse with/without hospitalization, treatment discontinuation, AEs suicide risk	1 year	3 months
Abdall-Razak et al. (34)	Decision tree, cohort	Incorporating relapse, remission, AEs, diabetes complications	1 year	NA
Dutina et al. (35)	5-state Markov model, cohort	Remission without AEs, remission with AEs, relapse, second response, death	10 years	3 months
Arteaga et al. (36)	5-state Markov model, cohort	1st-line treatment, no active treatment, 2nd-line treatment, relapse, death	5 years	1 month
Yi et al. (37)	5-state Markov model, cohort	Acute phase, remission, relapse, death	Lifetime	1 year
Lin et al. (38)	Discrete event simulation, microsimulation	Incorporating adherence levels, relapse with/without hospitalization, stable and adverse events	1 year	NA
Jin et al. (39)	Discrete event simulation, microsimulation	Incorporating 4 module for different pathway with relevant interventions	Lifetime	NA

CHDs, coronary heart diseases; AP, antipsychotics; SEs, side effects; AEs, adverse events; NA, not applicable.

time horizon. It should be discussed whether the 1-year time horizon was sufficient to capture all important and interesting outcomes, since such a time horizon might fail to capture the impact on both health-related quality of life and costs of relevant clinical events among drugs. It is also notable that AEs with different durations should be clearly described to calculate the

TABLE 4 | Summary of the adverse events considered in the included economic evaluations.

References	Consideration and description of AEs	Types of AEs					
		EPS*	Weight gain	Diabetes	Hyperprolactinemia	Metabolic events**	Others
Einarson et al. (15)	×	×	×	×	×	×	NA
Lachaine et al. (16)	√	√	√	√	×	√	NA
Park et al. (17)	√	√	×	×	√	√	Agranulocytosis
Dilla et al. (18)	√	√	√	×	×	×	Somnolence, sexual dysfunction, postinjection syndrome, suicide
Anh et al. (19)	√	√	√	×	×	×	Agranulocytosis
Lubinga et al. (20)	√	√	√	√	×	×	Ischemic heart disease
Druais et al. (21)	√	√	√	√	×	×	NA
Lin et al. (22)	√	√	√	√	×	×	NA
Rajagopalan et al. (23)	√	√	√	√	×	×	NA
Einarson et al. (24)	×	×	×	×	×	×	NA
Einarson et al. (25)	×	×	×	×	×	×	NA
Barnes et al. (26)	√	√	√	×	×	√	Sexual dysfunction, aversive subjective experience, cardiac symptoms
Einarson et al. (27)	×	×	×	×	×	×	NA
Einarson et al. (28)	×	×	×	×	×	×	NA
Wiwat et al. (29)	√	√	√	√	√	×	NA
Nuhoho et al. (30)	×	×	×	×	×	×	NA
Aigbogun et al. (31)	√	√	√	×	×	√	NA
Németh et al. (32)	√	√	×	×	×	×	NA
Zhao et al. (33)	√	√	√	√	×	√	NA
Abdall-Razak et al. (34)	√	√	√	√	×	×	Diabetes complications: amputation, MI, stroke, IHD, HF
Dutina et al. (35)	√	√	×	×	×	√	Neutropenia
Arteaga et al. (36)	√	√	√	√	√	×	NA
Yi et al. (37)	√	√	√	×	√	√	Liver function damage
Lin et al. (38)	√	√	√	√	√	√	NA
Jin et al. (39)	√	√	√	√		√	Neutropenia

AEs, adverse events; MI, myocardial infarction; IHD, ischemic heart disease; HF, heart failure; NA, not applicable.

**EPS (effects of the extrapyramidal system) including akathisia, and tardive dyskinesia. **Metabolic events including pathoglycemia, dyslipidemia and hypertension.*

respective additional costs and disutilities. Park et al. (17) and Arteaga et al. (36) classified the reversible and irreversible AEs and assumed that reversible AEs would last for 18 weeks or 3 months while irreversible AEs would remain for the rest of the period. Rajagopalan et al. (23) classified the AEs into one-off AEs (such as EPS), persistent AEs (such as weight gain), and cumulatively occurred AEs (such as diabetes). Abdall-Razak et al. (34) clearly described the health-related utilization of the AEs and summarized the calculation of utilities of each AEs. However, more than half of the studies failed to clearly defined both costs and utilities considerations of the AEs.

Compliance and Persistence

Medication compliance (also known as adherence) can be defined as the extent to which the medication-taking of a patient matches that defined by the prescriber while medication persistence (also known as continuous adherence or discontinuation rate) refers to the act confirming to the recommended continuing treatment for the duration of time from the prescriber (43, 44). Both of them could influence the risk of relapse, rehospitalization, costs, quality of life through different aspects, especially for chronic disorders such as schizophrenia (44). Due to the different definitions and roles, it is important to not only take both compliance and persistence into account but also distinguish them when building economic models.

Information about the adoption of compliance or persistence in the included studies is listed in **Table 5**. The management of medication compliance or medication persistence can be summarized into three types: (1) Patients classified based on the compliance rates (adherence rates) from existing literature and then search for inputs under relevant compliance (15, 24, 25, 30, 33, 38). Such a method is usually applied in decision tree models and microsimulation models. (2) Non-persistence rates (discontinuation or dropout rates) are used rather than

compliance to reflect the medication behaviors (17, 18, 20–22, 27, 28, 31, 36, 39). In such studies, non-persistence rates were divided into lack of efficacy, adverse events, intolerance, patients' choice and so on. Patients with treatment withdrawn due to lack of efficacy, adverse events or intolerance would change their therapies according to the treatment sequence. Patients who stopped treatment due to their own choices or for other reasons were defined as not receiving any therapies in the next simulation. Such methods were found in Markov model evaluations (3). Compliance not considered in the analysis. Lachaine et al. (16) assumed that patients remained on their medication continually for 5 years which was chosen as relatively short period to reduce uncertainty. Additionally, Abdall-Razak et al. (34) and Németh et al. (32) did not introduce the non-persistence rate due to a lack of relevant data.

Various sources of reference for compliance or persistence were adopted in the evaluations, including retrospective studies, clinical trial studies, and naturalistic studies. Simple averaging was the major method adopted for multisource data. Most discontinuation rates were collected from clinical trials. Even though there might be differences between the definitions of compliance and persistence, most of the studies did not explain or discuss this issue. Considering the definition of compliance, data from real-world studies might be superior as no intervention has been implemented to influence the medication behaviors of patients.

Utility

According to the health states defined in the model, the most commonly used utilities in the studies were those for stable schizophrenia, relapse without hospitalization, relapse with hospitalization and the disutilities of EPS, weight gain, and diabetes. Utilities and references are summarized in **Tables 6**, **7**. Utilities of the stable state, relapse without hospitalization and relapse with hospitalization ranged from 0.65 to 0.919, 0.485 to 0.762, and 0.27 to 0.604, respectively. Apart from EPS, weight gain and diabetes, the utilities or disutilities of hypertension, coronary heart disease, stroke, and hyperprolactinemia were also considered in some studies. Utilities from Lenert et al. (45) and Briggs et al. (46) were the most frequently referenced among the studies.

It was noteworthy that the utilities for the same disease states varied greatly. Possible reasons included varieties in the classification of the researched states, selection of the population, and different methods or instruments applied among referenced quality of life studies.

Definitions or classifications of the health states were usually developed based on a literature review (45, 46), expert opinions (45, 46) and interviews with patients or laypersons (46) rather than through a unified method. Such states are usually framed by several items or descriptions; however, few studies discussed the applicability for states in decision-analytical models.

Layperson, patients with schizophrenia and caregivers are common responders in research on health-related quality of life. The differentiation of responders could induce heterogeneity among the results. For example, Briggs et al. (46) discovered significant differences between laypersons and patients, especially for relapse and EPS states. Regardless of the doubt regarding the response ability of patients with schizophrenia, studies have demonstrated that schizophrenia patients in the stable stage were able to provide valid and reliable answers, indicating the necessity to include such a population (48, 53).

Due to the specialty of mental disease as well as the choice of population such as laypersons, caregivers, or psychiatrists, the majority of the methods generated utilities using the standard gambling or time trade off approaches. The EuroQol-5 dimensions (EQ-5D) questionnaire is preferred by The National Institute for Health and Care Excellence (NICE). However, the sensitivity of the EQ-5D index to capture both social and psychological well-being for patients with schizophrenia is still controversial (65).

Results of the Economic Evaluations

The included studies compared the cost-effectiveness of commonly used SGAs (including long-acting injections). However, due to economic, political, cultural diversities among the different regions, the results of one economic evaluation may not be applicable beyond the defined setting (12). Thus, the results of the evaluation are not to be introduced here, but detailed information would be provided in the **Supplementary Material 1**. All of the studies adopted sensitivity analysis to verify the robustness of the base-case results. Notably, a change in the time horizon in different scenarios could lead to inverse results (17, 32). Accordingly, discussion about the time horizon may be required for schizophrenia therapy.

Quality Assessment of the Included Studies

The widely used QHES and CHEERS lists economic evaluation checklists were applied for a quantitative and qualitative review.

Assessed with the QHES list, scores ranged from 60 to 93 for 25 studies, where 21 (84.0%) studies scored between 75 and 93, and 4 (16.0%) studies scored between 60 and 74, indicating the relatively high quality of the majority studies. As summarized in **Table 8** and **Figure 2**, all of the studies met the requirements of item 1, item 4, item 6, and item 15 representing the descriptions of study objective, subgroup analysis, incremental analysis, and conclusion, respectively. However, no more than half of the studies met the requirements of item 8 (choice of appropriate time horizon and discount rate) and item 13 (statement and justification of the choice of model, assumptions, and limitations).

The quality reports evaluated with the CHEERS checklists were showed in **Table 9** and **Figure 3**. The fulfilled items ranged from 16 to 23 for each study. More than half of the studies failed to meet the requirements for time horizon, preference-based outcome measurement, and assumptions. A considerable number of the studies selected a relatively short time horizon, which may be insufficient to capture necessary events. Most of the studies did not fully explain the reasons for time horizon selections. A large number of the studies chose utility values from the published literature, while some studies did not describe the methods used to elicit preference for outcomes. Studies seldom reported or explained the assumptions

TABLE 5 | Summary of the methods used to integrate medication compliance.

References	Expression		Roles in the model	Source of the data				Statistical methods
	Compliance	Persistence		Retrospective study	Clinical trials	Observational study	Review	
Einarson et al. (15)	√	√	(a) Act as branches behind chance nodes, (b) influence the probabilities for events	√	√	√		Simple average
Lachaine et al. (16)	×	×						NA
Park et al. (17)	×	√	Lead to therapy changes		√			Kaplan-Meier discontinuation curves
Dilla et al. (18)	×	√	Lead to therapy changes		√			
Anh et al. (19)	√	×	Not specified				√	Simple average
Lubinga et al. (20)	×	√	Lead to relapse		√			NA
Druais et al. (21)	×	√	(a) Act as transition probabilities, (b) influence relapse of the disease		√			NA
Lin et al. (21)	×	√	Lead to change or discontinuation of the therapy				√	NA
Rajagopalan et al. (23)	×	√	Act as transition probabilities		√		√	Regression analysis, partial assumption
Einarson et al. (24)	√	√	(a) Act as branches behind chance nodes, (b) influence the probabilities of events	√	√	√		Partial assumption, simple average
Einarson et al. (25)	√	√	(a) Act as branches behind chance nodes, (b) influence the probabilities of events	√	√	√		Partial assumption, simple average
Barnes et al. (26)	Not specified							NA
Einarson et al. (27)	×	√	(a) Act as branches behind chance nodes, (b) influence the probabilities of events		√			NA
Einarson et al. (28)	×	√	(a) Lead to change or discontinuation of the therapy, (b) influence the relapse of the disease	√	√			NA
Wiwat et al. (29)	√	√	Influence relapse of the disease		√			NA
Nuhoho et al. (30)	√	√	(a) Act as branches behind chance nodes, (b) influence the probabilities of events	√				NA
Aigbogun et al. (31)	×	√	Lead to change or discontinuation of the therapy		√			Indirect comparison based on data from clinical trials
Németh et al. (32)	×	×						NA
Zhao et al. (33)	√	√	Classified different types of patients	√	√	√		Assumption
Abdall-Razak et al. (34)	×	×						NA
Dutina et al. (35)	Not specified							NA
Arteaga et al. (36)	×	√	Act as transition probabilities	√	√			NA
Yi et al. (37)	×	√	Act as transition probabilities					NA
Lin et al. (38)	√	√	Classified different types of patients	√	√	√		NA
Jin et al. (39)	√	√	Persistence rate acting as transition probabilities while non-compliance seen as reason for non-persistence	√			√	NA

NA, not applicable.

TABLE 6 | Summary of the utilities for health states of schizophrenia.

Study	Stable	Non-hospitalized relapse	Hospitalized relapse	References
Einarson et al. (15)	0.89	0.659	0.49	(45–49)
Lachaine et al. (16)	0.75	NA	NA	(45)
Park et al. (17)	0.856	NA	−0.358	(46)
Dilla et al. (18)	0.77	—	−0.18	From SOHO data
Druais et al. (21)	0.919	0.762	0.604	(46)
Lin et al. (22)	0.8	NA	0.67	(45)
Rajagopalan et al. (23)	0.799	NA	0.67	(45, 46, 50)
Einarson et al. (24)	0.89	0.659	0.49	(45–49)
Einarson et al. (25)	0.89	0.659	0.49	(45–49)
Barnes et al. (26)	0.696	NA	NA	AMICUS trial
Einarson et al. (27)	0.7/0.65*	0.485/0.469*	0.27	(21, 51, 52)
Einarson et al. (28)	0.890/0.840/0.795/0.790**	0.690/0.665/0.643/0.640**	0.49	(21, 51, 52)
Wiwat et al. (29)	0.69	NA	0.58	(22)
Nuhoho et al. (30)	0.89	0.659	0.49	(45–49, 53)
Aigbogun et al. (31)	0.88	0.74	0.53	(45, 54)
Németh et al. (32)	Not reported	Not reported	Not reported	(39)
Zhao et al. (33)	0.88	0.74	0.53	(45), expert opinion
Abdall-Razak et al. (34)	0.799	0.67	0.67	(45)
Dutina et al. (35)	0.919	0.604	0.604	(46)
Arteaga et al. (36)	0.916/0.865##	−0.358	−0.358	(46, 51)
Yi et al. (37)	0.92	0.74#	0.60	(45, 46)
Lin et al. (38)	0.88/0.75/0.75###	0.74/0.63/0.63###	0.53/0.53/0.42###	(45), expert opinion
Jin et al. (39)	0.80	0.67	NA	(45)

NA, not applicable.

**Data presented as utility for patients receiving injection therapy monthly/utility for patients receiving injection therapy every 3 months.*

***Data presented as utility for patients receiving paliperidone 3-month injection/paliperidone 1-month injection/risperidone long-acting injection/haloperidol decanoate injection, oral olanzapine and clozapine.*

#*Data refer to acute phase.*

##*Data presented as utility for patients receiving paliperidone 3-month injection/paliperidone 1-month injection.*

###*Data presented as utility for full compliance, partial compliance and non-compliance patients.*

in single paragraph or table, adding to the difficulty identifying all assumptions underpinning the decision-analytical model. In addition, descriptions were for the parameters included, such as selection of population, measurement of effectiveness, and choice of model type.

Unlike the CHEERS checklist acting as a recommendation of the report format, the QHES list was developed to appraise the quality of economic evaluation (13, 14). According to the assessment of the QHES and CHEERS lists, most of the studies could be identified as relatively high-quality analyses, but certain limitations existed regarding the report quality. The selection of an appropriate time horizon and description of assumptions are frequent limitations for the included studies or even for economic evaluations in other chronic diseases (66, 67).

To compare the quality among the included studies, model types, regions, and time horizons were used as the indicators to classify the studies. The average QHES score of Markov model studies was 84.46 (13 studies) which was higher than that of decision tree model studies (77.14, 7 studies). The average score of the studies applying microsimulation was 80.75. The average numbers of the items consistent with the CHEERS recommendations were 19.23, 17.71, and 20 for Markov model studies, decision tree model studies, and microsimulation model studies. As a result, the Markov model and microsimulation model rather than the decision tree model are more appropriate model types for the study of schizophrenia. The quality of studies among different regions was also slightly different. The average QHES scores of the studies from North America, Asia, and European countries were 90.67, 81.00, and 80.07, respectively. It should be noticed that certain discrepancies exist among the scores of the studies from European countries where the maximum and minimum scores were 96 and 64. The numbers of the items consistent with the CHEERS recommendations (21.3, 18.14, and 18.86, respectively) were similar. However, even though the studies from North America seemed to be of higher quality, the numbers of the studies from the three regions differed a lot (three studies from North America, 7 studies from Asia, and 14 studies from European countries) and this might introduce bias when assessing the qualities.

TABLE 7 | Summary of the utilities of adverse events or complications.

Study	EPS	Weight gain	Diabetes	Others	References
Einarson et al. (15)	NA				
Lachaine et al. (16)	−0.074	−0.031	−0.06/−0.05*	Hypertension: −0.02 CHD: −0.07/−0.06* stroke: −0.17/−0.18*	(45, 55)
Park et al. (17)	−0.256	NA	−0.151	Hyperprolactinemia: −0.089 CHD: −0.151	(46)
Dilla et al. (18)	−0.054	−0.003	NA	Sexual disfunction: −0.066	From SOHO data
Druais et al. (21)	−0.197	−0.094	−0.15		(46)
Lin et al. (22)	0.72***	0.77***	0.77***	myocardial infarction: 0.74*** stroke: 0.64*** poststroke: 0.70***	(45, 56, 57)
Rajagopalan et al. (23)	89%**	96%**	−0.15	NA	(45, 46, 50)
Einarson et al. (24)	NA				
Einarson et al. (25)	NA				
Barnes et al. (26)	NA	NA	NA	Adverse events-0.006	AMICUS trial
Einarson et al. (27)	NA	NA	NA	NA	NA
Einarson et al. (28)	NA	NA	NA	NA	NA
Wiwat et al. (29)	0.62***	0.66***	0.66***	Hyperprolactinemia: 0.62	(22, 58)
Nuhoho et al. (30)	NA				
Aigbogun et al. (31)	−0.099	−0.036	NA	Akathisia: −0.09 pathoglycemia: −0.067 dyslipidemia: −0.099 sedation: −0.084	(45, 59–61)
Németh et al. (32)	Not reported	Not reported	Not reported	Not reported	(62)
Zhao et al. (33)	88.8%**	95.9%**	NA	NA	(45)
Abdall-Razak et al. (34)	88.8%**	95.9%**	0.76***	Amputation: −0.109, non-fatal myocardial infarction: −0.129, non-fatal stroke: −0.181, heart failure: −0.108, ischemic heart disease: −0.132	(45, 50, 56, 63)
Dutina et al. (35)	−0.256	NA	NA	Metabolic syndrome: −0.132	(46)
Arteaga et al. (36)	−0.256	−0.089	−0.151	Prolactin-related syndrome: −0.089	(46)
Yi et al. (37)	0.72***	0.83***	NA	increased blood glucose level: 0.77***, liver function damage 0.75***, hyperprolactinemia: 0.82***	(45, 64)
Lin et al. (38)	88.8%**	95.9%**	88.8%**	hyperlipidemia/hyperprolactinemia: 88.8%**	(45)
Jin et al. (39)	−0.07	−0.03	−0.09	NA	(45, 56)

Data presented as utility for male/utility for female.

***Data presented as percentage reduction in utility for the presence of adverse effects.*

****Data presented as utility values.*

To analyze the quality differences of studies with different time horizons, we classified the studies into two categories: short-term studies, i.e., the time horizon was 1 year or less, and long-term studies, i.e., the time horizon was longer than 1 year. The averaged QHES scores of the short-term studies (78.2, 10 studies) were lower than that of the longer-term studies (84.3, 15 studies). However, the number of the items consistent with the CHEERS recommendations are similar (18.3 for short-term studies vs. 19.53 for long-term studies). As mentioned above, the QHES list was developed to appraise the quality of economic evaluation while the CHEERS checklist was developed to recommend the report format. It can be inferred from the description of the time horizon from the two lists that the QHES list (Did the analytic horizon allow time for all relevant and important outcomes?) was more subjective and focused on the relationship between the item assessed and model outcomes. While the CHEERS checklist [State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate] highlighted the fact that the statement of relevant aspect was provided and with no requirement to judge the appropriateness for the evaluation. Thus, attention should be paid when choosing checklists and interpreting the results.

TABLE 8 | Quality assessment of economic evaluations with the QHES checklist.

Study	QHES items																Scores
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Einarson et al. (15)	√	×	×	√	√	√	√	×	√	√	√	√	√	√	√	√	81
Lachaine et al. (16)	√	√	√	√	√	√	√	√	√	√	√	√	×	√	√	√	93
Park et al. (17)	√	√	√	√	√	√	√	√	√	√	×	√	√	√	√	√	93
Dilla et al. (18)	√	√	√	√	√	√	×	√	√	√	×	√	√	√	√	×	85
Anh et al. (19)	√	√	×	√	√	√	√	√	√	√	√	√	×	×	√	×	76
Lubinga et al. (20)	√	√	√	√	√	√	√	√	√	√	√	√	×	×	√	√	87
Druais et al. (21)	√	√	√	√	√	√	√	×	√	√	√	√	√	√	√	√	93
Lin et al. (22)	√	√	√	√	√	√	√	√	×	√	√	√	×	√	√	√	85
Rajagopalan et al. (23)	√	√	×	√	√	√	√	√	√	√	√	√	√	×	√	√	86
Einarson et al. (24)	√	√	√	√	√	√	×	×	×	√	√	√	×	√	√	√	73
Einarson et al. (25)	√	√	√	√	√	√	×	×	√	√	√	√	×	√	√	√	81
Barnes et al. (26)	√	√	√	√	√	√	√	×	√	√	√	√	×	√	√	√	86
Einarson et al. (27)	√	√	√	√	√	√	√	×	√	√	√	√	×	√	√	√	86
Einarson et al. (28)	√	√	√	√	√	√	√	×	×	√	√	√	×	√	√	√	78
Wiwat et al. (29)	√	√	√	√	√	√	√	√	×	√	√	√	√	×	√	√	86
Nuhoho et al. (30)	√	√	×	√	√	√	√	×	×	√	√	√	√	√	√	√	77
Aigbogun et al. (31)	√	√	√	√	√	√	√	×	√	√	√	√	×	√	√	√	86
Németh et al. (32)	√	×	√	√	√	√	×	×	√	×	√	×	√	√	√	√	70
Zhao et al. (33)	√	√	×	√	√	√	√	×	√	√	×	√	√	√	√	√	78
Abdall-Razak et al. (34)	√	√	×	√	×	√	×	×	√	√	√	√	×	√	√	√	64
Dutina et al. (35)	√	√	×	√	√	√	×	√	×	√	√	√	×	×	√	√	60
Arteaga et al. (36)	√	×	√	√	√	√	√	√	√	√	√	√	√	√	√	√	96
Yi et al. (37)	√	√	√	√	√	√	√	√	√	√	√	√	×	×	√	√	87
Lin et al. (38)	√	×	√	√	√	√	×	×	√	√	√	√	√	×	√	√	78
Jin et al. (39)	√	×	×	√	√	√	√	√	√	√	√	√	√	×	√	√	82
Qualified studies	25/25	20/25	17/25	25/25	24/25	25/25	18/25	12/25	19/25	23/25	22/25	24/25	12/25	17/25	25/25	23/25	

DISCUSSION

Purpose of Systematic Review of Economic Evaluations

With the increasing number of publications on health economic studies in recent years, systematic reviews in this filed have caught the attention of decision makers as useful tools to generate evidence (68). However, concerns have been voiced regarding whether cost-effectiveness findings can be transferred from one setting to another (12). Anderson et al. discussed the generalizability of the results of health economic studies and concluded that differences in methods, context, intervention costs, and effects contributed to the limitations on evidence synthesis (12). Gomersall et al. also discussed the debate over futility vs. utility of systematic reviews of economic evidence, emphasizing the inability to compare resources between countries and the differences in context and population (69). Pigone et al. also pointed out the challenges in the presentation of economic systematic reviews due to the large amounts of both synthesized data and generated results (70).

Despite challenges in generating results of economic evaluations via systematic reviews, it was suggested that systematic reviews should focus on methods of model development, sources of both efficacy and utility data, and resources used for specific diseases. It might be valuable for researchers and decision makers to identify the differences among studies (69, 70). For model-based economic evaluations, in particular, model structure selection was recommended based on the summarized existing studies, which could provide relatively comprehensive consideration for the necessary model states and link clinical practice and hypothetical model transitions. Notably, compared with differences in national contexts, it was found that variability in published economic evaluations was related more to the variety of study (71), confirming the importance of summarizing the model methods applied to existing studies. Thus, this systematic review focuses on the methods and study quality of the 25 eligible studies.

Main Findings

Among the included studies, most compared the cost-effectiveness of SGAs or long-acting injections. Fifteen studies considered the treatment sequences in model development, which could enlighten the future model development.

Despite the burden and productivity loss due to schizophrenia, few studies chose the societal perspective covering

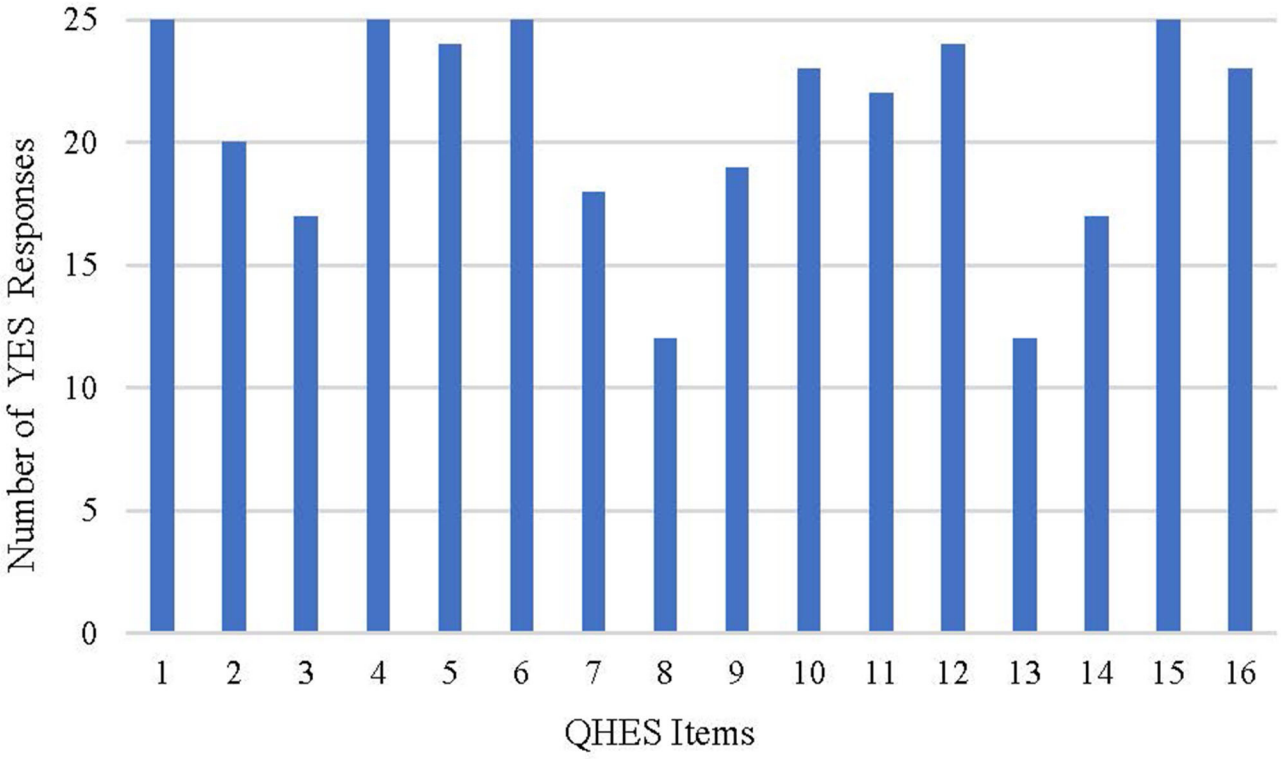


FIGURE 2 | Results of the assessment with the QHES list.

the indirect costs. Due to the early onset of schizophrenia, the average age of these patients is younger than that of patient with other chronic diseases. It would be necessary to include indirect costs in the evaluation. A retrospective study in the US concluded that indirect and non-health care costs were strong contributors and could be more than 70% of the total burden (72). A systematic review of the indirect costs of schizophrenia in Europe found that the average proportion of indirect costs of total disease expenditure was 44% (73). In China, the per case per annum indirect costs of schizophrenia were approximately US$1723.4 in 2013, accounting for 66.6% of the total costs (74). Therefore, a societal perspective covering both direct and indirect costs is preferable.

Description of the treatment sequences from most of the included studies could improve the model design and reflect the clinical prescription especially for chronic diseases or patients with high rate of therapy change. However, there remains challenges considering treatment sequences in economic evaluation. Medication treatment may vary among individuals due to the genotypes, metabolism, comorbidities, adverse events and so on (75). Also, the followed medication therapy should be impact by the previous medication choices. Thus, it may be questioned to apply a uniform sequency for patients especially in the cohort model. Cost and effectiveness data for the multiple drugs and the analytical methods are other challenges for treatment sequences. Even though choice of single drug based on market share or expert opinions and weighted or unweighted averaged data from multiple drugs are common methods in studies, the appropriateness requires further discussion.

According to the summary of the models applied, the Markov model was the most frequently used and treatment sequences, relapse, remission, and adverse events were the important health state elements in model development. The time horizons varied from 5 years to lifetime for the Markov models. While for the decision tree models, a 1 year time horizon was preferred. Due to the uncertainty in the time frame of treatment, it is recommended the impact of the time horizon be explored in a sensitivity analysis. Adverse events such as EPS, weight gain, and diabetes should be considered in the models for schizophrenia since these factors have a recognized influence on the treatment effect. Also, consideration of different types of AEs should be properly defined to estimate the impact on health outcomes and costs in the economic evaluation.

Based on the criteria studies, compliance and persistence were not clearly classified, thus definition is recommended for economic evaluations since it might determine the choice of appropriate data source. When integrating compliance or persistence, data are required on both health outcomes and costs for patients who are non-compliant or discontinued treatment (76). Evidence for compliance or persistence could be collected from retrospective studies, clinical trials, observational studies, or reviews.

Utility values, derived from the literature may contribute to the heterogeneity among results when they are applied to

TABLE 9 | Quality assessment report of economic evaluations with the CHEERS checklist.

Study	CHEERS items																								Fulfilled items
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	
Einarson et al. (15)	×	√	√	×	√	×	√	×	√	√	√	×	√	√	√	×	√	√	√	√	√	√	√	√	18/24
Lachaine et al. (16)	√	√	√	√	√	√	√	√	√	√	×	×	√	√	√	×	√	√	√	√	√	√	√	√	21/24
Park et al. (17)	√	√	√	×	√	√	√	√	√	√	√	×	√	√	×	√	√	√	√	√	√	√	√	√	21/24
Dilla et al. (18)	√	√	√	√	√	√	√	√	√	√	√	×	√	√	√	×	√	√	√	√	√	√	×	√	21/24
Anh et al. (19)	×	×	√	√	√	√	√	√	√	√	√	√	√	√	√	×	√	√	√	×	√	√	×	×	18/24
Lubinga et al. (20)	×	√	√	√	√	√	√	√	√	√	√	×	√	√	×	√	√	√	√	√	√	√	√	√	21/24
Druais et al. (21)	√	√	√	√	√	√	√	×	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	23/24
Lin et al. (22)	√	×	√	√	√	√	√	√	×	√	√	×	×	√	√	×	√	√	√	√	√	√	√	√	19/24
Rajagopalan et al. (23)	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	×	√	√	√	√	√	√	23/24
Einarson et al. (24)	√	√	√	√	√	√	√	×	√	√	√	×	×	√	√	×	√	×	√	×	×	√	√	×	16/24
Einarson et al. (25)	√	√	√	√	√	√	√	×	√	√	√	×	√	√	√	×	√	×	√	√	×	√	√	√	19/24
Barnes et al. (26)	√	√	√	×	√	√	√	×	√	√	√	√	×	√	×	×	×	×	√	×	×	√	√	√	15/24
Einarson et al. (27)	√	√	√	√	√	√	√	×	×	√	√	√	√	√	√	×	√	√	√	√	√	√	√	√	21/24
Einarson et al. (28)	√	√	√	×	√	√	√	×	√	√	√	√	×	√	×	×	√	×	√	√	√	√	√	√	18/24
Wiwat et al. (29)	√	√	√	√	√	×	√	√	√	√	×	×	√	×	√	√	√	√	√	√	√	√	√	×	19/24
Nuhoho et al. (30)	√	√	√	×	√	√	√	×	√	√	×	×	√	×	√	×	√	×	√	√	√	√	√	√	17/24
Aigbogun et al. (31)	√	√	√	√	√	√	√	×	√	√	√	√	√	√	×	√	√	√	√	√	√	√	√	√	22/24
Németh et al. (32)	√	√	×	√	×	√	√	×	√	√	×	√	√	√	×	√	√	√	√	√	√	√	√	√	19/24
Zhao et al. (33)	√	√	√	×	√	√	√	×	√	√	×	√	√	√	√	√	√	×	√	√	√	√	√	√	20/24
Abdall-Razak et al. (34)	√	√	√	×	√	√	√	×	√	√	×	×	√	√	×	×	×	×	√	×	√	√	√	√	15/24
Dutina et al. (35)	√	√	√	×	√	√	√	√	√	√	×	×	×	√	√	×	×	×	√	√	×	√	√	√	16/24
Arteaga et al. (36)	√	√	×	√	×	√	√	×	√	√	√	×	√	×	√	√	√	√	√	√	√	×	√	√	18/24
Yi et al. (37)	√	√	√	×	×	√	√	√	×	√	×	×	√	×	√	×	√	√	√	√	√	√	√	√	17/24
Lin et al. (38)	√	√	×	√	×	√	√	×	√	√	×	×	√	×	√	√	×	√	√	√	√	×	√	√	17/24
Jin et al. (39)	√	√	√	×	×	√	√	√	√	√	√	×	√	√	√	√	√	√	√	√	√	√	√	√	22/24
Qualified studies	22/25	23/25	23/25	15/25	20/25	23/25	25/25	12/25	22/25	25/25	16/21	9/25	20/25	20/25	18/25	11/25	21/25	16/25	25/25	21/25	20/25	24/25	23/25	22/25	

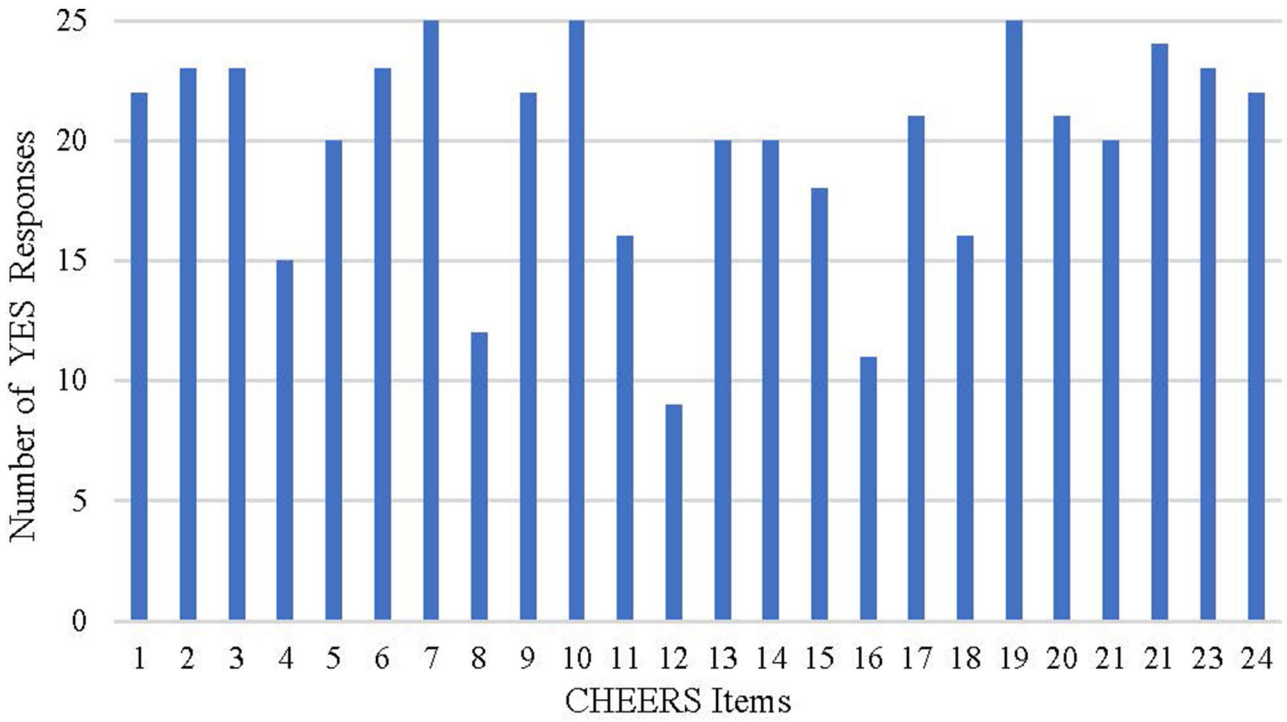


FIGURE 3 | Results of the assessment with CHEERS checklist.

the same health states in different studies. Differences in the classifications of health states, survey responders, elicitation methods, and regions were the main factors influencing the utility values. Thus, it is recommended that researchers choose proper sources based on the factors above, as well as the publication year or update of methods.

Certain limitations to study quality have been identified, such as the description of appropriate time horizon selection, discount rate, statement, and justification of the choice of model type, assumptions and limitations to the evaluations. For the reporting quality of the studies, time horizon, preference-based outcome measurement, and assumptions were the major missing parts. To improve both the quality of the study and the quality of the report, it is suggested that researchers conduct the evaluation and generate the manuscript under the respective guidance and checklists.

Though there exist studies reviewed the economic evaluation of treatment for schizophrenia (8–10, 77), few fully discussed the treatment sequences, AEs, compliance and persistence of the included studies. Thus, this review provides more comprehensive and detailed information of modeling methodology for economic evaluation.

Limitations

There remain some limitations of this review. First, the review only included studies published after 2014 and does not represent the economic methods used in earlier years. Studies published recently may be more valuable for analysis, considering the relatively high quality, most recent treatment options and updated clinical evidence. Second, this review only included model-based economic evaluations. Even though trial-based economic evaluations for schizophrenia are also important evidence, this study aims to generate summaries and suggestions for model methodology rather than synthesizing economic evidence. In addition, trial-based studies may not provide long-term clinical outcomes and source consumption, especially for chronic diseases.

Suggestions

Based on the results of this review, it is suggested that future research focus on methods to integrate compliance or persistence data for chronic diseases. Due to the diverse utilities cited in the models, characteristics of study groups and measuring approach of preference-based health outcomes from the health-related quality of life research should be explained to provide appropriate options for the studies. Publications of economic evaluations should be designed and reported according to applicable gelines and checklists to improve study quality and provide both scientific and valuable evidence for decision makers. Future research could pay more attention to the economic evaluation of long-acting injection antipsychotics.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**,

further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

LW and HL contributed to the study design, analysis, and writing. FS, XG, and HX contributed to the review work. JL contributed to the manuscript revise. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.689123/full#supplementary-material

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The Anti-Colon Cancer Effects of Essential Oil of *Curcuma phaeocaulis* Through Tumour Vessel Normalisation

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Background: Normalising tumour vessels had become a significant research focus in tumour treatment research in recent years. *Curcumae rhizoma* (CR) is an essential plant in traditional Chinese medicine as it promotes blood circulation and removes blood stasis. Similarly, CR improves local blood circulation.

Purpose: We explored the anti-colon cancer effects of essential oil from CR (OCR) by investigating its role in normalising tumour vessels. We also provided a basis for research and development into new anti-cancer drugs.

Methods: We used colon cancer as a research focus to investigate OCR. We established an *in vitro* co-culture model of colon cancer cells and human umbilical vein endothelial cells (HUVEC). We also established an *in vivo* subcutaneous implant colon cancer model in nude mice. These studies allowed us to evaluate the comprehensive effects of OCR in *in vivo* and *in vitro* colon cancer and its role in normalising tumour blood vessels.

Results: *In vitro*, we found that OCR inhibited Human colon cancer cells (HCT116) and HUVEC cell proliferation and inhibited vascular endothelial growth factor-a (VEGFa) mRNA and protein expression in HUVECs in a co-culture system. Our *in vivo* studies showed that OCR inhibited colon cancer tumour growth, reduced angiogenesis in tumours and increased vascular endothelial (VE)-cadherin and pericyte coverage in tumour vessels.

Conclusions: OCR inhibited colon cancer growth both in *in vivo* and *in vitro* models, reduced angiogenesis in tumours, improved tumour vessel structures and normalised tumour vessels.

Keywords: ***Curcumae rhizoma*, tumour vessel, normalisation, colon cancer, vessel structure**

Abbreviations: CR, *Curcumae Rhizoma*; OCR, essential oil from CR; HUVEC, Human umbilical vein endothelial cells; VEGFa, Vascular endothelial growth factor-a.

BACKGROUND

Angiogenesis is an important physiological process during embryonic development, growth and tissue repair. Imbalanced angiogenesis can lead to various pathological consequences and is a particular hallmark feature of tumours (1). From an anatomical perspective, tumour blood vessels are generally disorderly; their generation and distribution are not controlled by normal physiology, leading to spatial abnormalities in blood flow. At the cellular level, the vascular endothelium and pericytes in tumours are missing and cause serious leakage of vascular contents (2–4). This alteration exacerbates local hypoxia and acidosis in tumour environments, eventually converting tumour cells to malignant phenotypes and affecting the killing capacity of immune cells and therapeutics toward tumours (5).

For these reasons, studies have focused on tumour vessel biology. In 1971, researchers pioneered starving tumours to death (6), where tumour formation was inhibited by inhibiting tumour angiogenesis. However, over-pruning tumour vessels had the same effect as blood vessels' overgrowth. Tumour vessels cannot achieve their normal vascular functions (7). After this, scientists turned their attention to normalising tumour vessels. By regulating the balance of pro- and anti-angiogenic factors, tumour vessel functions and structures could be normalised (8). Recent studies showed that particular drugs could reduce tumour metastases, enhance chemotherapeutic drug delivery and increase the anti-cancer effects of chemotherapeutic drugs after effective vascular normalisation (9–12).

In recent years, bioactive compounds from traditional Chinese medicine and associated derivatives have gained scientific acceptance as potentially promising complementary and alternative medicines to treat various diseases (13–16).

Curcumae rhizoma (CR) is the dried rhizome of Curcuma phaeocaulis Valeton, Curcuma kwangsiensis S. G. Lee et C. F. Liang or Curcuma wenyujin Y. H. Chen et C. Ling plant (13). Traditional Chinese medicine proposes that local tumours suffer from stagnation of 'qi', blood and poor metabolism (17). Therefore, for tumour treatment, drugs that promote blood circulation and remove blood stasis are combined to improve local blood circulation. CR is an important traditional Chinese plant that promotes blood circulation and removes blood stasis.

The essential oil from CR (OCR) is the main medicinal active ingredient. The main components are ketones, olefins and aromatic hydrocarbons. Of these, furanodiene, furanodienone, curcumol, β-elemene, curedione and gemmazone are more abundant (17, 18). Studies have shown that CR reduces blood viscosity and improves blood flow rates (19). In addition, evidence suggests that β-elemene increases (VE)-cadherin expression in tumour tissues (20). For these reasons, it is hypothesised that OCR normalises blood vessels in colon cancer tumours.

In this study, we examined OCR's effects on cell viability, proliferation and vascular endothelial growth factor-a (VEGFa) expression in cultured cell lines human colon cancer cells (HCT116) and human umbilical vein endothelial cells (HUVEC)) *in vitro*. In addition, we simulated HUVEC growth in a tumour environment *in vitro* to study the effects of OCR on the expression of key angiogenic factors. Then, the inhibitory effects of OCR on colon cancer and its effects on tumour vessels were studied *in vivo*. We aimed to explore the promotion of blood circulation to remove blood stasis and provide a basis for developing potential new tumour drugs for colon cancer.

METHODS

Materials

Cells: HUVECs and HCT116 cells were obtained from the National Engineering Research Centre for Biomaterials of Sichuan University.

Animals: Four-week-old male BALB/C-NU mice were purchased from Sibefu Biotechnology Co., Ltd. (Experimental Animal Licence: SCXK (Beijing) 2019-0010). Nude mice were adaptively fed for one week. Studies were conducted per protocols approved by the Animal Ethics Committee of Chengdu University of Traditional Chinese Medicine (Animal Ethics Approval Number: 2017-08).

Drugs: OCR was diluted in normal saline (Chroma, Chengdu, China). The daily dose was 0.1 mg/g. Oxaliplatin (Solarbio, Beijing, China) was diluted in a 5% glucose solution.

Cell Culture

HCT116 cells and HUVECs were cultured in RPMI-1640 (Gibco, USA) complete medium containing 10% foetal bovine serum (Gibco) at 37°C in a 5% CO_2 environment. The indirect co-cultivation system method is adopted to simulate the tumor environment. HCT116 and HUVEC were seeded on the upper or lower layers of the transwell chamber, and the two kinds of cells were placed in the same culture environment. After 24 h of different drug intervention, characterisation studies were performed.

Animal Studies

In vivo studies: Animals were adaptively fed for one week, after which a colon cancer subcutaneous transplantation model was prepared. HCT116 cells were prepared at 1.5×10^6 cells/100 µl normal saline. A 1 ml injection needle was used to subcutaneously inject 100 µl cell suspension into the armpit of mice. Tumour size was measured using a Vernier calliper every three days and tumour volumes calculated according to the formula; $V = 1/2 \times \text{length} \times \text{width}^2$.

When the average tumour volume was > 100 mm^3, we randomly divided the mice into four groups; OCR, OCR + oxaliplatin, oxaliplatin only and model groups. Mice in OCR and OCR + oxaliplatin groups received daily OCR intragastric doses (**Figure 1**). Mice in OCR + oxaliplatin and oxaliplatin groups received intraperitoneal injections with oxaliplatin every 3 days. The model group received no treatment. After study completion, the mice were anesthetised with 2% sodium pentobarbital (0.25 ml/100 g) and sacrificed by cervical dislocation, and subcutaneous tumours removed for immunofluorescence.

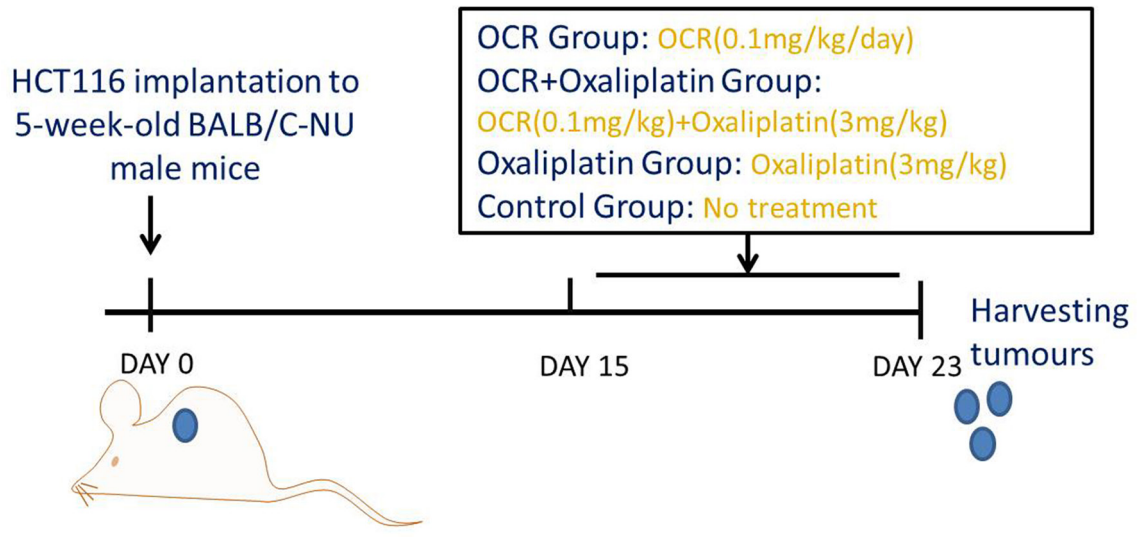


FIGURE 1 | Animal study design.

CCK-8 Assay

Cells were seeded in 96-well plates at appropriate densities. After drug intervention, a complete medium containing 10% CCK-8 (Meilunbio, Dalian, China) was added to well for 1 h in the dark. Optical density values at 450 nm were measured using a microplate reader. Cell viability was then calculated.

The 5-Ethynyl-2′-Deoxyuridine Assay

Cells were seeded in 6-well plates at appropriate densities. After a 24 h drug treatment, an EdU kit (Meilunbio) was used for staining. Cells were observed under a microscope (green fluorescence\ blue fluorescence).

Quantitative Polymerase Chain Reaction

After extracting RNA, reverse transcription was performed using the HiScript III RT SuperMix kit (Vazyme, Nanjing, China). Then enzyme (Vazyme) was added and PCR instrumentation used (QuantStudio 3, Thermo) for amplification.

Western Blotting

After lysing cells, lysates were centrifuged and supernatants assayed for protein determination using the bicinchoninic acid (BCA) protein quantification kit (Thermo Fisher Scientific). VEGFa expression (Abcam) was detected, and β-actin (Proteintech, Wuhan, China) used as a loading control.

Immunofluorescence

Fresh tumour tissue was embedded in paraffin and sectioned. Sections were subjected to antigen retrieval and incubated with CD31 (Servicebio, Wuhan, China), anti- platelet-derived growth factor receptor-β (PDGFR-β) (Abcam) and CD144 antibodies (Thermo) which was used to label vascular endothelial (VE)-cadherin depending on the investigation. Images were viewed under a microscope and acquired and processed using.

Statistical Analysis

Data were processed using a one-way analysis of variance. A P value < 0.05 was considered statistically significant. Data were displayed as the mean ± standard deviation (SD).

RESULTS

The Effects of OCR on HCT116 Cells

Different OCR concentrations were incubated with HCT116 cells for a 24 h period and cell viability assessed using the CCK-8 method. HCT116 viability decreased with increasing OCR concentrations. HCT116 cells were less tolerant to OCR at IC_{50} = 678.5 μg/ml (**Figures 2A, B**). Based on the OCR intervention curve, two safe doses were selected for drug intervention follow-up studies; a low concentration dose of 20 μg/ml and a medium concentration dose of 50 μg/ml.

To observe the effects of OCR on HCT116 proliferation, we pre-treated the cells with low (20 μg/ml: HCT116 20 group) and medium OCR concentrations (50 μg/ml: HCT116 50 group) for 24 h, and the EdU assay performed to assess proliferation. EdU staining showed that the ratio of EdU-labelled cells at 24 h for both experimental groups was significantly lower than the HT116 control group ($P < 0.001$). In addition, the ratio of EdU-labelled cells in the HCT116 50 group at 24 h was significantly lower than the HCT116 20 group ($P < 0.05$) (**Figures 2C, D**). These data suggested that the inhibitory effects of OCR in HCT116 cells were concentration-dependent.

To observe the effects of OCR on VEGFa mRNA expression in HCT116 cells, we pre-treated the cells with low and medium OCR concentrations for 24 h, after which VEGFa mRNA expression was quantified. We observed no significant differences in expression between groups, including the control group (**Figure 2E**).

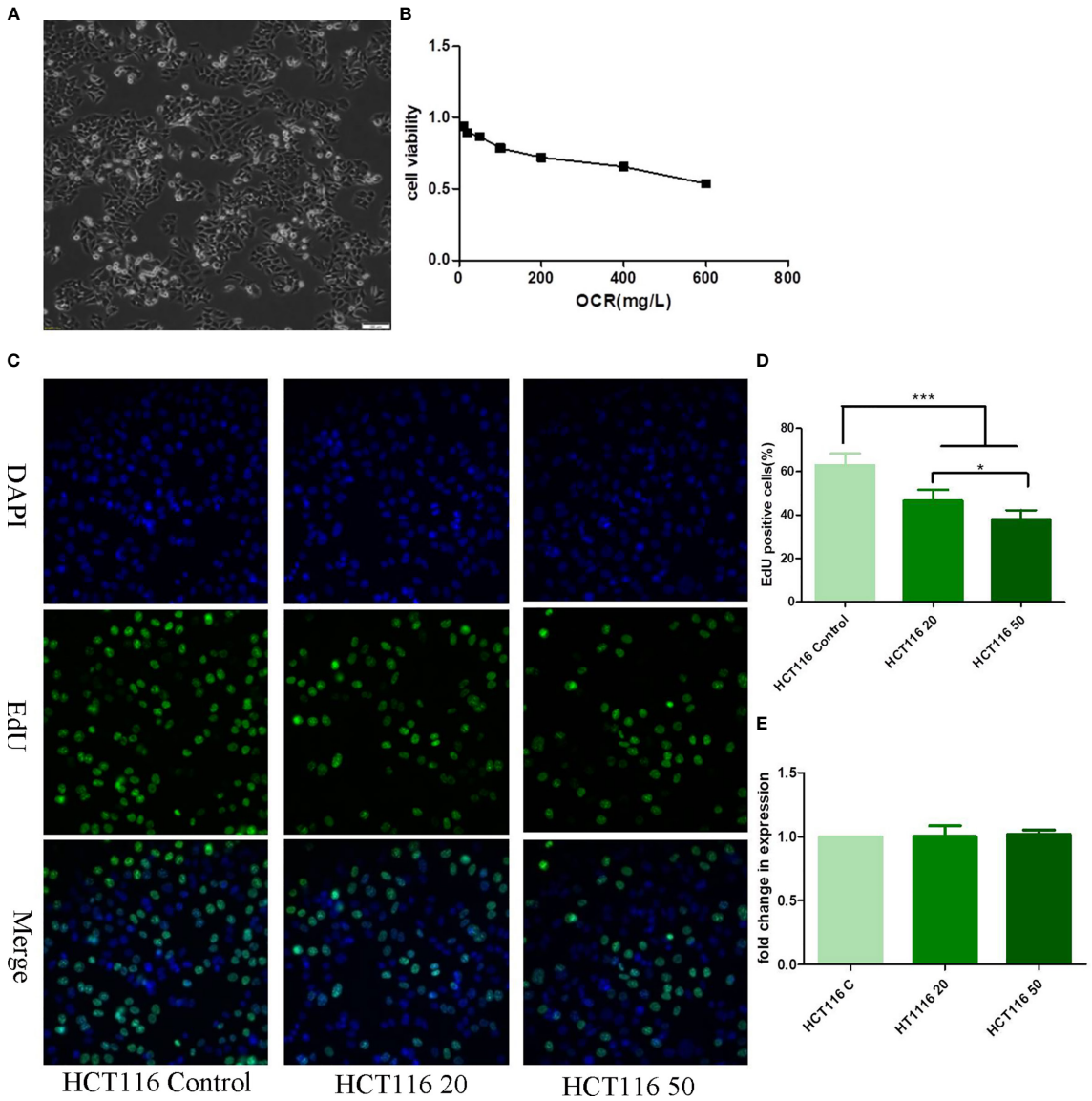


FIGURE 2 | The effects of essential oil from *Curcumae rhizoma* (CR) (OCR) on HCT116 cells. **(A)** HCT116 cell morphology. **(B)** The effects of different OCR concentrations on HCT116 viability. **(C, D)** The effects of OCR on HCT116 proliferation. **(E)** The effects of OCR on VEGFa mRNA expression in HCT116 cells. (n = 3, mean ± standard deviation (SD), ***P < 0.001, *P < 0.05 compared with the control group).

The Effects of OCR in HUVECs

Different OCR concentrations were incubated with HUVECs for a 24 h period and cell viability assessed using the CCK-8 method. HUVEC viability decreased with increasing OCR concentration. When compared with HCT116 cells, HUVECs were more resistant to OCR, with an IC_{50} = 950μg/ml (**Figures 3A, B**). Based on the OCR intervention curve, two relatively safe doses were selected for drug intervention follow-up studies with HUVECs; a low concentration dose of 50 μg/ml and a medium concentration of 150 μg/ml.

To observe the effects of OCR on HUVEC proliferation, we pre-treated the cells with low (50 μg/ml: OCR 50 group) and medium OCR concentrations (150 μg/ml: OCR 150 group) for 24 h. EdU staining showed that the ratio of EdU-labelled cells at 24 h in the OCR 50 group was not significantly different to the control group. However, the ratio of EdU cells in the OCR 150 group was significantly lower than both control (P < 0.001) and OCR50 groups (P < 0.001) (**Figures 3C, D**).

To determine the effects of OCR on VEGFa RNA expression in HUVECs, we pre-treated the cells with low and medium OCR concentrations for 24 h, after which expression was quantified. VEGFa mRNA expression in both experimental groups were significantly lower than the control group (P < 0.05) (**Figure 3E**).

To observe the effects of OCR on VEGFa protein expression, HUVECs were pre-treated with low and medium OCR

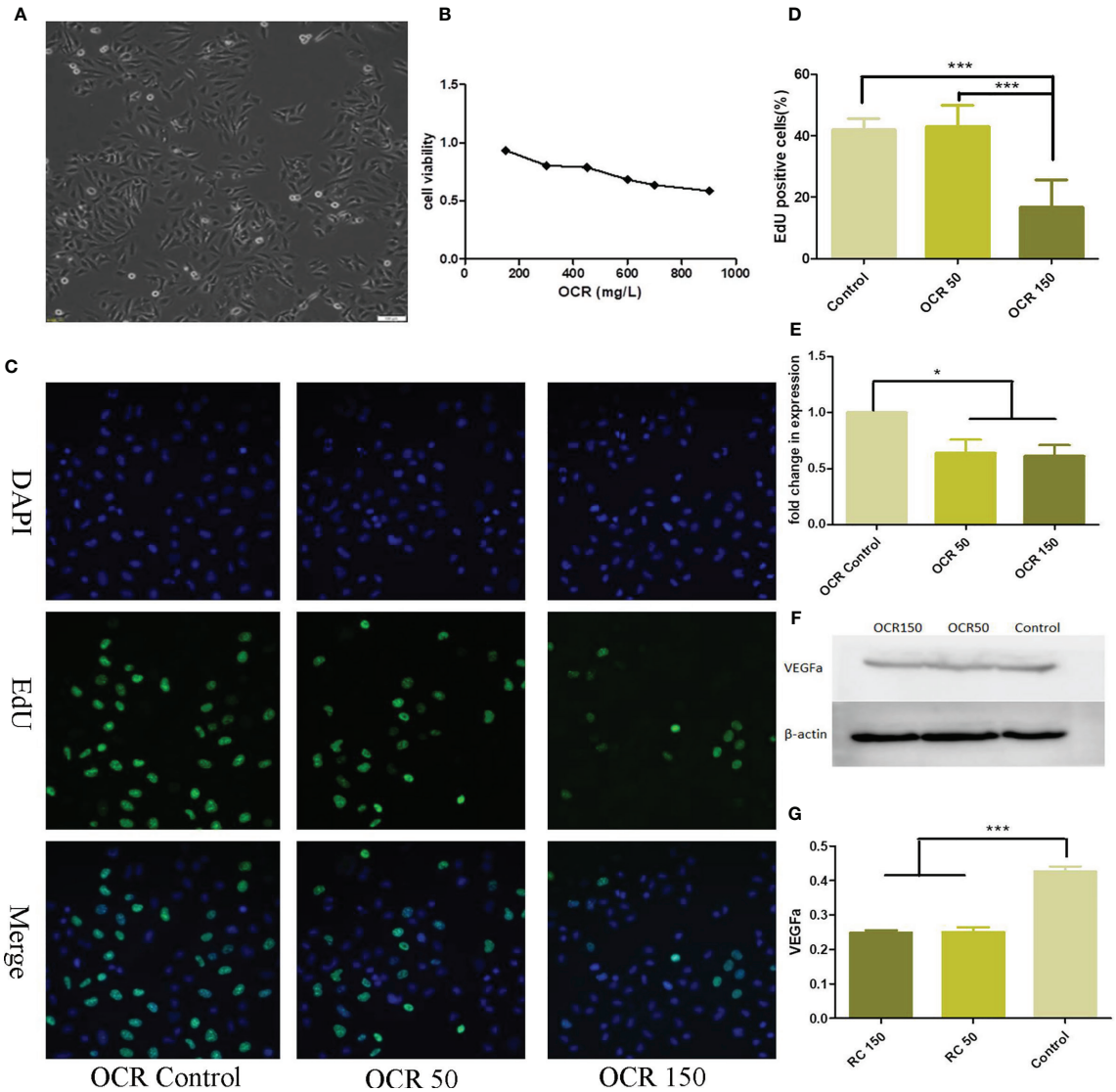


FIGURE 3 | The effects of essential oil from *Curcumae rhizoma* (CR) (OCR) on HUVECs. **(A)** HUVEC morphology. **(B)** The effects of different OCR concentrations on HUVEC viability. **(C, D)** The effects of OCR on HUVEC proliferation. **(E)** The effects of OCR on VEGFa mRNA expression in HUVECs. **(F, G)** The effects of OCR on VEGFa protein expression in HUVECs. (n = 3, mean ± standard deviation (SD), ***P < 0.001, *P < 0.05 compared with the control group).

concentrations for 24 h, after which western blotting was performed. VEGFa protein expression in both experimental groups was significantly lower than the control group (P < 0.05) (**Figures 3F, G**).

The Effects of OCR on HUVECs Co-Cultured With HCT116 Cells

To observe the effects of OCR on HUVEC morphology in a co-culture system, we incubated different OCR concentrations (20 μg/ml, 50 μg/ml and 150 μg/ml) with HUVECs in a co-culture system for 24 h, after which cell morphology was investigated. HUVECs in the co-cultured control group exhibited an irregular cell morphology, longer cell antennae and poor general cell status. In contrast, HUVEC morphology in the co-culture system plus OCR supplementation was relatively regular and cells were in good general condition (**Figure 4A**).

To quantify the effects of OCR on VEGFa mRNA expression in HUVECs in the co-culture system, we pre-treated the system with different OCR concentrations for 24 h and tested. VEGFa mRNA expression in HUVECs in the co-culture system increased significantly compared with HUVECs cultured alone (P < 0.001). When compared with the co-culture control group (co-culture with no OCR treatment), the OCR 50 μg/mland 150 μg/ml intervention groups significantly reduced VEGFa mRNA expression in the co-culture system (P < 0.01, P < 0.05). These data suggested that co-culturing with HCT116 cells increased VEGFa mRNA expression in HUVECs, and the intervention of

an OCR dose (50 μg/ml and/or 150 μg/ml) reduced this expression (**Figure 4B**).

To further investigate the effects of OCR on VEGFa protein expression in HUVECs in the co-culture system, the system was pre-treated with different OCR concentrations for 24 h. Western blotting showed that VEGFa protein expression in co-cultured 50 μg/ml and 150 μg/ml OCR groups was significantly lower than the co-cultured control group ($P < 0.001$). In addition, VEGFa protein expression in the 150 μg/ml co-culture group was significantly lower than the 50 μg/ml co-culture group ($P < 0.001$) (**Figures 4C, D**). These effects were concentration-dependent.

The Inhibitory Effects of OCR on Subcutaneously Transplanted Colon Cancer Tumours

We investigated the effects of OCR on the general state and weight of nude mice. After cells were subcutaneously transplanted, mouse weight was recorded every 3 days. The ratio of body weight to initial body weight after transplantation was taken as the weight multiple of the nude mice. Weight multiple results showed that the weight of nude mice in each group increased variably within 15 days of subcutaneous transplantation; the weight of nude mice in each group decreased to different degrees after 15 days. We observed no differences in this trend between groups, which may have been related to tumour growth (**Figure 5A**).

As specified, tumour growth was recorded every 3 days after transplantation. Tumour volume change data for each group suggested no significant differences between groups within 15 days of transplantation. After OCR administration, tumour growth appeared to differentiate between groups (**Figures 5B, C**). We observed that tumour volume in OCR and combination groups increased slowly.

The Effects of OCR Blood Vessel Normalisation in Tumours

When compared with the model group, the number of microangiogenesis vessels which was labelled by CD31 in the other groups was significantly reduced ($P < 0.001$). Also, the number of microangiogenesis vessels in tumours in the OCR + oxaliplatin group were significantly lower than OCR and oxaliplatin groups ($P < 0.05$) (**Figures 5D, E**). These results suggested that both OCR and oxaliplatin inhibited microangiogenesis vessel formation in tumours, whereas combined use exerted better inhibitory effects in tumour vessels.

Compared with the model group, PDGFR positive rates in tumour vessels in the other groups significantly increased ($P < 0.001$). In addition, PDGFR positive rates in the OCR + oxaliplatin group were significantly higher than individual oxaliplatin groups ($P < 0.05$) (**Figures 6A, B**). These results suggested that both OCR and oxaliplatin increased PDGFR coverage in tumour perivascular cells.

Compared with the model group, the positive rates for vascular endothelial VE-cadherin in tumour vessels of the other groups were significantly increased (**Figures 6C, D**). Also, the positive rate for VE-cadherin in the OCR +

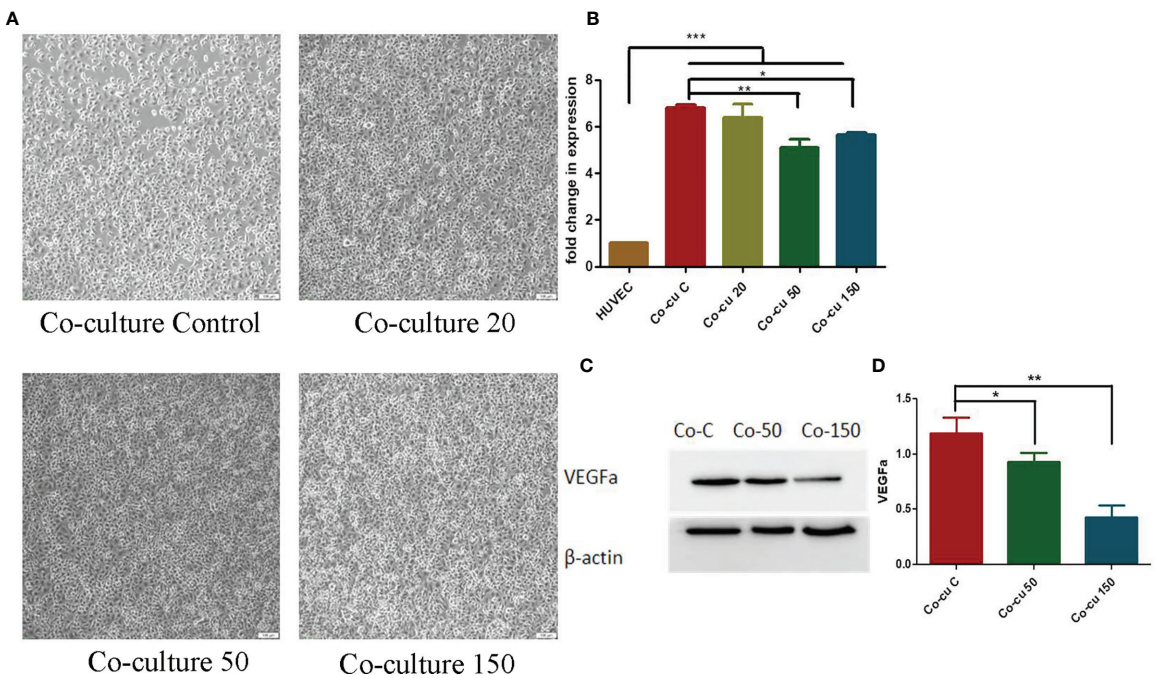


FIGURE 4 | The effects of essential oil from *Curcumae rhizoma* (CR) (OCR) on HUVECs co-cultured with HCT116 cells. **(A)** Changes in HUVEC morphology in the co-culture system at different OCR concentrations. **(B)** The effects of OCR on VEGFa mRNA expression in HUVECs. **(C, D)** The effects of OCR on VEGFa protein expression in HUVECs. (n = 3, mean ± standard deviation (SD), ***P < 0.001, **P < 0.01, *P < 0.05 compared with the control group).

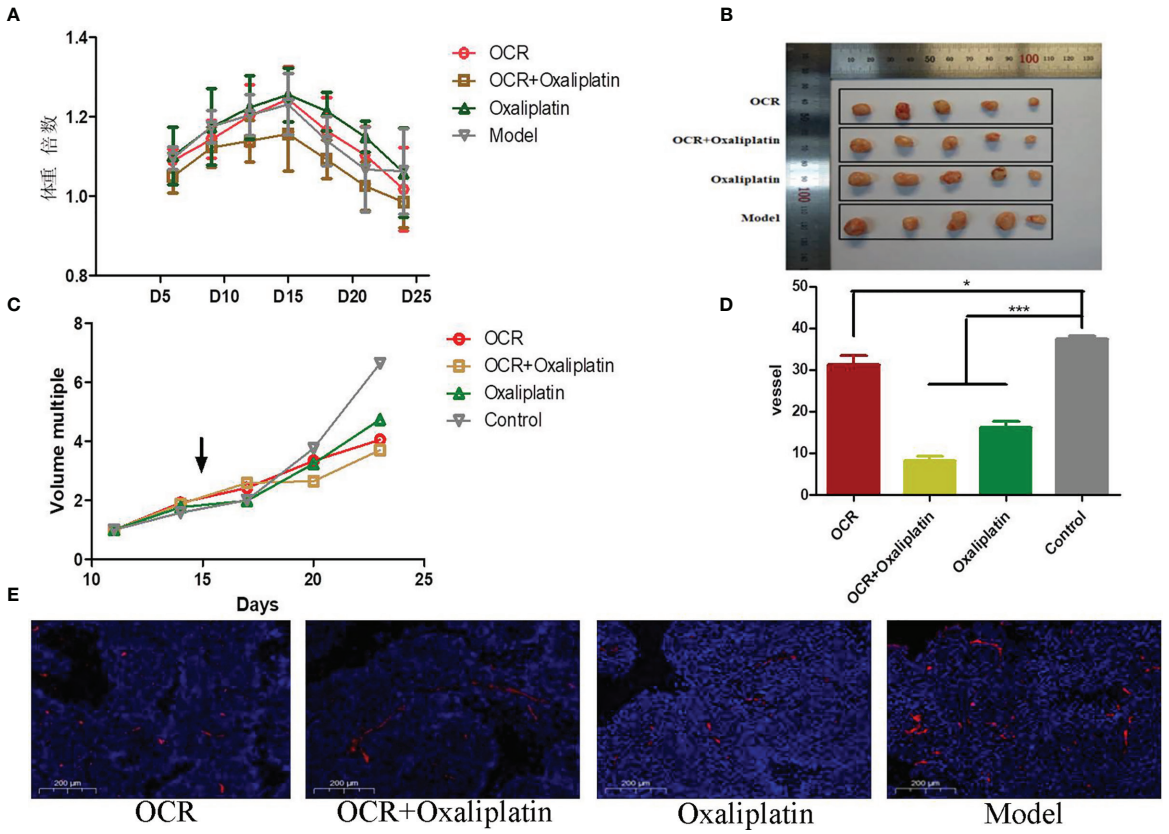


FIGURE 5 | The inhibitory effects of essential oil from *Curcumae rhizoma* (CR) (OCR) on subcutaneously transplanted colon cancer tumours. **(A)** Changes in mice body weight in different groups. **(B, C)** Tumour size in different groups. **(D, E)** CD31 marker expression in tumours in different groups. (n = 5, mean ± standard deviation (SD), ***P < 0.001, *P < 0.05 compared with the control group).

oxaliplatin group was significantly higher than the individual OCR and oxaliplatin groups. These results suggested that when combined, OCR and oxaliplatin increased VE-cadherin coverage in tumour vessels.

DISCUSSION

Previous studies have shown that OCR exerts anti-cancer, anti-inflammatory, liver protection, immune regulation and chemoprevention effects (17). However, no systematic research has yet shown the effects of OCR on tumour vessel normalisation. Therefore, we explored whether OCR inhibited tumour growth by regulating tumour vessels.

OCR elicited inhibitory effects on HUVEC and HCT116 proliferation, with the effects in HCT116 cells concentration-dependent. Also, when compared with HCT116 cells, HUVECs were more resistant to OCR. This tolerance difference between normal and disease model cells suggested OCR exerted a unique intervention effect on diseases. Equally, drug dosage is a great concern for clinicians; we identified that OCR dosage differences in inhibiting normal cell activity and disease model cell activity was a distinct OCR advantage. Thus, when selecting reasonable therapeutic dosages, clinicians can theoretically protect normal cells while inhibiting diseased cells.

VEGFa is an important angiogenic factor. Its vascular permeability allows macromolecular proteins such as fibrinogen to leak from blood vessels, thereby forming capillary blood networks (5). Also, VEGFa selectively acts on vascular endothelial cells to promote proliferation and migration, to ultimately form new blood vessels (21). In the tumour environment, massive tumour metabolic consumption, severe local tumour hypoxia and large metabolite accumulation feeds back to stimulate tumour cell secretion of a variety of angiogenesis-related factors, thereby rapidly forming new blood vessels. VEGFa is one such fast-response angiogenic factor (22). Studies have confirmed VEGFa is highly expressed in various tumours in the liver, breast, colon and melanoma cancer (23–27). We observed that OCR inhibited VEGF RNA and protein expression in HUVECs. When co-cultured with colon cancer cells, HUVECs displayed abnormal morphology. Also, VEGFa expression in HUVECs in the disease co-culture model was significantly higher than in HUVECs cultured alone.

These data verified the traditional tumour vessel theory to a certain extent. During HUVEC co-cultivation with HCT116 cells, these cells secreted molecules that acted on HUVECs, thereby

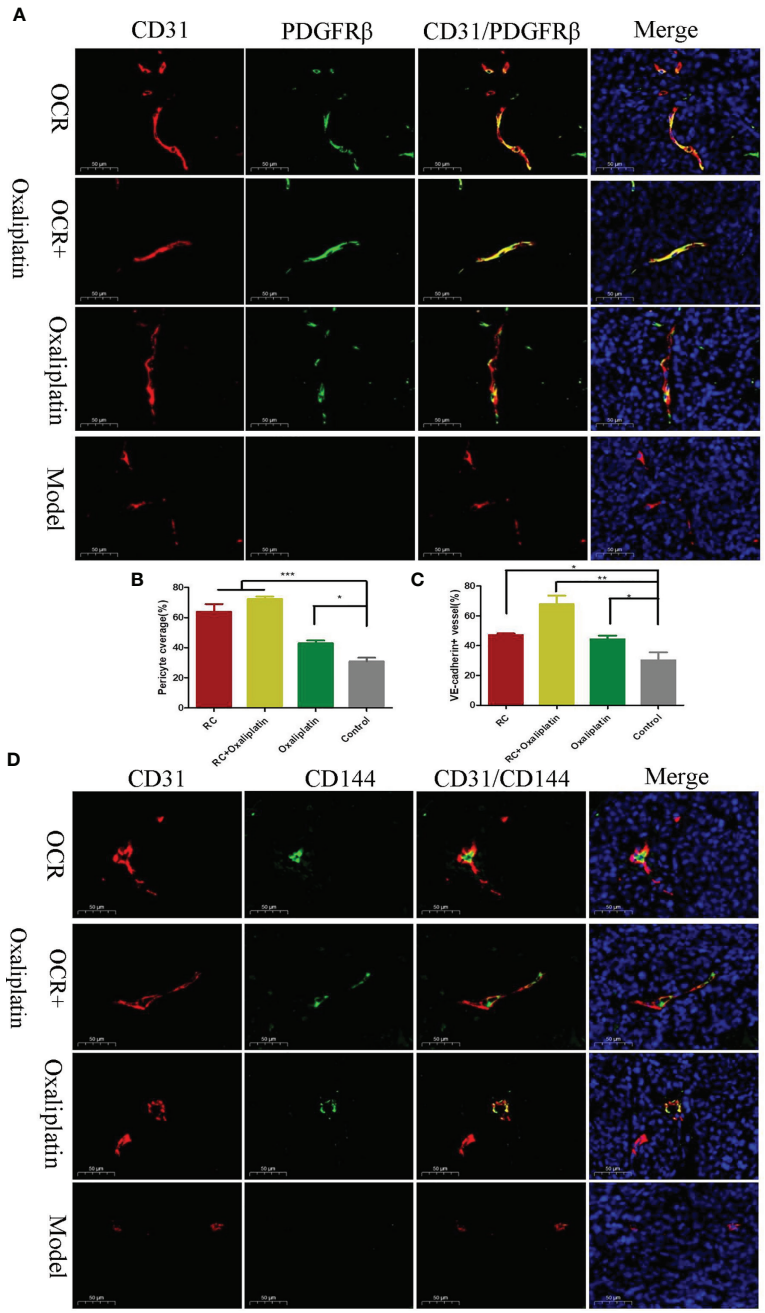


FIGURE 6 | The effects of essential oil from *Curcumae rhizoma* (CR) (OCR) on tumour blood vessel normalisation. **(A, B)** Tumour pericyte coverage in different groups. **(C, D)** VE-cadherin tumour coverage in different groups. (n = 5, mean ± standard deviation (SD), ***P < 0.001, **P < 0.01, *P < 0.05 compared with the control group).

facilitating a significant increase in VEGFa mRNA expression. This observation indicated that the co-culture system accurately reflected changes in endothelial cells during tumour pathology. Our data also suggested that an OCR intervention (50 μg/ml and 150 μg/ml) reversed this rapid increase in VEGFa RNA expression in HUVECs. Western blotting evidence also suggested that OCR (50 μg/ml and 150 μg/ml) treatments significantly reduced VEGFa protein expression in HUVECs cultured alone and co-cultured HUVECs. Importantly, these inhibitory effects were concentration-dependent. Therefore, these *in vitro* investigations suggested that OCR may inhibit endothelial cells' overgrowth during cancer pathological conditions.

Many factors in the body promote angiogenesis, with compensatory mechanisms operating under certain conditions

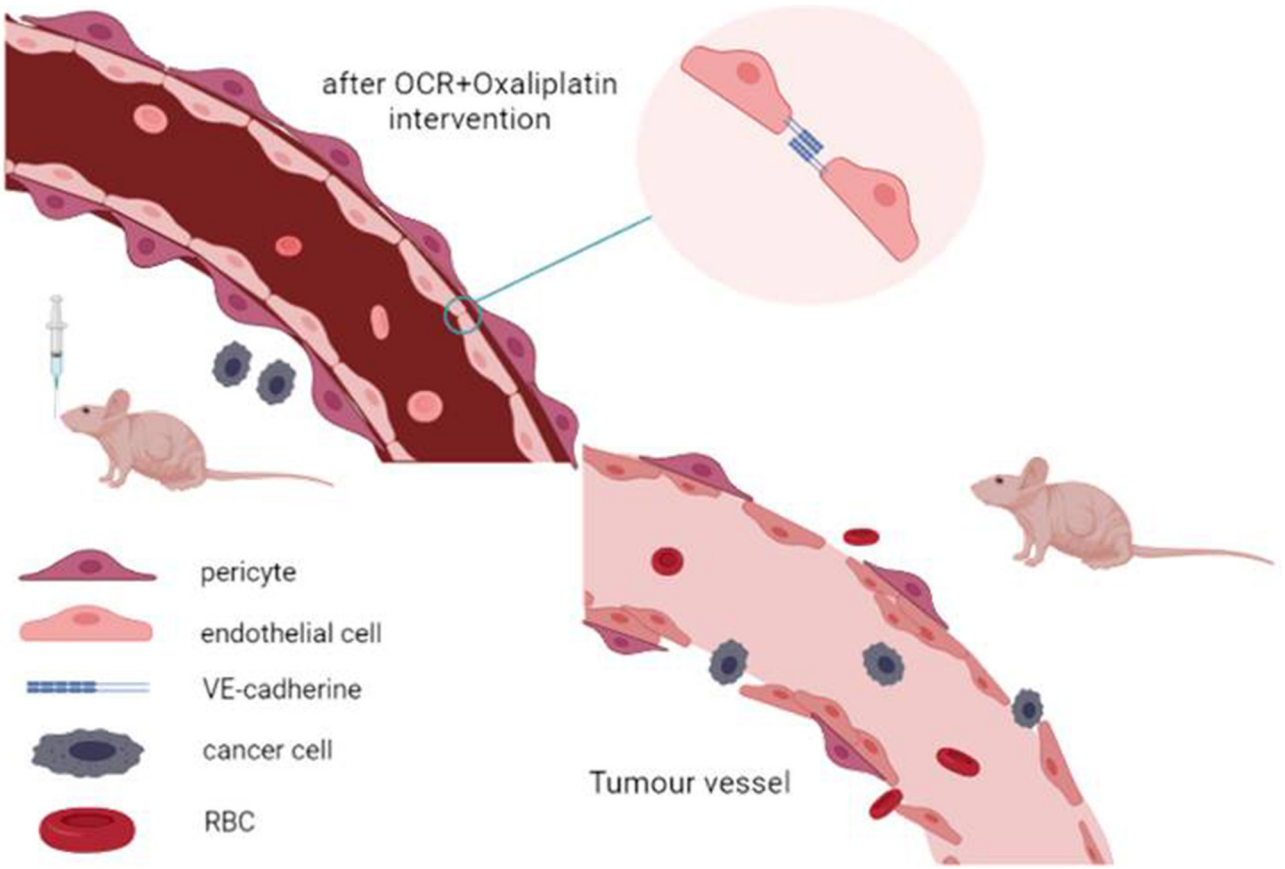


FIGURE 7 | Conclusion diagram.

(28). Currently, no single characteristic factor reflects the maturity of tumour vessels (29). Therefore, to further dissect the effects of OCR on tumour vessels and closely observe these effects on tumour vessel morphology and structure, we conducted comprehensive *in vivo* studies. Our weight results in mice showed that OCR combined with oxaliplatin had no significant effects on these data. Also, tumour volume changes in mice showed that individual OCR and combined with oxaliplatin slowed down tumour growth rates.

According to tumour vessel characteristics, reducing tumour angiogenesis rates and improving vessel structure are effective strategies in normalising tumour vessels. Therefore, we explored the impact of OCR on blood vessels in solid tumours. Platelet endothelial cell adhesion molecule-1 (CD31) is located at tight junctions between vascular endothelial cells and may be used to assess tumour angiogenesis. Studies have shown CD31 is expressed in both mature and immature tumour vessels. When compared with other endothelial cell marker factors, CD31 more accurately reflected the number and density of tumour microvessels (30). Our CD31 data indicated that the number of microangiogenesis vessels in the model group was higher than other groups. This was consistent with the literature where blood vessels are rapidly and disorderly formed in tumours. In our work, OCR reduced the numbers of microangiogenesis vessels in tumours, whereas the combination with oxaliplatin increased them. In addition, this combination altered disordered tumour microvessels to continuous and orderly vessels.

Pericytes are important components of arterioles, veins, capillaries (31), providing support for endothelial cells (32). Within the vascular structure, endothelial cells surround to form a lumen. Pericytes adhere to endothelial cells and the basement membrane which surrounds them (33). Thus, pericytes cover endothelial cells and help quiescent endothelial cells maintain a non-proliferative state. However, during tumour growth, pericytes lose their monitoring capabilities which cause endothelial cells to become activated in the presence of stimulating angiogenic factors (34). Studies have shown that it is vital to restore pericyte coverage in the vasculature in a tumour state (35). From our study, OCR appeared to restore perivascular cell coverage in the tumour, and similarly, OCR and oxaliplatin combined increased this effect.

VE-cadherin is an endothelial cell membrane protein. Physiologically, it regulates contact inhibition between vascular endothelial cells (36). VE-cadherin also generates a dynamic balance between endothelial cell growth and pericyte coverage in blood vessels and helps maintain blood vessel homeostasis.

Also, VE-cadherin regulates the growth rate of vascular endothelial cells by regulating angiogenic factors (37, 38). Studies have shown that *VE-cadherin* knockout mice experience difficulties forming initial continuous blood vessels due to adhesion barriers between endothelial cells, causing death within 10 days of embryonic development (39). Similarly, in *VE-cadherin* knockout newborn mice, new endothelial cells cannot connect to form new blood vessels, whereas existing endothelial cells in original blood vessels were released (40). Under normal physiological conditions, VE-cadherin is tightly connected to endothelial cells so that cells are ordered and structurally complete. When VE-cadherin expression is lacking (knocked out), endothelial cells cannot undergo monolayer formation and arrangement. In our study, OCR improved VE-cadherin coverage in tumours, and similarly, when combined with oxaliplatin, these effects were enhanced. Thus, OCR inhibited tumour growth, reduced tumour angiogenesis and improved abnormal vascular structures in mouse tumours.

CONCLUSIONS

OCR inhibited HCT116 and HUVEC activity, proliferation and also VEGFA mRNA and protein expression in HUVECs. It reversed VEGFA mRNA and protein overexpression in HUVEC cells under pathological condition. OCR also inhibited subcutaneously transplanted colon cancer tumour growth rates in mice. Finally, OCR combined with oxaliplatin reduced tumour angiogenesis and increased VE-cadherin and pericyte coverage, thus normalising tumour vascular structure (**Figure 7**).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by Animal Ethics Committee of Chengdu University of Traditional Chinese Medicine (Animal Ethics Approval Number: 2017-08).

AUTHOR CONTRIBUTIONS

YF: Validation, methodology, and writing-original draft. LD: Methodology. HG: Methodology. YZ: Validation. FP: Conceptualization, writing-reviewing. and editing. GW: Writing-reviewing and editing ideas. CY: Conceptualization, writing-reviewing and editing, and project administration. All authors contributed to the article and approved the submitted version.

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Risk Prediction Model for Esophageal Cancer Among General Population: A Systematic Review

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Objective: The risk prediction model is an effective tool for risk stratification and is expected to play an important role in the early detection and prevention of esophageal cancer. This study sought to summarize the available evidence of esophageal cancer risk predictions models and provide references for their development, validation, and application.

Methods: We searched PubMed, EMBASE, and Cochrane Library databases for original articles published in English up to October 22, 2021. Studies that developed or validated a risk prediction model of esophageal cancer and its precancerous lesions were included. Two reviewers independently extracted study characteristics including predictors, model performance and methodology, and assessed risk of bias and applicability with PROBAST (Prediction model Risk Of Bias Assessment Tool).

Results: A total of 20 studies including 30 original models were identified. The median area under the receiver operating characteristic curve of risk prediction models was 0.78, ranging from 0.68 to 0.94. Age, smoking, body mass index, sex, upper gastrointestinal symptoms, and family history were the most commonly included predictors. None of the models were assessed as low risk of bias based on PROBST. The major methodological deficiencies were inappropriate date sources, inconsistent definition of predictors and outcomes, and the insufficient number of participants with the outcome.

Conclusions: This study systematically reviewed available evidence on risk prediction models for esophageal cancer in general populations. The findings indicate a high risk of bias due to several methodological pitfalls in model development and validation, which limit their application in practice.

Keywords: methodology, risk of bias, systematic review, esophageal cancer, risk prediction model

INTRODUCTION

Esophageal cancer is one of the most common cancers worldwide, with an estimated 6,04,100 new cases and 5,44,076 cancer deaths in 2020 (1). In China, esophageal cancer is the sixth most common cancer and the fourth most common cause of cancer deaths (2). The two primary histologic subtypes of esophageal cancer are esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC), and squamous dysplasia (SD) and Barrett's esophagus (BE) are known precursors of esophageal cancer for ESCC and EAC, respectively (3). Several factors have been found to be associated with an increased risk for esophageal cancer, including older age, male, family history, smoking, and alcohol consumption (4).

The prognosis of esophageal cancer is poor since most cancers were diagnosed at a late stage. Endoscopic screening plays a key role in the prevention of esophageal cancer. It can reduce the incidence and mortality through early detection, early diagnosis, and early treatment of cancer and precancerous lesions (5, 6). However, population-wide endoscopic screening is less cost-effective due to low detection rate and low compliance, while opportunistic screening is limited in clinical practice due to the high requirement for equipment, technic, and personnel (7).

The risk prediction model is an effective tool for risk stratification and prediction and has been widely used in screening for lung cancer (8), colorectal cancer (9), and breast cancer (10). It is also expected to be applied to esophageal cancer screening to optimize the screening strategy and provide patients with individualized screening guidance. By predicting the probability of esophageal cancer and precancerous lesions in the general population based on predictive factors, risk prediction models can identify high-risk individuals eligible for endoscopic screening, which could concentrate the subjects needed to be screened, reduce the cost and increase the efficiency and compliance of screening, as well as avoid over-screening (11, 12).

In recent years, several risk prediction models with various risk factors have been developed for esophageal cancer. However, it is not clear whether these models are developed or validated appropriately or whether they are applicable to screening for the general population. Therefore, it is important to evaluate the methodology underpinning model development and validation, and also risk factors and performance to guide decisions regarding the use and choice of models for risk predictions. The aim of this systematic review was to provide an overview on the models developed to predict the risk of esophageal cancer in general population, including methodological characteristics, predictors, and risk of bias.

MATERIALS AND METHODS

This systematic review was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) (13). A pre-specified protocol was followed when this study was conducted.

Literature Search

We comprehensively searched the PubMed, EMBASE, and Cochrane Library electronic databases to identify relevant publications on December 31, 2020, and updated the search on October 22, 2021. The search strategy consisted of medical subject headings (MeSH) and text words for risk prediction models of esophageal cancer and its precancerous lesions, with the results restricted to human studies. The main search terms were as follows: [("cancer" OR "carcinoma" OR "neoplasia" OR "tumor" OR "malignancy") AND ("esophageal" OR "esophagus" OR "gastrointestinal" OR "digestive" OR "alimentary") OR "esophageal neoplasms" [MeSH]] AND ("predict" OR "predictive" OR "prediction") AND "model" AND "risk." Further studies were sought by manually searching for the relevant articles in public databases.

Selection of Studies

After the removal of duplicates, studies were screened according to the inclusion and exclusion criteria based on titles and abstracts. If a decision could not be made based on abstracts, full articles were retrieved. Studies were selected if they met with the following criteria: (1) published as an original research article in a peer-reviewed journal; (2) developing or validating a risk prediction model of esophageal cancer and/or its precancerous lesions; (3) considering more than one predictors in the prediction model, including traditional and genetic risk factor, laboratory test, or risk scores that combing multiple risk factors; (4) had the outcome as cases with cancer or precancerous lesions vs. non-cases. Two independent authors (RC and JZ) screened the search results to assess conformity with selection criteria, with disagreement resolved with a third author (SW).

Data Extraction and Synthesis

The same authors independently performed data extraction and quality assessment using standardized protocols. The general characteristics of studies were extracted, including first author, publication year, country, outcome, study design, study period, sample size, and model-related information (statistical methods, model performance, validation method, and included predictors). In this process, the methods of studies published for each risk model were classified according to the TRIPOD guidelines (14). For studies which included multiple models, for example separate models for different outcomes or age groups, all were included separately.

Assessment of Risk of Bias

The risk of bias was assessed using PROBAST (Prediction model Risk Of Bias Assessment Tool) (15). The tool contains a total of 20 signaling questions to facilitate structured judgment of risk of bias covering four domains on model development and validation: participants, predictors, outcome, and analysis. Any initial disagreement was resolved through further discussion among the authors.

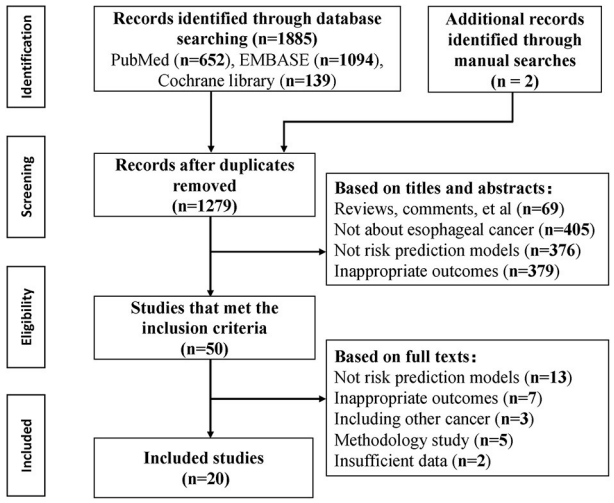


FIGURE 1 | Flowchart of literature search for risk prediction models of esophageal cancer.

RESULTS

The initial search identified 1,885 records, and 20 articles were included according to the inclusion criteria (**Figure 1**). A total of nine cohorts, 11 case-control studies, and two cross-sectional studies were involved since two studies applied two study designs. Three articles (16–18) reported independent models for different outcomes, three articles reported (19–21) independent models with different predictive factors, one article (22) reported sex-specific models, and one article (11) reported four age-stratified models; thus a total of 30 models were identified on risk prediction for esophageal cancer and precancerous lesions.

Overview of Risk Prediction Models

Table 1 presents the primary characteristics of the included studies. The publication year ranged from 2008 to 2021. There are 10 models for EAC and BE, 19 models for ESCC and SD, and one model for unspecified esophageal cancer. The sample size of included studies ranged from 355 to 5,55,011, involving 20,776 cases in total. All models on EAC and BE are for people from Western countries, whereas most models on ESCC and SD are for Asians, especially those in East Asian countries including Japan and China. Among the 30 reported models, model discrimination (C statistic) ranged from 0.68 to 0.94, with a median area under the receiver operating characteristic curve (AUC) of 0.78.

Predictive Factors

An overview of the predictive factors that were included in the risk prediction models are summarized in **Table 2**. The number of predictors included in the final models ranged from three to 10, with a median of five predictors. The most common predictors were age, smoking, body mass index (BMI), sex, upper gastrointestinal symptoms, and family history. Besides, genetic variants were included in four studies (16, 21, 24, 28), two of them were ALDH2 genotypes (21, 28), and the other two were single nucleotide polymorphisms (SNPs) or polygenic risk score generated from genome-wide association studies (16, 24).

Methodology of Risk Prediction Models

The methodological characteristics of the included models are summarized in **Table 3**. The number of events per variables (EPVs) in the final multivariate analysis was <10 for eight models, and ranged between 10 and 20 for eight models. One third of the models keep continuous variables whereas about half of the models transformed continuous variables to multicategorical variables. Candidate predictors were selected based on multivariable screening in 15 models and clinical experience combined with statistical analysis in 10 models. Eighteen models reported missing values and excluded them from analysis, whereas other studies did not report the issue of missing data. All models reported discrimination with C statistic, of which eight models reported both C statistic and Somers' D statistic. Model calibration was reported in 10 models with Hosmer-Lemeshow test and seven models with calibration plot. Twenty-three models were internally validated using cross validation, bootstrapping, or resampling. Only four models performed independent external validation.

Risk of Bias

A summary of the risk of bias analysis is shown in **Table 4**. None of the models were identified as at low risk of bias. The high risk of bias in participants is mainly due to inappropriate date source, such as cases and non-cases from different populations in case-control studies, which also causes inconsistent definition of predictors and outcomes and makes the domain of predictors and outcome high risk. Major deficiencies in the analysis domain relate to number of participants with the outcome and evaluation of model performance. The relatively recommended prediction model for subjects with high risk of ESCC were Chen's model (25) and Han's model (26), and the model by Kunzmann was recommended for identifying individuals at risk for EAC (18).

DISCUSSION

This systematic review summarizes the available evidence on risk prediction for esophageal cancer in general populations and evaluated the methodology of the included models comprehensively. The findings indicate a high risk of bias in the existing models due in part to limitations in study design and poor reporting and are expected to guide efforts to improve the development, validation, and transparent reporting of risk prediction models for esophageal cancer as well as other related diseases.

Unlike breast cancer (34), colorectal cancer (35, 36), and lung cancer (37), which already have a large number of models with externally validations, the development and validation of risk prediction models of esophageal cancer is still insufficient. Although the included models showed a relatively acceptable performance on discrimination, less than half models evaluated the calibration, and few models have independent external validation. The results of risk of bias assessment indicated that the predictive performance may be overestimated in the

TABLE 1 | Characteristics of included studies.

References	Country	Study design	Study type†	Study period	Outcome	No. of participants	Number of events	AUC (95%CI)
Baldwin-Hunter et al. (23)	USA	Cross-sectional	1b	2015–2017	BE	2,931	57	0.71 (0.64–0.77)
Chang et al. (24)	China	Case-control	2a	NR	ESCC	20,298	9,805	0.71 (0.70–0.72)
Chen et al. (25)	China	Cohort	1b	2007–2012	ESCC	86,447	298	0.81 (0.78–0.83)
Dong et al. (16)	UK	Case-control	2a	NR	BE EAC	7,976	3,288 (BE) 2,511 (EAC)	0.80 (0.78–0.82) (BE) 0.75 (0.73–0.78) (EAC)
Etemadi et al. (17)	Iran	Case-control	2a	2003–2007	ESCC	871 (ESCC)	300 (ESCC)	0.77 (0.74–0.80) (ESCC)
		Cohort	2a	2003–2007	SD	724 (SD)	26 (SD)	0.71 (0.64–0.79) (SD)
Han et al. (26)	China	Cohort	3	2012–2019	ESCC	115,686 (d) 54,750 (v)	186 (d) 120 (v)	0.80 (0.77–0.83) (d) 0.79 (0.75–0.82) (v)
Ireland et al. (27)	Australia	Case-control	1a	2015	BE	355	120	0.82 (0.78–0.87)
Koyanagi et al. (28)	Japan	Case-control	3	2001–2005 (d) 2005–2013 (v)	EC	1,260 (d) 654 (v)	265 (d) 328 (v)	0.94 (9.92–0.95) (d) 0.91 (0.89–0.93) (v)
Kunzmann et al. (18)	UK	Cohort	1b	2006–2010	ESCC EAC	355,034	64 (ESCC) 220 (EAC)	0.71 (0.66–0.78) (ESCC) 0.80 (0.77–0.82) (EAC)
Liu et al. (11)	China	Cohort	2a	2012–2015	SDA MDA	15,073	112 (SDA) 194 (MDA)	0.80 (0.74–0.85) (SAD, <=60 years) 0.68 (0.62–0.74) (SAD, >60 years) 0.77 (MAD, <=60 years) 0.68 (MAD, >60 years)
Liu et al. (29)	China	Cross-sectional Cohort	3	2017–2019	SDA	5,624 (d) 5,767 (v)	87 (d) 34 (v)	0.87 (0.84–0.95) (d) 0.84 (0.79–0.89) (v)
Rubenstein et al. (30)	USA	Cross-sectional	1a	2008–2011	BE	822	70	0.72 (0.66–0.79)
Shen et al. (31)	China	Case-control	2a	2014–2016	ESCC	1,220	244	0.79 (0.75–0.82)
Thrift et al. (12)	Australia	Case-control	2a	2002–2005	EAC	1,944	364	0.76 (0.73–0.79)
Wang et al. (19)	Sweden	Case-control	1b	1994–1997	ESCC	987	167	0.81 (0.77–0.84) (full) 0.79 (0.75–0.82) (simple)
Wang et al. (32)	Norway, UK	Cohort	3	1984–2016 (d) 2006–2010 (v)	ESCC	77,476 (d) 477,535 (v)	53 (d) 105 (v)	0.76 (0.58–0.93) (5 years) (d) 0.70 (0.64–0.75) (5 years) (v)
Xie et al. (20)	Sweden	Case-control	2a	1995–1997	EAC	1,009	189	0.84 (0.81–0.87) (full) 0.82 (0.78–0.85) (simple)
Xie et al. (33)	Norway	Cohort	2a	1995–2015	EAC	62,576	29	0.81 (0.70–0.91) (10 years) 0.88 (0.83–0.93) (15 years)
Yang et al. (22)	China	Case-control	1a	2010–2013	ESCC	3,410	1,418	0.81 (0.79–0.84) (men) 0.88 (0.85–0.90) (women)
Yokoyama et al. (21)	Japan	Case-control	2a	NR	ESCC	868	234	0.86 (HRA-G) 0.84 (HRA-F)

GC, gastric cancer; ESCC, esophageal squamous cell carcinoma; EC, esophageal cell; EAC, esophageal adenocarcinoma; SD, Squamous Dysplasia; BE, Barrett's esophagus; SDA, severe dysplasia and above (lesions including severe dysplasia and higher-grade lesions); MDA, moderate dysplasia and above (lesions including moderate dysplasia and higher-grade lesions); d, derivation/development; v, validation.

†*Type of study according to the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines. 1a, development only; 1b, development and validation using resampling; 2a, random split-sample development and validation; 2b, non-random split-sample development and validation; 3, development and validation using separate data; 4, validation study.*

derivation dataset and is probably lower than that reported when used in practice. In addition, all EAC/BE models were developed in Western countries, and half ESCC/SD models were developed in China. Due to difference in risk factors among populations, the existing models may not be applicable for people in other high risk areas of esophageal cancer such as Eastern Asia, Southern and Eastern Africa. To ensure the generalizability of models in populations with different characteristics, more models with external validation are needed in further studies (38).

The most common predictors included in the models are well-known risk factors of esophageal cancer, such as age, sex, smoking, and BMI, although there was a variety of predictive factors between different pathological types. For example, ESCC is more related to eating habits including eating rapidly, irregular eating, intake of hot food, intake of fresh fruit, and so on, whereas the more common predictor of EAC is gastroesophageal reflux disease (GERD) (39). However, none of these risk factors are included as predictors by all models. Approximately 80% of the models included age and smoking as predictors, and about half

TABLE 2 | Overview of risk factors included in the risk prediction models.

References	Age	Sex	Smoking	Alcohol	Family history	BMI	UGI symptoms†	Other risk factors
Baldwin-Hunter et al. (23)		√	√		√*		√	
Chang et al. (24)‡	√	√	√	√				17 G SNPs and 8 GE SNPs, genetic risk factors interaction with drinking
Chen et al. (25)	√*	√*	√*		√*		√*	fresh fruit*, salted food*, relative disease history*
Dong et al. (16) (EAC/BE)‡	√	√	√			√	√	polygenic risk score, non-steroidal anti-inflammatory drugs
Etemadi et al. (17) (SD/ESCC)‡	√		√		√			education, ethnicity, opium use, oral health, marital status, tea temperature, water source
Han et al. (26)	√*	√*	√*	√*		√		fresh fruit*
Ireland et al. (27)‡	√	√		√		√	√	family reflux history, history of hypertension
Koyanagi et al. (28)‡	√	√	√	√				ALDH2 genotype
Kunzmann et al. (18) (EAC)	√*	√*	√*			√*	√*	
Kunzmann et al. (18) (ESCC)	√*		√*					asthma inhaler use*
Liu et al. (11) (SDA, ≤60 years)	√*					√	√*	use of coal or wood as a main source of cooking fuel*, rapid ingestion of food
Liu et al. (11) (SDA, >60 years)	√*		√*		√	√*		pesticide exposure*, irregular eating habits, high-temperature food intake, eating rapidly, intake of leftover food in summer*
Liu et al. (11)(MDA, ≤60 years)	√*				√*		√*	use of coal or wood as a main source of cooking fuel*, cooking fumes exposure*
Liu et al. (11) (MDA, >60 years)	√*				√*	√*		irregular eating habits, high-temperature food intake*, eating rapidly, intake of leftover food in summer*
Liu et al. (29)	√*		√*			√*	√*	
Rubenstein et al. (30)	√*		√*				√*	waist-to-hip ratio
Shen et al. (31)	√*	√	√	√*				education, intake of hot food*, intake of pickled/salted food*, intake of fresh fruit*
Thrift et al. (12)			√*			√*	√*	education*, non-steroidal anti-inflammatory drugs*
Wang et al. (19) (full model)	√*	√*	√*	√*				education and duration of living with a partner*, place of residence during childhood*
Wang et al. (19) (simple model)	√	√*	√*	√*				
Wang et al. (32)	√*	√	√*	√		√		
Xie et al. (20) (full model)			√			√*	√*	living with a partner for <1 year, previous diagnoses of esophagitis and diaphragmatic hernia and previous surgery for esophagitis, diaphragmatic hernia or severe reflux or gastric or duodenal ulcer
Xie et al. (20) (simple model)			√*			√*	√*	
Xie et al. (33)	√*	√	√			√	√*	
Yang et al. (22) (men)	√*		√*	√*	√*			education*, family wealth score*, adult height*, tooth brushing times*, missing and filled teeth*, tea temperature*
Yang et al. (22) (women)	√*				√*			education*, family wealth score*, adult height*, tooth brushing times*, missing and filled teeth*
Yokoyama et al. (21) (HRA-F)			√*					alcohol flushing*, strong alcohol beverages*, green-yellow vegetables*, fruit
Yokoyama et al. (21) (HRA-G)			√*					ALDH2 genotype*, strong alcohol beverages*, green-yellow vegetables*, fruit*

√*Risk factors included in the model,* **Significant risk factors.*

†*Including gastroesophageal reflux disease and related symptoms, alarming symptoms of retrosternal pain, back pain or neck pain, epigastric pain and dyspepsia.*

‡*Significance of risk factors is not reported.*

TABLE 3 | Methodology of included models.

Characteristics of analysis	Number of studies (%)
EPV in final model	
<10	8 (26.67)
10–20	8 (26.67)
≥21	14 (46.66)
Handling of continuous variables	
Transforming to multi-categorical variables	16 (53.34)
Keep continuous variables	10 (33.33)
Not report	4 (13.33)
Variable selection	
Multivariable screening	15 (50.00)
Clinical experience and statistical analysis	10 (33.33)
Not report	5 (16.67)
Missing values	
Exclusion from analysis	18 (60.00)
Not report	12 (40.00)
Model performance	
Discrimination	
C statistic/AUC	22 (73.33)
C statistic/ACU and Somers' D statistic	8 (26.67)
Calibration	
Hosmer-Lemeshow test	7 (23.33)
Calibration plot	4 (13.33)
Hosmer-Lemeshow test and calibration plot	3 (10.00)
Not report	16 (53.34)
Validation	
Internal validation	23 (76.66)
External validation	2 (6.67)
Internal and external validation	2 (6.67)
Not report	3 (10.00)
Internal validation ($N = 25$)	
Cross validation	19 (76.00)
Bootstrapping	3 (12.00)
Cross validation and bootstrapping	2 (8.00)
Resampling	1 (4.00)

TABLE 4 | Risk of bias of included studies using PROBAST.

References	Risk of bias				Overall
	Participants	Predictors	Outcome	Analysis	
Baldwin-Hunter et al. (23)	Low	Low	Low	High	High
Chang et al. (24)	High	High	High	High	High
Chen et al. (25)	Low	Low	Low	High	High
Dong et al. (16)	High	High	High	High	High
Etemadi et al. (17)	High	High	High	Unclear	High
Han et al. (26)	Low	Low	Low	High	High
Koyanagi et al. (28)	High	Low	Low	High	High
Ireland et al. (27)	High	High	High	High	High
Kunzmann et al. (18)	Low	Low	High	Unclear	High
Liu et al. (11)	Low	Low	Low	High	High
Liu et al. (29)	Low	Low	Low	High	High
Rubenstein et al. (30)	High	Low	Low	High	High
Shen et al. (31)	High	Low	Low	High	High
Thrift et al. (12)	High	High	High	High	High
Wang et al. (19)	Low	High	High	Unclear	High
Wang et al. (32)	Low	Low	Low	High	High
Xie et al. (20)	Low	High	Low	High	High
Xie et al. (33)	Low	Low	Low	High	High
Yang et al. (22)	Low	Low	Low	High	High
Yokoyama et al. (21)	High	High	High	High	High

of the models involved sex and BMI. One possible explanation is that these known risk factors did not reach statistical significance in the derivation dataset. A better method to handle these well-established predictors and those with clinical credibility in multivariate modeling is to include them in a prediction model regardless of any statistical significance (40). Some models also incorporate less common predictive factors related to data set features and population characteristics. The predictors only reported by one study include asthma inhaler use (18), waist-to-hip ratio (30), use of coal or wood as the main source of cooking fuel (11), pesticide exposure (24), opium use (17), oral health (12), and alcohol flushing (21). More evidence is needed to verify that their selection is not based on accidental association with esophageal cancer. In addition, there are models that combined genetic risk factors such as genetic polymorphisms or polygenic risk score as predictors to produce better performance. When applied to the general population in both population-based screening and opportunistic screening, the predictors included in the models must be readily obtained in primary care settings. The inclusion of genetic risk predictors may reduce the applicability of the models because they require additional measurement and costs. In summary, the selection of a suitable risk prediction model should comprehensively take the performance, the quality, and the feasibility into consideration.

The results of the risk of bias assessment show that none of the models meet all the requirements of PROBAST (40). The risk of bias in a section of participants, predictors, and outcomes is mainly caused by pitfalls in the study design. In a non-nested case–control study, case patients from a hospital with advanced conditions may be overrepresented, leading to overestimated model performance and reduced model applicability. The methodological limitations in the analysis section are as follows: (1) About 60% of the studies have an EPV lower than 10 and are likely to be overfitting in general (41, 42). For predictors with low-prevalence presented in a model, such as non-steroidal anti-inflammatory drugs (NSAIDs) use (16) and pesticide exposure (11), higher EPV is needed to eliminate bias in regression coefficients and improve predictive accuracy (41). (2) Continuous variables are transformed to multicategorical variables in more than half of the prediction models, the most common of which is categorizing age into groups. However, categorization of continuous predictors might lead to loss of information and weaken the performance of risk prediction models (43). (3) Most of the models either did not report any missing information or exclude missing value in the analysis, which may reduce the available sample size and cause selection

bias (44, 45). It should be noted that risk assessment relies on the transparent reporting of studies, and poor reporting could cause the items to be evaluated as high risk or unknown risk. However, to be clear, the clinicians and policy makers, who decide which clinical prediction models should be promoted in evidence-based guidelines or implemented in practice, should refer to reviews like current study at the very beginning. Meanwhile, the high prevalence of models with a high risk of bias emphasizes the need to improve methodological quality of prediction research.

To our knowledge, this is the first review that summarizes the risk prediction models of esophageal cancer in the average-risk population. We used the recently published tool PROBAST to assess the risk of bias and applicability of the included prediction model studies and then evaluated their methodological characteristics and performance. Risk prediction models by Chen (25), Han (26), and Kunzmann (18) were recommended based on the relatively standardized measurement of predictors and outcome, large sample size, complete evaluation, and good result of model performance. The results of this study will provide a reference for the further development, validation, and application of risk prediction models in the target subjects for endoscopic screening.

A limitation of the present study is the methodological shortcomings and inadequate reporting in the included articles. It is not possible to objectively evaluate and directly compare the models based on the poor reporting. Due to the lack of validation studies, we cannot perform meta-analysis of calibration measures for the prediction models. In addition, the variation of predictors and ethnic differences contribute to the poor implementation of the existing models.

CONCLUSIONS

There have been a few risk prediction models developed for esophageal cancer with acceptable predictive ability, although certain methodological limitations, especially the low rate of external validation, should be noted. Further researches are needed to develop a reliable risk prediction model for esophageal cancer based on general population and validate the existing models in an independent dataset.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

RC, RZ, SW, and WW designed and supervised the study. RC, JZ, and SW carried out the literature research, extracted data, and wrote the original draft. All authors critically reviewed the manuscript and approved the final draft.

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