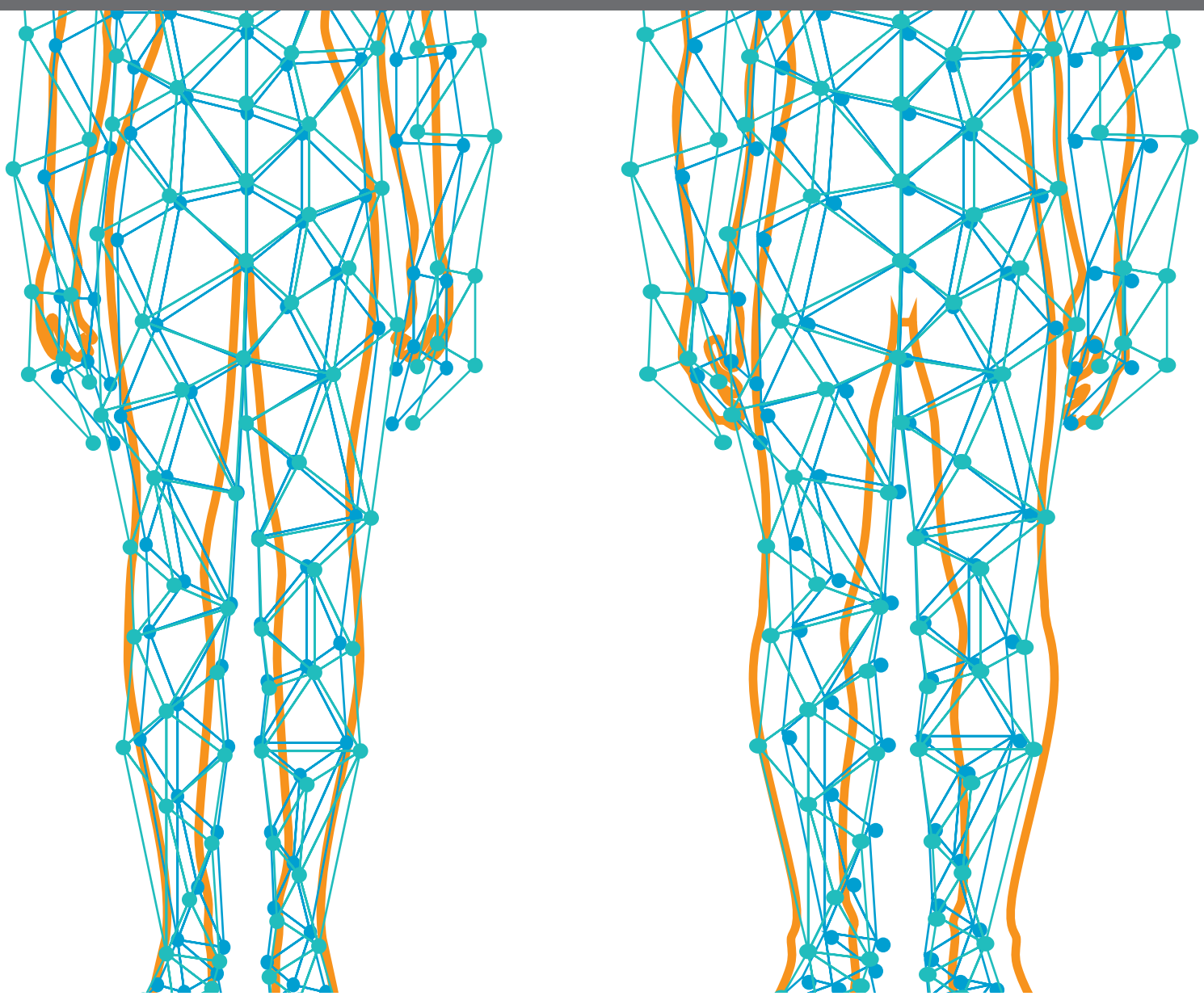
IMPACTS OF COMMON GERIATRIC SYNDROMES AND THEIR INTERACTION WITH CHRONIC DISEASES ON HEALTH

EDITED BY: Ming Yang, Jinhui Wu, Lin Kang and Andrea P. Rossi

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IMPACTS OF COMMON GERIATRIC SYNDROMES AND THEIR INTERACTION WITH CHRONIC DISEASES ON HEALTH

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Editorial: Impacts of common geriatric syndromes and their interaction with chronic diseases on health

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Editorial on the Research Topic
Impacts of common geriatric syndromes and their interaction with chronic diseases on health

One of the most critical tasks of geriatric care is maintaining and improving the function and health of the elderly (1). In addition to chronic diseases, geriatric syndromes (e.g., sarcopenia, frailty, functional disability, and malnutrition) substantially affect elderly health (2). Geriatric syndromes may interact with chronic diseases but their effects on elderly health are not fully understood (3).

This Research Topic includes not only original studies but also narrative reviews and systematic reviews, which provide updated knowledge on important geriatric syndromes and their interactions with chronic diseases on elderly health.

Relevant new findings in this series

Frailty

Setiati et al. conducted a multi-center cross-sectional study in Indonesia in 2020. Among the included 908 individuals, 167 (18.70%) had frailty. The authors reported that frailty was related to functional dependence, malnutrition risk, depression, a history of falls, a history of hospitalization, and polypharmacy. Functional dependence defined by the Barthel Index was related to an approximately seven-fold higher risk of frailty, while depression was correlated with an approximately three-fold higher risk of frailty. Malnutrition risk or malnutrition was related to an increasingly higher risk for frailty. A history of falls or hospitalization was associated with frailty. Polypharmacy was associated with a two-fold higher risk for frailty.

Shi et al. investigated the frailty status among 1,246 older adults and its association with mortality. The authors reported that women were frailer than men. In the whole study population, frailty was associated with an increased risk of death. The authors also found that frailty posed a more significant mortality risk than age, which emphasizes the importance of the management of frailty.

Liang et al. evaluated the relationship between frailty, hospitalization, and costs in Chinese older patients. Frailty was determined by an electronic frailty index (eFI) according to routine electronic health records. Among the 42,821 individuals with enough data, 33.8% had eFI-defined frailty. The eFI-defined frailty was independently associated with prolonged hospital stays and in-hospital death. Besides, the costs were positively associated with the level of frailty.

Liu et al. provided new insights into the trajectory and correlation between intrinsic capacity (IC) and frailty. This longitudinal observational study recruited 230 older adults and followed them for 2 years. The prevalence of frailty and IC impairment was 23.0 and 67.9% in the baseline and increased to 41.8% and 81.6% at the end of the follow-up, respectively. The authors concluded that loss of IC and frailty overlapped and co-existed in their study population.

Meng et al. explored the potential biomarkers and possible biological mechanisms related to frailty. They used 246 serum samples from Chinese men to detect metabolic profiles by targeted high-performance liquid chromatography-tandem mass spectrometry, including amino acids, carnitines, acylcarnitines, and lysophosphatidylcholines (LPCs). Older adults with frailty had lower tryptophan and higher glycine levels than those without frailty. Several characterized biomarkers, such as LPC16:0, LPC18:2, and tryptophan, were associated with frailty.

Similarly, Pan et al. used metabolomics to find frailty biomarkers and putative frailty pathogenic processes. Liquid chromatography-mass spectrometry-based metabolomics was applied to evaluate 349 metabolites in Chinese serum samples. The results showed that intermediates of carbohydrate metabolism, saturated fatty acids, unsaturated fatty acids, and certain essential amino acids might be the candidate biomarkers for the early screening and assessment of frailty. The authors suggested the potential mechanisms of frailty as well.

Additionally, Chang et al. evaluated the association between videofluoroscopic swallowing study (VFSS) findings and the incidence of pneumonia in patients with dysphagia due to frailty. They recruited 190 patients and followed them for 3 months after the VFSS. During the follow-up, 47 (24.7%) patients had pneumonia. Airway penetration and aspiration were associated with an increased risk of pneumonia.

She et al. reviewed the literature focused on frailty in older patients with the 2019 coronavirus disease (COVID-19), including potential pathogenesis, evaluation methods, and intervention measures. The authors suggested that older patients with COVID-19 should have an assessment of their frailty status as soon as feasible. They offered a scientific reference for clinicians to comprehensively manage frailty in older patients with COVID-19, from assessment to diagnosis and intervention.

Dai et al. performed a systematic review to assess the predictive value of frailty in lung cancer. Six studies with 2,359 patients were enrolled. The results showed that pre-frail or frail patients were more likely to experience therapeutic toxicity and all-cause death. The authors concluded that frailty was a significant predictor of all-cause death and treatment toxicity in patients with lung cancer.

In a study of Chinese older individuals in the community, Zhang, Ruan et al. evaluated the association between physical frailty and health-related quality of life (HRQoL). Based on 429 individuals, the results showed that physical frailty was an independent determinant of overall HRQoL. This study provides new evidence on the association between frailty and HRQoL and emphasizes the importance of timely management of frailty.

Malnutrition

Using a multi-stage random sampling method, Liu et al. built a large cohort of 86,514 older individuals living in the community in Xinjiang, China. Low BMI was defined as BMI <18.5 kg/m^2 (for individuals aged <70 years) or BMI <20 kg/m^2 (for individuals aged ≥ 70 years). The prevalence of low BMI varied by geography and age. As latitude declined and age grew, the prevalence of low BMI steadily increased. This finding needs to be validated in other populations.

By using an open-access database from the National Health and Nutrition Examination Survey, Yen et al. found that patients with different comorbidities were affected differently by alcohol drinking.

Lastly, based on a sample of 669 elderly hospitalized adults, Chen et al. found that albumin was negatively associated with inflammatory indexes. They also reported that patients with poor nutritional status were more prone to having pneumonia in older adults.

Sarcopenia

Jing et al. explored the relationship of activities of daily living (ADL) disability with trunk muscle mass and quality metrics determined from computed tomography (CT) in older inpatients. They found that CT-derived muscle quality indicators, instead of muscle mass index, were associated with ADL disability. This finding reinforces the importance of muscle quality for assessing muscle health in sarcopenia research.

Chung et al. performed a meta-analysis with six studies to explore the prevalence of sarcopenia and its relationship

to diabetes in community-dwelling individuals. The prevalence of sarcopenia, as determined by the Asian Working Group for Sarcopenia criteria, was 15.9% in people with diabetes and 10.8% in those without. Compared to people without diabetes, diabetics showed a noticeably greater risk of sarcopenia.

Kwack et al. proposed a new method to evaluate muscle mass. In a small cross-sectional study conducted in hemodialysis patients, the author's calculated psoas muscle (PM) index and normal-density psoas muscle (NPM) index using the whole PM area (-29–100 HU, as usual) or the normal-density PM area (35–100 HU, the new method) divided by height squared. The results suggested that in hemodialysis patients, the NPM index can be a practical predictor of muscle strength and physical performance. Muscle mass and muscle quality are both taken into account in this new method, and it deserves further investigation.

Huang and Wang reviewed the current evidence of sex hormones for treating sarcopenia. They also discussed the possible advantages of combining sex hormone treatments with exercise and dietary supplements.

Gao et al. reanalyzed the data from the China Health and Retirement Longitudinal Study (CHARLS) to explore the association between sarcopenia and depressive symptoms in Chinese older individuals. They included 7,706 participants aged $\geq$ 60 years. In the baseline, both probable sarcopenia and sarcopenia were positively associated with depressive symptoms. During the 3.7-year follow-up, 956 (20.6%) participants experienced depressive symptoms. Participants with probable sarcopenia or sarcopenia were more prone to having newly developed depressive symptoms. These findings provided new evidence that sarcopenia should be evaluated when fighting against depressive symptoms.

Lee et al. investigated the association between acute vertebral osteoporotic compression fractures (VOCF) and body composition in 461 older patients. The risk of acute VOCF was the highest in patients with sarcopenic obesity. Sarcopenic obesity was strongly linked with acute VOCF rate, particularly in women, according to multivariate analysis.

Functional disability

Zhang, Liu et al. developed a novel screening tool named function impairment screening tool (FIST) for assessing physical function. Based on a cohort of 489 Chinese older adults, they proved that the FIST tool had good test-retest reliability and validity. However, its diagnostic value for screening functional impairment needs to be further validated in different populations.

Sun et al. reanalyzed the data of 13,959 adults aged $\geq$ 45 years from the CHARLS study and concluded that short or long sleep duration was associated with vision impairment. This finding is interesting and merits further research.

Moreover, Peng et al. reanalyzed the differentially expressed genes from two microarray data sets to explore prognostic gene expression signatures for age-related hearing loss. They concluded that distinct levels of hearing loss in presbycusis were correlated with different autophagy indicators and immunological microenvironments.

Lastly, Prell et al. showed that dizziness syndromes were completely different between older adults and their young counterparts. Younger individuals reported more severe dizziness-related distress, whereas older individuals reported experiencing dizzy symptoms for longer than younger individuals. Older individuals experienced fewer depressive symptoms and less anxiety than younger individuals. Younger individuals were more likely to be hospitalized and had more doctor consultations than older individuals.

Cardiovascular disease

Some studies addressed cardiovascular diseases in older adults. For example, Zhang, Xiang et al. reviewed the evidence regarding the contribution of nursing to the treatment of cardiovascular diseases and concluded that nursing significantly improved the outcomes of heart failure and myocardial ischemia in older patients. This finding emphasized the importance of nursing in older patients with heart disease, which deserves further research in the future.

Additionally, in a prospective cohort study with 271 patients with acute non-ST-segment elevation myocardial infarction, Zhang, Wang et al. reported that elevated plasma myeloperoxidase level was related to high inflammatory status and a coronary events risk score.

Zhang, Xian et al. tested the diagnostic value of AMAZFIT®, a wearable electrocardiogram-recording device, for detecting arrhythmia in 291 older adults. This new tool appeared to have a considerable sensitivity and specificity for detecting atrial fibrillation, premature arterial contractions, and premature ventricular contractions when using a standard 12-lead ECG device as the gold standard.

Lastly, Miao et al. performed a systematic review to evaluate the possible value of serum uric acid (SUA) for predicting outcomes in patients with chronic heart failure. A total of 18 publications were included. The results showed that serum SUA was positively associated with an increased risk of all-cause mortality, cardiovascular mortality, and the composite of death or cardiac events.

Osteoarthritis

In a meta-analysis involving 24 randomized controlled trials (RCTs) with 1,275 participants, Wang et al. evaluated the benefits of proprioceptive training for improving symptoms,

function, and proprioception in patients with knee osteoarthritis (KOA). Proprioceptive training could substantially improve pain, stiffness, and physical function, and enhance joint position sense (JPS), muscular strength, mobility, and knee range of motion when compared to no intervention. Additionally, proprioceptive training provided better results in terms of JPS and mobility when compared to the control groups.

Traditional Chinese Yijinjing Qigong Exercise (YJJQE) is a popular exercise in China. Zhang, Guo et al. designed an RCT to assess the effectiveness of YJJQE for treating KOA. They randomly assigned 50 KOA patients to the YJJQE group (n = 25) or the stretching training exercise (STE) group (n = 25). For a period of 12 weeks, each participant had two 40-min exercise sessions (YJJQE or STE) twice per week. They found no difference between groups with regards to the primary outcome, the Western Ontario and McMaster Universities Osteoarthritis Index Scale score. However, YJJQE seemed to be related to an improvement in psychological wellbeing.

Miscellaneous

Huang, Jia et al. reviewed recent findings on *Helicobacter pylori* (H. pylori) diagnosis, management, and treatment in older adults, highlighting the differences between older patients and their younger counterparts. The use of routine therapy in older patients was constrained by health issues, such as comorbidities and polypharmacy. However, eradication treatment may still be advantageous for older patients. New methods, such as complementary and dual therapies, may also be used to treat elderly people with H. pylori infection.

In a systematic review with 29 RCTs with 1,994 participants, Zhang, Ou et al. summarized current evidence regarding transcutaneous electrical acupoint stimulation (TEAS) for preventing postoperative cognitive dysfunction. The results demonstrated that the perioperative use of TEAS reduced postoperative cognitive dysfunction rates and protected early postoperative cognition.

To describe the impact of new androgen receptor axis-target (ARAT) drugs on diarrhea and constipation, Xiong et al. performed a systematic review including 13 trials with 15,117 participants. They compared four drugs (abiraterone, enzalutamide, apalutamide, and darolutamide) with placebo. These novel ARAT drugs were related to 1.3 times increased risk of any-grade diarrhea. Patients with metastatic hormone-sensitive and castration-resistant prostate cancer were most likely to experience diarrhea when using abiraterone.

Future research

This collection highlights new information and new trends regarding the epidemiology, dynamics, and management of common geriatric syndromes, such as frailty, sarcopenia, disability, and malnutrition, and their interaction with chronic diseases, with a particular focus on cardiovascular disease and osteoarthritis. Not surprisingly, most of the studies in this collection focused on frailty and sarcopenia, the two new "geriatric giants" and to a lesser extent, malnutrition (4). Unfortunately, other geriatric giants, such as cognitive impairment/dementia, delirium, and dysphagia, were less addressed in this collection and should be the topic for future special issues. Moreover, except for Huang, Wang et al. review of the literature, most of the included studies were observational and/or cross-sectional observations. In particular for sarcopenia and frailty, future research should concentrate on the treatment of those conditions with ad hoc clinical trials.

Here, we proposed some considerations for further research:

- Older adults with geriatric syndromes are more likely to suffer from chronic diseases (e.g., diabetes and cardiovascular disease) (5), while chronic diseases are associated with an increased number of geriatric syndromes (3). The cross-talk between different geriatric syndromes and chronic diseases and their synergistic effects on health require more future research.
- Although some authors argued that vascular diseases are key etiological of geriatric syndromes (6), the potential mechanism of geriatric syndromes remains unclarified. Further disentangling of the mechanisms of different organ aging may help us understand geriatric syndromes.
- More well-designed clinical trials are required to focus on the optimal interventions for preventing and treating geriatric syndromes. The interventions may include pharmacotherapy, lifestyle management, and rehabilitation/prerehabilitation. Some interventions (e.g., resistance training and vitamin D) that benefit both chronic diseases (e.g., osteoporosis) and geriatric syndromes (e.g., sarcopenia and frailty) may have priority. The study populations may focus on people who are prone to geriatric syndromes, such as the oldest old, institutional residents, and older patients in different clinical settings. The outcomes should include patient-reported outcomes and HRQoL.

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Frailty and Its Associated Risk Factors: First Phase Analysis of Multicentre Indonesia Longitudinal Aging Study

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Background: National long-term care development requires updated epidemiological data related to frailty. We aimed to find the prevalence of frailty and its associated factors among Indonesian elderly.

Methods: We conducted first-phase cross-sectional analysis of Indonesia Longitudinal Aging Study (INALAS) data collected from community-dwelling outpatients aged 60 years and older without acute illness in nine geriatric service care centres. Descriptive, bivariate and multivariate analyses were conducted.

Results: Among 908 elderly in this study, 15.10% were robust, 66.20% were pre-frail, and 18.70% were frail. Functional dependence was associated with frailty among Indonesian elderly (OR 5.97, 95% CI 4.04–8.80). Being depressed and at risk for malnutrition were also associated with frailty with OR 2.54, 95% CI 1.56–4.12, and OR 2.56, 95% CI 1.68–3.90, respectively. Prior history of fall (OR 1.77, 95% CI 1.16–2.72) and hospitalization (OR 1.46, 95% CI 0.97–2.20) in the previous 12 months were associated with frailty. There is also significant association between poly pharmacy and frailty (OR 2.42, 95% CI 1.50–3.91).

Conclusion: Approximately one in five Indonesian community-dwelling elderly was frail. Frailty is associated with functional dependence, being at risk for malnutrition or being malnourished, depression, history of fall, history of hospitalization, and poly pharmacy. There may be bidirectional relationships between the risk factors and frailty. The development of long-term care in Indonesia should be considered, without forcing the elderly who need it.

Keywords: frailty, prevalence, Indonesia, community-dwelling elderly, long-term care, risk factors

INTRODUCTION

Indonesia is facing an increase in elderly population. Currently, there are more than 26 million people aged 60 years and older nationwide. This group of people contribute to 9.92% of total Indonesian population in 2020 (1). It is expected that elderly will make up 12.9% of total Indonesian population in 2030 (2). Frailty is a major problem among Indonesian elderly. This modern geriatric syndrome is closely related to high risk for devastating conditions, such as falls, hospitalization, disability, and death (3, 4).

Physiological decline of organs in the elderly and the comorbidities contribute to the change in functional status, depression state, cognitive function, and nutritional status, resulting in frail state. Frailty is a state of increased vulnerability to stressor resulting from a decline in physiological reserve and function capacity of an elderly. This vulnerable state may bring about inadequacy to recover after destabilization (5).

Frail older people are at higher risk of needing long-term care (LTC) (6). At the moment, Indonesia is in the process of developing LTC service for elderly population with significant loss of capacity. The funding of the development requires involvement of the policy makers, who make decisions based on the cost-efficiency and the urgency from the latest national prevalence of frailty. The data related to frailty are also essential for the development of other healthcare services that should be available in Indonesia to support World Health Organization (WHO) framework on healthy aging. However, the updated epidemiological data are lacking. Our previous multicentre cross-sectional study in 2014 suggested that frailty was found in 27.2% Indonesian elderly. Only 13.2% of Indonesian elderly were in robust condition (5).

We aimed to find the current prevalence of frailty and its associated factors among Indonesian community-dwelling elderly in this cross-sectional study. This first phase analysis is a part of the national multicentre data analyses of Indonesia Longitudinal Aging Study (INALAS).

MATERIALS AND METHODS

Study Design and Subjects

This cross-sectional study was conducted in several geriatric service care centers in different islands of Indonesia from March to October 2020. In this study, we randomly selected 9 out of 17 elderly healthcare centers in Indonesia, namely Dr. Wahidin Sudirohusodo Hospital (RSWS), Makassar, South Sulawesi; Sanglah Hospital (RSUP Sanglah), Denpasar, Bali; Hasan Sadikin Hospital (RSHS) Bandung, West Java; Dr. M. Djamil Hospital (RSUP Dr. M. Djamil) Padang, West Sumatera; Dr. Moewardi Hospital (RSUD Moewardi), Solo, Central Java; Teja Husada Hospital (RSK Geriatri Teja Husada) and Ben Mari Hospital, Malang, East Java; Atma Jaya Hospital, and Cipto Mangunkusumo National General Hospital (RSCM), Jakarta. The data analysis was a part of INALAS. INALAS is a multicenter longitudinal aging study focusing on the health of older adults in Indonesia involving several geriatric service care centers in different islands. We planned to document the changes in a prospective manner every 6 months with target follow-up period of 5 years.

The inclusion criteria were community-dwelling elderly in the geriatric outpatient clinics of all selected hospitals who agreed to participate in the study. The definition of elderly was individuals aged 60 years and above. We recruited the patients consecutively. The exclusion criteria were elderly patients with an acute illness, such as acute confusional state, acute infection, and acute cerebrovascular and/or cardiovascular events.

The sample size needed for the study was determined based on the formula for the sample size of the estimated proportion (7). The minimum number of subjects to be recruited was 485 subjects. Ethical approval was obtained from the Faculty of Medicine, Universitas Indonesia. All subjects or their representing family members signed the written informed consent form.

Data Collection

We used primary data from questionnaires and secondary data from medical records to collect the data related to the list of medications and comorbidities. Frailty state was assessed using the FRAIL scale, consisting of fatigue, resistance (defined as the ability to climb one flight of stairs), ambulation (walk a block), number of comorbid illnesses <5, and weight loss of more than 5% in the previous year. One point was given if the patients answered yes to each question. If the total score was 0, the patient was categorized as robust or fit. If the total score was 1 or 2, the patient was categorized as pre frail, and if the total score was 3 or higher, the patient was categorized as frail (8).

The data collected for the cross-sectional study included (a) demographic data (i.e., age, sex, last completed formal education, having caregiver or not, and marriage status); (b) History of fall and/or hospitalization in the past 12 months (c) frailty state based on the FRAIL questionnaire; (c) functional status based on the Barthel Index of Activity of Daily Living (ADL) questionnaire: totally dependent (score 0–4), severely dependent (score 5–8), moderately dependent (score 9–11), slightly dependent (score 12–19), independent (score 20); (d) nutritional status based on the Mini Nutritional Assessment Short-Form: normal nutritional status (score 12–14), at risk for malnutrition (score 8–11), malnourished (score 0–7); (e) depression status based on 15-item version of Geriatric Depression Scale: normal (score < 5), depressed (score 5–15); (f) cognitive function based on Mini-Cog©: low likelihood of dementia (score 3–5) and high likelihood of dementia (score 0–2); (g) total number of the medications administered daily from self-report and/or medical record; (h) comorbidities obtained from medical record. All screening and diagnostic activities were done by physicians in internal medicine - geriatric medicine care centers.

Statistical Analysis

The prevalence of frailty was obtained by calculating the proportion of patients who were categorized as frail divided by total study subjects. For the statistical analysis, frailty status was divided into: (1) non-frail (robust and pre frail), and (2) frail. Categories of age group were: (1) < 70 years, and (2) ≥70 years. We determined the age groups based on the latest life

expectancy of Indonesian population, approximately 70 years for both male and female individuals (1). The subjects were categorized based on their sex into male and female. Categories of the level of education were: (1) senior high school or higher, (2) junior high school or lower. Categories of the marriage status were: (1) married and (2) not married or widowed. Categories of the functional status were divided into two categories: (1) independent, (2) dependent (for subjects with total, severe, moderate and slight dependency). Categories of the depression status were: (1) normal and (2) depressed. Categories of cognitive function were: (1) low likelihood and (2) high likelihood of dementia. Categories according to nutritional status were: (1) normal and (2) at risk for malnutrition or malnourished (for subjects with score <12). Categories according the history of fall were: (1) no history of fall and (2) prior history of fall. Categories according the history of hospitalization were: (1) no history of hospitalization and (2) prior history of hospitalization. Poly pharmacy was determined based on the number of drugs that the patients consumed routinely and/or based on the medical records. An individual experiences poly pharmacy if he/she takes five or more medications daily (9).

Analyses were performed with SPSS Version 21 (IBM, Armonk, New York, USA). We used Chi-square test to perform the bivariate analysis, followed by multivariate analysis to assess the association between frailty and the independent variables. Variables with p-value < 0.25 in bivariate analysis were included for multivariate analysis using multiple logistic regression method. P-value < 0.05 was considered statistically significant.

RESULTS

We collected data from 908 individuals from different geriatric care centers. Male-to-female ratio of study subject was nearly 1:1. The characteristics of the subjects are shown in **Table 1**. Among the elderly in this study, 15.10% were robust, 66.20% were pre-frail, and 18.70% were frail, see **Figure 1**.

Three out of five frail elderly were female, see **Table 2**. A higher proportion of frail elderly was aged 70 years and older (54.7%), completed senior high school and higher education (63.5%), was married (64.1%), and had caregiver (76.5%). More than 60% of frail subjects were functionally dependent. More than half of the frail elderly were also at risk for malnutrition or even were malnourished. On the other hand, a larger proportion of frail elderly was not depressed (68.2%), and had low likelihood of dementia (85.9%), no prior history of fall (65.9%), and no history of hospitalization (57.1%). Seventy-nine percent of frail elderly experienced poly pharmacy. The most common comorbidities of frail elderly were hypertension (70.0%), diabetes mellitus (52.4%), and coronary heart disease (43.5%). Based on the p-value of the results of bivariate analysis, all variables, except educational background, were included in the multivariate analysis.

The results of multivariate analysis showed that functional dependence was associated with frailty among Indonesian elderly [OR 5.97, 95% Confidence Interval (CI) 4.04–8.80], see **Table 3**. Being at risk for malnutrition or being malnourished was associated with frailty (OR 2.56, 95% CI 1.63–3.90). Depression was also associated with frailty with OR 2.54, 95% CI 1.56–4.12. Prior history of fall and hospitalization were also associated with frailty (OR of history of fall 1.77, 95% CI 1.16–2.72; OR of history of hospitalization 1.46, 95% CI 0.97–2.20). There is also

TABLE 1 | Characteristics of Subjects ($n = 908$).

Characteristics	*n* (%)
Sex	
Male	438 (48.2)
Female	470 (51.8)
Age	
60–69 years old	484 (53.3)
> 70 years old	424 (46.7)
Educational background	
Senior high school and higher	571 (62.9)
Junior high school and lower	337 (37.1)
Marital status	
Married	649 (71.5)
Not married/widowed	259 (28.5)
Caregiver	
Yes	531 (58.5)
No	377 (41.5)
Functional status	
Independent	667 (73.5)
Dependent	241 (26.5)
Depression status	
Normal	783 (86.2)
Depressed	125 (13.8)
Nutritional status	
Normal	644 (70.9)
At risk for malnutrition or malnourished	264 (29.1)
Cognitive function	
Low likelihood of dementia	806 (88.8)
High likelihood of dementia	102 (11.2)
History of fall	
No	726 (80.0)
Yes	182 (20.0)
History of hospitalization	
No	628 (69.2)
Yes	280 (30.8)
Poly pharmacy	
No	265 (29.2)
Yes	643 (70.8)
Comorbidities	
Hypertension	686 (75.6)
Diabetes mellitus	449 (49.4)
Coronary heart disease	295 (32.5)
Dyslipidaemia	396 (43.6)
Osteoarthritis	82 (9.0)
Chronic kidney disease	231 (25.4)
Visual impairment	78 (8.6)
Osteoporosis	16 (1.8)

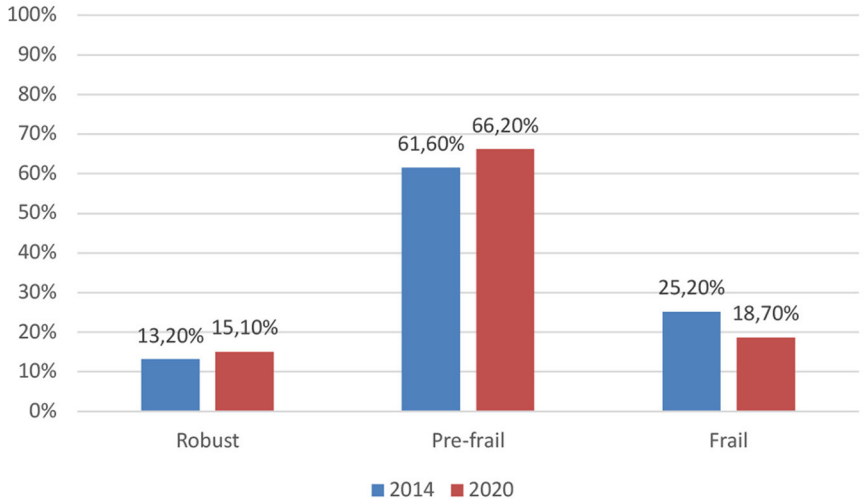


FIGURE 1 | Prevalence of frailty among Indonesian elderly in 2014 and 2020.

TABLE 2 | The results of bivariate analysis of study variables.

Variables	Frailty state		*P* Value	OR (95% CI)
	Non-frail [n (%)]	Frail [n (%)]		
Sex				
Male	367 (49.7)	71 (41.8)	0.06	1
Female	371 (50.3)	99 (58.2)		1.38 (0.98–1.93)
Age				
60–69 years old	407 (55.1)	77 (45.3)	0.02	1
> 70 years old	331 (44.9)	93 (54.7)		1.48 (1.06–2.08)
Educational background				
Senior high school and higher	463 (62.7)	108 (63.5)	0.85	1
Junior high school and lower	275 (37.3)	62 (36.5)		0.97(0.68–1.237)
Marital status				
Married	540 (73.2)	109 (64.1)	0.02	1
Not married or widowed	198 (26.8)	61 (35.9)		0.66 (0.46–0.93)
Functional status				
Independent	605 (82.0)	62 (36.5)	<0.001	1
Dependent	133 (18.0)	108 (63.5)		7.92 (5.50–11.41)
Depression status				
Normal	667 (90.4)	116 (68.2)	<0.001	1
Depressed	71 (9.6)	54 (31.8)		4.37 (2.92–6.56)
Nutritional status				
Normal	560 (75.9)	84 (49.4)	<0.001	1
At risk for malnutrition or malnourished	178 (24.1)	86 (50.6)		3.22 (2.28–4.55)
Cognitive function				
Low likelihood of dementia	660 (89.4)	146 (85.9)	0.19	1
High likelihood of dementia	78 (10.6)	24 (14.1)		1.39 (0.85–2.27)
History of fall				
No	614 (83.2)	112 (65.9)	<0.001	1
Yes	124 (16.8)	58 (34.1)		2.56 (1.77–3.72)
History of hospitalization				
No	531 (72.0)	97 (57.1)	<0.001	1
Yes	207 (28.0)	73 (42.9)		1.93 (1.37–2.72)
Poly pharmacy				
No	229 (31.0)	36 (29.2)	0.01	1
Yes	509 (69.0)	134 (78.8)		1.68 (1.12–2.49)

TABLE 3 | The risk factors associated with frailty in Indonesian elderly.

Risk factors	Coefficient B	Standard error	*P*-value	OR (95% CI)
Functional dependence	1.79	0.20	<0.001	5.97 (4.04–8.798)
At risk for malnutrition or being malnourished	0.94	0.22	<0.001	2.56 (1.68–3.90)
Depression	0.93	0.25	<0.001	2.54 (1.56–4.12)
Prior history of fall	0.58	0.22	0.01	1.77 (1.16–2.72)
Prior history of hospitalization	0.38	0.21	0.06	1.46 (0.97–2.20)
Poly pharmacy	0.89	0.24	<0.001	2.42 (1.50–3.91)

significant association between poly pharmacy and frailty (OR 2.42, 95% CI 1.50–3.91).

DISCUSSION

Among Indonesian community-dwelling elderly in this study, 15.10% were robust, 66.20% were pre-frail, and 18.70% were frail. Frailty is significantly associated with functional dependence, being at risk for malnutrition or being malnourished, depression, history of falls, history of hospitalization, and poly pharmacy. In contrast, age 70 years and older, female sex, high likelihood of dementia, lower level of education, or marital status was not associated with frailty.

We decided to use FRAIL scale instead of FI-40 for clinical practice and research purposes during COVID-19 pandemic, to protect the community-dwelling elderly by minimizing the time spent in healthcare centres. The feasibility of FRAIL scale in clinical setting allows the use of the promising tool to facilitate the translation of clinical research into medical practice (10). Routine screening of adults aged 70 years and older was recommended in The Asia-Pacific clinical practice guideline for the management of frailty (11).

The prevalence of frailty among Indonesian elderly was 18.70% in 2020, which is slightly lower than the estimated prevalence in 2014 (5). The Percentage of pre-frail and robust elderly in 2020 were higher than in 2014 (66.20% prevalence of pre-frailty in 2020 vs. 61.60%; 15.10% prevalence of robust elderly in 2020 vs. 13.20%). Follow-ups of frailty status are mandatory and regularly updated prevalence of frailty are crucial, both of which are incorporated in INALAS. Should frailty prevalence become high, it will be a threat to the elderly, as well as an alarm to health care professionals, researchers, and policy makers (12). The health system must be prepared for the care of older people with frailty (13). Despite the reversibility of frailty to robust state, emphasis should be placed on the prevention, detection, and management of the risk factors associated with frailty. This is because annual mean healthcare cost of frail elderly is more than twice higher than the estimated cost for robust elderly (13).

The prevalence of frailty in Indonesian in 2020 is similar to the prevalence of frailty in East Coast of Peninsular Malaysia based on Fried's phenotype of frailty (18.30%) (14). The prevalence of frailty was 15.9% in Bangkok metropolitan area (15), and 13.9% in Northern Thailand (16). On the other hand, the prevalence of frailty in urban district setting in Malaysia was only 5.7% (17). Previous study in Singapore, a developed city-state in Southeast Asia, found that the prevalence of frailty and prefrailty islandwide was 6.2% and 37%, respectively (18). A recent systematic review and meta-analysis of 56 studies (not including Indonesian data) related to the prevalence of frailty in community-dwelling elderly in low-income and middle-income countries (LMICs) suggested that the pooled prevalence of pre frailty was 49.3% (95% CI 46.4%−52.2%, $I^2 = 97.5\%$) and frailty was 17.4% (95% CI 14.4%-20.7%, $I^2 = 99.2\%$) (19).

We can infer that despite the decreasing prevalence of frailty in Indonesia in 2020 compared to 2014, the prevalence is among the highest in Southeast Asia. The national prevalence of frailty in 2020 was also higher than the pooled prevalence of frailty in other LMICs. In addition, nearly half of Indonesian elderly with disability in 2020 relied on self-medication without proper outpatient treatment for their health problems. Six percent of elderly with disability did not even treat themselves (1). Therefore, development of LTC in Indonesia should be considered. Currently, Indonesia still relies on the accessible integrated service center for older adults (Posyandu Lansia) that involves volunteers to do regular medical check-up services in the community. It was suggested that the elderly care service should be culturally accepted by the service recipients. Cultural and religious values should be incorporated in the care service to increase the efficacy of the programme in Indonesia (20).

However, once LTC is available in Indonesia, physicians could not simply force the elderly in need to receive it. It requires informed consent from the patients who need and want the LTC. This is due to the culture of Indonesian people in terms of respecting and taking care of the elderly until death occurred. In general, filial piety is an important moral tenet in Asian countries. Asian children are expected to provide care for their aging parents (20). Among all Indonesian older adults in 2020, 39.10% lived in three-generation homes, 27.85% lived with other family members (not in a three-generation household), 20.51% lived with his/her spouse, and only 9.80% lived alone (1).

There are still other conditions supporting the development of LTC in Indonesia. Following the discharge from the isolation ward, several dependent older adults were still equipped with nasogastric tube and/or indwelling catheter. During COVID-19 pandemic, several home care teams and/or the family caregivers at home may not provide optimal continuous care after discharge. Not all caregivers at home were able to accompany elderly with functional dependence all the time. Living at home with family members do not guarantee the surveillance and good

quality of care for dependent elderly. The sustainability of home-based care by family members in the future were also a concern in Thailand, accompanied by possible increase in out-migration of adult children. Decreasing fertility rates in Asian countries, including Indonesia, may signify fewer caregivers for the elderly in the future (20).

Indonesia is not the only Association of Southeast Asian Nations (ASEAN) Plus Three (APT) country being ill prepared to cope with the demand for LTC. The Philippines, Vietnam, Lao People's Democratic Republic, Cambodia, and Myanmar also have underdeveloped LTC system. Those countries also have gross domestic product (GDP) per capita lower than $20,000. Although the population is still relatively young compared with Western societies, those countries should establish a sustainable LTC system to meet the increasing demands of LTC amidst limited economic resources (20). LTC is essential to ensure a dignified late life, and to support behaviors to enhance intrinsic and functional capacity of the elderly. Expenditure on health systems on older populations should be seen as an investment, not a cost (21).

By involving more geriatric service care centres in the country and higher number of samples compared to previous national study in 2014 (5), we identified more risk factors associated with frailty, see **Table 3**. Based on the data in 2014, frailty in Indonesia is associated with age 70 years and older (OR 2.72, 95% CI 1.58–4.76), functional dependence (OR 2.89, 95% CI 1.79–4.67), and being at risk for malnutrition or malnourished (OR 3.75, 95% CI 2.29–6.13). Unlike the result of previous national data analysis, age 70 years and older was not associated with frailty in the current study. The findings related to functional dependence and nutritional status in the current study supported the previous Indonesian data.

Functional dependence based on Barthel Index of ADL is associated with nearly 7 times higher risk for frailty than control group. The risk is much higher than previously reported in previous national study. There is inverted association between ADL and frailty (5). A recent meta-analysis of 12 studies concluded that frail elderly were nearly three times more likely to develop or have worsened disabilities in ADL. In other words, frailty is considered as a precursor of disability (22).

Frailty and malnutrition are related syndromes (23), regardless of whether the former or the latter occurs first (24). Being at risk for malnutrition or malnourished is associated with 2-fold higher risk for frailty in this study. Another longitudinal aging study in Asia suggested a possible closed-loop cyclical association between the two. This may in turn lead to a combined malnutrition-frailty state (24). Malnutrition has major impact on the health and social care services. Similar to the burden of healthcare cost of frail elderly (13), community-dwelling individuals with malnutrition were reported to have healthcare costs that are double the cost for non-malnourished individuals (25).

In this study, depression is associated with nearly three times higher risk for frailty in elderly. A systematic review and meta-analysis of 24 studies suggested a reciprocal interaction between frailty and depression. Each condition may be a risk factor for the development of the other. In addition, there is an association between each condition and increased incidence and prevalence of the other (26). There are several potential explanations for the relationship between depression and physical frailty. Both syndromes have common pathophysiological mechanisms including hormonal changes in hypothalamic-pituitary-adrenal (HPA) axis, impaired HPA-axis response to stressful events, and elevated diurnal cortisol. Higher level of salivary cortisol level has been reported to be associated with frailty among community-dwelling female elderly. Moreover, severely depressed elderly may have inactivity, reduced physical activity, and medication non-compliance. Such lifestyle factors are related to frailty syndrome of older people (27). In addition, social isolation is related to depression in the elderly (26). Essential public health strategy in 2020 during the COVID-19 pandemic includes social distancing and stay-at-home measures (28). Since stay-at-home measures may increase social isolation (28), thus physicians and the community should also pay attention to the psychosocial health of the elderly.

There is an association between prior self-reported history of fall in the previous 12 months and 2-fold risk for frailty in our study. Older people who experienced falls had significantly more health problems than patients without falls. Besides, the risk of falling in elderly is also linked to frailty. One of the tools to use in hospital admission setting was "Identification of Seniors at Risk" (ISAR) screening, which is supplementary to vital sign measurement for the elderly to predict both falls and frailty (29). Not only is fall a significant risk factor for frailty, history of hospitalization in the previous 12 months is also associated with frailty. This finding is concordant with the results of previous systematic review and meta-analysis of 8 studies suggesting that elderly with frailty had the highest risk for hospitalization, followed by pre frail and robust elderly (30).

Poly pharmacy has been long known to be related to frailty. In this study, poly pharmacy is associated with 2-fold higher risk for frailty. A meta-analysis of 25 observational studies suggested a bidirectional relationship between poly pharmacy and frailty. The former appeared to be a major contributing factor for development of frailty (31). Poly pharmacy itself is related to the use of inappropriate drugs that are either contraindicated or pose a high risk to the elderly (32). Approximately 70% of Indonesian elderly in our study experienced poly pharmacy. Moreover, potentially inappropriate medication is highly prevalent among Indonesian elderly in primary healthcare centres (52.2%) (33). Therefore, appropriate reduction of poly pharmacy should be a strategy in preventing and managing frailty (31). Physicians should utilize prescribing tools, e.g., START/STOPP and Beers criteria, for appropriate medication reconciliation in elderly population (32).

To the best of our knowledge, this multicentre cross-sectional data analysis had the largest number of samples among other frailty studies in the region. Indonesia is a multiracial archipelago and our study population may represent the real population better by involving different centres and islands. Since transition between robust and frailty state is a dynamic process, we determined to follow up the changes in upcoming years to provide recent data related to geriatric medicine in Indonesia through INALAS for policy makers, guideline development, and

physicians. We also suggested new risk factors associated with frailty in Indonesia, which were not analyzed in the previous multicentre study. The data analysis also included appropriate adjustment for possible confounders.

In conclusion, among Indonesian elderly in this study, 15.10% were robust, 66.20% were pre-frail, and 18.70% were frail. The development of LTC in Indonesia should be considered, accompanied by respecting the local cultural values without forcing the elderly who need it. Frailty is significantly associated with functional dependence, being at risk for malnutrition or being malnourished, depression, history of falls, history of hospitalization, and poly pharmacy. There may be bidirectional relationships between aforementioned risk factors and frailty. Detection and prevention of either one of the factors, including frailty itself, should be emphasized in clinical practice for better outcome of elderly patients and lower healthcare costs.

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 was obtained from the Faculty of Medicine, Universitas Indonesia. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SSe, CS, KH, ND, IA, SSu, FB, RM, LD, AS, RR, RI, MA, and JM contributed to development of study concept and design. SSe, CS, KH, ND, IA, SSu, FB, RM, LD, AS, RR, and RI contributed to Acquisition of data. SSe, RI, MA, and JM contributed to analysis and interpretation of data. SSe, CS, KH, ND, RI, MA, and JM contributed to drafting of the manuscript. All authors contributed to the article and approved the submitted version.

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Prevalence of Sarcopenia and Its Association With Diabetes: A Meta-Analysis of Community-Dwelling Asian Population

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Purpose: Sarcopenia is a major disease affecting mortality and quality of life in the elderly population. We performed a meta-analysis of studies on the community-dwelling population to investigate the prevalence of sarcopenia and its association with diabetes.

Methods: Databases were searched for studies published up to February 3, 2021, reporting the prevalence of sarcopenia in patients with and without diabetes. Data extraction and quality assessment were performed according to the Newcastle-Ottawa scale.

Results: Six articles were included in the systematic review. All the patients were Asian, aged ≥60 years (women 53.4%), and the diabetic and non-diabetic population was 1,537 and 5,485, respectively. In all six studies, the Asian Working Group for Sarcopenia criteria were used to diagnose sarcopenia. The prevalence of sarcopenia was 15.9% in diabetics and 10.8% in non-diabetics. Diabetics showed a significantly higher risk of sarcopenia than non-diabetics (pooled OR = 1.518, 95% CI = 1.110 to 2.076, Z-value = 2.611, $p = 0.009$).

Conclusion: Among the Asian community-dwelling geriatric population, the prevalence of sarcopenia was significantly higher in diabetics than in non-diabetics. These results suggest that strategies for the management of sarcopenia are required in Asian elderly patients, especially with diabetes.

Keywords: diabetes mellitus, type 2, geriatrics, sarcopenia, prevalence, meta-analysis

INTRODUCTION

Globally, rapid increase in the aging population has led to social and health issues associated with age-related chronic diseases. Sarcopenia is a syndrome of age-related degenerative skeletal disease characterized by a progressive and generalized reduction in muscular mass, strength, and function (1). Although controversies remain regarding definitions, assessment tools, diagnostic criteria, and treatment, sarcopenia is developing into a critical public health burden among the elderly, being related to adverse outcomes such as frailty, disability, poor quality of life, and increased mortality. Previous meta-analyses have reported the prevalence of sarcopenia in community-dwelling older

adults, and the range varied from 9.9 to 40.4% depending on the definition of sarcopenia used (2, 3). Whereas, the earlier criterion was based only on muscle mass assessment (4), the recent definitions (5–7) include ethnic differences as well as muscle strength and function, which are more strongly associated with outcomes such as mortality (8).

The incidence of type 2 diabetes increases with age, and recent studies have revealed that both sarcopenia and diabetes have a bidirectional relationship (9). Age-related skeletal muscle degeneration could deteriorate insulin sensitivity and lead to the development of metabolic disorders such as diabetes, and vice versa. Diabetes-related decline in muscle mass, strength, and function leads to sarcopenia and increased disability, fracture, and mortality (10–12).

Although the decline of muscle mass and muscle strength has been compared between diabetic and non-diabetic patients in previous studies (13–16), few studies have compared diabetic and non-diabetic patients using the standardized sarcopenia diagnostic criteria reflecting qualitative changes in the skeletal muscles. To evaluate the prevalence of sarcopenia in diabetics and to compare it to that in non-diabetics, a meta-analysis of studies on the community-dwelling population using standardized criteria is required. Therefore, we systematically reviewed the literature and performed a meta-analysis to evaluate the impact of diabetes on the occurrence of sarcopenia in geriatric adults.

METHODS

Search Strategy

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. We systematically searched for relevant articles in the PubMed, Embase, Cochrane Library, SCOPUS, KoreaMed, Wangfang, and Ichushi databases for studies published from January 01, 1979 to February 03, 2021. The following keywords were used in the search: (sarcopenia OR muscle mass OR muscle strength) AND (prevalence OR epidemiology OR frequency OR incidence) AND (diabetes).

Study Selection

We applied the following inclusion criteria for the selection of articles: (1) the prevalence rate of sarcopenia was evaluated in the community-dwelling general population, (2) the prevalence rate of sarcopenia was investigated in diabetic and non-diabetic populations, (3) the age of included subjects was $\geq$60 years, and (4) loss of appendicular muscle mass and functional decline were considered for the diagnosis of sarcopenia. The exclusion criteria were as follows: (1) repeat publications and (2) lack of reporting on study outcomes.

Data Extraction

After discarding duplicate studies, two reviewers (SC and MC) independently evaluated the potentially eligible studies. The articles were screened for eligibility based on a review of the title and abstract, and disagreements were resolved through consensus. After screening, the full texts of the eligible articles were read independently by the two reviewers, and the eligibility of each article was re-assessed. Subsequently, the data, including the first author, publication date, study type, number of patients, and demographic information (age, sex, and other participant details) were extracted.

Quality Assessment

The Newcastle-Ottawa scale (NOS) for cross-sectional study was used for quality assessment (17), considering the three aspects: selection of subjects, comparability of groups, and assessment of outcome. The NOS allows four stars for selection of subjects, two for comparability of groups, and three for assessment of outcomes, a maximum of nine stars in total. Judgment of bias was expressed as "unsatisfactory studies," "satisfactory studies," "good studies," or "very good studies." The quality of each study was graded as low (0–3), moderate (4–6), or high (7–9). All divergences were resolved by consensus.

Grading of Evidence

The overall quality (certainty) of evidence was assessed using the GRADE system which grades evidence as high, moderate, low, or very low quality. Randomized controlled trials are graded as high-quality evidence by default. Scores can then be downgraded on the basis of the following prespecified criteria: risk of bias (weight of studies shows important risk of bias), inconsistency (substantial unexplained interstudy heterogeneity), indirectness (present of factors that limit the generalizability of the results), imprecision (95% confidence interval [CI] for risk estimates are wide), and publication bias (evidence of small-study effects) (18).

Statistical Analyses

The extracted data were analyzed statistically using Comprehensive Meta-analysis Version 2.0 (Biostat Inc., Englewood, New Jersey). For each analysis, a heterogeneity test was conducted using the I^2 statistic, which helps to evaluate the extent of inconsistency among the results. If I^2 values were $\geq$50%, the data were considered to have substantial heterogeneity, and the random-effects model was used for data analysis. In contrast, if I^2 values were $<$50%, the pooled data were considered homogenous, and the fixed-effects model was applied for data analysis.

The pooled prevalence and 95% CI for sarcopenia were also calculated. Additionally, to analyze the difference in the risk of sarcopenia between diabetes and non-diabetes, we analyzed the odds ratio (OR), and 95% CIs from the raw prevalence data. Statistical significance was set at $P < 0.05$.

RESULTS

Study Selection

A total of 7,239 potentially relevant studies were selected for the preliminary search from all databases (**Figure 1**). We initially excluded 1,119 duplicate studies, and excluded an additional 6,016 publications after reviewing their titles and abstracts. The remaining studies were assessed through a full text review of the articles. The European Working Group on Sarcopenia (EWGS) and Asian Working Group for Sarcopenia (AWGS)

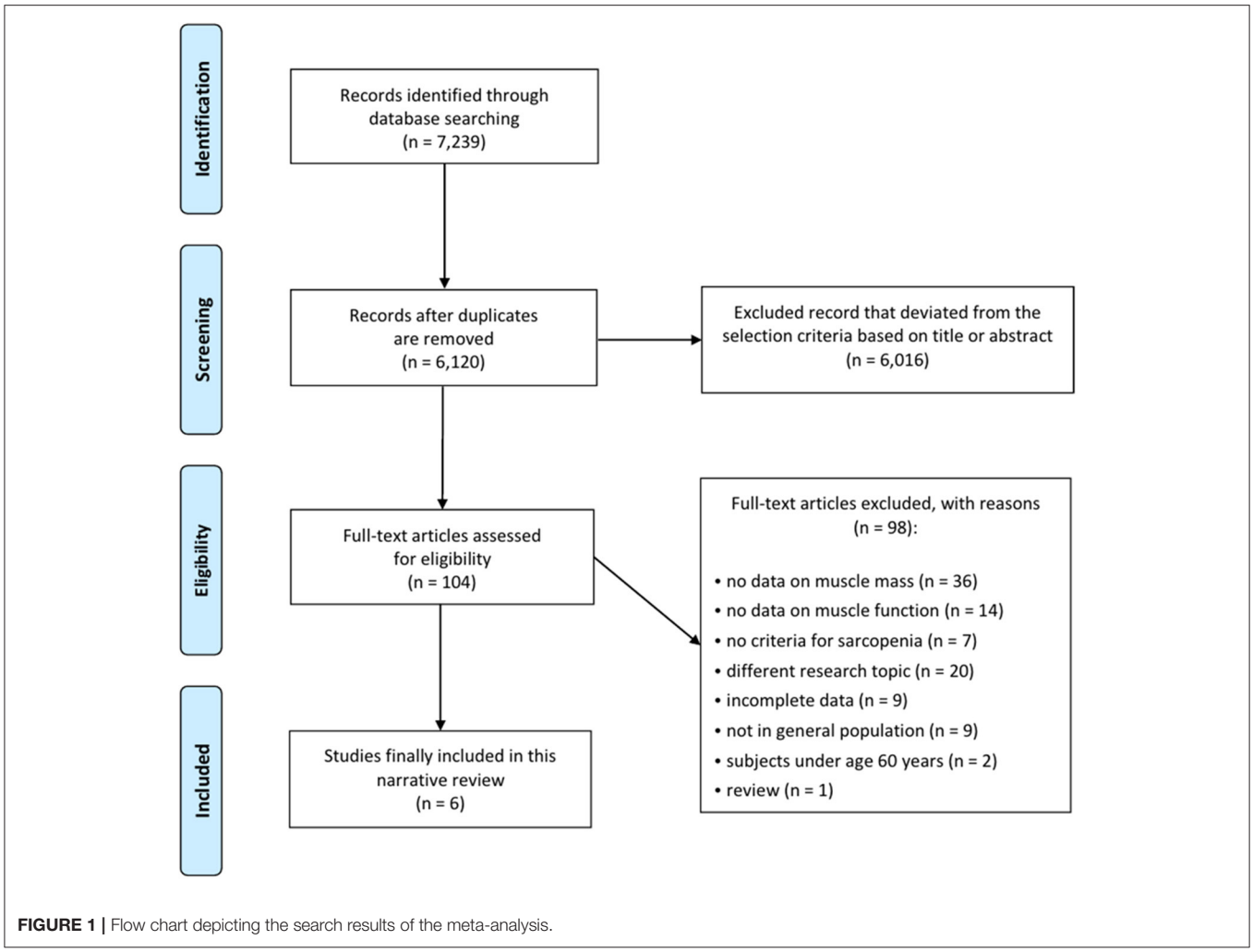


FIGURE 1 | Flow chart depicting the search results of the meta-analysis.

were considered as the standard criteria for the diagnosis of sarcopenia (6, 7). After the systematic review, six articles were included (**Table 1**) (19–24). In all six articles, the AWGS criteria were used to diagnose sarcopenia (7).

Study Characteristics

The selected studies included 1,537 diabetics and 5,485 non-diabetics. All patients were aged ≥60 years, and 53.4% were women. One study used dual-energy X-ray absorptiometry (DXA) to evaluate body composition, and another used bioelectrical impedance analysis (BIA).

Risk of Bias

Three included studies [by Han et al. (19), Kang et al. (21), Nakamura et al. (23), and Wang et al. (24)] were rated nine stars (selection of subjects: fout stars; comparability of groups: two stars; and assessment of outcome: three stars). The remaining two studies [by Han et al. (20) and Keng et al. (22)] were rated eight stars (selection of subjects: four stars; comparability of groups: one star; and assessment of outcome: three stars). Therefore, the quality of all included studies assessed using NOS was considered high.

Grading of Evidence

The overall quality (certainty) of evidence of all the included studies was rated as low.

Meta-Analysis Results

To evaluate the prevalence of sarcopenia among the diabetic and non-diabetic population, the random effects model was used (diabetic: $I^2 = 88.472$; non-diabetic: $I^2 = 89.158$), and the total prevalence was 15.9% (95% CI = 10.6 to 23.2%) (**Figure 2A**) and 10.8% (95% CI = 8.4 to 13.7%) (**Figure 2B**), respectively.

To analyze the difference in the risk of sarcopenia between the diabetics and non-diabetics, the random effects model was used ($I^2 = 65.292$). The diabetics showed a significantly higher risk of sarcopenia than the non-diabetics (pooled OR = 1.518, 95% CI = 1.110 to 2.076, Z-value = 2.611, $p = 0.009$) (**Figure 3**).

Publication Bias

Funnel plot analysis was performed, which showed visually a symmetrical distribution of published studies in all the analyses

TABLE 1 | Characteristics of the included studies.

No.	References	Country	Study design	No. of patients	Age (years)	Men: Women (*n*)	Sarcopenia/ Diabetes (*n*)	Sarcopenia/ non-diabetes (*n*)	Definition of sarcopenia	Body composition assessment	Participants recruitment method	Quality of evidence
1	Han et al. (19)	China	Cross-sectional	1,069	≥60	467:602	21/139	78/930	AWGS	BIA	Residents from three areas (Hougu, East Chadian, and West Chadian) of Tianjin, China.	⊕⊕ (low)
2	Han et al. (20)	China	Cross-sectional	711	≥60	349:362	18/80	59/631	AWGS	BIA	Residents from three areas (Hougu, East Chadian, and West Chadian) of Tianjin, China.	⊕⊕ (low)
3	Kang et al. (21)	Korea	Cross-sectional	2,403	70–84	1135:1268	88/670	196/1733	AWGS	DXA	Part of Korean Frailty and Aging Cohort Study	⊕⊕ (low)
4	Keng et al. (22)	Singapore	Cross-sectional	378	≥65	197:181	26/75	62/303	AWGS	BIA	Part of Singapore Chinese Health study	⊕⊕ (low)
5	Nakamura et al. (23)	Japan	Cross-sectional	1,371	≥65	601:770	22/337	79/1034	AWGS	BIA	Part of Japan Hisayama Study	⊕⊕ (low)
6	Wang et al. (24)	China	Cross-sectional	1,090	60–95	520:570	35/236	96/854	AWGS	BIA	Community-dwelling citizens living in Zhenjiang city of Jiangsu province, China.	⊕⊕ (low)

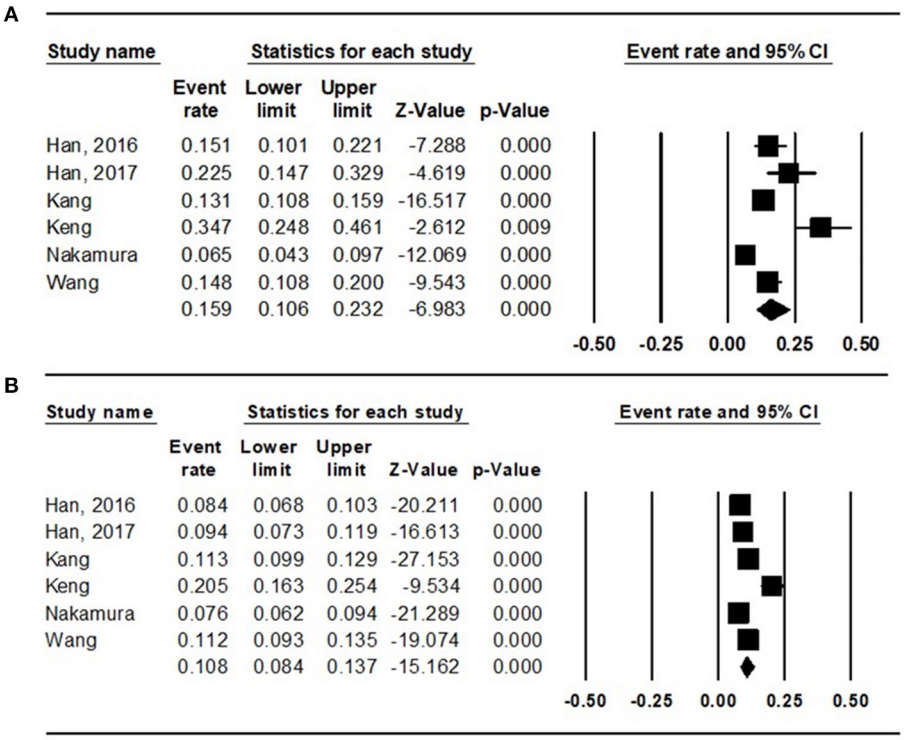


FIGURE 2 | Results of the meta-analysis on sarcopenia prevalence among the **(A)** diabetes population and that among the **(B)** non-diabetes population.

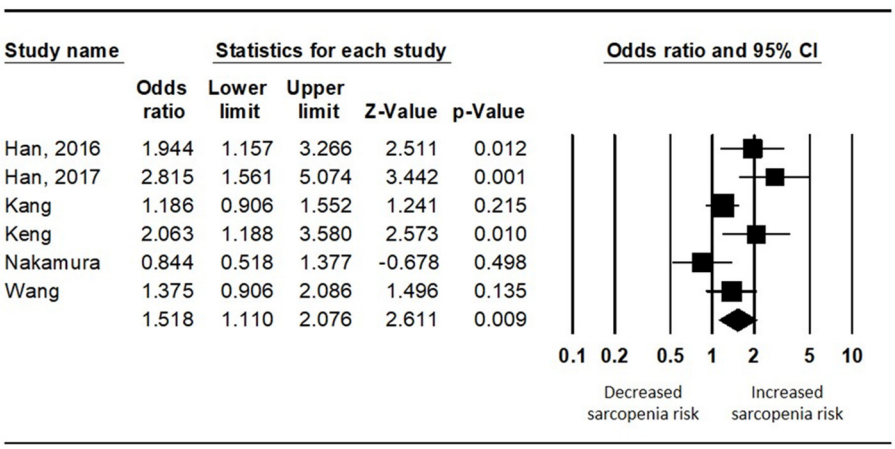


FIGURE 3 | Results of the meta-analysis on the difference in the risk of sarcopenia between the diabetes population and the non-diabetes population.

(prevalence of sarcopenia among the diabetics and non-diabetics and difference in the risk of sarcopenia between the diabetics and non-diabetics) (**Figure 4**).

DISCUSSION

In this meta-analysis, we analyzed studies that evaluated the prevalence of sarcopenia in diabetes and analyzed all the following parameters: muscle strength, quality, and function in the community-dwelling general population aged $\geq$ 60 years. During the systemic review, we found that most studies assessed either muscle strength or quality or did not target the general population. A total of six studies, which fulfilled all inclusion criteria were finally enrolled. The prevalence of sarcopenia was significantly higher in diabetics (15.9%) than non-diabetics (10.8%).

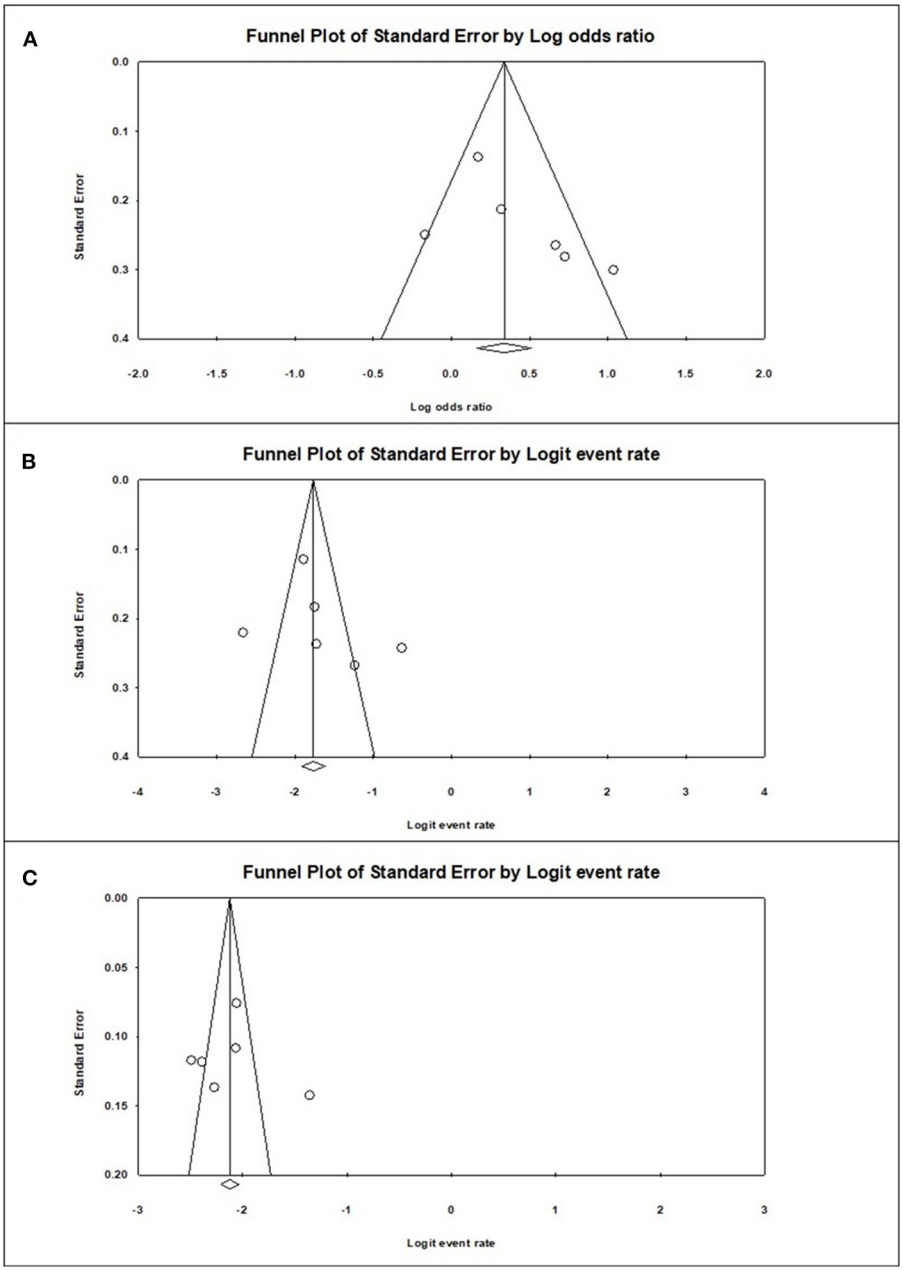


FIGURE 4 | Graphic funnel plots of the included studies **(A)**, diabetes population vs. non-diabetic population; **(B)**, prevalence of sarcopenia among the diabetes population; **(C)**, prevalence of sarcopenia among the non-diabetic population.

After the concept of "sarcopenia" was introduced by Baumgartner et al. (4), various definitions and diagnostic criteria have been introduced. The earlier diagnostic criteria were simply to assess skeletal muscle mass (25, 26), but recently, indicators to evaluate muscle function and quality are known to be considered an important portion of sarcopenia (5–7). Therefore, both components should be evaluated, and the diagnostic criteria reflecting them are widely accepted. Previous meta-analysis results included a number of studies using inconsistent criteria that demonstrated a wide range of the prevalence (2, 3). Since it is well-known that not only quantitative but also a qualitative assessment of body composition reflects the clinical outcomes such as frailty (21), fall risk (27), and mortality (28), we only included studies evaluated by EWGS or AWGS criteria recognized as the standard criteria (6, 7). Therefore, our findings have an advantage including the clinical studies conducted with more relevant criteria that are more closely related to actual clinical outcomes than previous studies. In

addition, the risk of selection bias was less affected because only included the studies target the general population, not patients admitted to hospitals or patients receiving treatment for other diseases.

The evil synergistic effects between sarcopenia and metabolic disease (such as diabetes) are already established from large population studies which lead to critical outcomes such as cardiovascular disease or mortality. In a study on 6,021 (2,593 men, 3,429 women) individuals from the general population in South Korean aged 30–93 years, a low muscle mass increased the risk of metabolically unhealthy status (≥2 components of metabolic syndrome or the presence of hypertension, diabetes, or cardiovascular disease) in non-obese men by 1.88 folds (29). Of 347,130 individuals from the general population (158,959 men, 188,171 women; mean age, 55.9) in the United Kingdom, 4% were diabetic, and diabetics with low handgrip strength had a 4.05 times higher risk for cardiovascular disease mortality compared to the high handgrip strength group (30). Of 610 (diabetics, 306, non-diabetics, 304) patients who were hospitalized at a single center in Brazil, the risk of mortality after discharge was significantly higher in those with diabetes and sarcopenia (OR = 1.78) (28). Insulin resistance is known to be the one of major factors involving the development of sarcopenia (31, 32). In patients with diabetes, age-related anabolic resistance worsens, fat mass increases, and lean mass decreases more rapidly than in non-diabetics (33). Insulin plays a role in inhibiting protein catabolism in muscles, and insulin resistance induces protein dysregulation (31). Insulin resistance causes dysregulation of the potential mediators of glucose and protein metabolism in the skeletal muscles, which are as follows: those regulated by the hypothalamic-pituitary axis [glucocorticoids, insulin-like growth factor 1 (IGF-1), and androgen], as well as Akt/mammalian target of rapamycin signaling, AMP-activated protein kinase, myostatin, urocortins, and vitamin D (34). In addition, advanced glycation end-products accumulate in the skeletal muscles in chronic conditions, resulting in muscle mass reduction and sarcopenia (35). Tumor necrosis factor-α (TNF-α) and TNF-like weak inducer of apoptosis increase the risk of sarcopenia, while IGF-1, insulin, and adiponectin reduce the risk of sarcopenia (36). In elderly diabetes patients, the incidence of sarcopenic obesity (high body fat and low body mass) (37) should be evaluated and should be prevented by nutrition intake and exercise giving anabolic stimulus to skeletal muscle (38).

Among diabetic patients, there are differences in the risk of sarcopenia depending on the duration of diabetes and glucose variability. In a Japanese study on diabetic individuals aged ≥ 60 years (108 men and 105 women), the prevalence of sarcopenia was 19.2%. The risk of sarcopenia increased with increase in the duration of diabetes in women (OR = 1.43) (39). In another Japanese study on 746 diabetic patients aged 38–96 years, the prevalence of sarcopenia was 7%. The risk of sarcopenia was 7.2 times higher in the patients with glycated hemoglobin (HbA1c) ≥8% than that in patients with HbA1c <6.5% when blood glucose control was poor (40). In another study on Japanese diabetics aged 65–87 years (69 men, 33 women), the prevalence of sarcopenia was found to be 11.6%. Low muscle mass, low grip strength, and slow walking speed were associated with larger glucose fluctuations. Glucose fluctuation was reported to increase the risk of sarcopenia (OR = 1.045) (41). Our study assessed the association of diabetes and sarcopenia from the community-dwelling population but have some limitations regarding the effects of glycemic control status, disease duration, level of exercise, malnutrition, and hypoglycemic medications on sarcopenia in peoples with diabetes. Further large epidemiologic studies are warranted in the future. Interestingly, recent anti-diabetic therapeutics might be candidate for prevention of sarcopenia: the use of metformin, glucagon-like peptide-1(GLP-1) receptor agonists, and sodium-glucose co-transporter-2 (SGLT2) inhibitors, and metabolic surgery has been suggested as a potential strategy to reduce fat mass (33). Further prospective studies for the impact of glucose control and body composition modification by appropriate diabetes treatment strategy on sarcopenia prevention are needed.

A limitation of the current meta-analysis is that a relatively small number of relevant studies have been published that used standardized diagnostic criteria for sarcopenia in the community-dwelling general population. Despite this limitation, this systematic review retrieved comparatively large data on the difference in prevalence of sarcopenia among the diabetic and non-diabetic Asian populations.

In conclusion, this meta-analysis revealed that sarcopenia was more prevalent in the diabetic population than in the non-diabetic population. The presence of diabetes significantly affects the occurrence of sarcopenia. To reduce sarcopenia-related complications, proper nutrition intake and resistance exercises are essential. Especially in elderly individuals with diabetes, strategies to reduce glucose variability and maintain healthy body composition while managing cognitive dysfunction and accompanying cardiovascular risks are warranted.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: this is a meta-analysis so the original dataset of reviewed studies is unavailable. Requests to access these datasets should be directed to Seung Min Chung, smchung@ynu.ac.kr.

AUTHOR CONTRIBUTIONS

SMC, JSM, and MCC: conception or design and drafting the work or revising. SMC and MCC: acquisition, analysis, or interpretation of data. All authors: final approval of the 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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The Auxiliary Diagnostic Value of a Novel Wearable Electrocardiogram-Recording System for Arrhythmia Detection: Diagnostic Trial

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Background: AMAZFIT®, a novel wearable electrocardiogram (ECG)-recording system is used for the measurement, acquisition, and storage of single-lead cardiac waveforms for adults. The aim of the study was to evaluate the accuracy of AMAZFIT® for diagnosing arrhythmia in older patients.

Methods: From May to December 2019, we recruited 291 elderly individuals with an average age of 78±10 years old, and 41.9% women. All cardiac waveforms were obtained from the AMAZFIT® which included limb and chest leads. Two trained technicians reviewed all ECG data to determine cardiac rhythm using standard diagnostic criteria. We evaluated the accuracy of AMAZFIT® for identifying arrhythmia by comparing the sensitivity, specificity, accuracy, positive predictive value (PPV), negative predictive value (NPV), and positive and negative likelihood ratios with those of a standard 12-lead ECG.

Results: Of the 291 participants, 197 older adults had arrhythmias, including AF (n = 119), first-degree AVB (n = 28), PACs (n = 25), and PVCs (n = 28). Three of these participants had arrhythmias of AF and PVCs. Chest lead data from 100% and limb lead data from 4.7% of the participants were analyzed. An evaluation of AMAZFIT® for atrial fibrillation (AF) reported a sensitivity, specificity, PPV, NPV PLR, and negative likelihood ratio (NLR) of 93.28, 95.35, 93.28, 95.35, 20.06, and 0.07%, respectively. AMAZFIT® also demonstrated excellent sensitivity for premature atrial contractions (PACs) (84.00%) and premature ventricular contractions (PVCs) (89.29%). However, the device demonstrated a low sensitivity for first-degree atrioventricular block (32.14%).

Conclusions: The AMAZFIT® showed significantly higher sensitivity and specificity for AF, PACs, and PVCs. This portable ECG-recording device based on an algorithm has a potential auxiliary diagnostic value for identifying arrhythmia compared with a standard 12-lead ECG device.

Keywords: arrhythmia, atrial fibrillation, AMAZFIT, detection, diagnostic trial

INTRODUCTION

The incidence and prevalence rates of arrhythmias, which include atrial fibrillation (AF), premature heart beats, and conduction block, are showing increasing trends, particularly in the elderly population. AF is one of the world's most common serious cardiac rhythm problems. Arrhythmias are significantly associated with increased morbidity and higher mortality (1–3). The prevalence of arrhythmia is doubled in people over 40 years of age (4, 5). Earlier identification of AF may reduce the risk of stroke and other consequences. A diagnostic challenge is that AF is often asymptomatic (6). An invasive cardiac monitoring strategy is the gold-standard for high-risk patients (7, 8). Insertable leadless cardiac monitors are associated with higher AF detection rates; however, this strategy is not easily adopted due to its inconvenience, and invasive characteristics, among other reasons.

Wearable arrhythmia detection devices are becoming increasingly popular (9). There is an increasing interest in the use of smartwatch-based technology for AF detection, with some initial data indicating that these devices may be used for population-level AF screening. While there is high clinician interest in the diagnostic precision from these devices, there is a paucity of data that evaluates their accuracy for the diagnosis of arrhythmia (10).

Some smartwatches such as the Apple Watch, Kadia Band, Kadia Mobile, and Simband, have been used for cardiac rhythm analyses (11–14). Unlike these smartwatches, the AMAZFIT® (Huami Corporation, Anhui, China) can collect single-lead cardiac waveforms from the chest lead, which could be used for the measurement, acquisition, and storage of single-lead cardiac waveforms for adults. We aimed to evaluate the accuracy of the AMAZFIT® as a detection tool for the diagnosis of arrhythmia in older patients.

METHODS

This was a diagnostic trial. A 12-lead ECG was used as the gold-standard to evaluate the diagnostic value of a wearable dynamic ECG recorder (AMAZFIT®) for the detection of arrhythmia.

Study Population

We continuously invited patients ($\geq$ 65 years of age) who were admitted to the Center of Gerontology and Geriatrics of West China Hospital from May to December 2019 who had a complaint of palpitation to participate in this study. The exclusion criteria were as follows: (1) a history of cognitive impairment (MMSE $<$ 10 score); (2) a history of skin disorders around the wrist or chest; (3) those who had unstable vital signs; and (4) those who refused to participate. All patients gave written informed consent.

Data Collection

For all participants, after obtaining informed consent, baseline demographic, clinical comorbidities and medications were abstracted from their medical records by a trained staff member. The arrhythmia and the type of arrhythmia were determined according to the results of conventional 12-lead ECG.

All participants were asked to hold the AMAZFIT® wearable dynamic ECG recorder (Model No DL4310/03; Production Permit No 20180012; Product Registration No 20182210012) on their wrist and chest wall for 1 min, during which time the pulse waveform was recorded in the AMAZFIT® Health App. Participants wore an AMAZFIT® on either wrist to collect limb lead data, which was firmly secured above the ulnar styloid. To collect chest lead data, the AMAZFIT® was applied with medical electrode stickers. AMAZFIT® is attached to the left side of the chest wall as shown in **Figure 1**. The mobile phone software was connected to the AMAZFIT®, and then the chest patch mode was selected to start the measurement.

At the same time, all participants were simultaneously acquiring regular 12-lead ECG waveforms. The 12-lead electrode has 10 electrode heads, which are placed on the human chest C1, C2, C3, C4, C5, C6, and the limbs RA(right arm), LA(left arm), RL(right leg), LL(left leg) positions, thereby obtaining 12-lead ECG(I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, and V6). For both techniques, the high pass and low pass filters used for ECG signal processing were respectively 0.6 and 25 Hz for 12-lead ECG and 0.67 and 40 Hz for the AMAZFIT®. Two trained ECG technicians reviewed all ECG data that was collected by AMAZFIT® to determine heart rhythm using standard criteria. In case of disagreement about the diagnosis between the reviewers, an electrophysiologist was consulted. The comparison between conventional 12-lead ECG and chest lead ECG data collected by AMAZFIT® are shown in **Figure 2**.

Statistical Analysis

Statistical analyses were performed using the SPSS 22.0 software program. Continuous variables were described as means $\pm$ standard deviations and categorical variables were described as numbers (percentages). We then calculated test characteristics, including sensitivity, specificity, accuracy, PPV, NPV, positive likelihood ratio and negative likelihood ratio for the AMAZFIT® wearable dynamic ECG recorder detection for AF, first-degree AVB, PACs, and PVCs compared with the expert reviewer diagnosis (criterion standard) of sinus rhythm based on 12-lead ECG.

RESULTS

The characteristics of the 291 participants included in our study are shown in **Table 1**. The mean age of the cohort was 78 $\pm$ 10 years, and 41.9% were women. A total of 119 participants were included in the AF cohort. There was no atrial flutter cases in the AF cohort. The other arrhythmia cohort included 81 participants with: first-degree atrioventricular block (n = 28), PACs (n = 25), and PVCs (n = 28), while the normal ECG cohort included 94 participants.

We used AMAZFIT® to collect cardiac waveform data for all participants, including limb lead and chest lead data. Chest lead data were successfully collected from 291 participants, while limb lead data were successfully collected from 43 participants. A total of 291 (100%) chest lead data recordings

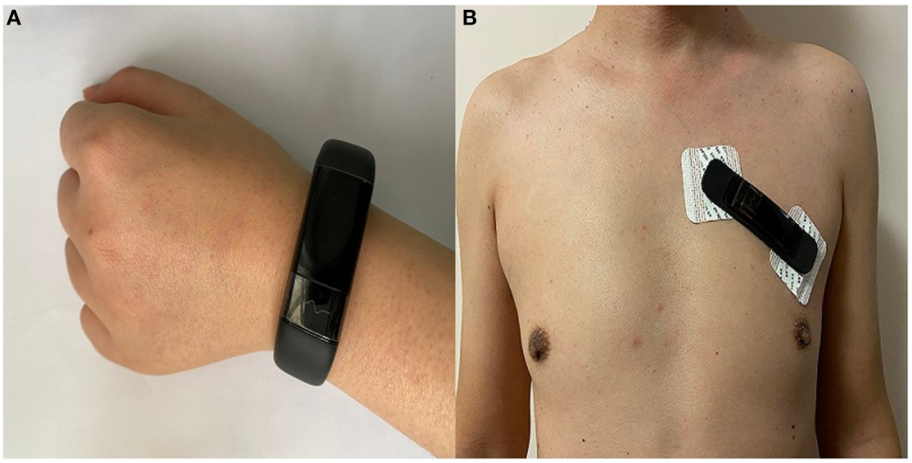


FIGURE 1 | AMAZFIT® location diagram. **(A)**: wrist **(B)**: chest wall.

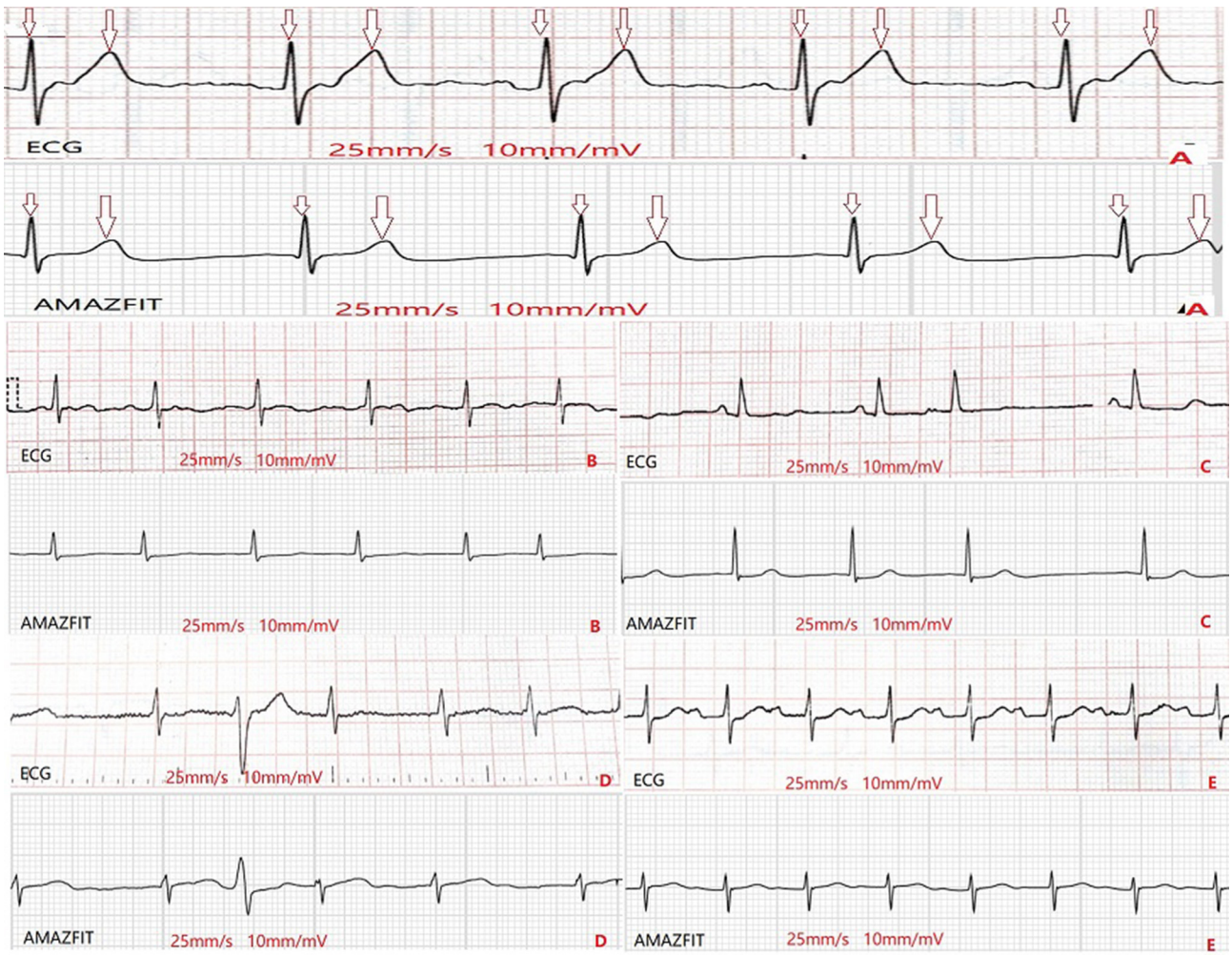


FIGURE 2 | Comparison of the waveforms from ECG and from AMAZFIT®**. (A)**: sinus rhythm; **(B)**: AF; **(C)**: PACs; **(D)**: PVCs; **(E)**: first-degree AVB. AF, arterial fibrillation; PACs, premature arterial contractions; PVCs, premature ventricular contractions; AVB, atrioventricular block.

TABLE 1 | Baseline characteristics of the study population.

	AF (*n* = 119)	AVB (*n* = 28)	PACs (*n* = 25)	PVCs (*n* = 28)	Normal ECG (*n* = 94)
Age, mean (SD), years	76 ± 10	84 ± 9	80 ± 10	76 ± 9	79 ± 9
Female	56(47.1)	7(25.0)	13(52.0)	6(21.4)	38(40.4)
Comorbidity					
Hypertension	65(54.6)	23(82.1)	19(76.0)	20(71.4)	59(62.8)
COPD	22(18.5)	11(39.3)	4(16.0)	5(17.9)	24(25.5)
Diabetes	19(16.0)	12(42.9)	5(20.0)	5(17.9)	25(26.6)
Coronary artery disease	27(22.7)	12(42.9)	7(28.0)	6(21.4)	26(27.7)
Stroke	22(18.5)	6(21.4)	8(32.0)	6(21.4)	9(9.6)
Anti-arrhythmic drug					
β- blocker	45(37.8)	7(25.0)	11(44.0)	14(50.0)	28(29.8)
CCB	34(28.6)	13(46.4)	13(52.0)	10(35.70)	24(25.5)
Digoxin	18(15.1)	0(0.0)	0(0.0)	2(7.1)	1(1.1)
Amiodarone	21(17.6)	1(3.6)	6(24.0)	3(10.7)	7(7.5)

AF, atrial fibrillation; AVB, atrioventricular block; PACs, premature atrial contraction; PVCs, premature ventricular contraction; ECG, electrocardiography; COPD, chronic obstructive pulmonary disease; CCB, calcium channel blockers.

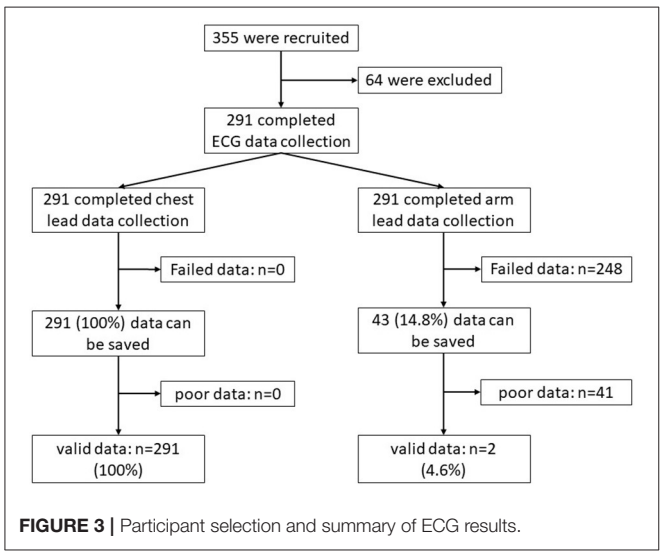


FIGURE 3 | Participant selection and summary of ECG results.

were analyzed, while only two (4.7%) limb lead data recordings were analyzed (**Figure 3**).

Compared with standard 12-lead ECG recordings, the AMAZFIT® detected AF, first-degree AVB, PACs, PVCs and normal ECG with similar accuracy (**Table 2**). An evaluation of the wearable dynamic ECG recorder for AF reported a sensitivity of 93.28%, a specificity of 95.35%, a PPV of 93.28%, an NPV of 95.35%, a PLR 20.06 and an NLR 0.07. This indicates that the smartwatch has excellent sensitivity and specificity for the detection of an irregular pulse from AF. The smartwatch also demonstrated superior sensitivity for PACs (84.00%) and PVCs (89.29%), respectively. However, the device demonstrated a low sensitivity for first-degree AVB (32.14%). The specificity of the AMAZFIT for first-degree AVB (97.72%), PACs (96.62%), PVCs (93.92%), and normal ECG (89.34%) detection was excellent.

We measured the HR of patients with AF using AMAZFIT® and 12-lead ECG. The intraclass correlation coefficients (ICC) of each device with a Bland-Altman plot of the induced SVT HR measurements are shown in **Figure 4**.

DISCUSSION

Our findings revealed that detection of arrhythmia with AMAZFIT® was feasible, and showed high diagnostic accuracy. The AMAZFIT® smart watch displayed excellent sensitivity for AF, PACs and PVCs, and a low sensitivity for first-degree AVB. In addition, we measured the HR of patients with AF using AMAZFIT® and with a 12-lead ECG. The results showed that the device can accurately measure the HR of AF similarly to the 12-lead ECG.

Arrhythmia is a common disease in the elderly, and AF is one of the world's most common serious heart rhythm problems. AF increases the risk of stroke and heart failure in elderly patients, which in turn reduces the quality of life and increases the burden of care for elderly patients (15, 16). Although the 12-lead ECG remains the gold-standard diagnostic test for AF, a major challenge in diagnosis is the often paroxysmal nature of arrhythmia, particularly in its early stages. As such, periodic 24-h Holter monitoring is frequently used to determine the adequacy of rate control and guides medical therapy. The most commonly prescribed non-invasive AF monitors, including Holter and 30-day event monitors, have severe methodological shortcomings that result in low compliance, diagnosis delay, high cost, and adverse patient outcomes. Monitors with automated AF detection capabilities are approved for clinical use, but the invasive nature, cost, and technical limitations have limited their widespread application (17, 18).

There is increasing interest in the use of smartphone-based technology in arrhythmias especially in AF detection with numerous published feasibility and screening studies (19–21). Recently, several different types of smartwatches were used for cardiac rhythm analysis, including the Apple Watch, Kardia Band, Kardia Mobile and Simband (Samsung Electronics

TABLE 2 | Diagnostic accuracy of AMAZFIT® against ECG.

	n	Sensitivity (100%)	Specificity (100%)	Accuracy (100%)	PPV (100%)	NPV (100%)	PLR	NLR
Arrhythmia	197	89.34	92.55	97.59	96.17	80.56	11.99	0.12
AF	119	93.28	95.35	94.50	93.28	95.35	20.06	0.07
First-degree AVB	28	32.14	97.72	91.41	60.00	93.12	14.10	0.69
PACs	25	84.00	96.62	95.53	70.00	98.47	24.00	0.16
PVCs	28	89.29	93.92	93.47	60.98	98.80	14.69	0.11
Normal ECG	94	92.55	89.34	90.38	80.56	96.17	8.68	0.08

PPV, positive predictive value; NPV, negative predictive value; PLR, positive likelihood ratio; NLR, negative likelihood ratio; AF, atrial fibrillation; AVB, atrioventricular block; PACs, premature atrial contraction; PVCs, premature ventricular contraction; ECG, electrocardiography.

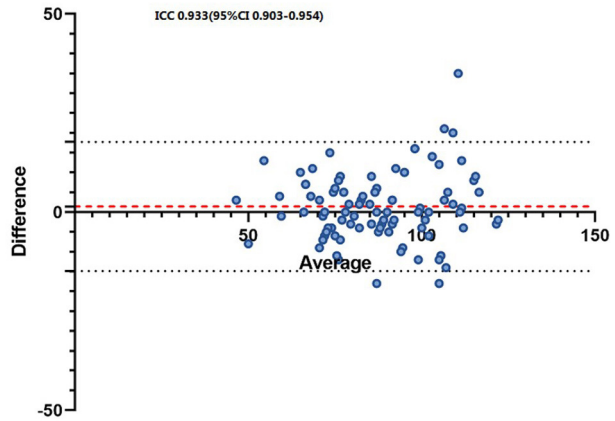


FIGURE 4 | Bland-Altman plots of the heart ratio between the ECG and AMAZFIT®.

Co.) (11–14). The Apple Watch includes an irregular rhythm notification feature that detects PPG-based irregularity at rest, and can notify the user of potential AF (22). In our study, we demonstrated that the AMAZFIT® could reliably distinguish an irregular pulse between AF and other rhythms, including sinus rhythm, PACs,and PVCs. The AMAZFIT® for AF was found to have a sensitivity of 93.28%, a specificity of 95.35%, a PPV of 93.28%, an NPV of 95.35%, a PLR 20.06 and an NLR 0.07. Rajakariar et al. (23) reported sensitivity and specificity using the Kardia Band for identifying AF was 94.4 and 81.9% respectively, with positive and negative predictive values of 54.8 and 98.4%, respectively. These findings indicate that the AMAZFIT® has excellent sensitivity and specificity for the detection of an irregular pulse from AF. In this study, we also report the sensitivity, specificity and accuracy of the AMAZFIT for PACs and PVCs. The results show that the AMAZFIT can accurately discriminate between AF, PACs, PVCs and normal ECG. McManus et al. (24) reported that a smartphone-based app showed good accuracy for PACs, at 95.5%, and for discrimination of PVCs at 96.0%. The results of our study indicate that compared with standard 12-lead ECG recordings, the AMAZFIT® had excellent sensitivity and specificity for diagnosing arrhythmia such as AF, PACs and PVCs, in the older patients.

Because slower heartbeat rates can be observed in normal aging and in disease progression, bradycardia and conduction abnormalities are more commonly identified in the elderly (25). Atrioventricular block that occurs frequently or during exercise, can cause dizziness or symptoms of exertional intolerance. There have been no reports on the identification of atrioventricular block using smartwatches. In our study, we tried to explore the sensitivity and specificity of AMAZFIT® for the diagnosis of first-degree atrioventricular block. The results demonstrated that AMAZFIT® had a low sensitivity (32.14%) for the detection of an irregular pulse from first-degree AVB. However, the specificity of AMAZFIT® for first-degree AVB (97.72%) detection was excellent. Whether AMAZFIT® may serve as a useful complementary tool for first-degree AVB screening needs to be evaluated in a larger -population-based study in the future.

Unlike other smartwatches, AMAZFIT® can collect single-lead ECG recordings from the chest lead in addition to limb single-lead ECG. We obtained chest lead data from all of the participants. While we collected arm lead data from only 43 (14.78%) participants, only two (4.7%) arm lead data recordings could be analyzed. Regrettably, the two recordings could not accurately reflect the heart rhythm of the patients. The advantages of AMAZFIT®, which collects single-lead ECG recordings of the chest lead, include convenience, small size, and long wearability. Accurate measurements with a smartwatch depend on an adequate blood flow and skin contact, and can be altered by the patient, movement of the device, environmental conditions, and ectopic beats (26). The population of this study includes adults 65 years and older. Elderly people may have loose and dry skin, which may affect the electrical conductivity of the skin, and reduce the quality of the AMAZFIT® performance.

As the use of wearable devices and direct-to-consumer medical devices increases in the general population, the potential abnormalities detected by these devices are brought to the attention of clinicians. For patients diagnosed with AF, proper clinical evaluation and confirmatory ECG testing are essential. New devices such as the AMAZFIT® are recommended to be integrated into patient care under physician supervision. Although important questions remain, wearable medical technology should be employed along with physician expertise.

CONCLUSIONS

Technological limitations may prevent the widespread use of AMAZFIT® arrhythmia screening in elderly patients, especially for first-degree AVB. However, AMAZFIT remains favorable compared with the conventional Holter monitoring system for symptomatic arrhythmia monitoring, despite the relatively low wearing rate in the elderly population. In the future, we look forward to more specialized arrhythmia screening tools. Cost-effective, convenient, reliable, and easy-to-apply tools for extended non-invasive AF detection would be helpful.

Study Strenghs

This diagnostic trial revealed that detection of arrhythmia with AMAZFIT® was feasible and showed a high diagnostic accuracy. The AMAZFIT® smart device displayed excellent sensitivity for AF, PACs and PVCs, and a low sensitivity for first-degree AVB. In addition, we measured the HR of patients with AF using AMAZFIT® and with a 12-lead ECG. The results showed that the device can accurately measure the HR of AF similarly to the 12-lead ECG.

Study Limitations

Our study has some limitations. First, the sample size was relatively small, especially the non-AF arrhythmia cohort. Second, we only measured the cardiac rhythm in very stable patients in a motionless state. Third, all of our patients were Asian; therefore, we did not consider whether the skin color could affect the accuracy of the AMAZFIT®.

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 Institutional Review Board of West China Hospital of Sichuan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JW and MY designed and supervised the study. SZ collected the data, and wrote the article. HX, YC, YL, and NZ collected the data and assisted with wrote the article. XG was responsible for the statistical design of the study and for carrying out the 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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BRIEF RESEARCH REPORT
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Videofluoroscopic Swallowing Study Findings Associated With Subsequent Pneumonia in Patients With Dysphagia Due to Frailty

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Dysphagia in frailty or deconditioning without specific diagnosis that may cause dysphagia such as stroke, traumatic brain injury, or laryngeal pathology, has been reported in previous studies; however, little is known about which findings of the videofluoroscopic swallowing study (VFSS) are associated with subsequent pneumonia and how many patients actually develop subsequent pneumonia in this population. In this study, we followed 190 patients with dysphagia due to frailty or deconditioning without specific diagnosis that may cause dysphagia for 3 months after VFSS and analyzed VFSS findings for the risk of developing pneumonia. During the study period, the incidence of subsequent pneumonia was 24.74%; regarding the VFSS findings, (1) airway penetration (PAS 3) and aspiration (PAS 7 and 8) were associated with increased risk of developing pneumonia, and (2) the functional dysphagia scale (FDS) scores of the patients who developed subsequent pneumonia were higher than those of the patients who did not develop subsequent pneumonia. Our study findings might assist clinicians in making clinical decisions based on the VFSS findings in this population.

Keywords: dysphagia, aspiration pneumonia, frailty, video fluoroscopic swallowing study, penetration-aspiration scale, functional dysphagia scale

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INTRODUCTION

Frailty is a complex syndrome associated with a progressive decline in physical, mental, and social functions (1). In most cases, frailty develops because of an age-related decline in multiple physiological systems and increases the risk of catastrophic deterioration of physiological function and health in older adults (1). Moreover, persistent illness can cause frailty. Frailty is associated with muscle loss, weakness, reduced activity, slowness, and disability (2). In frailty, there is a decline in not only overall body function, but also swallowing function (3). Although the accurate prevalence of dysphagia has not been evaluated, many studies have reported that frailty is an important cause of dysphagia and that the prevalence of dysphagia increases with higher degrees of frailty (3–5).

Effective and safe swallowing is a basic requirement for sustaining life. Dysphagia greatly affects general health due to malnutrition, limits social life, and deteriorates the quality of life. Furthermore, dysphagia frequently causes aspiration pneumonia, a leading cause of mortality (6, 7). Therefore, clinicians should thoroughly investigate the presence of dysphagia. Furthermore, knowledge of factors that influence the occurrence of aspiration pneumonia or predictive findings for aspiration pneumonia allows clinicians to observe and manage individuals at risk of pneumonia and prevent its development.

Videofluoroscopic swallowing study (VFSS) is a standard diagnostic tool for dysphagia (8). It provides information related to swallowing function, such as the presence of penetration or aspiration, oral or pharyngeal transit time, and the presence of residue in the pyriform sinuses and valleculae (8). VFSS can show the involvement of every phase of swallowing in detail. Based on the results of the VFSS, clinicians provide a dietary prescription and develop a treatment plan. We propose that some findings of VFSS be used to evaluate the risk of pneumonia in a person with frailty.

In the current study, we evaluated the VFSS findings that increased the likelihood of developing pneumonia in a person with frailty.

METHODS

Patient Selection and Data Collection

This study was approved by the Institutional Review Board of the University Hospital. All inpatient VFSS conducted at our hospital over two consecutive years from January 2019 to December 2020 were reviewed retrospectively. In addition, further data were obtained from the medical records, including age, sex, etiology of dysphagia, and subsequent pneumonia or death after VFSS. The etiology of dysphagia was determined according to the admission diagnosis or the reason for VFSS referral. A case of pneumonia was identified based on the antibiotic prescription record plus chest imaging, and the follow-up period for the detection of subsequent pneumonia or death was 3 months after VFSS.

The inclusion criteria were as follows: (1) age at VFSS $>$ 20 years and (2) oropharyngeal dysphagia due to frailty or deconditioning without specific diagnosis that may cause dysphagia such as stroke, traumatic brain injury, or laryngeal pathology. The exclusion criteria were as follows: (1) esophageal dysphagia; (2) dysphagia due to known neurologic conditions including stroke, traumatic brain injury, anoxic brain injury, brain tumor, amyotrophic lateral sclerosis, Parkinson's disease, or Alzheimer's disease; (3) dysphagia from laryngeal pathology, including laryngeal cancer, stenosis, paralysis, and postoperative head and neck surgery; and (4) patients who had been undergoing antibiotic treatment at VFSS.

VFSS was performed using an X-ray flat panel detector system (FPD, Zexira®, Canon Medical Systems, Otawara, Tochigi, Japan), and fluoroscopic images were saved as digital media at 30 frames per second using a scan converter. Bonorex 300 injection (iohexol 647 mg/mL, Central Medical Service, Seoul, Korea) was used as the contrast medium, and the test sequence was (1) 3 mL and 10 mL of contrast medium, (2) 5 mL of yogurt and contrast medium mixture (2 mL of contrast medium mixed with 10 g of yogurt), (3) 5 mL of banana and contrast medium mixture (2 mL of contrast medium mixed with 10 g of banana), and (4) 10 mL of contrast medium in a cup. For patient safety, the test was stopped when second aspiration was observed at any stage; therefore, not all types of foods were given to all patients. The results of VFSS were graded using the penetration-aspiration scale (PAS) (9) and functional dysphagia scale (FDS) (10) (**Supplementary Table 1**). The highest score for any type of food tested in the VFSS was used for analysis.

Statistical Evaluation

Data were analyzed using the Statistical Package for Social Sciences version 20.0 (IBM Corp., Armonk, NY). The patients were divided into two groups according to the presence or absence of pneumonia during the 3 months after VFSS. Differences in demographic characteristics between the two groups were compared using the independent *t*-test and the chi-square test. The PAS scores of the VFSS results were analyzed using a logistic regression test, as proposed in a previous study (11), and the FDS scores were analyzed using the independent *t*-test. Receiver operating characteristic (ROC) analysis was performed to evaluate the predictive accuracy of FDS for developing pneumonia. A sensitivity analysis was performed including only patients aged 60 years and older to investigate whether there is any difference in the study outcomes as older patients are known to be vulnerable to develop frailty syndrome. Statistical significance was set at $P < 0.05$.

RESULTS

A total of 1,051 inpatient VFSS reports were identified from January 2019 to December 2020. Of these, 190 patients were included in the analysis; the mean age of the patients was 75 ± 11 (range, 41–94) years, and 96 out of 190 patients (50.53%) were male. Among these, 47 patients (24.74%) had been diagnosed with pneumonia and no patient had died in the 3 months after VFSS. The demographic data of the patients with and without pneumonia are presented in **Table 1**. When comparing patients with and without pneumonia, no significant differences were found in age and sex between the two groups (**Table 1**).

The distribution of PAS scores of patients with and without pneumonia is depicted in **Figure 1**. The results of the logistic regression analysis to determine the relative risk of developing pneumonia according to the PAS score are shown in **Table 2**. Patients who scored PAS 3, 7, and 8 had 5.829-, 3.176-, and 5.009-times higher risk of developing pneumonia, respectively, compared to patients who scored PAS 1 on the VFSS ($p = 0.024$, $p = 0.020$, and $p = 0.004$, respectively).

The mean value of the FDS scores was 22.15 ± 19.48 in the patients without pneumonia and 31.28 ± 19.72 in the patients with pneumonia; the mean value of the FDS appeared significantly different between the two groups ($p = 0.006$) (**Table 1**). When analyzing subscores of the FDS, statistically significant differences were found in the "residue in the oral cavity" ($p = 0.035$), "laryngeal elevation and epiglottic closure" ($p = 0.003$), "residue in the valleculae" ($p = 0.002$), and "residue in the pyriform sinuses" ($p = 0.009$). For predicting pneumonia after VFSS, the area under the ROC curve of FDS was 0.639 (95% confidence interval, 0.549–0.728, $p = 0.004$) (**Figure 2**). The optimal cutoff value obtained from the maximum Youden's index (*J*) was 23.50 (sensitivity, 61.7%; specificity, 61.5%).

In the sensitivity analysis,168 patients were aged 60 years and older were included. Among these, 39 patients

TABLE 1 | Demographic data of the study population and functional dysphagia scale (FDS) scores of the patients with and without subsequent pneumonia after VFSS.

	Patients without subsequent pneumonia	Patients with subsequent pneumonia	*p*-value
Age	75.57 ± 11.59	72.89 ± 9.45	0.154†
Gender (M:F)	68:75	27:20	0.239‡
FDS total score	22.15 ± 19.48	31.28 ± 19.72	**0.006†**
FDS subscore			
Lip closure	0.52 ± 1.75	0.74 ± 0.80	0.459†
Bolus formation	0.84 ± 1.49	1.34 ± 1.51	0.051†
Residue in oral cavity	1.24 ± 1.46	1.79 ± 1.68	**0.035†**
Oral transit time	1.59 ± 2.66	2.17 ± 2.01	0.234†
Triggering of pharyngeal swallow	3.02 ± 4.63	3.40 ± 4.79	0.626†
Laryngeal elevation and epiglottic closure	3.86 ± 5.63	6.89 ± 6.00	**0.003†**
Nasal penetration	0.00 ± 0.00	0.09 ± 1.58	0.323†
Residue in valleculae	4.42 ± 3.31	6.21 ± 3.52	**0.002†**
Residue in pyriform sinuses	3.64 ± 3.45	5.36 ± 3.94	**0.009†**
Coating of pharyngeal wall after swallow	1.94 ± 3.96	1.91 ± 3.98	0.965†
Pharyngeal transit time	1.06 ± 1.77	1.36 ± 1.92	0.327†

Values are presented as number or mean ± standard deviation.
†p-value was calculated using an independent t-test.
‡p-value was calculated using the chi-square test.
Bold numbers are significant at p < 0.05.

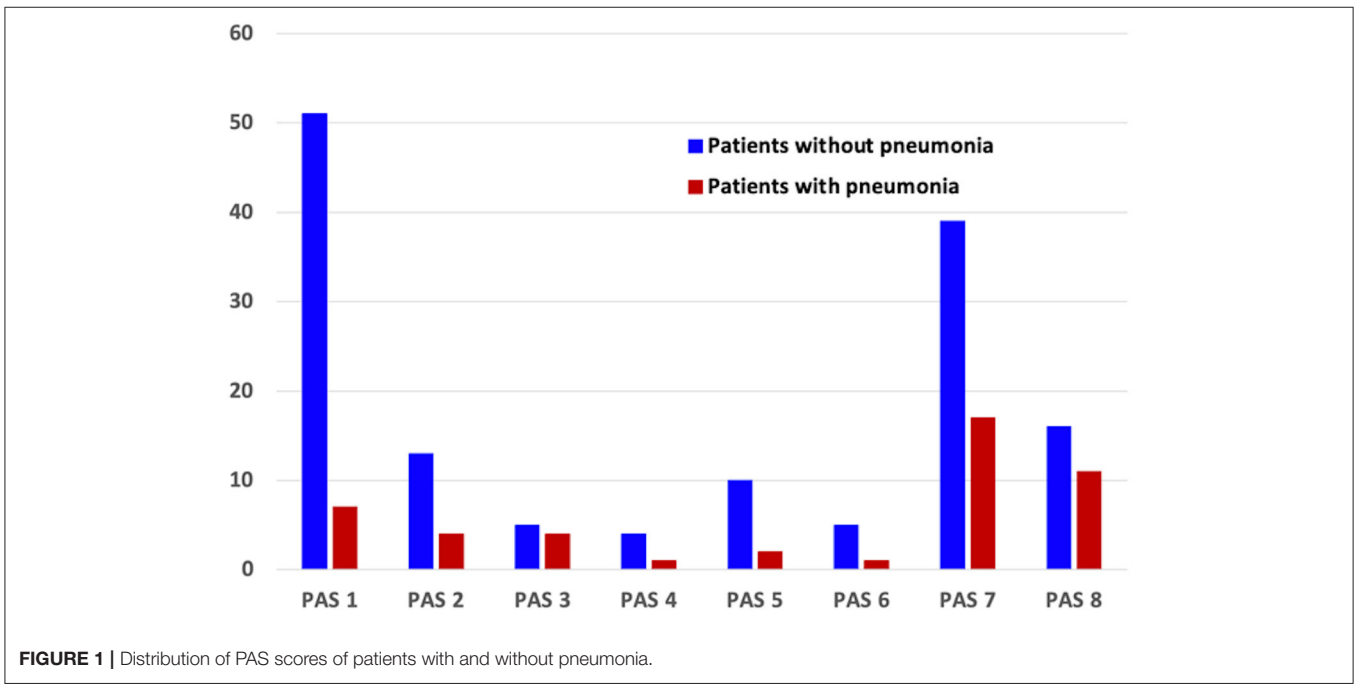


FIGURE 1 | Distribution of PAS scores of patients with and without pneumonia.

(23.21%) had been diagnosed with pneumonia. No significant difference was found in age and sex between patients with and without pneumonia (**Supplementary Table 2**), and the results of the logistic regression analysis of the PAS score showed similar results when compared to patients of all ages in that patients who scored PAS 3, 7, and 8 had significantly higher risk of developing pneumonia compared to patients who scored PAS 1 (OR = 7.200, $p = 0.028$; OR = 4.800, $p = 0.010$; and OR = 10.000, $p = 0.001$, respectively) (**Supplementary Table 3**). The mean value of the FDS scores was significantly higher in patients with pneumonia when compared to patients without pneumonia (31.03 ± 19.84 and 22.48 ± 19.46, respectively; $p = 0.018$), (**Supplementary Table 2**). In FDS subscore analysis, statistically differences were found in the "bolus formation" ($p = 0.038$), "laryngeal elevation and epiglottic closure" ($p = 0.008$), "residue in the valleculae" ($p = 0.002$), and "residue in the pyriform sinuses" ($p = 0.013$).

TABLE 2 | Odds ratio for development of subsequent pneumonia after VFSS according to PAS scores.

PAS score	OR	95% Confidence interval		*p*-value†
		Lower bound	Upper bound	
1	1.0			
2	2.242	0.569	8.832	0.249
3	5.829	1.257-	27.022	**0.024**
4	1.821	0.177	18.709	0.614
5	1.457	0.263	8.068	0.666
6	1.457	0.148	14.357	0.747
7	3.176	1.199	8.411	**0.020**
8	5.009	1.665	15.071	**0.004**

†*p-value was calculated using logistic regression test.*
Bold numbers are significant at $p < 0.05$.
PAS, penetration-aspiration scale.

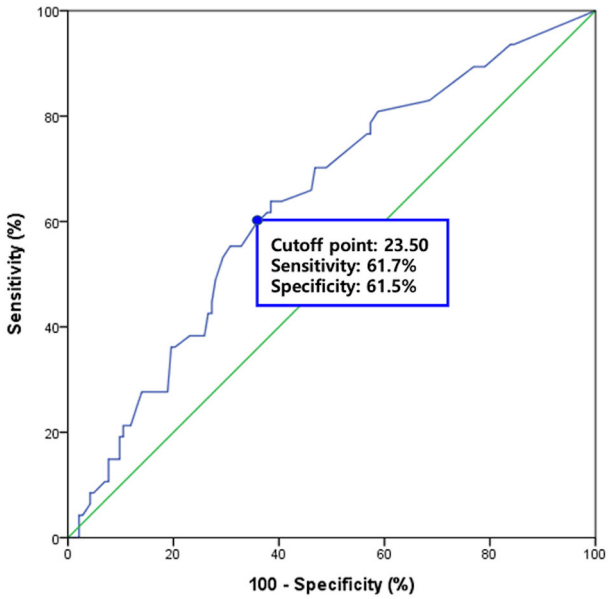


FIGURE 2 | The diagnostic value of the functional dysphagia scale (FDS) for predicting subsequent pneumonia after VFSS. The area under the receiver operating characteristic (ROC) curve of FDS for the prediction of subsequent pneumonia was 0.639 (95% confidence interval, 0.549–0.728, $p = 0.004$). The optimal cutoff value obtained from the maximum Youden's index (*J*) was 23.50 (sensitivity, 61.7%; specificity, 61.5%).

DISCUSSION

Aspiration pneumonia is a subtype of lung infection that is part of a continuum rather than a distinct entity, regardless of whether it is community-acquired pneumonia or hospital-acquired pneumonia (12). Among the known risk factors for aspiration pneumonia, including dysphagia, reduced consciousness, neurologic disorders, poor oral hygiene, dependency for feeding, tube feeding, sarcopenia, and gastroesophageal reflux disease (13), dysphagia is one of the most consistent factors, and it is prevalent not only in patients with neurologic diseases and head and neck diseases, but also in patients with frailty or general weakness without a specific diagnosis that may cause dysphagia (14–19). However, less is known regarding the incidence of subsequent pneumonia in this population, and the findings of VFSS are associated with an increased risk. This study followed 190 patients with dysphagia due to frailty or deconditioning without a specific diagnosis that may cause dysphagia for 3 months and analyzed VFSS findings for the risk of developing pneumonia. To the best of our knowledge, this is the first study to investigate this topic. During the study period, the incidence of subsequent pneumonia was 24.74%; regarding the VFSS findings, (1) airway penetration (PAS 3) and aspiration (PAS 7 and 8) were associated with increased risk of developing pneumonia, and (2) the FDS scores of the patients who developed subsequent pneumonia were higher than those of the patients who did not develop subsequent pneumonia.

The PAS was developed in 1996 by Rosenbek et al. to characterize the severity of airway invasion seen on VFSS by indicating the anatomical depth at which the food material enters and to allow clinicians to track changes in swallowing function over time (9). The association between airway invasion on VFSS and pneumonia has been well-documented in previous studies (20–22). Our data are consistent with those of previous studies in this regard. However, statistically significant results were only found for PAS scores of 3, 7, and 8. This might be explained by the relatively small number of patients with PAS 4, 5, and 6 in our study (5, 12, and 6 persons, respectively). In addition, previous studies have reported that PAS 2 is no longer regarded as abnormal (23), and PAS 4 and 6 are rarely observed (24, 25), which is consistent with our findings.

In addition to PAS, we evaluated the swallowing status using FDS. It was originally developed for quantifying functional dysphagia in stroke patients (10), but it has also been used to evaluate swallowing function in patients with various diseases, including stroke, Parkinson's disease, and head and neck cancer (20, 26–28). Our data suggest that FDS might be useful for evaluating patients with dysphagia due to frailty or general weakness. In addition, significantly larger amounts of oral and pharyngeal residues, as well as reduced laryngeal elevation and epiglottic closure, were observed in patients with pneumonia compared to patients without pneumonia, consistent with previous studies (29, 30). However, in the ROC analysis, the area under the ROC curve was 0.639, which indicated poor diagnostic value of FDS in predicting subsequent pneumonia in this population (31), that might have resulted from the fact that the FDS was originally tested for detecting aspiration and not pneumonia (10). Not every patient with documented aspiration on an instrumental test develops subsequent pneumonia, although airway aspiration significantly increases the risk of pneumonia (15).

The results of the sensitivity analysis, in which only patients ≥ 60 years were included, were similar to original test results except for the fact that scores for the "residue in the oral cavity," which was significantly different between the two groups in the original

analysis, was not significantly different in the sensitivity analysis. Instead, the scores for the "bolus formation" was significantly higher in patients with subsequent pneumonia in the sensitivity analysis. However, although these were statistically significant, they might not be clinically significant, considering the small mean differences of the two subscores between patients with and without pneumonia.

Considering the rapid aging of the global population, it is expected that the prevalence of dysphagia in frailty might also increase. In addition, a recent study found that the prognosis of dysphagia outcome, a higher mortality rate during the 54-month follow-up period after VFSS, is affected by the etiology of dysphagia rather than the severity of aspiration determined by PAS, and the worst outcome was observed in patients with dysphagia due to frailty or generalized deconditioning when compared to patients with dysphagia due to stroke, neurologic diseases, trauma, surgery, or laryngeal pathologies (32). However, only patients with aspiration (a PAS score $\geq$ 5) were included and VFSS findings other than PAS scores were not considered in that study. Therefore, it remains unclear which findings of the VFSS are associated with subsequent pneumonia and how many patients actually develop subsequent pneumonia in this population. We tried to obtain more comprehensive clinical information by including all inpatient VFSS conducted at our hospital during the study period so that all patients with symptoms or signs of dysphagia could be included in the analysis. Our study findings might assist clinicians in making clinical decisions based on the VFSS findings in this population.

However, this study had several limitations. First, this is a retrospective study; therefore, some data that might add more value to the study were not available, such as frailty scores or the severity of disease at the time of VFSS because the tests required for calculating them were not routinely performed. In addition, patients who developed pneumonia but did not come to our institution for follow-up care after they were discharged home or to other institutions such as secondary hospitals or long-term care facilities might have been omitted from the calculation of the incidence of pneumonia, therefore underestimating the prevalence of subsequent pneumonia. Second, the follow-up period was relatively short: the 3 months after the VFSS. Lastly, this study was conducted in a single tertiary academic hospital, which might affect the generalizability of the interpretation of the study findings. Further large-scale prospective studies are required to achieve a comprehensive understanding of dysphagia in frailty or general weakness, without specific diseases that cause dysphagia.

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 Institutional Review Board of Yeungnam University Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MC and SK conceived the idea, determined the study design, collected data, performed the statistical analysis, and drafted and revised the manuscript. All authors contributed to the article and approved the submitted version.

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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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REVIEW
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Frailty Pathogenesis, Assessment, and Management in Older Adults With COVID-19

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The 2019 coronavirus disease (COVID-19) is a highly contagious and deadly disease. The elderly people are often accompanied by chronic inflammation and immunodeficiency, showing a frail state. The strength, endurance, and physiological function of the elderly are significantly decreased, and the ability to deal with stress response is weakened. They are the high-risk group that suffering from COVID-19, and rapidly developing to critical illness. Several recent studies suggest that the incidence rate of COVID-19 in elderly patients with frailty is high. Early assessment, detection, and effective intervention of frailty in COVID-19 patients are conducive to significantly improve the quality of life and improve prognosis. However, there are insufficient understanding and standards for the current evaluation methods, pathogenesis and intervention measures for COVID-19 combined with frailty. This study reviews the progress of the research on the potential pathogenesis, evaluation methods and intervention measures of the elderly COVID-19 patients with frailty, which provides a reference for scientific and reasonable comprehensive diagnosis and treatment in clinical.

Keywords: COVID-19, frailty, pathogenesis, assessment, management

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INTRODUCTION

Novel coronavirus SARS-CoV-2, named "coronavirus disease 2019" (COVID-19) by the World Health Organization (WHO) on February 11, 2020, is one of the highly pathogenic β-coronaviruses. This coronavirus spreading through the respiratory tract to cause pneumonia showed high infectivity and mortality. As of March 1, 2021, the COVID-19 pandemic has spread to 192 countries with over 114.2 million confirmed cases and 2.3 million deaths (1). It is reported that the mortality of COVID-19 rose exponentially with age, from 0.4% among those aged 40–49 years to 3.6% among those aged 60–69 years and 14.8% among those aged >80 years (2). The possible reasons for this phenomenon are changes of physiological structure and function, accompanied by chronic inflammation, immune decline, and decreased anti-stress ability, which are not conducive to the prognosis of COVID-19. In this paper, the epidemiology, potential pathogenesis, evaluation methods, and intervention measures of old COVID-19 patients combined with frailty are reviewed, which can provide reference for scientific and reasonable clinical comprehensive diagnosis and treatment.

DEFINITION OF FRAILTY

Frailty, which is common in all countries, is a major cause of functional decline and early death in the elderly (3, 4). This syndrome is either physical or psychological or a combination of both, and is a dynamic process that can improve or worsen over time. In 2013, a consensus group defined frailty as "A medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death," consisting of delegates from six major international, European, and US societies (5). There are two principal models. In Fried's phenotype model, frailty is based on three or more components of poor grip strength, slow walking speed, low physical activity, exhaustion, and unintentional weight loss (6). The frailty index, or cumulative deficit model, defines frailty in terms of the accumulation of "deficits" (symptoms, signs, diseases, and disabilities). A frailty index score reflects the proportion of potential deficits present (7). The phenotype model defines frailty in physical terms, whereas the cumulative deficit model uses a broader definition of frailty.

EPIDEMIOLOGY

Frailty can occur before the age of 65, but the probability of frailty is on the rise in the elderly aged 70 and above (8). Studies suggest that the incidence of frailty reaches 15% in the elderly over 65 years old and more than 25% in people over 85 years old (9). Incidence rate in women is higher than in men (10, 11). An important reason suggested is that old women with frailty have more abdominal fat than old men (12). Abdominal adiposity is associated with systemic inflammation by mediating its link with metabolic syndromes, which are important markers of oxidative stress and result in skeletal muscle damage and low grip strength (12). This factor might be a core mechanism leading to sex-associated frailty. Besides, lower education level, lower income, lower socioeconomic status, and minority are all positively related to the frailty (13, 14). These persons tend to be frailer, lonelier, and more isolated than others. A prospective study demonstrated high levels of loneliness were associated with increased risk of physical frailty (15).

One study enrolled 1,564 COVID-19 patients with the median age of 74 years old. According to the clinical frailty scale (CFS), the incidence of frailty (CFS score 5–9) was 49.4%. Results showed that frail patients had both an increased risk of mortality and longer duration of hospital stay compared with patients who were not frail, which worsened with increasing frailty (16). In a meta-analysis of 3,817 patients with COVID-19, the pooled prevalence for CFS 1–3 was 34% (32–36%), CFS 4–9 was 65% (61–70%). Each 1-point increase in CFS was associated with 12% increase in mortality rate (17). A series of studies in this field have shown that older patients with COVID-19 have a higher incidence of frailty, and frailty has a significant negative effect on the prognosis of COVID-19 patients.

POTENTIAL PATHOGENESIS

At present, the exact pathogenesis of frailty in old adults with COVID-19 has not been fully elucidated. A large number of studies have found that the levels of inflammatory factors are increased in both COVID-19 and frailty patients (18–21). Inflammatory response may be involved in the potential pathogenesis. During the acute phase of viral infection, circulating inflammatory cytokines are elevated in old patients with COVID-19. Upregulated Interleukin-6 (IL-6), activates STAT3 by tyrosine phosphorylation to trigger inflammatory response through the JAK/STAT signaling pathway (22). The resulting inflammation can generate Reactive Oxygen Species (ROS) causing both oxidative damage and eliciting an amplification of the cytokines' release, inducing a positive feedback loop resulting in a chronic systemic pro-inflammatory state where tissue injury and healing mechanisms proceed simultaneously (23). Besides, increased inflammation contributes to markers of blood clotting elevate, and long-term high coagulation state increases the risk of blood clots (24). High levels of inflammatory cytokines are also associated with a risk of muscle insufficiency, decreased skeletal muscle mass and loss of strength, leading to sarcopenia (25). These accumulative impairments can lead to a decline in multi-system function in elderly patients with COVID-19, which we called frailty.

Interleukin-6 also has a broad effect on cells of the immune system. It can induce the transcription factor Bcl-6 to transform naive T cells into follicular helper T cells, helping to initiate the adaptive immune response and to regulate auto-tolerance, to prevent autoimmunity (26, 27). However, high levels of IL-6 in old patients with COVID-19 can inhibit the response of alveolar macrophages and dendritic cells to influenza virus to produce antiviral interferon. It can further inhibit virus-specific CD8 T-cell responses (28, 29), and immune repertoire would be skewed to the memory phenotype, T cell clonal expansion, increased autoimmune antibody production that leads to frailty (30) (**Figure 1**). Meanwhile, because of suppressed virus-specific CD8 T-cell responses, it is difficult to clear coronavirus. Thus, frailty interacts with COVID-19 in a vicious cycle, and early identification of COVID-19 combined with frailty and timely intervention measures would significantly improve the quality of life and improve prognosis.

Malnutrition plays a key role in the pathogenesis of both frailty and sarcopenia. Elderly patients with COVID-19 often show low intake during hospitalization, forming an acute negative nutritional balance, which is characterized by the deficiency of multiple nutrients. If there are insufficient proteins and lipids to keep organ function and muscle activity, muscle will be catabolized to provide energy leading to sarcopenia (31). If old COVID-19 patients are lack of 25-hydroxyvitamin D, they will develop osteoporosis, and are susceptible to systemic infection, damage immune response, and even autoimmunity (32), promoting the occurrence of frailty. Meanwhile, with the appearance of frailty, the appetite would slough to aggravate malnutrition (33), which is not conductive to the prognosis of COVID-19. Therefore, early nutritional intake of elderly patients with COVID-19 is of great significance to prevent frailty.

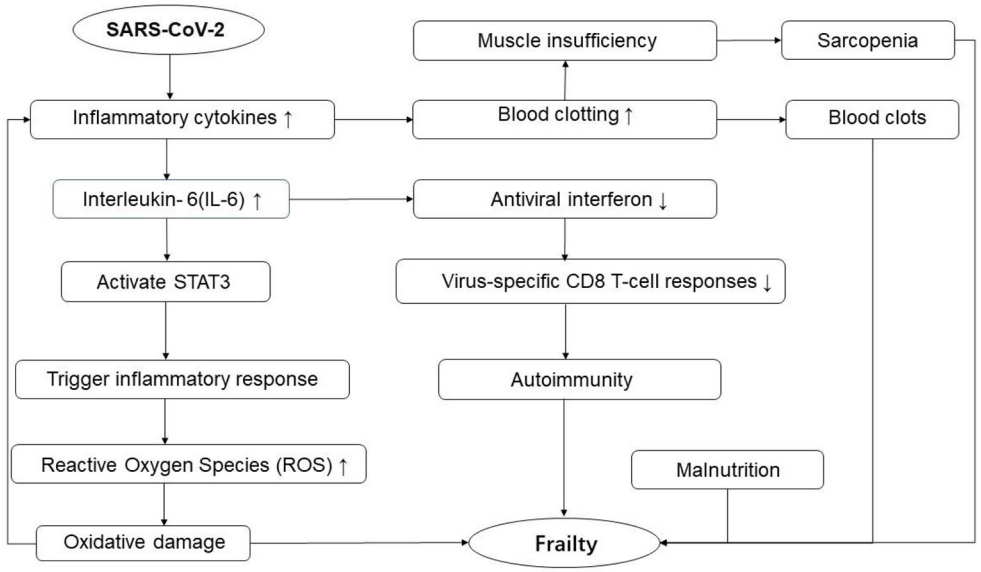


FIGURE 1 | Potential pathogenesis of frailty in elderly patients with COVID-19.

POST-COVID-19 IMPLICATIONS

The old COVID-19 persons combined with frailty tend to experience substantially more severe symptoms and lethality. Infection produces biological damage and loss of homeostasis. This ultimately contributes to accelerated aging and the development of age-related diseases (34).

About the impact of infections on physical function, only three studies performed objective physical and motor function tests, which targeted different physical domains (35–37). Despite the methodological heterogeneity, most studies support the hypothesis that infections impair physical function. The potential mechanisms are multiple. Prolonged immobility during hospitalization accentuates muscle-atrophy and levels of proinflammatory cytokines, which further lead to muscle loss and sarcopenia (38, 39). Decreased caloric and nutritional intake is a common feature of infectious diseases; this can negatively affect muscle health and function.

About the impact of infections on cognitive function, many studies supported the possibility that pneumonia, and virus infection to a lesser extent, negatively affect cognition. The neurotrophic propensity of the virus and the sustained pro-inflammatory status induced by the infection may trigger or accelerate neurodegenerative processes through increased deposition of beta-amyloid and microglia activation (35, 40–42). Similarly, the systemic inflammatory status and the boost in the oxidative processes might explain the impact of pneumonia on cognition. Further, pneumonia-related hypoxia is also linked to neurodegeneration and cerebrovascular lesions, which has been shown to predispose individuals to cognitive impairment and dementia (43).

EVALUATION METHOD

During the pandemic, an appropriate evaluation method for early identification of elderly COVID-19 patients who are prone to frailty is needed. Early intervention measures and reasonable allocation of medical resources are conducive to improving the prognosis. However, so far, there is no standard evaluation method for COVID-19 with frailty. Frequently used frailty evaluation methods recommended by the International Conference of Frailty and Sarcopenia Research (ICFSR) in 2019 include the following (discussed later and summarized in **Table 1**).

Clinical Frailty Scale

In 2020, the National Institute for Health and Care Excellence (NICE) published a quick guidance on the care of patients with COVID-19, which recommended to access patients aged 65 and over with CFS. Clinical frailty scale is a simple and inexpensive frailty scale that scores patients based on their daily function (44). A lot of studies revealed that the CFS has been widely used in multiple settings. The association of CFS score with clinical outcomes highlights its utility in the care of the aging population (45). Labenz et al. (46) believed that CFS is independent of comorbidities or age, and regular testing with CFS at hospital admission may identify patients at higher risk for worse disease progression and improve the prognosis for COVID-19 patients. Sablerolles et al. (47) believed that CFS score is a suitable risk marker for hospital mortality in patients with COVID-19 over 65 years. Frail patients (CFS 6–9) of all ages admitted with COVID-19 have a significantly higher hospital mortality than fit patients (CFS 1–3). But there is no significant difference in hospital mortality between mildly frail patients (CFS 4–5) and

TABLE 1 | Performance of different evaluation methods to identify frailty among patients with COVID-19.

	Cutoffs	Strengths	Weaknesses
CFS	Score according to considered variables, in general frail if CFS score >4	Simple; no physical testing required; score associated with mortality	Scoring somewhat subjective
FI	Ratio of accumulated deficits and considered variables, in general frail if FI >0.25	Meaningful results in all patients; irrespective from age and disability	Time-consuming; need for comprehensive geriatric assessment
FP	Five pre-defined criteria to categorize a patient as robust (none of the criteria), pre-frail (one or two criteria), and frail (three or more criteria)	Possible before comprehensive geriatric assessment; pre-clinical evaluation	Not applicable to disabled older patients
FRAIL	Five pre-defined criteria to categorize a patient as robust (one or none of the criteria), pre-frail (two criteria), and frailty (three or more criteria)	Simple; cheap; no physical testing required	Scoring somewhat subjective
EFS	Score according to considered variables, in general frail if EFS score>6	Good poly-dimension, credibility, and internal consistency; no physical testing required; a reliable predictor for mortality	Scoring somewhat complicated

fits patients who were admitted to intensive care. Therefore, CFS is an appropriate scale to assess frailty in elderly patients with COVID-19, and patients with CFS 6–9 points should be given more medical resources and a higher level of care.

Frailty Index

The calculation method of FI is the ratio of the number of defects existing in patients to the total number of defects designed, including social characteristics, clinical signs, symptoms, comorbidities, laboratory examination, and imaging examinations. These items can be adjusted according to individual differences. Kojima et al. (48, 49) believed that FI is a good indicator of mortality risk for all patients, irrespective from age and disability. Moreover, FI can evaluate frailty status in a graded manner to make a more precise risk prediction, rather than just three frailty categorization by frailty phenotype (robust, pre-frail, and frail). However, the evaluation method of FI is time-consuming and needs comprehensive geriatric assessment (49). The establishment of electronic FI simplifies the use of FI, and Clegg et al. demonstrated that electronic FI is a reliable predictor for mortality (50). With the popularization of electronic medical records in hospitals, the use of electronic FI to predict mortality in elderly patients with COVID-19 is considered convenient and feasible (51).

Frailty Phenotype

Frailty phenotype, developed and verified by Fried et al. in 2001, is a commonly used evaluation method to identify frailty or pre-frailty in current studies (5). Subjects were diagnosed as frailty if three or more of the following five criteria are met: decreased walking speed, decreased grip strength, decreased physical activity, fatigue, and unexplained weight loss. Fried et al. demonstrated that FP provides a potential basis for clinical assessment for those who are frail or at risk, which could be used for pre-clinical evaluation (49), and for future research to develop interventions for frailty based on a standardized ascertainment of frailty (6). Cesari et al. FP is deemed to have a high relation with nutritional status (52), which may be more suitable for the evaluation of elderly COVID-19 patients with anorexia. It is also more reasonable to give nutritional supplements to patients based on FP. Petermann-Rocha et al. (53) found that there is no significant difference between FP and FI in evaluating COVID-19 patients combined with frailty. However, FP is not applicable to disabled older patients for that it requires objective measurement of stride speed and grip strength (49).

The Frail Scale

As FP is not applicable for patients with impaired physical function or patients in the acute phase whose grip strength and gait speed can't be accurately measured, The FRAIL scale was provided by the International Society of Nutrition and Aging. The assessment of FRAIL is similar to FP. However, the assessment of FP is based entirely on patients themselves, without any measurement tools. Aprahamian et al. proved that FRAIL can be used as a screening instrument for frailty (time and cost-effective) (54). As a simple and easy scale, it has been adopted by many countries and regions (55). May et al. (56) conducted a prospective cohort study of 114 elderly COVID-19 patients to examine the association between frailty and COVID-19, and it was demonstrated that the FRAIL scale can help to predict the risk of frailty in elderly COVID-19 patients at an early stage. Clinical work is busy, and frailty assessment for elderly patients is labor- and time-consuming. FRAIL is of high sensitivity and convenience, but accuracy is insufficient for that evaluation methods based on the patient's description alone. As a result, it can be used for preliminary screening of frail patients to improve clinical work efficiency.

Edmonton Frailty Scale

Compared with the above four evaluation methods, EFS covers a wider range of assessment items, such as nutrition, mood, and medication, which has good poly-dimension, credibility, and internal consistency. Perna et al. (57) proved that EFS could not only reflect the frailty risk of patients reliably, but also reveal the reason for frailty. Similarly, EFS has an important relationship with independent evaluation scales in various fields. Chan et al. (58) found an important association between EFS and the Geriatric Depression Scale (GDS). Faria et al. (59) found an

important association between EFS and the Mini-Mental State Examination (MMSE). Izawa et al. (60) found an important association between EFS and the Mini-Nutritional Assessment (MNA). Therefore, providing EFS for elderly patients with COVID-19 and selecting appropriate independent assessment scale according to EFS to give etiological therapy may be beneficial to improve the prognosis of old COVID-19 patients. At present, there is a lack of relevant literature on evaluating elderly COVID-19 patients with EFS, which needs to be studied urgently.

INTERVENTION MEASURE

Frailty is a dynamic and manageable process that can be prevented, delayed or even reversed with interventions and health strategies. At present, there is no recognized intervention measures for COVID-19 with frailty. All reviews suggested the adoption of regular physical exercise and nutrition support (34, 61, 62).

Physical Exercise

As people get older, their motion decreases and physical function declines, increasing the risk of frailty. The American College of Sports Medicine (ACSM) recommends multicomponent exercise, including resistance exercise, aerobic exercise, and coordination and balance exercises, as the best physical intervention for preventing and improving frailty.

First of all, sarcopenia, as a common potential factor in frailty, is characteristic of progressive and general loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death (63). Resistance exercise can improve muscle quality and function by damaging the ultrastructural of muscle, releasing inflammatory cytokines and growth factors, and increasing protein synthesis (64). One meta-analysis found that intensities ranging from 70 to 95% of 1-RM significantly increase muscle strength, but decreasing the intensity of the weights to 30–40% of 1-RM during the first 2 weeks of the program to reduce muscle soreness may be more reasonable (65). Besides, resistance exercise also exerts a mechanical load on bones consequently leading to increase in the bone strength so as to reduce the incidence of osteoporosis (66). Secondly, aerobic exercise (such as swimming, cycling, and walking) is also indispensable. Aerobic exercise ensures adequate oxygen supply and transport of nutrients and metabolites and maintains the normal functioning of tissues and organs. It is beneficial to increase brain blood flow in old people, nourish nerve, and help improve cognitive function (67). Finally, fall is a common problem for older people, and coordination and balance exercises can help old people adjust their posture. At the same time, resistance exercise can strengthen the skeletal system, and aerobic exercise can improve the nervous system, which can all prevent patients from fall (68). A random controlled experiment showed that there are 29–60% proportional reductions in the incidence, duration, and overall severity of acute respiratory infection in the group in which patients insist on physical exercise at a moderate intensity (69). More and more researchers believed that physical exercise can enhance the immune response and mitochondrial antiviral ability to improve the prognosis of COVID-19 (70). Meanwhile, it is necessary for elderly COVID-19 patients to do physical exercise at home to help control COVID-19 transmission during a pandemic (71).

Nutrition Support

As the main contributor of muscle anabolism in the elderly, protein is an indispensable energy substance. A long-term study suggested that protein supplementation for 24 weeks (15 g of milk protein daily at breakfast and lunch), coupled with resistance training, can improve muscle mass, strength, and physical function (72). More protein intake does not mean healthier, and excessive intake may increase the risk of frailty (73). The distribution of protein intake is more important than the total protein intake, and frailty patients tend to consume more protein at noon, and less in the morning (74). Supplementing protein according to the consumption may be much conducive to the prevention and relief of frailty. At the same time, the source of protein is important, and plant protein and soy protein are better for lowering LDL-c and protecting the cardiovascular system (75).

The endogenous antioxidant function of the elderly decreases with age, and the sensitivity to oxidative stress increases. Oxidative stress can accelerate the generation of osteoclasts and the apoptosis of osteoblasts, which does not only lead to osteoporosis, but also impair heart and brain function, and increase the risk of frailty in old people (76). Carotenoids from fruits and vegetables have obvious antioxidant effect and reduce oxidative stress by destroying the formation of oxygen free radicals. It can also reduce the inflammatory cytokines induced by Aβ42 and inhibit the inflammatory response which could be beneficial in inhibiting the inflammatory progression of COVID-19 (77). It also plays an important role in the cognitive impairment. Carotenoids have a high binding force with Alzheimer's disease-related receptors (histone deacetylase and P53 kinase receptors) (78), which could become antagonists of Alzheimer's disease. According to relevant studies, long-term carotenoid supplementation at a dose of 10 mg/day is safe and effective. Excessive consumption of carotenoids increases the risk of lung cancer that is not conducive to the prognosis of COVID-19 (79, 80).

Elderly people are chronically low in calories. Schoufour et al. observed that with every 418·4 kJ (100 kcal) increase, the odds to be frail are 5% lower (81). But there is no evidence to support the benefits of a high-calorie diet. Kim et al. (82) suggested that maintaining a daily energy supplement of 400 Kcal and 25 g of protein can significantly improve physical fitness and prognosis of elderly patients with COVID-19.

Low levels of vitamins (such as A, D, E, B6, and B12) and minerals (such as calcium, zinc, and selenium) are found to be independent risk factors for frailty, which play important roles in inhibiting inflammation, reducing oxidative stress, maintaining muscle function, improving osteoporosis, and preventing falling. Research showed the benefits on balance and muscle strength with daily doses of 800 IU or more of vitamin D (83).

In addition, a reasonable diet structure is much conducive to the absorption of nutrients. Mediterranean diet is generally considered as a reasonable dietary structure, which is

characterized by more intake of fresh fruits, vegetables, and high-quality protein, less intake of red meat and dairy, and moderate intake of drinking, mainly with wine. Multiple studies showed that the Mediterranean diet is beneficial for prognosis of old frail people (84).

Medical Intervention

It has been suggested that defects in multiple hormonal systems are potential factors in the frailty (85). The main endocrine hormone suitable for the medical intervention of frailty include sex hormone, growth hormone, and insulin-like growth factor (IGF). Androgen, including testosterone and dehydroepiandrosterone, has the function of maintaining musculoskeletal growth. In the elderly patients, the decreasing androgens make them lose muscle mass and strength, so that androgen replacement therapy could be beneficial for them. However, Nair et al. (86) found that daily androgen supplementation of 50 mg was not beneficial for muscles of elderly men, and increased the risk of cardiovascular and prostate adverse events. Progesterone is used primarily to stimulate appetite to improve absorption of nutrient, but some studies suggested that supplementation with progesterone after high-intensity resistance training seems to impair the effects of exercise, leading to decreased muscle mass, and function after exercise (87). Growth hormone plays an important role in the skeletal muscle growth. Insulin-like growth factor can regulate the production of a variety of transcription factors, which participates in inflammation and the expression of autophagy-related genes that are key mechanisms associated with frailty (88). However, there are few studies on the use of these hormones in old COVID-19 patients combined with frailty, and the efficacy and safety of them are still uncertain. More related studies are needed for further confirmation.

In addition to hormone, a 16-week treatment with metformin (500 mg twice daily) has been shown to improve walking speed in frail patients (85). Probiotic can improve the physical strength and grip strength of the elderly by regulating gastrointestinal flora (89). Supplementation with L-carnitine (1.5 g/day) for 10 weeks significantly improved grip strength in the elderly, and some subjects even changed from a pre-frailty state to a healthy state after intervention (90). However, the above conclusions are lack of sufficient evidences and need to be proved by further researches. At present, the ICFSR does not recommend medical intervention for frailty because its effectiveness is unclear, and it is not possible to assess whether the benefits of medical intervention outweigh the adverse consequences (91).

CONCLUSION

A series of studies suggested that elderly COVID-19 patients have a high incidence of frailty, and frailty is detrimental to COVID-19 prognosis. Due to the interaction between frailty and COVID-19, a vicious cycle leads to the poor prognosis. At present, there is no generally accepted consensuses for the evaluation and intervention of frailty in elderly patients with COVID-19, and there is not enough clinical understanding of it. Therefore, it is of great significance to improve the awareness of clinicians on the importance of early recognition and intervention methods. In clinical work, the elderly COVID-19 patients should be evaluated as early as possible, and multi-component physical exercise including resistance exercise, aerobic exercise, and coordination and balance exercises should be recommended, following the Mediterranean diet and avoiding mindless drug use.

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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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Geographic and Age Variations in Low Body Mass Index Among Community-Dwelling Older People in Xinjiang: A Cross-Sectional Study

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Background: Studies have shown an association between undernutrition and increased adverse outcome, as well as substantial geographic and age variations in undernutrition. Body mass index (BMI), a core indicator of undernutrition, is easy to measure and reflects the nutritional and health status of the human body. It is a simple and suitable tool for epidemiological investigations in large sample populations. Herein, we provide the first description of geographic and age variations in the prevalence of low BMI among community-dwelling older people in Xinjiang.

Methods: From January 2019 to December 2019, using a multi-stage random sampling method, we conducted a cross-sectional epidemiological survey of the community-dwelling older people in Xinjiang at different latitudes. Of the 87,000 participants, the statistical analyses included 86,514 participants with complete data.

Results: In Xinjiang, the prevalence of low BMI was 7.7% in the community-dwelling older people. The BMI gradually decreased with increasing age and gradually increased with latitude. The prevalence of low BMI in northern Xinjiang was 5.3%, which was significantly lower than that in eastern (7.7%) and southern (9.3%) Xinjiang. In the 60–69-, 70–79-, 80–89-, and ≥90-year age groups, the prevalence rates of low BMI were 5.8, 7.9, 10.0, and 13.9%, respectively. After adjusting for confounding factors (sex, ethnic group, hypertension, diabetes, hyperlipemia, smoking, and drinking), multivariate logistic regression analysis showed that the odds ratios (95% CI) for low BMI in eastern and southern Xinjiang were 1.165 (1.056–1.285) and 1.400 (1.274–1.538), respectively, compared to northern Xinjiang. The adjusted odds ratios (95% CI) for low BMI in the 70–79-, 80–89-, and ≥90-year age groups were 1.511 (1.39–1.635), 2.233 (2.030–2.456), and 3.003 (2.439–3.696), respectively, compared to the 60–69-year age group.

Conclusion: The results of this study revealed geographic and age variations in the prevalence of low BMI in the community-dwelling older people in Xinjiang. The prevalence of low BMI gradually increased as the latitude decreased and as age increased.

Keywords: undernutrition, BMI, aging, community-dwelling older people, Xinjiang

INTRODUCTION

Research on aging has attracted significant attention worldwide. The World Health Organization has reported a rapidly aging global population. In the first 50 years of the 21st century, the proportion of the older population (≥60 years of age) globally is expected to increase from 11 to 22%, corresponding to an increase from 605 million to two billion individuals (1). In China, by the end of 2018, 17.9% of the population was aged ≥60 years; 11.9% of whom were aged ≥65 years. Hence, China is gradually becoming a super-aged society (2).

With aging, older individuals experience a series of inevitable nutritional problems such as chewing and swallowing difficulties caused by tooth loss, absorption and utilization obstacles due to decreased body tissue and organ function, anorexia caused by medication, and other diseases. As a result, the energy and nutrient intake of older people cannot meet the needs of their bodies, eventually leading to undernutrition or a risk of undernutrition. The "Nutrition and Health Report of the Chinese Older People (2015)" revealed the high nutritional risk of older individuals in China, with up to 48.4% of individuals having a poor nutritional status (2, 3). In 2012, the total economic burden associated with undernutrition among older people in China was 84.14 billion Yuan, of which the direct economic burden was 63.93 billion Yuan. This accounted for 10.6% of the treatment cost of all diseases among older people, thereby increasing the financial burden of millions of families, as well as other countries (4, 5). Therefore, undernutrition in older individuals requires attention.

Numerous screening tools have been developed to assess the presence and risk of undernutrition. Body mass index (BMI), a common indicator, is easy to measure and reflects the nutritional and health status of the human body. It is simple and suitable for use in epidemiological investigations in large sample populations. Among the numerous consensus or guidelines published at present, a low BMI is a relatively consistent standard measurement (or diagnostic criterion), which has always been the core index of undernutrition assessment (or diagnosis).

Previous studies have confirmed that compared to older people with good nutritional status, those with undernutrition or high undernutrition risk show low immunity, poor resistance, decreased quality of life, prolonged hospital stay, increased hospital costs, poor treatment effect, poor prognosis, and high incidence of complications (6–9). Numerous studies have demonstrated the association of undernutrition with a high incidence of and mortality due to fractures and various diseases in older individuals (10–15). Therefore, considering the increasing proportion of older individuals in China, the "Healthy China 2030 Program Outline" and improvements in the nutritional status and health of all citizens in China need to be implemented.

The prevalence of undernutrition can vary substantially based on geography and age. Thus, we hypothesized that the prevalence of undernutrition in older individuals differs in Xinjiang province due to geographic factors. Identifying variations in undernutrition among regions can help direct prevention efforts. Province-level maps are often created based on data available in each province. However, maps of undernutrition prevalence cannot identify disparities within a province. Although many epidemiological studies on undernutrition have been conducted in recent years, geographic and age variations in undernutrition prevalence in the older population in Xinjiang are unknown. Therefore, epidemiological surveys of the older population in Xinjiang are needed.

This cross-sectional, epidemiological investigation was conducted among the community-dwelling older people in Xinjiang to describe the geographic and age differences in the prevalence of low BMI, the core index of undernutrition assessment (or diagnosis), in this population. Thus, this study may provide a reference for the formulation of prevention and treatment strategies for undernutrition in the community-dwelling older people in Xinjiang.

MATERIALS AND METHODS

Study Participants

This cross-sectional study of the community-dwelling older people in Xinjiang was reviewed and approved by the Ethics Committee of People's Hospital of Xinjiang Uygur Autonomous Region. All research participants provided written informed consent.

Located in the hinterland of the Eurasia continent (73°40′–96°23′ E and 34°25′–48°10′ N), Xinjiang is divided into three distinct subregions (north, south, and east) according to its natural settings and climate patterns (16). From January to December 2019, a multilevel random sampling method was used to perform surveys of older individuals in Xinjiang. During the first stage, two regions were randomly selected from the northern (Altai and Tacheng, located at latitudes of 46°21′−48°00′ N), eastern (Hami and Turpan, located at latitudes of 40°52′−41°12′ N), and southern (Hotan and Kashgar, located at latitudes of 35°28′−37°12′ N) Xinjiang subregions (**Figure 1**). During the second stage, one city was randomly selected from each region. During the third stage, two counties were randomly selected from each city. During the fourth stage, 7,500 older individuals aged 60 years or older were randomly selected from each county. A total of 90,000 study participants were selected.

The inclusion criteria were age 60 years or older and the ability to complete the survey, understand the investigation, cooperate with the investigators, and provide signed informed consent. The exclusion criterion was the inability to cooperate with the investigators. A total of 87,000 individuals completed the survey, resulting in a response rate of 96.67%. We excluded 486 participants with incomplete data; therefore, the statistical analyses included data from a total of 86,514 participants (**Figure 2**).

Questionnaire Survey

A set of standardized questionnaires was completed under the physicians' guidance. The questionnaire survey included information on age, sex, ethnic group, education level, occupation, disease history, medication history, family history, drinking history, smoking history, and eating habits.

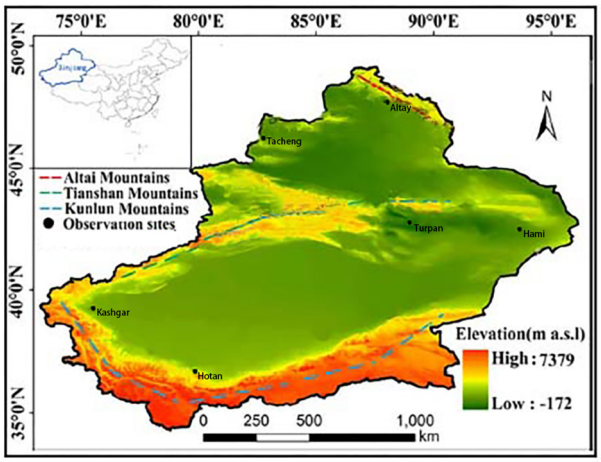


FIGURE 1 | Observation sites in the study, southern Xinjiang, northern Xinjiang, and eastern Xinjiang, China.

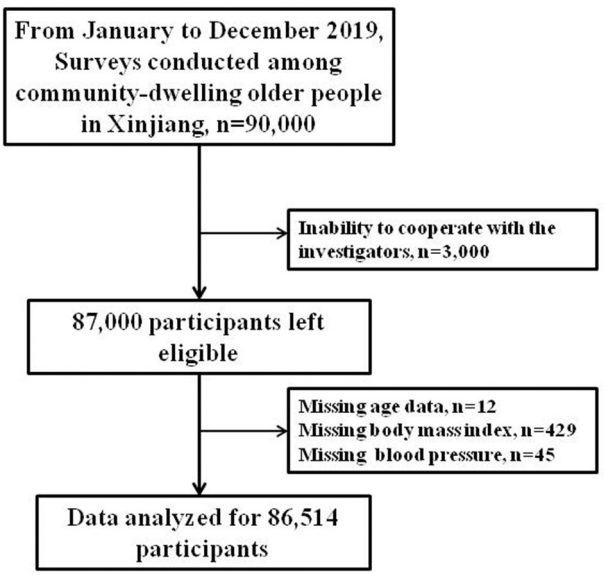


FIGURE 2 | Selection procedure of the study participants.

Physical Examination

Each participant underwent a detailed physical examination performed by a physician. Indicators such as blood pressure, weight, and height, were measured by qualified professionals using standard methods.

Blood Pressure Measurement

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured according to the methods recommended by the American Heart Federation. All participants were prohibited from smoking and drinking alcohol, tea, and coffee 30 min before blood pressure measurement. A desktop mercury sphygmomanometer was used to measure blood pressure. The blood pressure of the right upper arm of the participants in a seated position was measured by a medical specialist after a 10-min rest period. The blood pressure was measured three times consecutively every 2 min, at a room temperature of $>18^{\circ}$C.

Weight Measurement

The participants were required to not eat before undergoing measurements, to remove their shoes, and to wear light clothing. A calibrated medical scale was used for weight measurement. The participants were asked to relax and to stand upright in the middle of the chassis of the scale, which had a reading accuracy of 0.1 kg.

Height Measurement

A measuring ruler, with a minimum scale of 1 mm, was fixed vertically to the ground. The participants were instructed to stand upright with both heels together and with the shoulders and hips close to the measuring ruler. The surveyor placed a square ruler on top of the participants' head, with the side of the right angle near the measuring ruler and the other side near the participant's scalp. The measuring ruler was accurate to 1 mm. BMI was calculated as follows: BMI = weight (kg)/height (m) ^{2}.

Collection of Blood Samples and Laboratory Testing

Disposable blood collection equipment was used to draw 10 mL of peripheral venous blood in the morning from the participants who had fasted for at least 10 h. Plasma (serum) was immediately centrifuged and separated from the blood cells and stored at -80°C for testing. Levels of fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), serum creatinine (SCr), and serum urea nitrogen (SUN), and other biochemical indicators were examined within 1 month at the Clinical Laboratory Center of People's Hospital of Xinjiang Uygur Autonomous Region (a third-grade class A hospital) using a Hitachi 7600 automatic biochemical analyzer.

Related Diagnostic Criteria

Low BMI

According to the undernutrition assessment (diagnosis) criteria for Asians from the "Global Leadership Initiative on Malnutrition Consensus (2018)," participants aged <70 years with a BMI of <18.5 kg/m^2 or those aged ≥70 years with a BMI of <20 kg/ m^2 were considered to have a low BMI.

Overweight/Obesity

According to the standard Chinese guidelines for adults for the prevention and control of overweight and obesity, a BMI of 24.0 kg/m^2 ≤ BMI < 28.0 kg/m^2 was used to indicate "overweight" and a BMI ≥28.0 kg/m^2 was used to indicate "obesity."

Hypertension

Hypertension was defined as an SBP of ≥140 mmHg and/or a DBP of ≥90 mmHg or a previous hypertension diagnosis/treatment for hypertension.

TABLE 1 | Clinical characteristics of the study participants.

	Normal BMI group (n = 24,997)	Low BMI group (n = 6,662)	Overweight/obesity group (n = 54,855)	$F(\chi 2)$	P
Age (year)	74.01 ± 6.309	74.76 ± 6.548	73.04 ± 5.767	397.163	<0.001
SBP (mmHg)	131.9 ± 20.047	127.34 ± 20.754	137.98 ± 20.009	1361.266	<0.001
DBP (mmHG)	75.20 ± 12.068	73.27 ± 12.242	78.37 ± 12.228	924.282	<0.001
TC (mmol/L)	4.65 ± 1.300	4.49 ± 1.280	4.81 ± 1.304	275.672	<0.001
TG (mmol/L)	1.31 ± 0.856	1.15 ± 0.866	1.60 ± 1.031	1141.382	<0.001
HDL-c (mmol/L)	1.44 ± 0.809	1.48 ± 0.562	1.38 ± 0.854	57.806	<0.001
LDL-c (mmol/L)	2.57 ± 1.007	2.44 ± 0.923	2.68 ± 0.979	174.621	<0.001
ALT (U//L)	19.79 ± 13.166	18.37 ± 12.785	22.14 ± 13.746	137.297	<0.001
AST (U//L)	23.02 ± 10.737	23.60 ± 10.984	22.80 ± 10.338	1.509	0.221
SCr (umol/L)	73.36 ± 25.033	71.96 ± 22.871	74.07 ± 24.663	24.26	<0.001
SUN (mmol/L)	5.74 ± 2.534	5.92 ± 3.113	5.63 ± 2.465	46.301	<0.001
FBG (mmol/L)	5.66 ± 1.855	5.40 ± 1.590	6.16 ± 2.248	742.835	<0.001
Sex (Male, %)	51.8	47.2	45.8	246.889	<0.001
Smoking (Yes, %)	10.3	9.4	9.0	33.023	<0.001
Drinking (Yes, %)	5.0	3.7	5.8	60.349	<0.001
Hypertension (Yes, %)	43.0	34.3	57.5	2307.624	<0.001
Diabetes (Yes, %)	11.5	7.3	20.6	1447.149	<0.001
Hyperlipemia (Yes, %)	43.2	34.9	54.5	1073.696	<0.001
Geographic region					
Northern Xinjiang (%)	25.5	20.2	31.8	663.366	<0.001
Eastern Xinjiang (%)	28.3	27.3	26.7		
Southern Xinjiang (%)	46.2	52.7	41.5		
Ethnic group					
Han (%)	58.8	67.6	52.9	850.339	<0.001
Uygur (%)	32.3	24.5	33.8		
Kazakh (%)	4.1	3.7	7.0		
Others (%)	4.8	4.2	6.3		

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL-c, high density lipoprotein-cholesterol; LDL-c, low density lipoprotein-cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SCr, serum creatinine; SUN, serum urea nitrogen; FBG, fasting blood glucose.

Diabetes Mellitus

Diabetes mellitus was defined as an FBG level of ≥7.0 mmol/L or a previous diagnosis of type 2 diabetes mellitus requiring treatment.

Hyperlipidemia

According to the 2016 Prevention and Treatment Guidelines for Chinese Adults with Dyslipidemia, hyperlipidemia was defined as a TC level of >5.18 mmol/L, an LDL-C level of >3.37 mmol/L, or a TG level of >1.7 mmol/L.

Smoking and Drinking

According to the standards proposed by the World Health Organization, smokers were defined as participants who smoked continuously or had smoked for a cumulative period of at least 6 months, while drinkers were defined as those who drank alcohol once weekly, with an alcohol consumption of 8 g per week.

Quality Control

Standard methods and unified and standardized instruments (checked and corrected by professionals) were used to collect the relevant data. To control for observer error, all investigators underwent training on conducting accurate questionnaire surveys (the questionnaire survey was performed by a medical specialist). Furthermore, physical examinations; blood sample collection, transportation, separation, preservation, and marking; questionnaire review, data entry, etc. were all completed by specialists. Only qualified surveyors participated in the survey. According to the principle of double-blind data entry, two professionals entered the data in parallel and performed the statistical analyses after verification.

Statistical Analysis

Data analyses were performed using IBM SPSS Statistics for Windows, version 19.0 (IBM Corp., Armonk, NY, USA). Values were expressed as mean ± standard deviation. Counting data were expressed as percentages. The distributions of participants' characteristics between the low BMI, normal BMI, and overweight and obesity groups were analyzed using one-way analysis of variance (ANOVA) or chi-square tests. The differences in BMI and the prevalence of low BMI among individuals of different ages and geographic regions

were also analyzed by one-way ANOVA or chi-square tests. After adjusting for confounding factors (age, sex, ethnic group, hypertension, diabetes, hyperlipemia, smoking, drinking), multivariate logistic regression was used to analyze the influence of geographic variations on low BMI. $P<0.05$ was considered statistically significant.

RESULTS

Clinical Characteristics

Table 1 presents the clinical characteristics of the study participants. Age, SBP, DBP, TC, TG, LDL-c, HDL-c, alanine aminotransferase, SCr, SUN, FBG, sex, smoking, drinking, hypertension, diabetes, hyperlipemia, geographic region, and ethnic group differed significantly between the low BMI, normal BMI, and overweight and obesity groups (all $P < 0.001$). No significant differences in aspartate aminotransferase levels were observed between the three groups ($P = 0.221$).

TABLE 2 | Geographic and age disparities of low BMI in the community-dwelling older people in Xinjiang.

	BMI (kg/m^2)	Prevalence of low BMI (%)
Geographic region		
Counties in northern Xinjiang (46°21′−48°00′ N)	26.29 ± 4.310	5.3
Counties in eastern Xinjiang (40°52′−41°12′ N)	25.57 ± 4.568	7.7
Counties in southern Xinjiang (35°28′−37°12′ N)	25.32 ± 4.011	9.3
F (χ2)	332.490	326.46
P	<0.001	<0.001
Age group (year)		
60–69	26.22 ± 4.405	5.8
70–79	25.69 ± 4.366	7.9
80–89	24.92 ± 4.145	10
≥90	24.05 ± 4.018	13.9
F (χ2)	326.987	306.322
P	<0.001	<0.001

Geographic and Age Variations in the Prevalence of Low BMI Among the Community-Dwelling Older People in Xinjiang

Overall, the prevalence of low BMI was 7.7% in community-dwelling older people of Xinjiang. **Table 2** shows the geographic and age disparities of BMI and the prevalence of low BMI in the population. The BMI gradually decreased as age increased and gradually increased with latitude. The prevalence of low BMI in northern Xinjiang was 5.3%, which was significantly lower than that in eastern (7.7%) and southern (9.3%) Xinjiang. In the 60–69-, 70–79-, 80–89-, and ≥90-year age groups, the prevalence rates of low BMI were 5.8, 7.9, 10.0, and 13.9%, respectively.

After adjusting for confounding factors (sex, ethnic group, hypertension, diabetes, hyperlipemia, smoking, and drinking), multivariate logistic regression analysis showed that the odds ratios [95% confidence intervals (CIs)] for low BMI in eastern (40°52′−41°12′ N) and southern (35°28′−37°12′ N) Xinjiang were 1.165 (1.056–1.285) and 1.400 (1.274–1.538), respectively, compared to counties in northern Xinjiang (46°21′−48°00′ N) (**Table 3**). The adjusted odds ratios (95% CI) for low BMI in the 70–79-, 80–89-, and ≥90-year age groups were 1.511 (1.39–1.635), 2.233 (2.030–2.456), and 3.003 (2.439–3.696), respectively, compared to the 60–69-year age group (**Table 3**).

DISCUSSION

The results of the present study revealed the varying prevalence of low BMI among the community-dwelling older people across Xinjiang. The prevalence of low BMI gradually increased with decreasing latitude (5.3% in northern Xinjiang, 7.7% in eastern Xinjiang, and 9.3% in southern Xinjiang). Moreover, the prevalence of low BMI increased gradually with age (5.8, 7.9, 10.0, and 13.9% in the 60–69-, 70–79-, 80–89-, and ≥90-year age groups, respectively). The results reveal the geographic and

TABLE 3 | Adjusted odds ratios (95% confidence intervals) of low BMI vs. non-low BMI associated with age and latitude.

	B	Standard error	Odds ratios	95% Confidence intervals	*P*
Age group (year)*					
60–69			1.000		<0.001
70–79	0.413	0.040	1.511	1.397–1.635	<0.001
80–89	0.803	0.049	2.233	2.030–2.456	<0.001
≥90	1.099	0.106	3.003	2.439–3.696	<0.001
Latitude group**					
46°21′−48°00′ N			1.000		<0.001
40°52′−41°12′ N	0.153	0.050	1.165	1.056–1.285	0.002
35°28′−37°12′ N	0.336	0.048	1.400	1.274–1.538	<0.001

*The odds ratios for age grouping are adjusted for latitude, sex, ethnic group, hypertension, diabetes, hyperlipemia, smoking and drinking status.
**The odds ratios for latitude grouping are adjusted for age, sex, ethnic group, hypertension, diabetes, hyperlipemia, smoking and drinking status.
BMI, body mass index.

age disparities in low BMI among the community-dwelling older people in Xinjiang.

Age Differences in Low BMI

In the older population, as age increases, food intake decreases; this is affected by factors such as society, psychology, physiology, drugs, and behavior, and ultimately leads to a high incidence of undernutrition (17, 18). The reported risk of undernutrition in the people aged ≥60 years in China was 5.4%, while that in the hospitalized older individuals has been increasing continuously up to 50–70% (17, 19). Studies also revealed the presence of undernutrition in 5–30% of older people living at home, 6–70% of older people in nursing homes, and 20–60% of older inpatients (20, 21). The results of previous studies also confirmed the positive correlation between undernutrition prevalence and age; thus, undernutrition is also considered a geriatric syndrome (22, 23). The present study used a multi-stage random sampling method to perform an epidemiological survey of low BMIin the community-dwelling older people in Xinjiang. The prevalence of low BMI in this population was 7.7% and the prevalence of low BMI increased with age, indicating the need to screen for undernutrition and provide reasonable nutritional interventions in the older people.

Geographic Variations of Low BMI

Disease is not distributed randomly in the population; rather, it shows time and space distributions. Spatial attributes provide data related to the spatial entity and geographical location. The incidence and prevalence of disease in certain populations, climates, environments, are all related to the geographical location. Geographic variations in undernutrition and BMI have been documented in children, adolescents, adults, and older residents in nursing homes (24–27).

According to the "China Obesity Index Survey (2015)," the distribution of obesity (BMI ≥28.0 kg/m^2) in China decreased from north (high latitude) to south (low latitude). The prevalence of obesity in northern China (35%) was higher than that in southern China (27%). The main reasons for the higher BMI include higher latitude and colder weather, as well as individual factors such as less exercise, slower metabolism, and fat deposition. In contrast, lower latitude and hotter weather, as well as individual factors including increased exercise and faster metabolism were associated with a lower BMI. Moreover, the prevalence of obesity (increased BMI) gradually decreased in the Chinese urban population with decreasing latitude (28). Similarly, in this study, the prevalence of low BMI increased gradually as the latitude decreased (southern Xinjiang (35°28′−37°12′ N)> eastern Xinjiang (40°52′−41°12′ N)> northern Xinjiang (46°21′−48°00′ N).

The geographic variation may be related to objective factors such as regional climate and lifestyle of local residents at different latitudes.

The survey sites in northern Xinjiang (46°21′−48°00′ N) experience only cold and warm seasons a year. Winter lasts for 6 months, with the coldest temperature of −40°C. Summer lasts only briefly, with the potential for snowfall even during this season and a frost-free period of <90 days per year. The summer season is characterized by rain, humidity, and cool temperatures. In contrast, the survey sites in eastern Xinjiang (40°52′−41°12′ N) are characterized by a continental arid desert climate with long periods of sunshine, high temperatures, large temperature fluctuations between day and night, little precipitation, and strong winds. The annual average temperature is 14°C, while that in summer is approximately 30°C. Annually, eastern Xinjiang has an average of 99 hot days with temperatures >35°C and 28 days with temperatures >40°C. The survey sites in southern Xinjiang (35°28′−37°12′ N) have an arid climate with extreme droughts within a warm temperate zone. Temperatures are high in the summer and moderate in the winter, with little precipitation, sufficient light, abundant heat, long frost-free periods, large temperature differences between day and night, and average annual precipitation of 35 mm (29).

Thus, such unique geographical environments result in unique lifestyle among the local residents. The residents of northern Xinjiang have higher alcohol, beef, mutton, and spicy food consumption and lower vegetable consumption. These participants also preferred high-fat and high-protein diets (such as meat and dairy food) (30). Because the weather is not suitable for sports, these individuals exercise less often, which results in fat accumulation and subsequent high BMI. In contrast, residents in southern Xinjiang mainly consume carbohydrates such as dried fruits and wheat flour (30). The relatively warm weather is conducive for frequent exercise; hence, fat is not easily accumulated, leading to a high incidence of low BMI. It was reported that the residents in the eastern Xinjiang have a higher level of consumption of vegetables and fruits, compared to those in other regions (30). Vegetables and fruits are rich and contain a higher proportion of sugar in this region, which are mainly benefited from the huge difference in temperature between day and night. Moreover, the high temperature in summer in this area leads to decreased exercise and consequently increases the risk of fat accumulation. Therefore, geographic variations in the prevalence of low BMI may be due to geographic variations in other lifestyle risk factors. The various potential causes of geographic variations require further investigation to determine the contribution of each of those causes.

Our study has some notable limitations. First, we did not collect data on the participants' diet and exercise, which may be related to low BMI. Second, additional nutritional assessments were not performed; hence, we were unable to obtain further information on the prevalence of undernutrition in this population.

Despite these limitations, our study has several strengths. This is the first epidemiological survey of low BMI in Xinjiang with a large sample size. Owing to the multi-stage random sampling strategy used in this study, we were able to obtain a representative sample population and uniform data coverage across continental Xinjiang.

We have provided evidence of geographic and age differences in the prevalence of low BMI among the community-dwelling older people in Xinjiang. Our results confirmed that the prevalence of low BMI gradually increased with decreasing latitude and with increasing age. This information can be used

to establish prevention efforts targeted at particular populations within Xinjiang.

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 Ethics Committee of People's Hospital of Xinjiang Uygur Autonomous Region. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HW contributed to the study design, data collection and analysis, result interpretation, and provided critical manuscript revisions. QQ and JL wrote the article. SX, XB, LW, and HX were involved in the data analysis and interpretation and also provided critical manuscript revisions. All authors read and approved the submitted 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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Impacts of Frailty on Prognosis in Lung Cancer Patients: A Systematic Review and Meta-Analysis

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Background: Frailty is a common geriatric syndrome and is described as a limited ability to compensate and recover from stressors. Lung cancer is largely diagnosed in old age, when frailty is common and might have predictive value on prognosis. Therefore, we performed a systematic review to evaluate the prognostic role of frailty in lung cancer.

Methods: The online PubMed, Web of Science, CNKI and Wanfang literature databases were searched to identify all related articles that reported the predictive value of frailty for mortality and therapeutic toxicity. Review Manager 5.3 was used to analyze results by standard meta-analysis methodology.

Results: Seven studies were included in this review, and only six studies with 2,359 patients were enrolled in meta-analysis. Patients in two studies received chemotherapy, two studies radiotherapy, two studies surgery, one study not reported. Compared to non-frail patients, frail patients had a higher risk of overall mortality [Hazard Ratio (HR) = 1.57, 95% confidence interval (CI), 1.32–1.87], and therapeutic toxicity [Odds Ratio (OR) = 2.60, 95% CI, 0.82–8.24]. Prefrail patients also showed higher overall mortality and therapeutic toxicity than non-frail patients (HR = 1.20, 95% CI, 1.05–1.38; OR = 1.72, 95% CI, 1.18–2.51, respectively).

Conclusions: Frailty is a powerful predictor of overall mortality and therapeutic toxicity in lung cancer patients.

Keywords: frailty, lung cancer, mortality, therapeutic toxicity, prefrailty

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INTRODUCTION

Frailty is a common geriatric syndrome and is a state of age-related decline in biological reserve, decreased ability to maintain physiological balance and increased vulnerability to adverse health events (1, 2). Prefrailty is defined as a clinically silent process that predisposes individuals to frailty, and is an intermediate state between frailty and absence of frailty (3). Although the prevalence of frailty varies by the definition used, it increases with aging (4). Frailty can occur at any age, especially in those with chronic illnesses, but it is more prevalent in older adults (5). 17.4% of community-dwelling adults ages 60 years and older present with frailty, 49.3% with prefrailty, while that incidence increases to 29.5 and 59.3% respectively in those ages 85 years and older (6). The prevalence of frailty in patients with cancer is especially high (7), and it has been reported that more than half of older patients with cancer are frail at cancer diagnosis, which may increase the risk of chemotherapy intolerance, postoperative complications, and mortality (8).

Lung cancer is the leading cause of malignancy death, and causes almost one-quarter of all cancer deaths (9). Approximately 30–40% of lung cancers are diagnosed in patients aged 70 or more (10). Furthermore, the probability of developing invasive lung cancer increases with age, 0.6% among 50–59 years old, 1.8% among 60–69, 6.0% among over 70 (9). There are multiple treatment options in lung cancer, including surgery, chemotherapy, radiotherapy, etc. The prognosis of treatment is not only related to the cancer, but also related to the patient's physical and functional status. Comprehensive geriatric assessment (CGA) may help clinicians to define patients as fit, vulnerable or unfit to treatment (11, 12). Nevertheless, a phase III trail found the use of CGA to choose treatment did not improve survival but reduce treatment toxicity (13). Some studies found that frailty was associated with reduced overall survival in lung cancer patients (14, 15), and frailty assessment might inform toxicity risk (16). However, frailty was found to have no significant predictive value in postoperative outcomes (17).

In a word, frailty as a common geriatric syndrome has been tried to be used in the medical decision-making of lung cancer patients, while the predictive power and usefulness have not yet been clearly proven. Therefore, we conducted a systematic review to summarize the prognostic value of frailty in patients with lung cancer.

MATERIALS AND METHODS

Search Strategy

We conducted a systematic literature search on the online PubMed, Web of Science, CNKI and Wanfang literature databases from the start of each database up to 12 March 2021. For PubMed, the search items included: ("lung neoplasms"[MeSH Terms] OR ("lung" AND "neoplasms") OR ("lung" AND "cancer") OR "lung cancer") AND ("frailty"[MeSH Terms] OR "frailt" OR "frail") AND ("mortality"[MeSH Terms] OR "mortality" OR "mortalities" OR ("prognosis"[MeSH Terms] OR "prognosis" OR "prognoses") OR [("adverse" OR "adversely" OR "adverses") AND ("event" OR "events")] OR ("adverse effects") OR ("toxic" OR "toxicities" OR "toxicity")). For Web of Science, CNKI, and Wanfang, the same MeSH-terms were used in the search strategy. The reference lists of all included studies were also consulted to locate additional references of interest. This study was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (18) guidelines and has been registered in PROSPERO (registration number: CRD42021244311).

Inclusion and Exclusion Criteria

All eligible literatures had to meet the following criteria: (1) used a standardized index to assess frailty in clinically diagnosed lung cancer patients; (2) reported frailty association with at least one of the following outcomes: treatment adverse effects or complications, mortality; (3) the examined associations were reported by odds ratios (OR) or hazard ratios (HR) and 95% confidence intervals (CI), or these data could be calculated; (4) the full-text was published in Chinese or English. The exclusion criteria were: (1) studies on cancer in general without specific results for lung cancer; (2) meeting, abstracts, letters, reviews, editorials and case reports; (3) duplicate publications with same sample. Two authors (SPS and SSD) screened the titles and abstracts independently to select possible eligible articles and any inclusion discrepancies were resolved through discussion.

Data Extraction and Quality Assessment

The basic information of included studies was extracted by two reviewers (SPD and JS) including the following data: the name of the first author, publication year, country, follow-up time, sample size, frailty assessment scale, treatment methods, OR, HR, 95% CI. The extracted data of both authors were compared with one another, and any discrepancies were resolved by checking the original articles through a third reviewer (SSD).

The Newcastle-Ottawa Scale for cohort studies was used to assess the quality and risk of bias of the included studies (19). This scale contained three section: Selection, Comparability, and Outcome. A study was awarded a maximum of one point for each item within the Selection and Outcome categories, and a maximum of two points for Comparability, and a total of eight points might be achieved. The included literatures with score $\geq$ 6 were regarded as high-quality literatures, and those with score $<$ 6 were regarded as low-quality literatures. Two reviewers (JS and MY) independently assessed the included studies. If there was a discrepancy, all group members will discuss and solve the disagreements together.

Statistical Analyses

Review Manager 5.3 was used to perform this meta-analysis. The heterogeneity between studies was analyzed by I^2 test, which $I^2 > 50\%$ indicating that a potential heterogeneity existed. The pooled HR for overall mortality, OR for treatment adverse effects or complications, and corresponding 95% CI were calculated in fixed or random effects models. If substantial heterogeneity existed, the random-effects model was employed; otherwise, the fixed-effect model was applied. The potential publication bias was estimated by visually funnel plots. A two-sided P-value ≤ 0.05 was considered statistically significant.

RESULTS

Study Characteristics and Quality

As shown in **Figure 1**, a total of 567 articles were initially identified from the online database, of which 101 after duplication were excluded. After screening the titles and abstracts of remaining 466 records, 454 reports were excluded. 12 articles were assessed for eligibility by reading the full text, of which 2 reports excluded because of insufficient prognostic outcome data and 3 because of no separate results for lung cancer. Finally, 7 studies were included in this review (14–17, 21–23), and their characteristics were presented in **Table 1**. All of these studies were hospital-based registry cohort studies. A total of 3,921 lung cancer patients involved in these seven studies received different treatments, surgery in two (17, 21), radiotherapy in two (14, 15), chemotherapy in two (22), unreported in one. Three of these included studies classified patients as prefrail and frail, and one classified patients as mild, moderate and

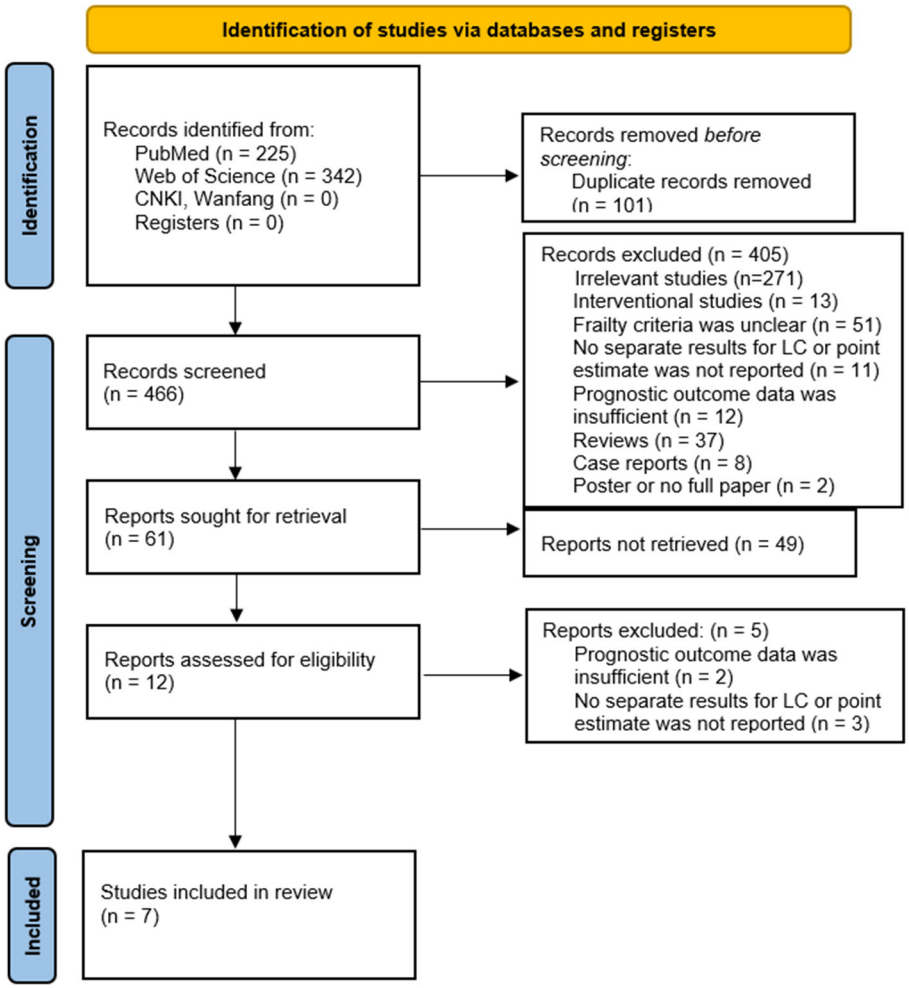


FIGURE 1 | The PRISMA diagram for study selection. PRISMA: preferred reporting items for systematic reviews and meta-analyses. From (20).

severe frailty. The assessment criteria for frailty were shown in **Supplementary Table 1**. All enrolled articles achieved a relatively high score equal or larger than 6 when evaluated by Newcastle-Ottawa Scale for cohort studies, and were regarded as high-quality papers. The assessment criteria of frailty used in different studies, showed in **Supplementary Table 2**. The largest paper (21) selected was not included in the meta-analysis because the frailty assessment measure was a cumulative risk factors score, including comorbidities and surgical factors, and had a loose conceptual relationship with frailty. Six other studies with 2,359 patients were included in meta-analysis.

Overall Mortality

Frailty in association with overall mortality risk was investigated in 5 cohort studies (14–16, 22, 23). The pooled HR from the combination of included studies was 1.57 (95%CI: 1.32–1.87), which demonstrated that compared to non-frail patients, frail patients had a higher risk of overall mortality. No significant heterogeneity was observed across these pooled studies ($Chi^2 = 7.82$, $df = 4$, $I^2 = 49\%$, $P = 0.10$) (**Figure 2A**). The funnel plot indicated no publication bias (**Figure 3**).

Two included studies explored the role of prefrailty in predicting the risks of overall mortality in patients with lung cancer (22, 23). **Figure 2B** showed forest plots, which showed the HR of the association between prefrailty and overall mortality. The pooled data indicated an association between prefrailty and higher overall mortality (HR = 1.20, 95% CI: 1.05–1.38). No significant heterogeneity was observed across these pooled studies ($Chi^2 = 1.55$, $df = 1$, $I^2 = 35\%$, $P = 0.21$).

Therapeutic Toxicity

Three articles assessed the role of frailty in predicting treatment toxicity, including postoperative complications, chemotherapy adverse reactions, chemotherapy toxicity (16, 17, 22). As shown in **Figure 4A**, the pooled OR was 2.60 (95% CI: 0.82–8.24), indicating frailty associated with higher odds of treatment toxicity. No significant heterogeneity was observed across these pooled studies ($Chi^2 = 4.02$, $df = 2$, $I^2 = 50\%$, $P = 0.13$). From

TABLE 1 | Baseline characteristics of the included studies.

Study	Year	Country	Recruitment	Follow up		Sample size	Age (years)		Frailty		Females	Stage	Treatment		Therapeutic toxicity		Overall mortality
				Length	Median	number	Range	Median or mean	Scale	Cut off (numbers)	(%)					OR (95% CI)	HR (95% CI)
Kaneda	2021	Japan	2016–2019	NR	NR	193	NR	70.4	Frailty phenotypic model	Non-frail (152), prefrail (28), frail (13)	37	1–3	Surgery	Prefrail	Postoperative complications	0.89 (0.28–2.79)	
														Frail		0.44 (0.055–3.58)	
Cespedes Feliciano	2020	America	1993–1998	19.9 years	5.8 years	822	50–79	63	Fried frailty phenotype	Non-frail (405), prefrail (239), frail (178)	100	NR	NR	Prefrail			1.09 (0.89–1.34)
														Frail			1.33 (1.05–1.68)
Wang	2019	China	2010–2017	8 years	3.9 years	1,020	≥60	65	FI-LAB	Non-frail (701), prefrail (269), frail (50)	28.6	1–4	Chemotherapy	Prefrail	Any adverse reactions	1.86 (1.25–2.77)	1.30 (1.08–1.57)
														Frail		3.48 (1.77–6.87)	2.13 (1.51–3.00)
Ruiz	2019	America	2010–2014	NR	NR	45	42–86	69	Fried Frailty Index	Frail (12), non-frail (23)	20.8	4	Chemotherapy	Frail	Treatment-related grade 3-5 toxicity	5.82 (1.06–31.81)	1.03 (0.51–2.11)
Raghavan	2018	Canada	2009–2014	76.1 months	38.8 months	140	NR	NR	Modified frailty index	Non-frail (91), frail (49)	63.9	1	Stereotactic body radiotherapy	Frail			1.98 (1.02–3.85)
Franco	2018	America	2009–2014	74.1 months	38.5 months	139	NR	74	Modified frailty index	Non-frail (101), frail (38)	51.8	1–2	Stereotactic body radiotherapy	frail			2.25 (1.44–4.44)
De la Garrza Ramos	2016	Canada	2002–2011	NR	NR	1,562	NR	62	Metastatic Spinal Tumor Frailty Index	Non-frail, mild frail, moderate frail, severe frail	NR	NR	Spine surgery	Mild frail	Complication	1.63 (0.93–2.89)	
														Moderate frail		3.52 (2.02–6.16)	
														Severe frail		5.27 (3.04–9.12)	

NR, not reported; FI-LAB, frailty index based on laboratory variable.

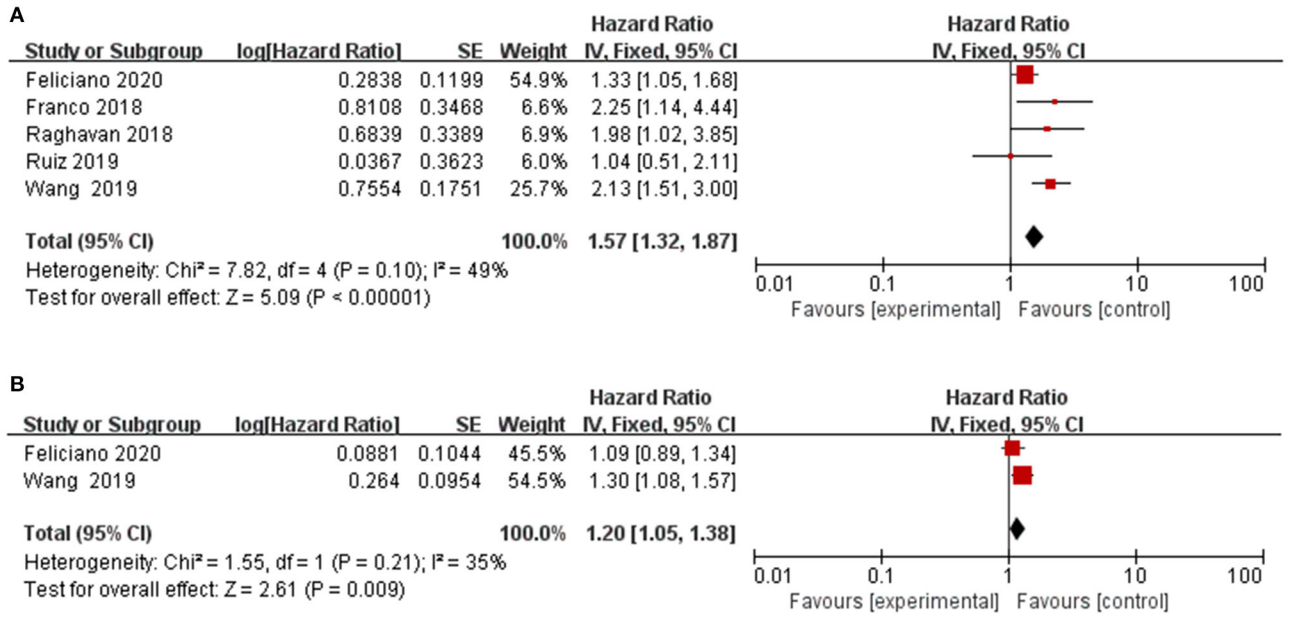


FIGURE 2 | Forest plot of the association between frailty and overall mortality. **(A)** frailty and overall mortality; **(B)** prefrailty and overall mortality.

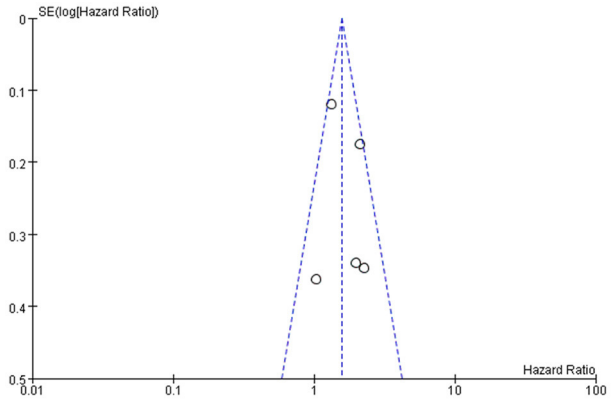


FIGURE 3 | Funnel plot of frailty and overall mortality.

the combination of included articles, prefrailty was associated with higher odds of treatment toxicity (OR = 1.72, 95% CI: 1.18–2.51) (**Figure 4B**).

De la Garza Ramos et al. (21), which assessed frailty by Metastatic Spinal Tumor Frailty Index, found that compared with patients with no frailty, patients with moderate frailty (OR = 5.15; 95% CI: 2.44–10.86), and severe frailty (OR = 5.74; 95% CI: 2.69–12.24) had significantly increased odds of inpatient mortality. Similarly, patients with mild frailty (OR = 1.88; 95% CI: 1.33–2.66), moderate frailty (OR = 3.83; 95% CI: 2.71–5.41), and severe frailty (OR = 6.97; 95% CI: 4.98–9.74) had significantly increased odds of developing a major in-hospital complication.

DISCUSSION

Our systematic review and meta-analysis showed poor prognosis in lung cancer patients with frailty or prefrailty. Compared to non-frail patients, frail patients had a higher risk of overall mortality and treatment toxicity. Similarly, prefrailty was associated with higher overall mortality and therapeutic toxicity.

Frailty was characterized by a decline in functioning across multiple physiological systems, while there is a progressive debate about how to define this condition (24, 25). The two most commonly used frailty assessment instruments are frailty phenotype (26) and frailty index (27). A previous review revealed that frailty prevalence greatly varies across studies, from 4 to 59%, because of lack of standardization of concepts or measures (28). Although the frailty assessment criteria were different among the studies included in this review, no significant heterogeneity was observed across these pooled studies. However, when metastatic spinal tumor frailty index (MSTFI) used in spinal patients, severely frail patients had significantly increased odds of developing a major in-hospital complication, and OR was 5.27 (95% CI, 3.04–9.12), which was higher than the pooled OR (2.60, 95% CI, 0.82–8.24) in our review. The components of MSTFI included comorbidities (e.g., anemia, chronic lung disease, and coagulopathy et al.), emergent/urgent case, and anterior or combined surgical approach, which was largely different from estimates components in other studies. At present, there are few studies comparing the predictive value of different frailty assessment instruments for prognosis. Therefore, more studies are needed in the future to explore the frailty assessment criteria suitable for different populations.

The studies included in this meta-analysis involved different therapeutic methods, including chemotherapy, radiotherapy, and

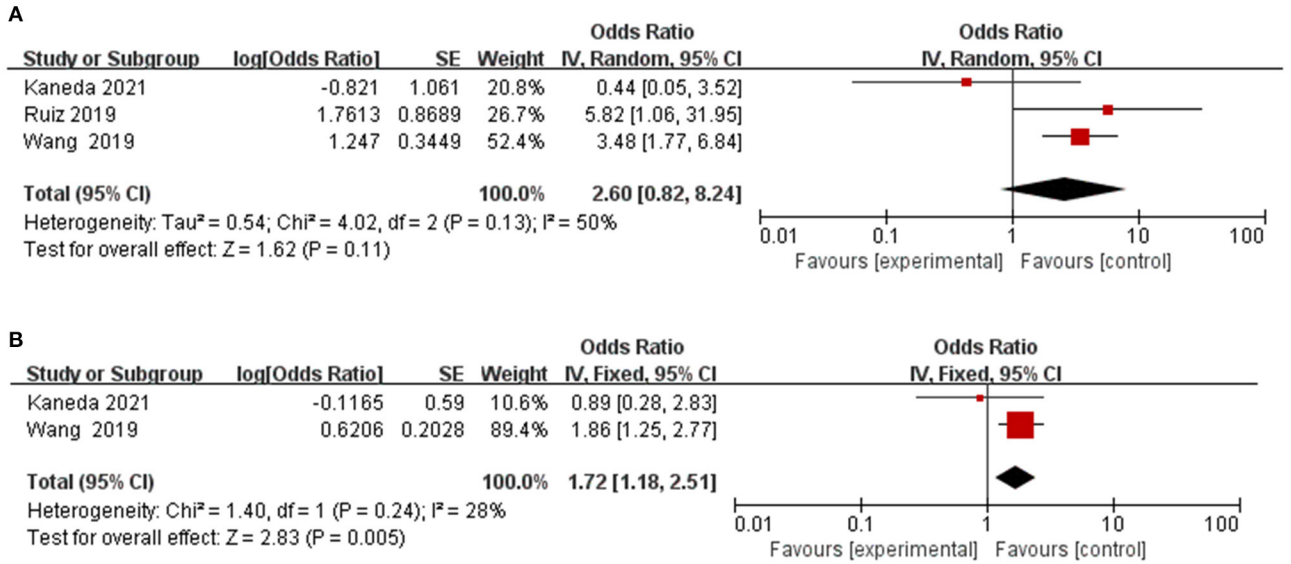


FIGURE 4 | Forest plot of the association between frailty and therapeutic toxicity. **(A)** frailty and therapeutic toxicity; **(B)** prefrailty and therapeutic toxicity.

surgery. Except one study found that frailty was not a significant predictor of postoperative outcomes (17), others revealed frailty was associated with overall mortality or therapeutic toxicity. Due to the small number of studies, we did not perform subgroup analyses for treatment methods. However, there may be potential differences in the predictive value of frailty for the prognosis of different treatments, which needs to be confirmed by future studies. The appearance of EGFR tyrosine kinase inhibitor and immune-checkpoint inhibitors has dramatically improved the prognosis of patients with non-small cell lung cancer, while frailty assessment is deficiency in these patients (29, 30), and prospective randomized trials addressing this question are warranted.

The patients included in this study included patients with different lung cancer stages, from stage 1 to stage 4. However, due to the limited number of studies, we did not conduct subgroup analysis on disease stages. From the early stage to the late stage of lung cancer, the proportion of frailty increased (22). However, there was no significant difference in the incidence of frailty between stage 1A and 1B/2A patients (14). Franco et al. (14) found that overall stage did not influence the survival of patients by univariate analysis (1B/2A vs. 1A, $P = 0.46$). A previous study confirmed that no significant interactions between frailty and disease stage in the recurrence-free survival ($P_{\text{interaction}} = 0.98$) and OS ($P_{\text{interaction}} = 0.96$) among colorectal cancer patients (31). The interactions between frailty and disease stage in the survival of lung cancer patients needs further studies to confirm.

Our review suggested that frailty was associated with prognosis of lung cancer, which was in accordance with those of studies conducted in patients with other type of cancer (7, 8). However, based on one study included in our meta-analysis, frailty seemed not to be associated with postoperative complications in lung cancer patients, which was not consistent with relevant results of studies on other types of cancer. These previous studies found that frailty was associated with increased risk of postoperative complications in patients with gastric cancer (32), pancreatic cancer (33), head and neck cancer (34), colorectal cancer (35), gynecologic cancer (36). The modified Frailty Index has been validated in several studies as a reliable measure of mortality in vascular (37), orthopedic (38), gynecologic (39), and general surgeries (40). Therefore, further studies are required to determine the association between frailty and surgery-related outcomes in lung cancer.

Many factors might affect the findings of the assessment of the impact of frailty on the prognosis of lung cancer. Studies found that unadjusted association estimates might overestimate the impacts of frailty on prognosis of lung cancer. Frailty was significantly associated with shorter OS on univariate analysis [HR = 2.22 (95% CI, 1.22–4.05)], while the value of HR decreased to 1.98 (95% CI, 1.02–3.85) (15). When adjusted for other factors, such as clinical stage and age et al., the value of HR decreased from 3.00 (95% CI, 2.15–4.18) to 2.13 (95% CI, 1.51–3.00) (22). When the factors associated with the prognosis were selected to constitute the frailty index components, the prognostic value of the frailty itself might be overestimated (21). Several studies included in this meta-analysis were derived from unadjusted association estimates and the pooled results confirmed the prognostic value of frailty. A previous study found that I^2 had a substantial bias when the number of studies was small (41). Although no significant heterogeneity was observed across the pooled studies in our meta-analysis, more future studies are needed to confirm the adjusted HR of frailty because of the limited number of studied include in our review.

This meta-analysis has some limitations. First, only a small number of studies are included in this review. Therefore, we did not perform the subgroup analyses according to the different treatments. Second, the frailty assessment instruments varied

across studies, and we did not perform the subgroup analyses due to limited number of studies of each assessment instruments. Third, it should be acknowledged that the number of available studies for prefrailty was small for robust conclusions to be drawn. Further studies are needed to establish the strength of association between prefrailty and lung cancer prognosis.

CONCLUSIONS

Frailty and prefrailty seem to have a significant impact on the mortality and therapeutic toxicity of patients with lung cancer. Therefore, frailty assessment is important before treatment, which may affection treatment decisions. More prospective studies are needed to explore the prognostic value of frailty in lung cancer patients receiving different treatments.

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

ShD, MY, and JW: conception or design and drafting the work or revising. ShD, JS, and SiD: acquisition, analysis, or interpretation of data. 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.2021.715513/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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Association Between the Normal-Density Psoas Muscle Index and Handgrip Strength or Gait Speed in Maintenance Hemodialysis Patients

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Introduction: This study aimed to evaluate the association between the psoas muscle (PM) index with or without fatty infiltration and various indices associated with muscle mass in hemodialysis (HD) patients.

Methods: We included stable HD patients (n = 83). The collected data included subjective global assessment (SGA) score, ASM/Ht^2 (appendicular skeletal muscle mass divided by the squared height in meters), gait speed (GS; m/s), and handgrip strength (HGS; kg). The abdominal computed tomography (CT) image was obtained using a CT scanner. The PM and normal-density PM (NPM) indices (mm^2/m^2) were calculated using the whole PM area or the area with an attenuation range of 35–100 HU divided by the squared height in meters.

Results: Correlation coefficients for the SGA score, ASM/Ht^2, HGS, and GS were greater for the NPM index than for the PM index. The linear regression analysis showed that, on multivariate analysis, the NPM index was significantly associated with the SGA score, ASM/Ht^2, and GS. However, the PM index was significantly associated with the SGA score and ASM/Ht^2 but not with HGS or GS. For calculating the low GS, the area under the receiver operating characteristic curve area was significantly greater for the NPM index than for the PM index (P = 0.012).

Conclusion: The present study suggested that the NPM index excluding fatty infiltration may be an early and useful indicator for detecting muscle strength and physical performance among HD patients.

Keywords: psoas muscle, hemodialysis, muscle strength, gait speed, fatty change

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INTRODUCTION

Hemodialysis (HD) is one of most commonly used dialysis modalities in end-stage renal disease patients requiring renal replacement therapy. With advances in HD technologies and cares, the survival of HD patients has improved. However, the prevalence of long-term complications increased over time with treatment and as the dialysis population ages (1). Decreased muscle mass is one complication that can develop in long-term HD patients (2). This is associated with decreased

quality of life and increased morbidity or mortality in HD patients (3). Therefore, accurate muscle mass measurement is important for predicting prognosis or physical performance in HD patients.

Computed tomography (CT) and dual X-ray absorptiometry (DXA) are commonly used for measuring muscle mass in HD patients (4, 5). Previous studies have shown that, among various muscle mass indices, the psoas muscle (PM) index measured on CT is associated with clinical outcomes in HD patients (6, 7). However, HD patients are prone to insulin resistance caused by various conditions such as diabetes mellitus (DM), chronic inflammation, or uremia (8). Insulin resistance can be associated with fatty changes in the muscle mass in HD patients and lead to overestimated muscle mass measurements. Both PM including or excluding fatty infiltration can predict the total muscle mass index and nutritional index. The two indices are positively correlated with total muscle mass. Both muscle mass and fatty infiltration can be increased by improving nutrition in dialysis patients. However, the predictability of muscle strength or physical performance differs between the two indices. Although the total amount of muscle mass was to be the same, muscle mass with fatty infiltration is associated with a greater decrease in muscle strength or physical performance than that without fatty infiltration. These reveal that muscle mass without fatty changes may be more closely associated with muscle strength or physical performance than total muscle mass *per se*. However, there are few studies of the association between muscle without fatty changes and indicators associated with muscle function in HD patients. This study aimed to evaluate the association between the PM index with or without fatty infiltration and various indices associated with muscle mass in HD patients.

MATERIALS AND METHODS

Study Design and Participants

Our study was a cross-sectional study and it was performed between September 2012 and March 2015 in a medical center. We included HD patients aged ≥20 years and with duration of dialysis ≥6 months, ability to ambulate without an assistive device, ability to communicate with the interviewer, and no hospitalization within the 3 months before enrollment. This study was approved by the institutional review board of a local medical center (approval no. 12-07). Informed consent was obtained from all participants before enrollment: a total of 83 patients were enrolled. None of the participants took medications associated with physical activity such as opioids, antihistamines, or antidepressants.

Baseline Variables

The collected baseline data included sex, age, presence of DM, dialysis vintage, hemoglobin (g/dL), C-reactive protein (CRP; mg/dL), blood urea nitrogen (mg/dL), creatinine (mg/dL), calcium (mg/dL), phosphorus (mg/dL), sodium (mEq/L), potassium (mEq/L), chloride (mEq/L), intact parathyroid hormone (i-PTH; pg/mL), total cholesterol (mg/dL), albumin (g/dL), and single pool measurement of solute removal during HD that focuses on urea ($spKt/V_{urea}$). All laboratory tests were performed prior to the HD sessions and repeated thrice in the following 3 weeks. The mean of three values was recorded for each parameter. DM was defined as a patient-reported history and medical record of a DM diagnosis or use of antiglycemic medication. The $spKt/V_{urea}$ values were calculated using the described as described previously (9).

Assessment of the Nutritional Status, Muscle Mass, Strength, and Gait Speed

The subjective global assessment (SGA) score was calculated based on scores from seven items (weight loss, dietary intake, gastrointestinal symptoms, functional capacity, comorbidity, decreased fat, and decreased muscle mass) as described previously (10). Muscle mass was evaluated using whole-body DXA (GE Medical Systems Lunar, Madison, WI, USA). Appendicular skeletal muscle mass (ASM; kg) was calculated using the sum of lean mass of both extremities. Finally, ASM/Ht^2 was calculated as ASM divided by the squared height in meters. Hand grip strength (HGS) was measured and each patient performed three trials with the dominant hand using a manual hydraulic dynamometer (Jamar® Hydraulic hand dynamometer; Sammons Preston, Chicago, IL, USA). Maximum values among the three trials were selected. Gait speed (GS; m/s) was evaluated using the timed 4-m walking test (11). A low GS group was defined based on their values <0.8 m/s, according to a previous guideline (11). We also defined the low SGA (<6 of total SGA score), low ASM/Ht^2 (<7.0 kg/m^2 for males and <5.4 kg/m^2 for females), and low HGS (<26 kg for males and <18 kg for females) groups based on the same guidelines (11).

PM Evaluation

The abdominal CT image was obtained using a 320-slice CT scanner (Aquilion ONE; Toshiba Medical Systems Corp., Tokyo, Japan). A single axial image was obtained at the lower border of the L3 vertebral level. The images were analyzed using an image analysis software (ImageJ 1.45S; National Institutes of Health, Bethesda, MD, USA). In our study, Hounsfield units (HU) of muscle were defined using a modified version described previously (12). Muscle attenuations at very low, low, or normal density were −29 to −1, 0–34, and 35–100 HU, respectively. A quantitative assessment of the whole PM was obtained and PM area (mm^2) was defined as the area with an attenuation range of −29 to 100 HU among the sum of the right and left whole PM areas, which includes very low-, low-, and normal-density muscle. The PM index (mm^2/m^2) was calculated using the PM area divided by the squared height in meters. Normal-density PM (NPM) area was defined as the area with an attenuation range of 35–100 HU among the sum of the right and left whole PM areas including normal-density muscle alone. The NPM index (mm^2/m^2) was calculated using the NPM area divided by the squared height in meters. Three measurements were taken of both PMs and the average was used for the analysis.

Statistical Analysis

The data were analyzed using IBM SPSS Statistics version 25 (SPSS Inc., Chicago, IL, USA). Categorical variables are expressed as counts (percentages). The distribution of the

continuous variables was evaluated using the Kolmogorov-Smirnov test. Continuous variables with normal distribution are expressed as means ± standard deviations. Those with non-normal distributions are expressed as medians (interquartile ranges). Comparisons between two groups were performed using *t*-tests. The correlations between two continuous variables were assessed using Pearson's correlation analysis. For linear regression analyses, the dependent variables were the SGA, ASM/Ht^2, HGS, and GS, and the independent variables were the PM and NPM indices. The multivariate analysis was adjusted for age, sex, and presence of DM and performed using the backward conditional method. Discrimination, which is the ability of the model to differentiate between participants who have a low GS and those who do not, was examined using the area under the receiver operating characteristic curve (AUROC). The statistical significance between the AUROCs was calculated using the DeLong method. SPSS version 25 did not compare the AUROC curves using the DeLong method. Therefore, we also used other software to compare and evaluate the statistical significance between the ROC curves. The AUROC was calculated using MedCalc version 11.6.1.0 (MedCalc, Mariakerke, Belgium). The level of statistical significance was set at $P < 0.05$.

RESULTS

The clinical characteristics of the 83 patients are shown in **Table 1**. The mean age was 56.7 ± 11.9 years; 44 (53%) of the participants were male. The dialysis duration was 3.0 (5.1) years. The mean SGA score, HGS, GS, and ASM/Ht^2 values were 6 (2), 26.0 (9) kg, 0.92 ± 0.20 m/s, and 6.58 ± 0.98 kg/m^2, respectively. The proportions of very low-, low-, or normal-density muscle among the entire PM area were 5.8 ± 3.1%, 17.2 ± 7.2%, and 77.0 ± 9.6%, respectively. The mean PM and NPM index values were 448.7 ± 138.7 mm^2/m^2 and 348.1 ± 126.3 mm^2/m^2, respectively.

TABLE 1 | Participants' clinical characteristics.

	***N* = 83**
Male sex	44 (53%)
Age, years	56.7 ± 11.9
Diabetes mellitus	43 (51.8%)
Dialysis vintage, years	3.0 (5.1)
Hemoglobin, mg/dL	10.9 (0.7)
C-reactive protein, mg/dL	0.20 (0.40)
Blood urea nitrogen, mg/dL	59.4 ± 14.8
Creatinine, mg/dL	10.2 (2.4)
Serum calcium, mg/dL	8.4 ± 0.7
Serum phosphorus, mg/dL	5.4 ± 1.3
Serum sodium, mEq/L	138 ± 3
Serum potassium, mEq/L	5.0 ± 0.6
Serum chloride, mEq/L	98.5 ± 3.4
Intact parathyroid hormone, pg/mL	223 (240.3)
Total cholesterol, mg/dL	154 ± 34
spKt/Vurea	1.37 ± 0.31

Data are expressed as mean ± standard deviation for continuous variables with normal distribution, median (interquartile range) for continuous variables with non-normal distribution, and as number (percentage) for categorical variables.

Correlation coefficients for the PM index were 0.309 for the SGA score ($P = 0.005$), 0.580 for ASM/Ht^2 ($P < 0.001$), 0.474 for HGS ($P < 0.001$), and 0.295 for GS ($P = 0.007$). Those for the NPM index were 0.338 for the SGA score ($P = 0.002$), 0.604 for ASM/Ht^2 ($P < 0.001$), 0.537 for HGS ($P < 0.001$), and 0.384 for GS ($P < 0.001$). Because age is an important confounding factor, we also performed subgroup analyses according to 30–49, 50–59, or 60–79 years of age (**Table 2**). For all the groups and variables except ASM/Ht^2 in the 30–49 age group, the correlation coefficients were greater in the NPM index than the PM index.

Comparisons between the low and normal groups are presented in **Table 3**. The PM and NPM indices in the low GS group were lower than those in the normal GS group. There were no significant differences in the PM and NPM indices between the low and normal groups for HGS, SGA, and ASM/Ht^2, but the trends of the mean differences between the two groups were consistently greater in the NPM index than the PM index. In addition, the difference between the low and normal groups was relatively greater in HGS or GS than in ASM/Ht^2.

The linear regression analysis showed that, on multivariate analysis, the NPM index was significantly associated with the SGA score, ASM/Ht^2, and GS (**Table 4**). However, the PM index was significantly associated with the SGA score and ASM/Ht^2 but not with HGS or GS. Multivariate linear regression analysis showed that statistical significance was not obtained the association between the two indices and HGS ($P = 0.251$ for PM index and $P = 0.053$ for NPM index). Non-significance between the NPM index and HGS may be associated with small sample size. However, considering lower *P*-values for NPM index compared to that for PM index, analyses with a larger sample size would lead to statistical significance between the NPM and HGS. **Figure 1** shows the AUROCs for predicting the low GS of the two indices. For calculating the low GS, the AUROC values of the PM index were 0.675 [95% confidence interval (CI), 0.562–0.774; $P = 0.007$]. The AUROC values of the NPM index were 0.725 (95% CI, 0.616–0.818; $P < 0.001$). The AUROC area was significantly greater for the NPM index than for the PM index ($P = 0.012$).

DISCUSSION

Previous studies have shown the importance of muscle quantity and quality in populations prone to the risk of sarcopenia and/or insulin resistance (13, 14). Muscle quality is generally associated with fat infiltration within or between the muscles. Fatty changes in the muscle can result from various conditions, such as age, obesity, DM, or surgery, that decrease muscle attenuation on CT images (15). A range of −190 HU and −30 HU is commonly used to define the fat mass on CT images. A previous study defined HU ranges of very low-, low-, or normal-density muscle of −29 to −1, 0–34, and 35–100, respectively (12). However, there were inconsistencies regarding HU attenuation cut-off values or muscle mass on CT. Low cut-off values for muscle mass ranged from −29 to 35 HU, while high cut-off values ranged from 100

TABLE 2 | Correlation coefficients between the PM indices and various variables according to age groups.

	30–49 years ($n = 27$)				50–59 years ($n = 25$)				60–79 years ($n = 31$)			
	PM index		NPM index		PM index		NPM index		PM index		NPM index	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
SGA score	0.153	0.447	0.188	0.346	0.095	0.651	0.187	0.370	0.507	0.004	0.550	0.001
ASM/Ht^2, kg/m^2	0.637	<0.001	0.618	0.001	0.302	0.143	0.338	0.098	0.605	<0.001	0.674	<0.001
Handgrip strength, kg	0.469	0.014	0.543	0.003	0.516	0.008	0.590	0.002	0.292	0.111	0.367	0.042
Gait speed, m/s	0.455	0.017	0.500	0.008	0.087	0.680	0.189	0.366	0.096	0.607	0.260	0.158

P-values were tested using Pearson's correlation analyses.
PM, psoas muscle; NPM, normal-density psoas muscle; ASM/Ht^2, appendicular skeletal muscle mass per height squared; SGA, subjective global assessment.

TABLE 3 | Comparison of the PM and NPM indices between the groups of HGS, SGA, ASM/Ht2, or GS.

	HGS				SGA			
	Low	Normal	MD (95% CI)	*P*	Low	Normal	MD (95% CI)	*P*
PM index	431 ± 146	450 ± 138	19 (−60, 99)	0.627	427 ± 117	462 ± 152	35 (−26, 96)	0.258
NPM index	308 ± 107	357 ± 129	48 (−23, 120)	0.182	321 ± 101	368 ± 140	47 (−9, 102)	0.097
	ASM/Ht^2				GS			
	Low	Normal	MD (95% CI)	*P*	Low	Normal	MD (95% CI)	*P*
PM index	423 ± 109	460 ± 152	36 (−27∼100)	0.257	416 ± 124	505 ± 149	89 (28, 150)	0.005
NPM index	322 ± 92	362 ± 140	41 (−17∼98)	0.161	312 ± 11	414 ± 140	102 (48, 156)	<0.001

P-values were tested using a t-test.
HGS, handgrip strength; SGA, subjective global assessment; ASM/Ht^2, appendicular skeletal muscle mass per height squared; GS, gait speed; MD, mean difference; CI, confidence interval; PM, psoas muscle; NPM, normal-density psoas muscle; PM, psoas muscle.

TABLE 4 | Comparison of nutritional and physical performance according to the PM indices.

	PM index				NPM index			
	Univariate		Multivariate		Univariate		Multivariate	
	St-β	*P*	St-β	*P*	St-β	*P*	St-β	*P*
SGA score	0.309 (0.001)	0.005	0.233 (0.001)	0.032	0.338 (0.001)	0.002	0.256 (0.001)	0.017
ASM/Ht^2, kg/m^2	0.580 (0.001)	<0.001	0.296 (0.001)	0.013	0.604 (0.001)	<0.001	0.380 (0.001)	0.001
Handgrip strength, kg	0.474 (0.005)	<0.001	0.136 (0.006)	0.251	0.537 (0.005)	<0.001	0.230 (0.007)	0.053
Gait speed, m/s	0.295 (0.000)	0.007	0.107 (0.000)	0.437	0.384 (0.000)	<0.001	0.298 (0.002)	0.005

P-values were tested using linear regression analysis. The dependent variables were the SGA, ASM/Ht^2, handgrip strength, and gait speed, and the independent variables were the PM and NPM indices. Multivariate analysis was adjusted for age, sex, and the presence of diabetes mellitus, and performed using the backward conditional method.
ASM/Ht^2, appendicular skeletal muscle mass per height squared; NPM, normal-density psoas muscle; PM, psoas muscle; SGA, subjective global assessment.

to 150 HU. The wide range of HU values of muscle mass can be useful for predicting whole muscle mass area regardless of the fatty infiltration status, but a narrow range of HU values of muscle mass would be more useful for measuring the mass of muscles without fatty changes. Therefore, in our study, we used normal-density muscle mass alone to represent muscle mass without fatty infiltration.

Previous studies evaluated the association between mean PM density and prognosis in patients with various malignancies, such as melanoma, adrenocortical carcinoma, prostate cancer, and biliary or gastrointestinal tract cancer (16–20). Trotter et al. evaluated patients who underwent emergency laparotomy and showed the positive association between sarcopenia, assessed using mean PM density, and prognosis (21). Lindström et al. showed the association between PM quality and prognosis in patients treated for abdominal aortic aneurysms (22). Three studies showed a significant association between PM quality and prognosis in patients who underwent cardiac surgery (23–25). HD patients are at risk of insulin resistance. A previous study calculated the fatty changes of 49 HD patients using mean whole PM values and showed that intramuscular fat infiltration was associated with GS and 6-min walk test performance (26).

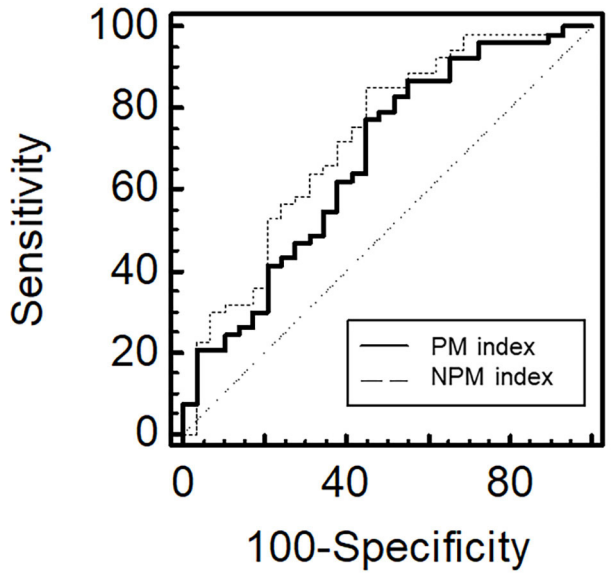


FIGURE 1 | The area under the receiver operating characteristic curve for the PM or NPM indices for predicting low gait speed. NPM, normal density-psoas muscle; PM, psoas muscle.

Physical performance such as GS is associated with muscle strength and/or mass (27, 28). Physical performance is also associated with various factors beyond muscle mass or strength, such as motor coordination, excitation-contraction coupling, or skeletal integrity. Therefore, decreases in physical performance can be addressed sooner than decreased muscle mass or strength. In addition, decreases in muscle strength would occur sooner than decreases in muscle mass. Although the associations among muscle mass, strength, and physical performance are complex, muscle mass with fatty changes would lead to lower strength and/or physical performance than that without fatty changes despite the same total muscle mass.

In our study, the SGA score as a nutritional index and ASM/Ht^2 as a total skeletal muscle mass index were associated with the PM index and NPM index. ASM/Ht^2 determined using DXA simply evaluates the total lean mass regardless of fatty changes within the muscle mass. The SGA score is a useful indicator for predicting nutritional status, but it does not discriminate whether the dominantly increased mass is muscle or fat. GS was associated with the NPM index alone. Statistical significance was not obtained, but trend showed a positive association between NPM index and HGS. Strength or physical performance can be influenced by muscle quantity and quality. Our results revealed that the NPM index as an indicator of muscle quality is more closely associated with strength or physical performance. In addition, the correlation coefficients for the SGA score, ASM/Ht^2, HGS, and GS were greater for the NPM index than for the PM index.

Our study has inherent limitations, including a cross-sectional design with a single-center setting and a small number of patients. Our study was performed without sample size calculation according to the hypothesis. In addition, our study had a relatively too small a sample size to draw definitive conclusions from. A cross-sectional study with a relatively small sample size, such as ours, would be useful in suggesting issues regarding the associations between the variables rather than drawing definitive conclusions. Second, we did not perform multivariate analyses with adjustment for all confounding factors, such as the presence of exercise, calcium, phosphorus, i-PTH, CRP, or 25-(OH) vitamin D levels. Multivariate analyses using all confounding factors may be optimal for evaluating the independent effects of a variable. However, our study had a relatively small sample size, and we did not perform multivariate analyses adjusting for all variables. Therefore, we selected three covariates (age, sex, and the presence of DM) that can be significantly influenced by outcome measurements and performed multivariate analyses including three covariates and one variable (PM or NPM index). A prospective longitudinal study including a large number of patients and additional indicators is warranted to overcome these limitations.

In conclusion, the present study suggested that the NPM index excluding fatty infiltration may be applicable as an early and useful indicator for detecting muscle strength and physical performance among HD patients. However, limitations regarding the small sample size and the cross-sectional design without sample size calculation according to the hypothesis should be noted. Prospective studies with a larger sample size are needed to identify the definitive associations between the NPM index and muscle strength or physical performance in HD 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 IRB of CHA Gumi medical center. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SK conceptualized and designed the study, performed the data analysis and interpretation, and wrote the manuscript. BK and JK generated and collected the data. JD and JK drafted and revised the manuscript. All authors approved the final version of the manuscript.

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frontiers in Medicine

ORIGINAL RESEARCH
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Frailty Status Among the Elderly of Different Genders and the Death Risk: A Follow-Up Study

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Background: Frailty in the elderly population is currently a frontier and focus in the field of health and aging. The goal of this study was to explore the frailty status among the elderly of different genders and its influence on the risk of death during 11 years.

Methods: Frailty index (FI) was used to evaluate the frailty status in the elderly based on the baseline data conducted in 2009; and death as outcome variables collected in 2020 were analyzed. The difference of the frailty level and mortality of different genders was compared. Cox regression and Kaplan–Meier curves were applied to evaluate the influence on the risk of death and the 11-year survival of the elderly at different level of frailty, respectively.

Results: Totally, 1,246 elderly people were recruited. The mortality in men (43.7%, 227/519) was statistically higher than that in women (34.3%, 249/727) ($x^2 = 11.546$, $P = 0.001$). Deficits accumulated exponentially with age, and at all ages, women accumulated more deficits than do men on average ($B = 0.030$ vs. 0.028, $t = 4.137$, $P = 0.023$). For any given level of frailty, the mortality rate is higher in men than in women, and the difference in mortality between genders reached the peak when FI value was 0.26. Cox regression analysis showed that FI value had a greater impact on the risk of death in older men ($HR = 1.171$, 95%CI: 1.139∼1.249)than that in older women ($HR = 1.119$, 95%CI: 1.039∼1.137). Survival analysis showed that the median 11-year survival time in women was longer than that in men (95.26 vs. 89.52 months, $Log\ rank = 9.249$, $P = 0.002$). Kaplan–Meier curves showed that the survival rate decreased with the increase of frailty, and at the same level of frailty, survival time in older women was longer than that in older men, except for severe frailty (FI $\geq$ 0.5).

Conclusion: The frailty status and its influence on mortality are different among the older people of different genders; therefore, specific interventions for frailty should be conducted in the elderly population of different genders, as well as of different degrees of frailty.

Keywords: frailty, elderly, different genders, death risk, follow-up study

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INTRODUCTION

The study on frailty in the elderly population is currently a frontier and focus in the field of health and aging. The concept of frailty was formally introduced at a meeting of the American Geriatrics Society in 1978 and used to describe a health status in the elderly population with various accumulated health problems requiring long-term support in activities of daily living (1). Since the phenotypic definition of frailty was first introduced by Fried et al. (2) in 2001, the concept of frailty has attracted attention in the field of geriatric medicine, and study publications on frailty have also rapidly increased. Studies have shown that frailty is closely associated with falls, dementia, fractures, and cardiovascular diseases in the elderly population, and the degree of frailty greatly impacts survival rates (3, 4). The degree of frailty in the elderly population has important predictive value for the risks of many adverse outcomes, such as disability, reduced activities of daily living, lengthening of hospitalization, and death events (5, 6).

The frailty index (FI) model, established by Canadian geriatric specialist Professor Kenneth Rockwood and his team, is based on the accumulation of health deficits and currently one of the most popular model to assess frailty in the elderly population (7). The assessment with the FI model successfully achieves a quantitative description of the frailty status in the elderly population and provides an effective way to quantitatively assess the health status of the elderly population. The assessment with FI provides a broader range than other indicators. Multiple health variables can be represented as a single indicator able to reflect a variety of biological processes and more accurately measure the overall health status of the elderly population, enhancing the statistical power of outcome estimation (8). One study demonstrated that the FI outperformed other frailty assessment tools in predicting adverse health prognoses, including death events (9). Due to physiological differences, the progression and manifestation of frailty vary in the elderly population of different genders (10–12). The results of foreign studies based on community population showed that frailty degree in women was higher than in men at the same age, and the mortality rate was higher in men than in women at the same degree of frailty (13). So far, there have been few studies on the FI model in the elderly population of different genders in Chinese communities or on the analysis of the impact of frailty on long-term mortality risk. The elderly population in Beijing urban communities were included in this study, and the prospective analysis utilized the FI model to assess differences in frailty in the elderly population of different genders and the impact on mortality risk, so as to provide a basis for further specific intervention measures to decrease adverse health prognosis caused by frailty.

MATERIALS AND METHODS

Study Setting and Participants

This is a secondary analysis of the Health Status and Fall Status Follow-up Survey database, a representative cohort of community dwelling elder people aged 60 years and older. In this study, the baseline survey population in 2009 were used as samples, and death events from this cohort collected in the follow-up survey in 2020 were used as the outcome variables. The baseline survey was conducted in 2009 in Longtan Sub-district Office jurisdiction of Beijing's Dongcheng District as the survey site using cluster random sampling. A total of 1,578 elderly residents were eligible. The inclusion criteria: the elderly who were $\geq$60 years during the survey and having lived in the survey site for more than 1 year. The exclusion criteria: the elderly who were not living in the survey site during the survey or were unable to cooperate to complete the survey. A total of 37 elderly residents refused the survey and 63 elderly residents were lost to follow-up (not at home on two visits during the survey). The actual number of survey subjects was 1,536, with a response rate of 95.2%; and a total of 1,512 valid questionnaires were obtained, with a total valid rate of 98.4%. In 2020, a follow-up study on the 1,478 baseline survey population was conducted, and information related to death events among this population was also collected. By 2020, 232 subjects were lost to follow-up, with a lost-to-follow-up rate of 14.0% (232/1,478). All were subjects who left or moved out of the survey site, with an average age of 68.24 $\pm$ 3.58 years, including 108 men (46.6%) and 124 women (53.4%). A total of 1,246 subjects were finally included in the analysis, including 519 men (41.7%) and 727 women (58.3%) with an average age of 72.05 $\pm$ 4.52 years. The age of the elderly who were lost-to-follow-up was lower than those included in the study ($t = 12.148$, $P = 0.000$), but there was no significant difference between both genders ($\chi^2 = 1.921$, $P = 0.166$). All subjects signed the informed consent forms.

Study Content and FI Construction

In this study, a standard questionnaire validated by multiple rounds of expert discussion was used and information was collected by face-to-face interview. The information included demographic characteristics, social support and economic status, health and physical status, diseases and signs, medications, cognition and emotion stats, balance function test, activities of daily living assessment (ADL, IADL), and comprehensive geriatric assessment. Based on the content of the questionnaire, a total of 37 variables were selected as the health deficits for calculating the FI according to the criterion of health deficits and standard procedure to construct the FI (14). The variables which made up the FI covered a range of health problems, including comprehensive geriatric assessment ($n = 7$), visual and hearing assessment ($n = 2$), walking and balance function ($n = 6$), diseases and medications ($n = 16$), activities of daily living (ADL and IADL) ($n = 2$), cognition and emotion ($n = 3$), and depression assessment ($n = 1$). At the same time, the variables were coded according to their types following the standard steps (14). For the binary variables, the presence of a deficit was coded as "1" and its absence was coded as "0." For the multilevel variables, intermediate response level was coded using an additional value to grade variables between "0" and "1," each lower rating of health was coded to represent a larger deficit (see **Appendix 1**). The FI is calculated using the formula: FI = number of health deficit scores/total number of items considered as health deficits (i.e., 37). The FI value ranges from 0 to 1. The

larger the value, the more health deficits the individual has, i.e., the greater degree of frailty.

Definition of Follow-Up Outcomes

Based on the standardized questionnaire, death events among the cohort were collected at follow-up in 2020, including whether the subject died, and the time and place of death. For subjects who died during the follow-up period, the staff used standard forms to confirm or obtain information or medical records related to their deaths from family members, local residential committees, or local police stations. A precision method was used for the follow-up duration. If the subject died during the follow-up, the follow-up duration was calculated as (death date–baseline date)/12; if the subject was still alive, it was calculated as (last follow-up date–baseline date)/12.

Quality Control

Quality controls were employed over the entire course of the baseline survey. The survey design (including the design of study protocol and questionnaire) was certified by experts and revised and validated many rounds using pre-survey. All investigators were medical professionals, and a uniform survey program was used for the training and qualification of investigators prior to the survey. The entire procedure of the survey was supervised and directed by the principal investigator, and each questionnaire was checked and reviewed. The data were double-entered by specially-assigned personnel and strictly checked for logic.

Statistical Analysis

SPSS 24.0 and Matlab 2020 software were used for data analysis and plotting, and the missing values of variables in the database were imputed using the MCMC method, one of the multiple imputation methods (15). Measurement data were expressed as $x \pm s$, and the independent sample t-test was used for comparison between two groups. Enumeration data were expressed as the number of cases (percentage), and the χ^2 test was used for comparison between groups. Nonlinear regression techniques were used to fit age-specific frailty index values as a function of age (an exponential function) and to fit the probability of death as a function of the frailty index (a logistic function). The Cox regression model was used to evaluate the hazard ratio (HR) for the impact of FI on mortality in the elderly population of different genders. In the multivariate analysis, as described by Kulminski et al. (16) the FI value was converted into 1% units, i.e., the FI value of each elderly subject was multiplied by 100 and rounded to the nearest whole number. The result obtained indicated the risk caused by each 1% increase in FI values. The Kaplan–Meier method was used to plot the 11-year follow-up survival curves of elderly subjects with different degrees of frailty and then tested using the log-rank method. $P < 0.05$ was considered statistically significant.

RESULTS

General Comparison in the Elderly Population of Different Genders

A total of 1,246 elderly subjects were finally included in the analysis, including 519 men (41.7%) and 727 women (58.3%), aged 60–101 years, with an average of 72.05 ± 4.52 years. The educational level of men was higher than women. In terms of health status, women suffered from more chronic diseases, and their IADL score was higher than men. However, there were no significant differences in the types of medication and ADL scores between the elderly of different genders. Compared with women, men had higher MMSE scores and lower CES-D scores, i.e., the cognitive function and depression status of men were better than women. Women had higher FI values than men, i.e., women had a higher degree of frailty than men. There were no significant differences in average age, marital status, or employment status between the elderly of different genders (all $P > 0.05$; see **Table 1**). As of 2020, a total of 476 subjects died, including 227 men (47.7%) with an 11-year mortality rate of 43.7% (227/519), and 249 females (52.3%) with a 11-year mortality rate of 34.3% (249/727). The mortality rate was higher in men than in women ($\chi^2 = 11.546$, $P = 0.001$).

Relationship Between Age and the Mean Value of FI in the Elderly Population of Different Genders

The relationship between age and the mean value of FI in the elderly population of different genders was analyzed. The results showed that the mean value of FI increased exponentially with age regardless of genders: $\mathrm{In(FI)} = \mathrm{A} + \mathrm{B} \times \mathrm{Age}$, where, $\mathrm{In(FI)} = -3.980 + 0.028 \times \mathrm{Age}$ for men and $\mathrm{In(FI)} = -3.974 + 0.030 \times \mathrm{Age}$ for women. The correlation coefficient between age and the logarithm of the FI was high for both men ($r = 0.986$, $P = 0.000$) and women ($r = 0.993$, $P = 0.000$). The FI values of women were higher than men at any age, i.e., women had a higher degree of frailty than men. On a logarithmic scale, the average annual relative increase rate of health deficits and FI values of women was higher than men ($B = 0.030$ vs. 0.028, $t = 4.137$, $P = 0.023$), i.e., the accumulation rate of health deficits in women was faster than men (see **Figure 1**).

Comparison of Mortality Rates in the Elderly Population of Different Genders With Different Degrees of Frailty

The trend of mortality rates with FI values in the elderly population of different genders was analyzed. The results showed that the FI was highly related to mortality, which was greater in men than in women. In other words, although women had more deficits than did men, the deficits were less lethal. The difference of the mortality rates between both genders with FI value of 0.2∼0.4 was higher than that with other FI values, with the peak occurring with FI value of 0.26, i.e., the difference of mortality rate between both genders was the largest with FI value of 0.26 (see **Figure 2**).

Multivariate Cox Regression Analysis of the Impact of FI on Mortality Risk in the Elderly Population of Different Genders

A multivariate Cox proportional hazards model was performed to evaluate the effect of FI on mortality after testing for the proportionality assumption. The results showed that after the adjustment for age, gender (men = 0, women = 1), years

TABLE 1 | Baseline characteristics of the study sample as separated by sex.

Variables	Men ($n = 519$)	Women ($n = 727$)	t/x^2	*P*-value
Age ($x \pm s$)	71.74 ± 4.41	72.16 ± 4.78	1.579	0.115
Years of education [*n* (%)]			152.645	<0.001
0	29 (5.6)	235 (32.3)		
1∼6	198 (38.2)	273 (37.6)		
≥7	292 (56.3)	219 (30.1)		
Marital Status [*n* (%)]			0.995	0.319
Married or cohabiting with spouse	279 (53.8)	370 (50.9)		
Others[a]	240 (46.2)	357 (49.1)		
Employment status [*n* (%)]			2.355	0.125
Working	27 (5.2)	25 (3.4)		
Retied	492 (94.8)	702 (96.6)		
N of chronic diseases ($x \pm s$)	2.16 ± 1.02	2.45 ± 1.18	4.521	<0.001
N of medication ($x \pm s$)	1.14 ± 1.03	1.17 ± 1.05	0.501	0.616
ADL score ($x \pm s$)	95.77 ± 11.07	94.85 ± 10.73	1.472	0.141
IADL score ($x \pm s$)	2.49 ± 0.19	3.42 ± 0.17	90.613	0.000
MMSE score ($x \pm s$)	25.51 ± 3.49	23.24 ± 4.21	10.061	0.000
CES-D score ($x \pm s$)	6.24 ± 4.08	7.16 ± 4.37	3.766	<0.001
FI ($x \pm s$)	0.12 ± 0.09	0.14 ± 0.11	3.407	<0.001

ADL, Activities of daily living; IADL, Instrumental activity of daily living; MMSE, Mini-mental status examination; CES-D, Center for epidemiologic studies depression scale; FI, frailty index; [a]*Including single, separated, divorce, and widowed.*

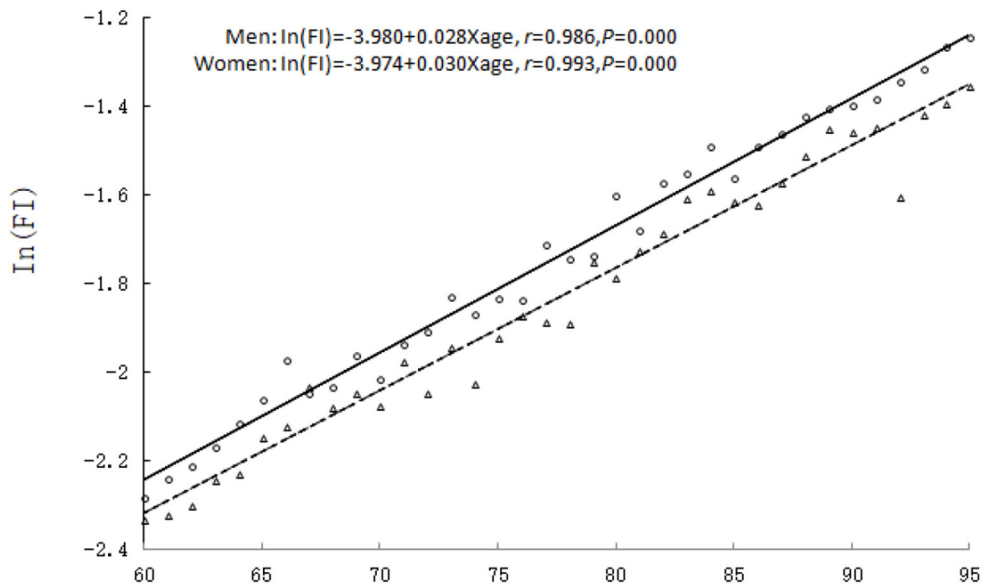


FIGURE 1 | The relationship between age and the mean value of FI. Men: triangle and dashed line; women: circles and solid line.

of education (0 years = 1, 1–6 years = 2, ≥7 years = 3), marital status (married or cohabiting with spouse = 1, other = 2), employment status (working = 1, retired = 2), the higher the FI value was associated with the higher the mortality risk, irrespective of the overall population or both genders, i.e., frailty increased mortality risk in the elderly population (all $P = 0.000$). Further comparison of the impact of FI on mortality risk by gender showed that the FI value had a greater impact on the mortality risk in men ($HR = 1.171$, 95%*CI*: 1.139–1.249) than women ($HR = 1.119$, 95%*CI*: 1.039–1.137). The FI also had a greater impact on the mortality risk than age ($HR = 1.145$ vs. 1.048; see **Table 2**).

TABLE 2 | Multivariate Cox regression analysis of the impact of FI on 10-year mortality risk in the elderly population of different genders.

Variables	Overall (n = 1,246)			Men (n = 519)			Women (n = 727)		
	B-value	*HR* (95%*CI*)	*P*-value	*B*-value	*HR* (95%*CI*)	*P*-value	*B*-value	*HR* (95%*CI*)	*P*-value
Age	0.047	1.048 (1.045∼1.061)	0.000	0.046	1.046 (1.039∼1.058)	0.000	0.049	1.051 (1.047∼1.063)	0.000
Sex	−0.439	0.645 (0.581∼0.692)	0.000	—	—	—	—	—	—
Year of education	−0.081	0.922 (0.854∼0.987)	0.032	−0.047	0.954 (0.871∼0.965)	0.027	−0.119	0.888 (0.739∼1.013)	0.054
Working status	−0.138	0.871 (0.629∼1.347)	0.584	−0.172	0.842 (0.528∼1.722)	0.342	−0.124	0.883 (0.817∼1.211)	0.865
Marriage status	0.276	1.318 (1.179∼1.452)	0.046	0.416	1.516 (1.324∼1.951)	0.037	0.112	1.119 (0.817∼1.193)	0.173
FI	0.135	1.145 (1.065∼1.217)	0.000	0.158	1.171 (1.139∼1.249)	0.000	0.112	1.119 (1.039∼1.137)	0.000

FI, frailty index.

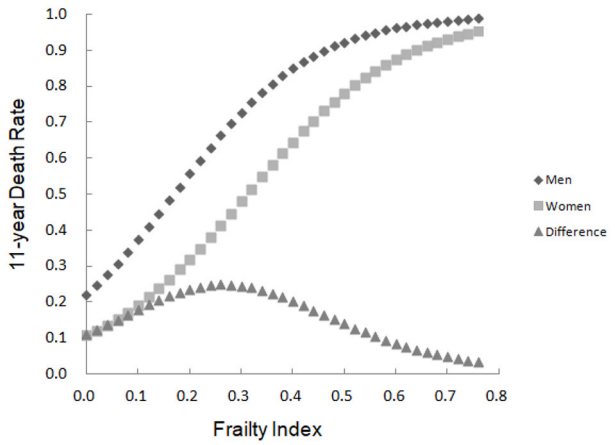


FIGURE 2 | The 10-year death rate as a function of the FI and the mortality difference between men and women.

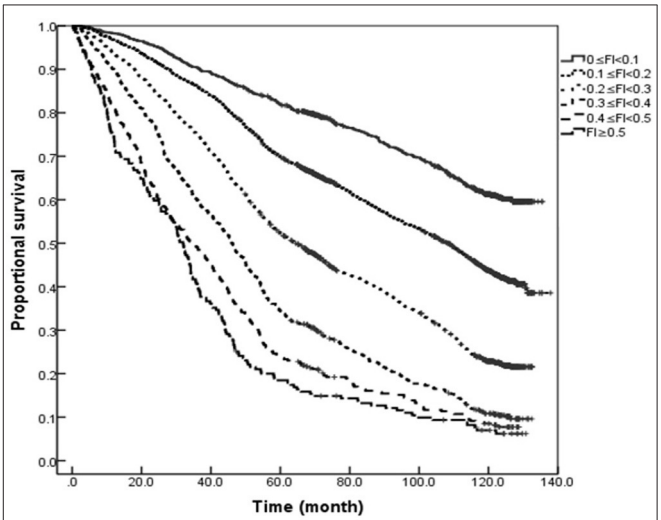


FIGURE 3 | Kaplan–Meier curves for the proportional survival of older men with different degrees of frailty.

Comparison of Kaplan–Meier Curves in the Elderly Population of Different Genders With Different Degrees of Frailty

The results of Kaplan–Meier analysis showed that the median survival for women followed up for 11 years was 95.26 months, which was higher than the 89.52 months for men (*Log-rank* = 9.249, $P = 0.002$). Further comparison of the Kaplan–Meier curves for the elderly population of different genders with different degrees of frailty ($0 \leq FI < 0.1$, $0.1 \leq FI < 0.2$, $0.2 \leq FI < 0.3$, $0.3 \leq FI < 0.4$, $0.4 \leq FI < 0.5$, and $FI \geq 0.5$) showed that increasing grades of the FI showed a dose-response effect in relation to survival for both men and women. The median survival with FI values of $0.1 \leq FI < 0.2$, $0.2 \leq FI < 0.3$, $0.3 \leq FI < 0.4$, $0.4 \leq FI < 0.5$, and $FI \geq 0.5$ were 108.11, 64.34, 46.00, 35.30, and 31.95 months for men, and 121.82, 77.53, 58.25, 41.38, and 30.58 months for women, respectively, i.e., the survival of women was longer than men with FI values of $0.1 \leq FI < 0.2$, $0.2 \leq FI < 0.3$, $0.3 \leq FI < 0.4$, and $0.4 \leq FI < 0.5$, and the difference was statistically significant (all $P < 0.05$). However, the difference in the survival rates between both genders with severe frailty ($FI \geq 0.5$) was not statistically significant ($P > 0.05$; see **Figures 3**, **4**).

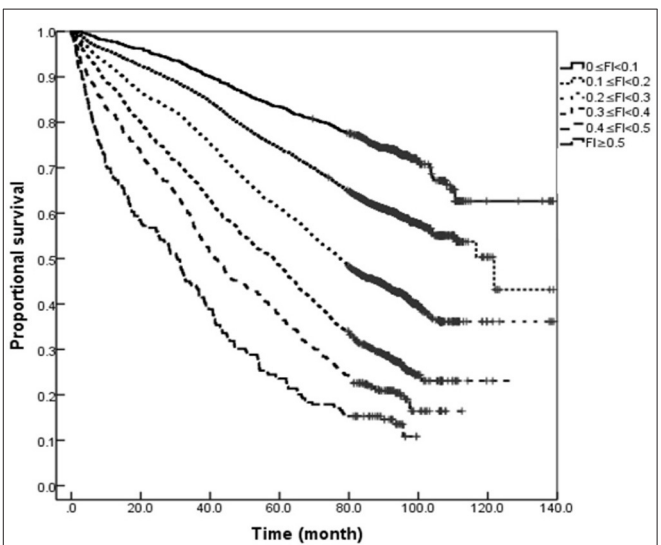


FIGURE 4 | Kaplan–Meier curves for the proportional survival of older women with different degrees of frailty.

DISCUSSION

In recent years, more and more geriatric researchers have begun to investigate the frailty in the elderly population. The systematic review has demonstrated that the FI is the only assessment tool that covers all factors related to frailty. It is the most useful tool for assessing frailty in the elderly population in routine care and community settings (9). In 2009, with the support from the China–Canada Collaboration on Aging and Longevity (CCCAL) (17), our team comprehensively and systematically utilized the FI to evaluate the health status of the elderly population in Mainland China and verify the applicability of the FI assessment tool in Chinese elderly population (18–20). In this study, our team used the FI model to assess frailty in the elderly population based on a follow-up survey of Beijing urban communities and analyzed the differences in the degree of frailty between elderly men and women, as well as the impact of frailty on mortality risk. The findings showed that the FI value increased exponentially with age for both genders and elderly women exhibited a higher degree of frailty than men at any age, i.e., elderly women had a faster accumulation rate of health deficits than men. It has been reported that the FI increases exponentially rather than linearly with age, and on a logarithmic scale, the average annual relative increase rate is about 3% (18), which is similar to the values of 3.0% for elderly men ($B = 0.030$) and 2.8% for elderly women ($B = 0.028$) in this study. It is noteworthy that the results of this study also showed that women had a higher degree of frailty than men, however, the mortality rate of men is higher than women for any degree of frailty, with the greatest difference at the mild to moderate degrees of frailty (FI = 0.26). That is, the cumulative risk of health deficits for elderly men is higher than for elderly women, especially for those with mild to moderate degrees of frailty. This conclusion has been verified in different countries, as well as in urban and rural areas of the same regions (21–24). This result also confirms the consensus that "men live better and women live longer." There is no definite conclusion on the specific mechanism. Some researchers believe that changes in sex hormone levels during aging are involved in the occurrence of frailty in the elderly population. The decline of sex hormone levels is directly related to muscle weakness, fatigue, and impaired function in the elderly population. One study suggested that frailty in elderly men was closely related to androgen levels, and high levels of free testosterone and dihydrotestosterone in serum reduced the risk of frailty in elderly men (25). In general, elderly women are more likely to exhibit various symptoms of frailty than elderly men. However, from a psychological perspective, men have a higher threshold for tolerating dysfunction and exhibit better physiological function, but the health reserves of elderly men are poorer than women. Therefore, the accumulated health deficits are more fatal to elderly men (26).

In order to further clarify the impact of FI on mortality risk in this study, a Cox regression analysis was performed after the adjustment for confounding factors, such as age, gender, and years of education. The results showed that greater FI value was associated with greater mortality risk for both genders. That is, frailty increases the mortality risk in the overall elderly population, and the FI value has a greater impact on mortality risk in elderly men than elderly women. Through the relative heterogeneity analysis of the degree of frailty in men and women, Yang et al. (26) pointed out that the ability of women to respond to external stimuli was more decreased with age than men, but at the same time, women were better able to resist adverse stimuli than men. Therefore, compared with men of the same age, women of frailty could more effectively retain their own responsiveness and maintain the system integrity for combating adverse environmental stimuli. This difference may also partially explain the higher health expectancy in women. At present, more and more scholars have begun to investigate the biological age of individuals, and findings show that the biological age of individuals is more effective in predicting adverse health outcomes, such as death (27–29), than the chronological age. This study also demonstrates that the FI value is a better indicator to predict death than age. The FI is also more closely related to the biological age of individuals than the chronological age, and the correlation has been used to calculate and determine the biological age of individuals by fitting the functional relationship between the age and the FI. Thus, compared with the chronological age, the FI can better reflect the age-related changes in the health status of individuals (30). In this study, the survival analysis of the elderly population with different degrees of frailty revealed that in severe frailty (FI $\geq$ 0.5), the superior survival rate of elderly women over elderly men disappeared. It is consistent with the study results reported by Yang et al. (26) that the difference change between genders decreased with the increase of age and degree of frailty. Therefore, the degree of frailty should be considered when conducting interventions for frailty in the elderly of different genders.

The following limitations of this study should be noted. Firstly, the baseline data were obtained based on the questionnaire, and there may be reporting bias, or recall bias because elderly subjects due to differ in understanding or recalling the content in the questionnaire. Therefore, in the course of training, it is essential for investigators to conduct the survey patiently and meticulously with both the individual subjects and their family members or nursing staff, so as to obtain detailed and true information as far as possible. Secondly, during the prospective observation period, the lost to follow-up subjects who left or moved from the survey site were all comparatively younger, and the lost to follow-up bias caused a certain impact on the results. Thirdly, this study did not collect causes of death, and the impact of other factors besides frailty on death cannot be ruled out. Moreover, although some objective physical function directors (static balance test, dynamic balance test, 5 times sit-to-stand test, up-and-go test) were included in the questionnaire, other important indicators that are strongly related to frailty, such as handgrip strength and walk speed, were not covered in the questionnaire due to practical limitation during the survey. The questionnaire requires future improvement and supplement with relevant information for more in-depth analysis.

CONCLUSION

In this study, the FI model was used to assess the frailty of the elderly population in the community of Beijing. The results are consistent with those studies conducted in developed countries.

The FI can better reflect the characteristics of frailty and is suitable to assess the health status or predict adverse outcomes in the elderly population. The study has once again verified the effectiveness of the FI model in the elderly population in China. The frailty of elderly men and elderly women, and the impact of frailty on mortality are various. Therefore, specific interventions for frailty should be conducted in the elderly population of different genders, as well as of different degrees of frailty.

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

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JS conducted the survey, performed statistical analysis of the data, and drafted the paper. YT helped with the analysis and assisted with manuscript preparation. LM and BZ conducted the survey and collected the data. CD assisted data analysis and result interpretation. HX and PY initiated and designed the study, revised the paper, and finally approved the version to be published. All authors read and approved the final version of the manuscript.

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APPENDIX

TABLE A1 | Variables for calculating the frailty index and their codes.

Variables	Codes
Comprehensive geriatric assessment	
Falls	No = 0, Yes = 1
Urinary incontinence	Never = 0, 1 time/week or less = 0.25, 2-3 times/week = 0.5, About 1 time/day = 0.75, Several times/day = 1
Pain	None = 0, Tolerable without affecting any activities = 0.33, Tolerable but affecting some activities = 0.66, intolerable but still able to make phone calls/watch TV/perform other activities = 1
Constipation	No = 0, Yes = 1
Weight loss	No = 0, Yes = 1
Sleep disorder	No = 0, Yes = 1
Usage of sleep aids	No = 0, Yes = 1
Visual and hearing assessment	
Vision	>4 m = 0, 1–3 m = 0.5, 1 m, or less = 1
Hearing	Completely clear = 0, Not very clear = 0.5, Not clear at all = 1
Walking balance function	
Usage of walking aids	No = 0, Yes = 1
Walking 400 m independently	Yes = 0, No = 1
Static balance test	> 10 s = 0, ≤10 s = 0.5, Unable to complete = 1
Dynamic balance test	> 10 s = 0, ≤10 s = 0.5, Unable to complete = 1
5 times sit-to-stand test	<10 s = 0, ≥10 s = 0.5, Unable to complete = 1
Up-and-go test	<12 s = 0, ≥12 s = 0.5, Unable to complete = 1
Diseases and medications	
Chronic diseases(15 types)[a]	Each no = 0, Each yes = 1
Number of medications	Infrequent medications = 0, 1–3 medications = 0.5, ≥4 = 1
Assessment of activities of daily living	
ADL	100 points = 0, 75–95 points = 0.25, 50–70 points = 0.5, 25–45 points = 0.75, 0–20 points = 1
IADL	≤5 points = 0, >5 points = 1
Cognition and emotion	
Memory is diminished	No = 0, Yes = 1
Emotional instability	Never = 0, Sometimes = 0.5, Often = 1
MMSE[b]	Cut-off value is normal = 0, Below cut-off is a cognitive deficit = 1
Depression assessment	
CES-D	<10 points = 0, ≥10 points = 1

ADL, activities of daily living; IADL, instrumental activities of daily living; MMSE, mini-mental state examination; CES-D, Center for Epidemiological Studies-Depression Scale (simplified version); [a]The 15 types of chronic diseases include hypertension, heart disease, diabetes, anemia, hyperlipidaemia, sleep apnea syndrome, gastrointestinal disease, cerebrovascular disease, dementia, tumor, protrusion of intervertebral disc, thyroid disease, osteoporosis, osteoarthritis, arthrolithiasis; [b]MMSE cut-off value is related to the level of education, 17 points for no education, 20 points for <6 years of education, 24 points for more than 6 years.

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REVIEW
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Roles of Nursing in the Management of Geriatric Cardiovascular Diseases

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The nursing field occupies the largest secion of the cardiovascular healthcare services. Despite this, the roles of nursing within the cardiovascular healthcare system has not been well displayed. The authors searched PubMed and Embase (between January 1, 1950, and June 17, 2021) and created a narrative review of recent publications regarding the role of nursing in the management of geriatric cardiovascular disease (CVD). Patients with geriatric CVD, which includes mainly myocardial ischemia and heart failure, were enrolled. Nursing can improve the outcomes of myocardial ischemia and heart failure. It plays a pivotal role in the recovery, rehabilitation, and outcomes of geriatric CVD, especially for chronic heart diseases. Taken together, this paper compiled is focused on the current status of cardiovascular nursing and may facilitate future treatment and rehabilitation in geriatric CVD.

Keywords: cardiovascular disease, geriatrics, nursing management, heart failure, cardiac rehabilitation

INTRODUCTION

Cardiovascular disease (CVD) remains a primary cause of mortality for people all over the world (1). According to statistical data from the American Heart Association (AHA), the age-adjusted prevalence of all types of heart disease was 10.6%. In 2017, CVD-induced deaths are about 17.8 million globally. The CVD-induced mortality is 219.4 per 100,000 in 2016. CVD has become a primary public health problem all over the world—far beyond cancer and unintentional injuries. Notably, 840,678 deaths from CVD were registered in the United States in 2016, which may contribute to significant economic and health burdens worldwide (2). According to the World Health Organization (WHO)'s World's Nursing Report 2020, there are over 27.9 million nurses globally, accounting for more than half (59%) of the number of medical workers in the world. Among them, 19.3 million are professional nurses (69%), and 6 million (22%) are professional nurse assistants (3).

In the nursing work of geriatric CVD, effective prevention of risk factors in nursing work is of great clinical significance to improve the quality of nursing and the early rehabilitation of geriatric CVD patients. As nurses have the most contact time with patients, they should not only be familiar with the characteristics of elderly cardiovascular disease, but they also acquire knowledge of the mental aspect of nursing, considering the social roles of the elderly.

China is now undergoing unprecedented economic growth and globalization, and this has resulted in an increase in the prevalence of chronic conditions, particularly CVD (4). CVD makes up 40% of all deaths in China, and it is thus the highest single cause of mortality. It is estimated that there are 290 million CVD patients in the world, which has created serious challenges for the improvement of public health. However, the population tends to have a low rate of awareness of CVD as well low popularization rates of CVD prevention in both urban and rural districts in China (5–7) (**Figure 1**). The world has witnessed huge changes in health services in China since 1978. Peking Union hospital trained the first nurses with bachelor's degrees (4). Cardiovascular nursing is dedicated to the nursing service and self-management of patients with CVD. It plays a pivotal role in the recovery, rehabilitation, and outcomes of geriatric CVD, especially chronic heart diseases. Nurse occupies the largest parts of cardiovascular healthcare services, whereas the roles of nursing within the cardiovascular healthcare system have not been highlighted well. There is therefore an emerging call for enhancing the roles of nursing in the whole process of CVD, especially geriatric CVD.

This narrative review is aimed at discussing the roles of nursing in the management of geriatric CVD. Firstly, we introduce the background of CVD and cardiovascular nursing, including the epidemiology and therapeutics of CVD as well as the current status of nursing. Secondly, we review the roles of nursing in the management of CVD such as heart failure and myocardial ischemia. Thirdly, we talk about the concept of nursing education. Finally, we discuss home- and clinic-based nursing, cardiac rehabilitation, and individual care. This article highlights the recent advances and provides an elaborate picture of cardiovascular nursing, which might be helpful in nursing care and therapy for CVD.

ROLES OF NURSING IN THE MANAGEMENT OF GERIATRIC CVD

Heart Failure

The symptoms of heart failure are characterized by shortness of breath, fluid retention, poor oxygen delivery, and impaired function of the heart itself (9). The prevalence of heart failure is increasing with age. There are 6.2 million adults ≥20 years of age who experienced heart failure (HF) between 2013 and 2016 in the United States of America (USA) (9).

In total, 127 patients with reduced ejection fractions (EFs) were prospectively allocated to standard care or intervention programs (1:2) at random from 2011 to 2013. Ortiz-Bautista et al. (10) found that readmissions for HF were reduced and life quality is significantly improved in the intervention group. A total of 59 patients were divided into three groups: collaborative management, self-management education, and usual care. The results show that the quality of life (QOL) score is improved in collaborative management compared to usual care at 18 and 24 months. Collaborative management

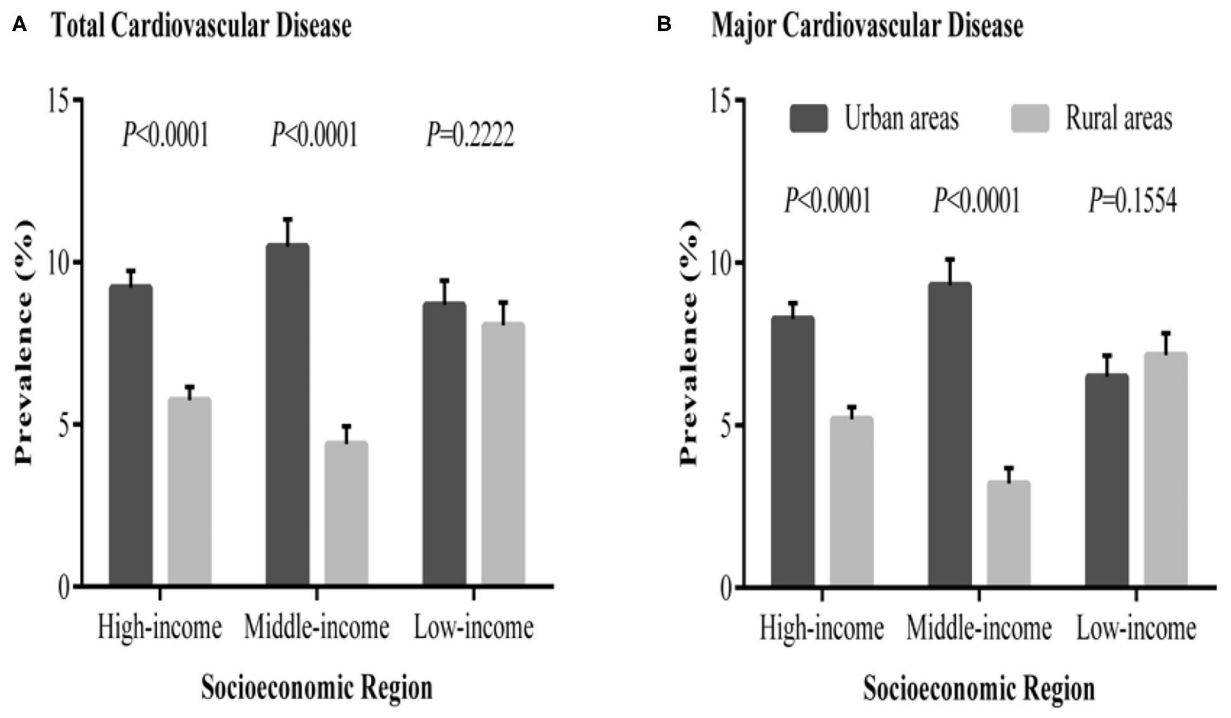


FIGURE 1 | Prevalence of total and major cardiovascular diseases in urban and rural communities in different socioeconomic regions of China. **(A)** The distribution of total cardiovascular disease prevalence. **(B)** The distribution of major cardiovascular disease prevalence (8).

may increase psychosocial status for HF patients and prevent HF-related rehospitalization (11).

HF may influence a patient's quality of life to a great extent. Rorth et al. (12) found that HF-led hospitalization is associated with increased nursing home admissions and domiciliary support. In total, 51 HF patients were enrolled and thereafter received adaptive servo-ventilation for trial evaluation. Results show that this treatment may improve the QOL of HF patients (13).

Myocardial Ischemia

Myocardial ischemia is referred to the insufficient flow of the coronary artery and is an early pathological stage of CVD, such as myocardial infarction and acute coronary syndrome (14). After the 12-month intervention, health-related QOL, cardiac risk factors, and health behaviors of the participants undergoing percutaneous coronary intervention (PCI) greatly improved compared to controls (15).

Psychological nursing used computed tomography angiography (CTA) technology-based nursing methods for patients with CHD. Systolic blood pressure, heart rate, diastolic blood pressure, self-rating anxiety scale, and the self-rating depression scale scores of patients in the observation group were notably lower than controls (16). Seidl et al. found that the cost-effectiveness of nurse-based case management is cost-neutral and contributes to a great improvement in health status among survivors. It was associated with higher quality of adjusted life years and lower costs in elderly patients with myocardial infarction (17). Moreover, Kirchberger et al. (18) reported that nurse-based management among elderly patients with acute myocardial infarction (AMI) improves functional status and malnutrition.

NURSING EDUCATION

Education of Nurses

There is no standardized protocol for HF education programs. Researchers and nursing staff are still exploring the best form of education. Breathett et al. added a novel tablet application to nurse practitioner (NP) education. They found that the addition of novel tablet applications may contribute to better patient satisfaction and teaching effects for HF patients (19). Addiction of nursing knowledge of electrocardiograms of myocardial ischemia and myocardial infarction will increase the mean score on the pretest in an urban hospital of the Midwest and improve patient outcomes (20).

Nurses' Education for Patients

Cardiosurgery nurses performed preoperative education for inpatients. They found that nurse-led preoperative education is helpful for reducing preoperative anxiety and postoperative cardiovascular/mortality complications, whereas it fails to reduce the possibility of second admissions and length of admission (21). Awoke and colleagues found that a nurse-led HF inpatient hospital education is suggested to improve reduce the 30-day possibility of second admission and self-care ability (22).

PERSPECTIVES

Home and Clinic-Based Nursing

Maru et al. enrolled 611 patients with subclinical cardiovascular diseases (without chronic heart failure) (23). In total, 13 patients recovering from acute coronary syndromes (ACS) were interviewed by telephone, and seven nurse mentors completed a survey after completing the program in Australia. There were positive signs that the program influenced patients' decisions to change unhealthy lifestyle behaviors. Outcomes highlighted both rewards and barriers associated with telephone-led patients follow-up visits (24). In Sweden, ∼40% of identified HF cohort was enrolled in a nurse-led HF clinic (25). In the USA, nurse-led clinic-based nursing was helpful in reducing 30-day second admission by ∼9% (26).

Cardiac Rehabilitation

Cardiac rehabilitation improves prognosis after an acute AMI, however, the optimal method of implementation is unknown. In total, 217 patients after an AMI received tailored care through a nurse-led cardiac rehabilitation program, and this achieved better control of total cholesterol, low-density lipoprotein (LDL) cholesterol, and systolic blood pressure. This suggests that a tailored, nurse-led cardiac rehabilitation program improves risk factor management in post-AMI patients.

CONCLUSIONS AND IMPLICATIONS

The elderly are usually faced with several major comorbidities/risk factors of CVD (2). The current problems of nursing in the management of elderly cardiovascular diseases still remain and are obstacles in the prevention and post-onset management. CVD is the first cause of disability and death in the elderly over 60 years old. Firstly, due to the particularity of the elderly group, in the process of nursing for geriatric CVD patients, we must pay attention to their psychological changes, and actively take measures to deal with their psychological situation (27). Secondly, the elderly often have a decreased understanding and learning ability, which causes difficulties for health education. The penetration degree of nursing health education is lacking in elderly CVD patients (28). There is a gap in nursing care for geriatric CVD patients. Thirdly, the importance of nursing has not been well-displayed for geriatric CVD compared with medical activity (consulting a cardiologist). Patients may seek help from doctors more than nurses.

In the nursing work of geriatric CVD, effective prevention of risk factors in nursing work is of great clinical significance to improve the quality of nursing and the early rehabilitation of geriatric CVD patients. As nurses who have the most contact time with patients, they should not only be familiar with the characteristics of elderly cardiovascular disease, but they should also have knowledge of mental nursing, considering the social roles of the elderly. Nurses should strengthen the study of etiology, pathogenesis, drug indications, and adverse reactions of CVD to improve the levels of professional technology. They should also actively communicate with patients, establish a relationship of mutual trust and understanding, and carry out

targeted psychological nursing, illness nursing, diet nursing, and discharge guidance according to elders' different conditions and personality characteristics so as to improve the quality of nursing and the recovery rate of geriatric CVD patients.

Though this narrative illustrates the most recent advances of nursing in the management of geriatric cardiovascular disease, there remain limitations and hope that further research/works can improve. Firstly, the authors failed to make a systematic review (evidence-based search) and only make a narrative review summary. Secondly, the authors failed to provide a comprehensive review: parts of the content are not analyzed in great detail, and this is possibly due to the length limitation of this narrative article and journal requirements.

CVD remains the main killer for people throughout the world (14, 29, 30). At the beginning of this manuscript, we introduce the background of CVD and nursing, followed by roles of nursing in the management of CVD such as HF and myocardial ischemia. Secondly, we discuss how nursing aims to provide a reference for cardiovascular nursing. Eventually, we analyze home- and clinic-based nursing, cardiac rehabilitation, and self-care. Taken together, this paper compiled here is devoted to the current status of cardiovascular nursing and may facilitate future research and progress in CVD.

AUTHOR CONTRIBUTIONS

TL, XW, and ZM: conceptualization. CZ and CX: writing – original draft. XT, JX, GH, and TL: writing – review and editing. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Development and Validation of an Electronic Frailty Index Using Routine Electronic Health Records: An Observational Study From a General Hospital in China

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Background: This study aimed to develop and validate an electronic frailty index (eFI) based on routine electronic health records (EHR) for older adult inpatients and to analyze the correlations between frailty and hospitalized events and costs.

Methods: We created an eFI from routine EHR and validated the effectiveness by the consistency of the comprehensive geriatric assessment-frailty index (CGA-FI) with an independent prospective cohort. Then, we analyzed the correlations between frailty and hospitalized events and costs by regressions.

Results: During the study period, 49,226 inpatients were included in the analysis, 42,821 (87.0%) of which had enough data to calculate an eFI. A strong correlation between the CGA-FI and eFI was shown in the validation cohort of 685 subjects (Pearson's $r = 0.716$, $P < 0.001$). The sensitivity and specificity for an eFI≥0.15, the upper tertile, to identify frailty, defined as a CGA-FI≥0.25, were 64.8 and 88.7%, respectively. After adjusting for age, sex, and operation, an eFI≥0.15 showed an independent association with long hospital stay (odds ratio [OR] = 2.889, $P < 0.001$) and death in hospital (OR = 19.97, $P < 0.001$). Moreover, eFI values (per 0.1) were positively associated with total costs ($\beta = 0.453$, $P < 0.001$), examination costs ($\beta = 0.269$, $P < 0.001$), treatment costs ($\beta = 0.414$, $P < 0.001$), nursing costs ($\beta = 0.381$, $P < 0.001$), pharmacy costs ($\beta = 0.524$, $P < 0.001$), and material costs ($\beta = 0.578$, $P < 0.001$) after adjusting aforementioned factors.

Conclusions: We successfully developed an effective eFI from routine EHR from a general hospital in China. Frailty is an independent risk factor for long hospital stay and death in hospital. As the degree of frailty increases, the hospitalized costs increase accordingly.

Keywords: frailty, electronic health records-EHR, long hospital stay, mortality, hospitalized costs

INTRODUCTION

As the population of older adults rises globally, the condition of frailty is gaining prominent attention (1). In China, the older adults aged 65 years and older has reached 190 million, accounting for 13.5% of the total population at the end of 2020 (2). Frailty describes a decline in physiological capacity across multiple organ systems, characterized by an increased vulnerability to stressors (3). The condition of frailty is associated not only with a myriad of adverse outcomes (4) but also with increased healthcare costs (5–16). However, there is no gold standard assessment instrument for frailty (17, 18). The most widely used instruments in clinical research are variations of the frailty phenotype (19) or frailty index (FI) based on the cumulative deficit model (20). Our previous study showed that the comprehensive geriatric assessment-FI (CGA-FI) may be an optimal assessment tool among five prevalent frailty measurements (21). Although numerous clinicians have embraced the concept of frailty, we are facing large challenges to make the translation from frailty research to clinical practice. The barriers include not only a lack of consensus among prevalent frailty measurements but also time and resource limitations in busy clinical environments.

To reduce the burden of frailty assessment on clinicians, Clegg et al. developed an electronic FI (eFI) using routine electronic health records (EHR) in UK primary care (22). Based on Clegg's eFI, Pajewski and his colleagues modeled another adapted eFI with more information on nursing and laboratory assessments using routine EHR in the US, which showed an independent predictive value for mortality, hospitalizations, emergency department visits, and injurious falls (23). Meanwhile, these time-saving assessments of frailty based on EHR have shown good consistency with traditional assessment methods, such as the Fried phenotype and CGA-FI (24, 25). However, there has been no relevant frailty research based on EHR in China, so we do not know whether an effective eFI can be developed from routine EHR in China.

Previous studies on frailty in inpatients have mainly focused on the population in a certain department or with a particular disease type, which cannot fully reflect conditions across all departments. Our previous research has found that the prevalence of frailty between medical and surgical departments was significantly different (21), but there has been no research that can show in detail the distribution of frailty in each department of a general hospital. Moreover, due to limitations in data acquisition, there is currently no study using EHR to analyze the relationship between frailty and hospitalized costs. Therefore, the effective utilization of EHR big data is particularly important, which can provide valuable information for clinical management.

This study aimed to develop and validate an eFI based on routine EHR for older adult inpatients and to analyze the correlations between frailty and hospitalized events and costs.

MATERIALS AND METHODS

Study Design

We conducted a cohort study on frailty using 6-year EHR of older adult inpatients from a general hospital in Beijing, China. The hospital is public, owned by government, with great attention to geriatrics and gerontology. We used a two-step approach to develop and validate an eFI based on the routine EHR for older adult inpatients. First, we followed published guidance on creating a FI using the cumulative deficit model to create an eFI from routine EHR, which involved diagnosis, nursing assessment, and laboratory tests (26). Second, in a validation cohort, we tested whether the eFI identified similar people as the CGA-FI. Then, we analyzed the correlation between frailty and hospitalized events and costs using the routine EHR.

Population in the EHR

The patients included were at least 65 years of age in the routine EHR database from July 1, 2013 to September 30, 2019. There were 96,393 hospitalizations involving 51,824 older adult inpatients in the records. During the study period, 34,612 patients had only one hospitalization, while 17,212 patients had two or more hospitalizations in the records. To avoid duplication, we chose the last hospitalization for these patients with two or more hospitalizations in the records for analysis. Considering the meaninglessness of hospital stays that were extremely short (1 day or less) and special issues regarding hospital stays that were extremely long, we excluded 5% of the patients, which included 2,006 (3.9%, 2006/51824) patients with hospital stay $\leq$ one day and 592 (1.1%, 592/51824) patients with hospital stay $>$ 66 days. Therefore, 49,226 inpatients were eligible (**Figure 1**).

Validation Cohort

For the validation exercise, we used a linked dataset on a prospective cohort of inpatients who had been assessed with the research standard CGA-FI. These participants were enrolled from September 2018 to February 2019 in the same hospital. The characteristics of the prospective cohort were described in detail in our previously published article (21). Among the 1,000 older adult patients in the cohort study, 703 participants were matched in the EHR database of 49,226 cases by hospitalized ID and admission time. There were 18 participants who did not have sufficient data to calculate the eFI. Finally, there were 685 older adult inpatients who had both the CGA-FI and eFI assessed. The CGA-FI was the result of the sum of all 48 variables' scores divided by 48. The threshold of 0.25 as the cut-off value of CGA-FI for identifying frailty. The details of all variables in CGA-FI are described in **Supplementary Table 1**.

Composition of the Electronic Frailty Index (eFI)

As shown in **Supplementary Table 2**, according to the core criteria of the Rockwood frailty index (26), we modeled our adapted eFI referring to the factors included in the eFI of Pajewski et al. (23). Forty-five variables were selected to construct the eFI,

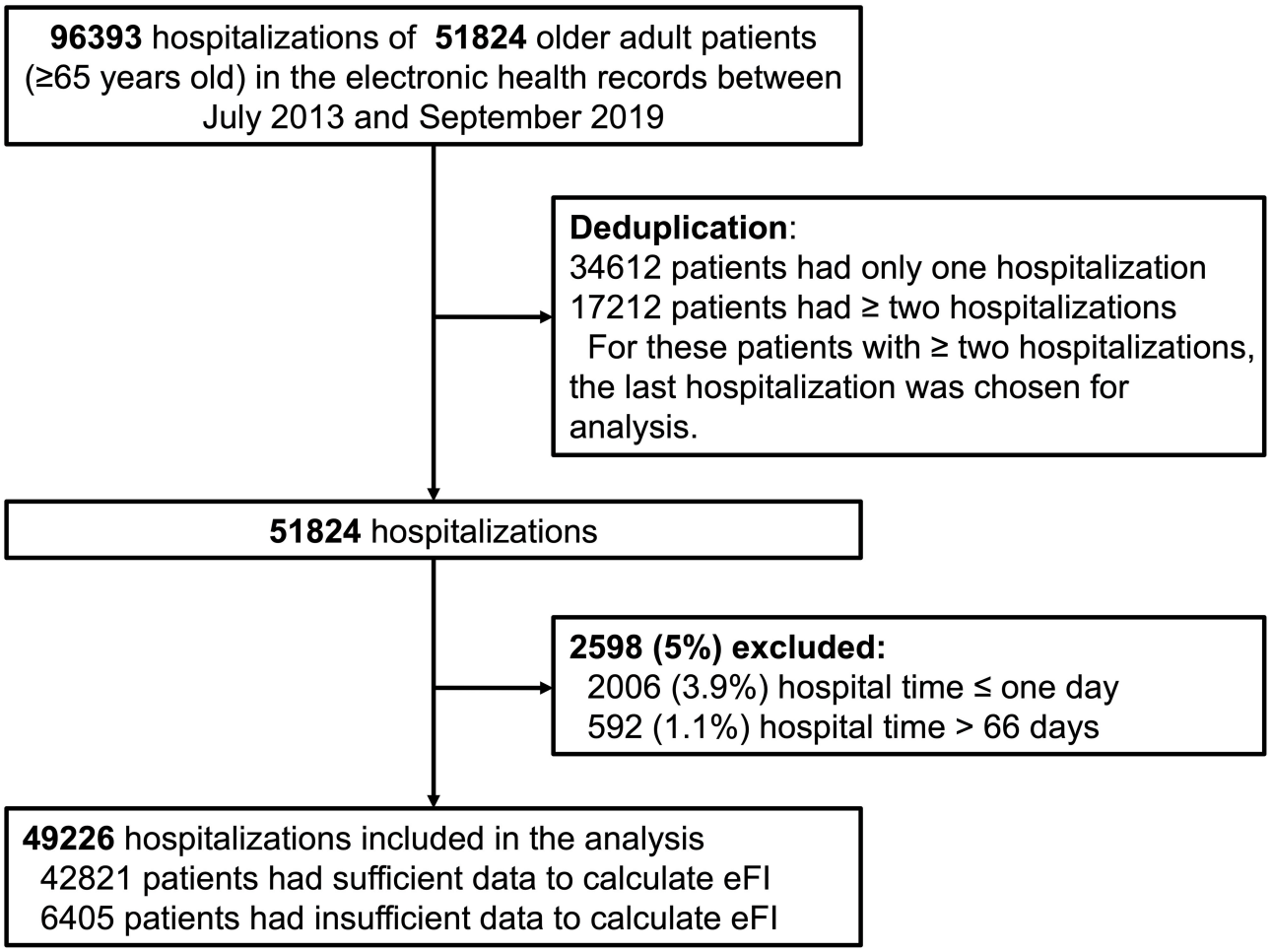


FIGURE 1 | Flow chart of the study cohort.

which included 20 items on the diagnosis of chronic diseases, 20 items on nursing assessments, and 5 items on laboratory tests.

These 20 items on the diagnosis of chronic diseases covered a range of systems, included hypertension, heart failure, myocardial infarction, atrial fibrillation/atrial flutter, peripheral arterial disease, venous thromboembolism, chronic lung disease, peptic ulcer, chronic kidney disease, diabetes, thyroid dysfunction, stroke, Parkinson's disease/parkinsonism, dementia, anxiety, depression, osteoporosis, arthritis, spondylosis/disc disorders, and malignancy. The international Classification of Diseases-tenth version (ICD-10) codes for each diagnosis were determined by three clinicians after discussion and according to the global standard for diagnostic health information from the World Health Organization website (https://icd.who.int/browse10/2010/en#/) (**Supplementary Table 3**).

These 20 items from the nursing assessments on the day of admission included the Barthel Index (containing 10 items: feeding, bathing, grooming, dressing, bowels, bladder, toilet use, transfers, mobility) (27), visual impairment, hearing impairment, insomnia, consciousness statement, constipation, appetite, pressure ulcer, BMI, heart rate, and blood pressure. The detailed cut-off values are shown in **Supplementary Table 2**.

Given the importance of laboratory tests for frailty assessment (28, 29), we included 5 routine laboratory items for constructing the eFI. Based on our previous study (21), we found that hemoglobin, albumin, sodium, and D-dimer were independently associated with frailty. Meanwhile, qualitative analysis of urine protein was widely tested and was useful to reflect renal function. Therefore, we selected these abovementioned 5 items from the routine laboratory tests. Usually, the blood and urine specimens were tested within 24 h after admission for inpatients. If a patient had more than one result for the same item, we chose the first result to construct the eFI. The detailed cut-off values are shown in **Supplementary Table 2**.

The eFI included a total of 45 factors and was calculated as the unweighted sum of the score for each factor, divided by the total number of non-missing items. There were no missing values regarding the diagnosis for all inpatients. Moreover, we did not want an absence of the Barthel Index, which contained 10 items and necessarily implied functional status. Therefore,

these abovementioned 30 items in the eFI were guaranteed. We additionally excluded individuals who did not have at least 6 of the 10 items on the nursing assessments (except Barthel Index) or at least 3 of the 5 items on the laboratory measurements. Finally, we required ≥39 non-missing items, which were consistent with recommendations for constructing the FI (26). The missing data elements from the routine EHR in calculating the eFI are described in detail in **Supplementary Table 4**. The upper tertile of the eFI scores (eFI ≥ 0.15) was defined as the cut-off value to indicate frailty.

Hospitalized Events and Costs

We defined hospitalized events as long hospital stay (>14 days) and death in hospital. Hospitalized costs included total costs, examination costs, treatment costs, nursing costs, pharmacy costs, and material costs. The total cost was the sum of all payments to the hospital for this hospitalization. Examination costs meant the payment for all examinations, such as laboratory measurements and imaging examinations. Treatment costs referred to payments for treatments, mainly by doctors and therapists, such as operation fees and consultation fees. Nursing costs referred to payments for all nursing care. Pharmacy costs referred to payments for all medications used during this hospitalization. Material costs referred to the payment for all medical consumable materials, of which surgical and interventional consumables accounted for a large proportion. We calculated hospitalized costs in United States dollars using the average exchange rate from 2013 to 2019 (1 USD = 6.46 CNY) for international comparisons.

Statistical Analysis

Descriptive statistics were compared between the groups using chi-square tests for categorical variables and *t*-tests or Mann-Whitney *U* for continuous variables. Pearson's correlation coefficient was used to describe the association between the continuous versions of the eFI and the CGA-FI. Additionally, a receiver operating characteristic (ROC) curve was calculated to estimate the area under the curve (AUC) for the eFI in relation to frailty, which was defined as CGA-FI≥0.25. We examined the association between frailty (eFI≥0.15) and hospitalized events using multivariate logistic regression, adjusting for age, sex, and operation [any surgery or intervention treatment in this hospitalization). Considering the influence of departments on hospitalization events, we divided 30 clinical departments into five groups (1) cardiology department; (2) internal medicine departments except cardiology; (3) orthopedics department; (4) surgical departments except orthopedics; (5) emergency department and intensive care units (ICUs)] and assessed the prevalence of frailty in different departments. We conducted a separate analysis for each subgroup. The results of the logistic regression models are presented as odds ratios (ORs) and 95% confidence intervals (95% CIs).

To investigate the impact of the eFI on hospitalized costs, generalized linear regression models (gamma-distributed and log-linked) adjusted for age, sex, and operation were used for all patients and each subgroup. For patients with two or more hospitalizations in the records, we chose the last hospitalization for analysis. The eFI values were multiplied by 10 to give equal 0.1 increments in the generalized linear regression models. The use of a gamma-distributed generalized linear model with a log-transformed link function has been shown to be a good method to estimate health-care cost distributions that are generally right-skewed (30). The results of the generalized linear regression models were presented as the β and 95% CIs for eFI values (per 0.1). A $P < 0.05$ was considered statistically significant.

We performed sensitivity analyses to assess the robustness of the eFI as an independent associated factor of hospitalized events and costs. For patients with two or more hospitalizations (17,212 out of 51,824 patients, 33.2%), we used the first hospitalization records instead of the last hospitalization records. We also excluded 5% patients with extremely short hospital stay (3.2%, 1,0656/51,824) or extremely long hospital stay (1.8%, 958/51,824). According to the method of constructing the eFI, 87.6% (43,116/49,210) of patients had sufficient data to calculate the eFI. For comparison with the original results, we still used 0.15 as the cut-off point of the eFI to identify frailty. Other statistical methods in the sensitivity analysis were the same as in the original analysis.

All analyzes were performed using the R software program, version 3.5.3.

RESULTS

Demographic and Clinical Characteristics

During the study period, 49,226 older adult inpatients from the EHR database were included (**Figure 1**). There were 50.5% males and the average age was 74.8 ± 6.9 years old. According to the method of constructing the eFI, there were 42,821 (87.0%) patients with sufficient data to calculate the eFI and 6,405 (13.0%) patients with insufficient data. The two groups had similar ages (74.8 ± 7.0 vs. 75.1 ± 6.7 years) and proportions of males (50.5 vs. 50.7%). However, the hospital days (9 [6, 14] vs. 4 [3, 7] days; $P < 0.001$) and death in hospital (3.4 vs. 0.7%; $P < 0.001$) were significantly different in these two groups. Moreover, the hospitalized costs in patients with insufficient data were significantly lower than those in the other group (all $P < 0.01$). Detailed information on the entire population is shown in **Table 1**. The departments of ophthalmology (54.5%, 3491/6405), general surgery (20.0%, 1284/6405), and traditional Chinese medicine (7.9%, 506/6405) were the top three leading contributors to the medical records with insufficient data (**Supplementary Table 5**). Among the 42,821 patients, 33.8% had an eFI≥0.15, and the median eFI was 0.111 (**Table 1**). **Figure 2** shows the prevalence of frailty in different departments. Females showed a significantly higher proportion of frailty than males (36.4 vs. 31.2%; $P < 0.001$).

Correlation Between the eFI and CGA-FI

In the validation cohort, there were 685 participants who had both the eFI and CGA-FI assessed. The average age was 74.6 ± 6.7 years old, and 48.0% were males. The prevalence of frailty, defined as a CGA-FI ≥ 0.25, was 31.5%. The median CGA-FI was 0.198, while the median eFI was 0.102. Detailed information on all subjects is shown in **Supplementary Table 6**. A strong

TABLE 1 | Demographics and hospitalized events and costs of all patients stratified by whether or not the eFI could be calculated from the electronic health records.

	All patients *n* = 49,226	Sufficient data to calculate eFI *n* = 42,821	Insufficient data to calculate eFI *n* = 6,405	*P* values
Demographics				
Age, years	74.8 ± 6.9	74.8 ± 7.0	75.1 ± 6.7	<0.001
Age, *n* (%)				<0.001
65 to <75 years	25,189 (51.2)	22,098 (51.6)	3,091 (48.3)	
75 to <85 years	19,185 (39.0)	16,458 (38.4)	2,727 (42.6)	
85 years or more	4,852 (9.9)	4,265 (10.0)	587 (9.2)	
Male	24,865 (50.5)	21,620 (50.5)	3,245 (50.7)	0.805
Hospitalized events				
Hospital days	8 [5, 14]	9 [6, 14]	4 [3, 7]	<0.001
>14 hospital days	10,806 (22.0)	10,439 (24.4)	367 (5.7)	<0.001
Death in hospital	1,496 (3.0)	1451 (3.4)	45 (0.7)	<0.001
Hospitalized costs				
Total costs, $	2,450 [1,390, 7,290]	2,840 [1,520, 8,300]	1,370 [858, 2,100]	<0.001
Examination costs, $	517 [254, 844]	573 [354, 905]	79.9 [12.7, 112]	<0.001
Treatment costs, $	456 [241, 822]	472 [243, 905]	326 [236, 535]	<0.001
Nursing costs, $	23.5 [10.8, 51.1]	26.2 [12.1, 55.1]	11.5 [5.4, 22.3]	<0.001
Pharmacy costs, $	446 [149, 1,090]	544 [208, 1,230]	57.6 [25.5, 184]	<0.001
Material costs, $	551 [155, 2,380]	522 [145, 3,120]	613 [446, 1,010]	0.003
eFI, median [IQR]	–	0.111 [0.067, 0.189]	–	–
eFI≥0.15, *n* (%)	–	14,472 (33.8)	–	–
eFI, *n* (%)				
eFI ≤ 0.10	–	18,384 (42.9)	–	
0.10 < eFI ≤0.20	–	14,502 (33.9)	–	
0.20 < eFI ≤0.30	–	6,169 (14.4)	-	
0.30 < eFI ≤0.40	–	2,844 (6.6)	–	
eFI > 0.40	-	922 (2.2)	–	

Values are showed as mean ± standard deviation, median [IQR], or n (%).
eFI, electronic frailty index; IQR, interquartile range.

correlation is shown between the CGA-FI and eFI (Pearson's $r = 0.716$, $P < 0.001$) (**Figure 3**). The AUC of the ROC for the eFI to identify frailty in the subjects was 0.859. The sensitivity and specificity to identify frailty were 64.8 and 88.7%, respectively, for an eFI≥0.15 (**Figure 4**).

Difference Between the Frail Group and Non-frail Group

We used 0.15 (tertile of eFI) as the cut-off value to indicate frailty in the 42,821 inpatients from the EHR database. Compared with the non-frail group, the frail group was significantly older (78.7 ± 7.1 vs. 72.8 ± 6.0 years; $P < 0.001$) and had a lower percentage of males (46.6 vs. 52.5%; $P < 0.001$). The department distributions and operations were clearly different between these two groups (both $P < 0.001$). The frail group had significantly longer hospital days (12 [8, 18] vs. 8 [5, 13] days, $P < 0.001$) and a higher mortality rate in the hospital (9.3 vs. 0.4%, $P < 0.001$) than the non-frail group. Meanwhile, the total hospitalized cost and each specific cost for the frail group were all significantly higher than those for the non-frail group (all $P < 0.001$) (**Table 2**).

Association of Frailty With Hospitalized Events and Costs

After adjusting for age, sex, and operation, an eFI≥0.15 showed independent correlations with long hospital stay (OR = 2.889, $P < 0.001$) and death in hospital (OR = 19.97, $P < 0.001$) for all older adult inpatients by multivariate logistic regression. In the subgroup analysis for different departments, the eFI was also independently associated with long hospital stay in all subgroups (ORs ranged from 1.392 to 4.750; all $P < 0.001$). The same results are presented for death in hospital (ORs ranged from 7.192 to 34.26; all $P < 0.001$) (**Table 3**).

In this study, the hospitalized cost averaged of non-frail and frail group were US $2,290 (1,370, 6,520) and US $4,790 (2,060, 10,700), respectively (**Table 1**). After adjusting for age, sex, and operation, the eFI was positively associated with total costs ($\beta = 0.453$, $P < 0.001$), examination costs ($\beta = 0.269$, $P < 0.001$), treatment costs ($\beta = 0.414$, $P < 0.001$), nursing costs ($\beta = 0.381$, $P < 0.001$), pharmacy costs ($\beta = 0.524$, $P < 0.001$), and material costs ($\beta = 0.578$, $P < 0.001$) for all older adult inpatients. Subgroups of different departments showed similar correlations between the eFI and hospitalized costs (all $P < 0.01$) (**Table 4**).

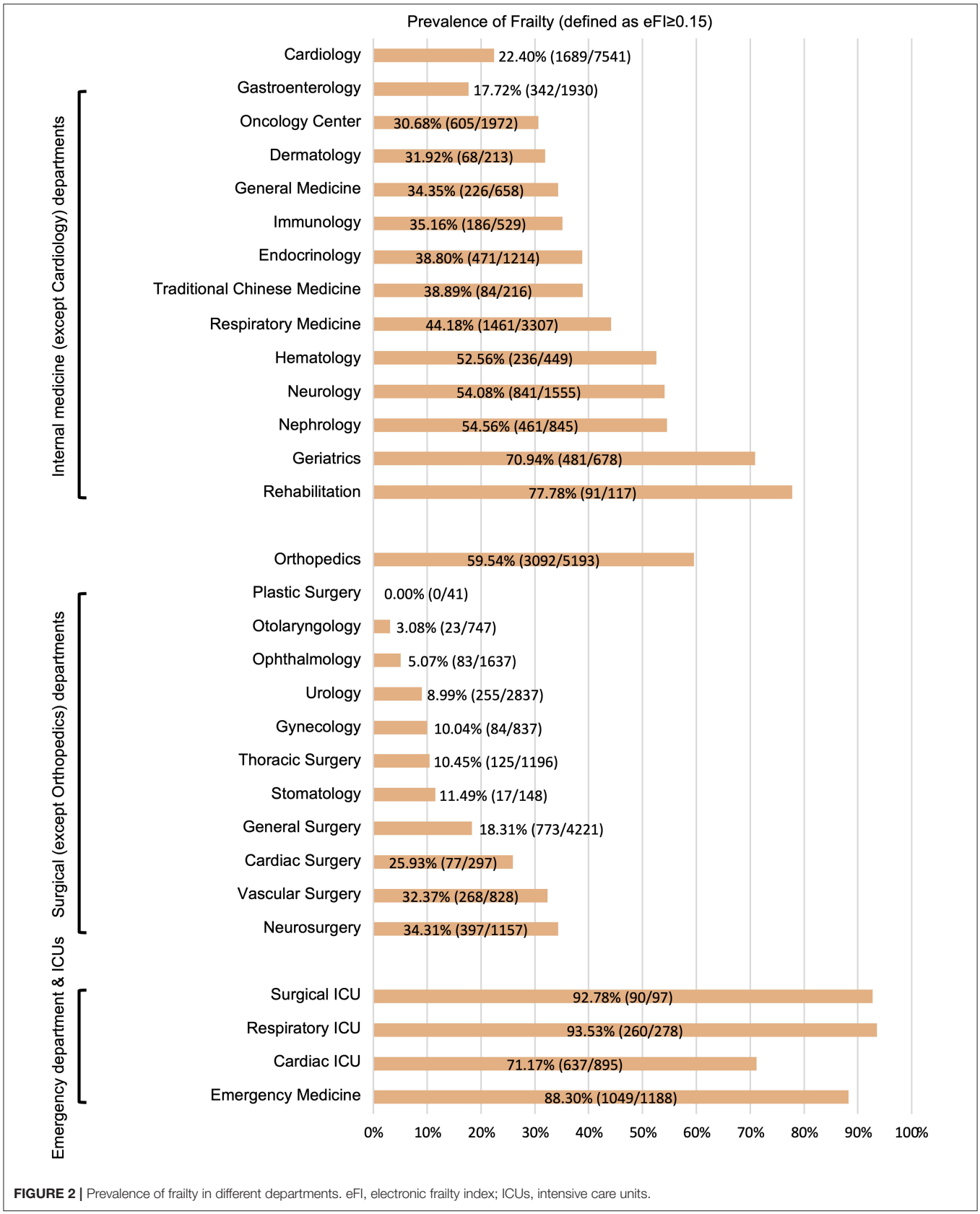


FIGURE 2 | Prevalence of frailty in different departments. eFI, electronic frailty index; ICUs, intensive care units.

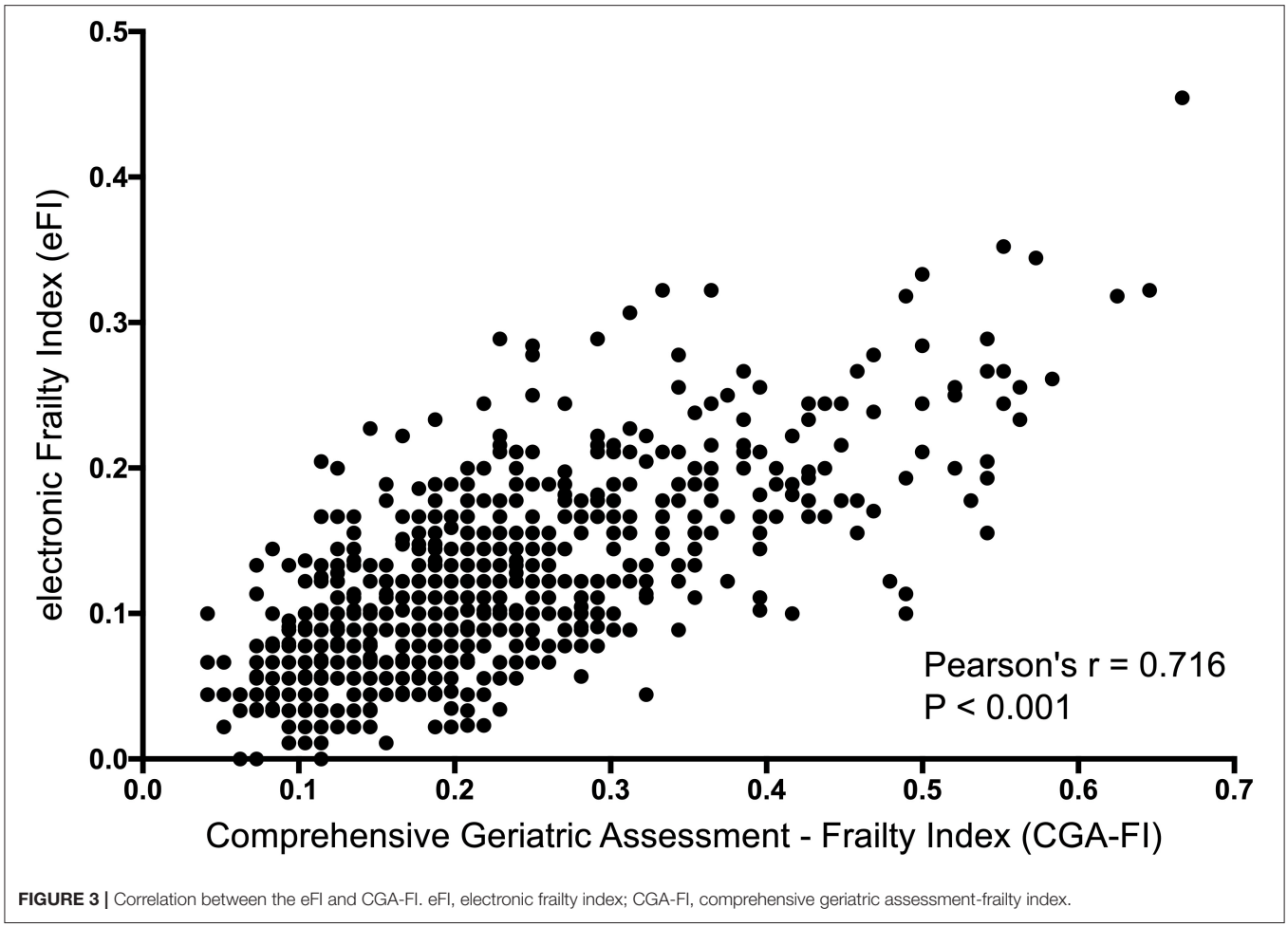


FIGURE 3 | Correlation between the eFI and CGA-FI. eFI, electronic frailty index; CGA-FI, comprehensive geriatric assessment-frailty index.

Sensitivity Analysis

When using the first hospitalization records instead of the last ones, the mortality in the hospital with sufficient data was 1.4%, which was lower than the 3.4% in the original data. There were 30.0% (12,934/43,116) of patients in the frail group, defined by an eFI≥0.15. All the trends between the frail group and the non-frail group were similar to those from the original analysis (**Supplementary Table 7**). After the sensitivity analysis, eFI≥0.15 remained an independent risk factor for long hospital stay and death in hospital (**Supplementary Table 8**). Moreover, the eFI was still independently associated with all kinds of increased hospitalized costs (**Supplementary Table 9**).

DISCUSSION

To our knowledge, this is the first study on detecting frailty in older adult inpatients by routine EHR in China. Our study demonstrates that an effective eFI by routine EHR for older adult inpatients can be developed from a general hospital in China, and the eFI was validated by agreement with the CGA-FI. Although the prevalence of frailty varied obviously among different departments, frailty was an independent risk factor for hospitalized events in each subgroup of different departments. As the degree of frailty increased, the hospitalized costs for older adult inpatients increased accordingly.

Frailty Assessment by Routine EHR

In this study, we constructed an eFI to assess frailty using routine EHR. Our results showed a strong correlation between eFI and CGA-FI, which was consistent with the findings of Brundle et al. in the UK (25) and Abbasi et al. in Canada (31). Previous studies have shown that eFI could predict mid-term adverse events in older adult patients (22, 23). Our study showed that the eFI was independently associated with long hospital stay and death in hospital. Although the eFI opens a new direction to fill the gap between research and clinical application, several details should be considered in clinical practices based on our results.

First, the cut-off value of the eFI for identifying frailty should be redefined according to the specific situation, instead of taking a generally accepted fixed value, such as 0.25 for the CGA-FI. Our study showed that the eFI was lower than the CGA-FI despite both having a strong correlation. The median CGA-FI was 0.198, while the median eFI was only 0.102 in the validation cohort. Therefore, applying cut-off value from CGA-FI to the eFI will underestimate the prevalence of the frail population. A similar study that simultaneously compared their own eFI

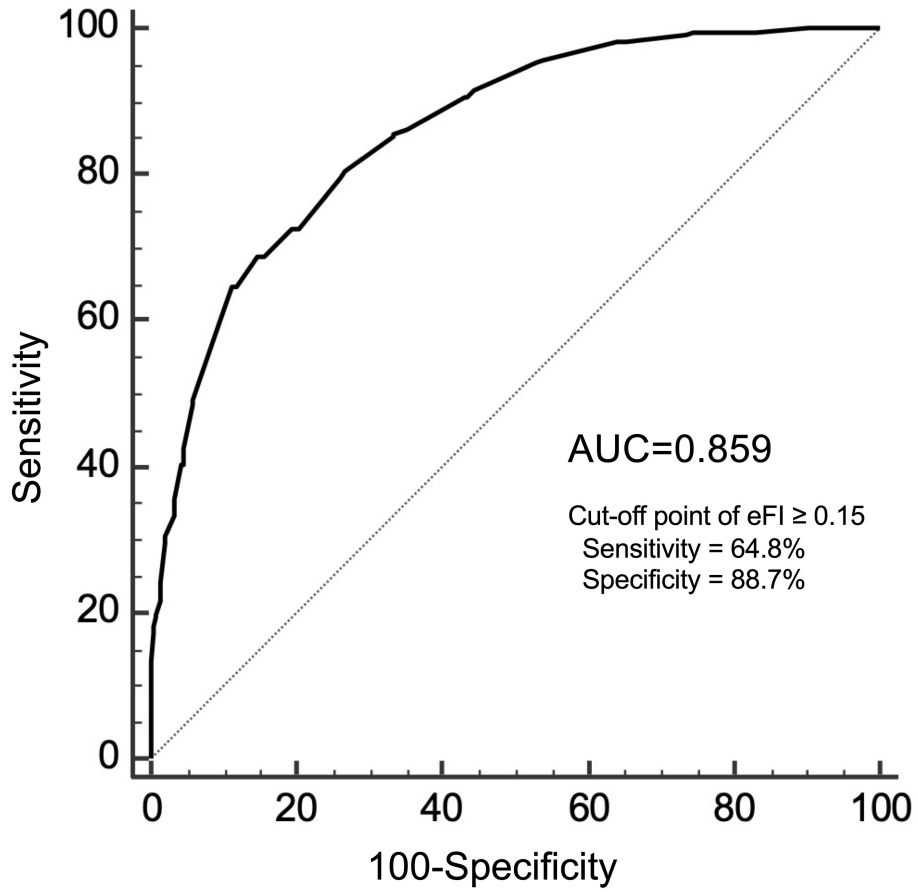


FIGURE 4 | The ROC analysis for the eFI against CGA-FI ≥0.25 to identify frailty. ROC, receiver operating characteristic; eFI, electronic frailty index; CGA-FI, comprehensive geriatric assessment-frailty index; AUC, area under the curve.

and CGA-FI also showed that eFI was relatively lower than the CGA-FI for 85 participants in a Canadian primary care program (31). There were several possible reasons why our eFI values were lower than those of the CGA-FI. Our eFI was based on routine EHR from a single hospitalization rather than a summary of medical records across multiple visits. In a single hospitalization, the diagnoses seemingly not highly-related to the current treatments, such as depression or anxiety, may be ignored, especially in surgical departments. Moreover, the nurses might not pay enough attention to the conditions related to frailty during the admission assessment, which might have led to the neglect of some positive manifestations. Given that the frailty prevalence was 35.1% by the CGA-FI in our previous survey for older adult inpatients (21), it was more reasonable to use the tertile of eFI values (0.15) as the cut-off value for identifying frailty. Perhaps each center needs to define its own cut-off value for the eFI according to its own situation and research results.

Second, the timeliness of constructing the eFI should be considered in clinical practice. The routine EHR used to construct the eFI could be mainly collected within 24 h after admission in our study except for the diagnostic codes. Compared with the well-checked, ICD-10 coded discharge diagnosis, the uncoded admission diagnosis was relatively difficult to analyze. Therefore, we used the discharge diagnosis to calculate the eFI. If the admission diagnosis is improved by coding in the future, we would be able to obtain the eFI within 24 h after admission, which would be not only useful in follow-up of frail patients after discharge, but also in guiding to manage older adult inpatients in a targeted manner during hospitalization. In previous studies, the eFI was mainly developed in primary care settings (22, 23, 31). Compared with relatively complete hospitalization records, the cleaning of primary medical data is more complicated. It is difficult to obtain all information from one setting at one visit. There often needs to be 1 or 2 years of medical records to construct an eFI, which leads to a time lag in the guidance of clinical practice.

Third, the eFI should reflect the variability in frail conditions. Frailty is a dynamic condition, and individuals can fluctuate between states of severity of frailty (32). In previous studies, researchers have rarely paid attention to this point when constructing an eFI (22). This might also be due to the limitations of electronic medical data, which caused frailty assessment to rely too much on diagnostic codes (24). Pajewski et al. and Abbasi et al. improved the composition of the eFI by adding some

TABLE 2 | Hospitalized events and costs in frail and non-frail groups classified by eFI ≥0.15.

	Non-frail group (eFI<0.15) *n* = 28,349	Frail group (eFI≥0.15) *n* = 14,472	*P* values
Demographics			
Age, years	72.8 ± 6.0	78.7 ± 7.1	<0.001
Age, n (%)			<0.001
65 to <75 years	17,939 (63.3)	4,159 (28.7)	
75 to <85 years	9,285 (32.8)	7,173 (49.6)	
85 years or more	1,125 (4.0)	3,140 (21.7)	
Male	14,874 (52.5)	6,746 (46.6)	<0.001
Departments			<0.001
Cardiology	5,852 (20.6)	1,689 (11.7)	
Internal (except Cardiology)	8,130 (28.7)	5,553 (38.4)	
Orthopedics	2,101 (7.4)	3,092 (21.4)	
Surgical (except Orthopedics)	11,844 (41.8)	2,102 (14.5)	
Emergency and ICUs	422 (1.5)	2,036 (14.1)	
Operation			<0.001
Yes	21,528 (75.9)	7,377 (51.0)	
No	6,821 (24.1)	7,095 (49.0)	
Hospitalized events			
Hospital days	8 [5, 13]	12 [8, 18]	<0.001
>14 hospital days	4,961 (17.5)	5,478 (37.9)	<0.001
Death in hospital	101 (0.4)	1,350 (9.3)	<0.001
Hospitalized costs			
Total costs, $	2,290 [1,370, 6,520]	4,790 [2,060, 10,700]	<0.001
Examination costs, $	514 [304, 788]	724 [465, 1,140]	<0.001
Treatment costs, $	429 [217, 766]	588 [303, 1,180]	<0.001
Nursing costs, $	23.2 [10.4, 46.4]	36.2 [16.7, 83.6]	<0.001
Pharmacy costs, $	417 [166, 914]	904 [375, 1,950]	<0.001
Material costs, $	506 [137, 2,590]	568 [160, 5,250]	<0.001

Values are showed as mean ± standard deviation, median [interquartile range], or n (%). eFI, electronic frailty index; ICUs, intensive care units.

laboratory tests and functional abilities (23, 31). We also agree with this improvement. Therefore, we added a 20-item set of nursing assessments and a 5-item set of laboratory tests to the factors of the eFI. A dynamic eFI during hospitalization can more effectively reflect the current condition of older adult inpatients, which would be more precisely guide clinical interventions.

The primary advantage of EHR data is its large volume, but the biggest challenge of EHR-based studies is the presence of missing data (33). Our study showed that 13.0% of patients had insufficient data to calculate the eFI, while Pajewski's study reported 29.6% (23), others did not report the details. We found that these 13% of patients had a significantly lower proportion of adverse events, which was consistent with the results of Pajewski's study (23). Our study showed that the department of ophthalmology contributed the majority of these patients (54.5%, 3491/6405), while the prevalence of frailty was only 5.07% in the department of ophthalmology. These results indicate that patients with insufficient data had a lower percentage of frailty. Therefore, the eFI can be applied to the vast majority of patients with a need for frailty assessment. Meanwhile, we should consider the tolerance for missing data when we select the factors for constructing an eFI.

Prevalence of Frailty Among Different Departments

We found that there were significant differences in the prevalence of frailty among the different departments. Generally, emergency departments and ICUs had the highest percentage of frailty (average: 82.8%), followed by internal medicine departments (average: 34.1%), and surgical departments (average: 27.1%). This trend was consistent with the results of a recent multicenter survey on frailty in older adult inpatients in China (34).

In this study, we found that the prevalence of frailty in the department of orthopedics (59.5%) was significantly higher than that in other surgical departments and most internal medicine departments. This was mainly because the conditions for most orthopedic patients were braked by osteoarthritis or fractures, especially hip fractures. The activities of daily living assessments for these inpatients in this state could not reflect their daily conditions. We should keep this point in mind when we use the eFI to guide clinical practice for inpatients in department of orthopedics. In our study, the prevalence of frailty in department of cardiology was lower than that in most internal medicine departments. This result was consistent with results in our previous cohort study (21). Since non-emergency percutaneous coronary intervention is not an outpatient procedure in China, it is easy to be explained. However, we were surprised to find that the prevalence of frailty in the gastroenterology ward (17.7%) was the lowest among all internal medicine departments. This might have been caused by the large amount of endoscopic procedures that lead to the development of gastroenterology near surgical departments. For hospitals that do not overly rely on endoscopic procedures, the prevalence of frailty in the gastroenterology ward may be closer to the average level among internal medical departments. In short, due to the differences in disease characteristics and treatment models, the prevalence of frailty varied significantly among different departments.

Association Between Frailty and Hospitalized Costs

Our findings showed that the hospitalized cost of patients with frailty was significantly higher than that patients without frailty. The eFI was positively associated with costs after adjusting age, sex and operation. This trend exists in all kinds of hospitalized costs (examination, treatment, nursing, pharmacy and material costs).

Previous studies has also suggested that frailty was associated with healthcare expenditure, both in developed and developing countries (5, 8–11, 15, 16). Several small-sample studies have shown that frailty was associated with increased hospitalized

TABLE 3 | Association between eFI and hospitalized events of elderly inpatients by logistic regression.

Variables	>14 hospital days				Death in hospital			
		95%CI				95%CI		
	OR	Lower	Upper	*P* values	OR	Lower	Upper	*P* values
All patients (*n* = 42,821)								
Age	1.004	1.000	1.007	0.033	1.018	1.011	1.026	<0.001
Sex (female = 1, male = 0)	0.821	0.785	0.860	<0.001	0.624	0.558	0.697	<0.001
Operation (Yes = 1, No = 0)	1.059	1.008	1.113	0.023	0.304	0.269	0.343	<0.001
eFI≥0.15	2.889	2.745	3.040	<0.001	19.97	16.18	24.63	<0.001
Department of cardiology (*n* = 7,541)								
Age	1.008	0.993	1.023	0.274	1.048	1.004	1.093	0.032
Sex (female = 1, male = 0)	0.990	0.823	1.189	0.911	0.832	0.490	1.414	0.497
Operation (Yes = 1, No = 0)	1.116	0.898	1.388	0.323	0.256	0.143	0.458	<0.001
eFI≥0.15	3.342	2.713	4.117	<0.001	7.966	3.903	16.26	<0.001
Departments of internal medicine (except cardiology) (*n* = 13,683)								
Age	1.012	1.006	1.018	<0.001	1.004	0.992	1.015	0.542
Sex (female = 1, male = 0)	0.901	0.836	0.971	0.006	0.679	0.577	0.799	<0.001
Operation (Yes = 1, No = 0)	1.264	1.166	1.370	<0.001	0.703	0.576	0.857	<0.001
eFI≥0.15	2.819	2.598	3.059	<0.001	16.44	12.40	21.78	<0.001
Department of orthopedics (*n* = 5,193)								
Age	1.001	0.993	1.011	0.695	1.092	1.047	1.138	<0.001
Sex (female = 1, male = 0)	0.784	0.691	0.889	<0.001	0.340	0.194	0.595	<0.001
Operation (Yes = 1, No = 0)	2.500	1.934	3.231	<0.001	0.098	0.056	0.169	<0.001
eFI≥0.15	1.392	1.214	1.597	<0.001	7.192	2.168	23.85	0.001
Surgical Departments (except orthopedics) (*n* = 13,946)								
Age	1.001	0.994	1.007	0.864	1.013	0.993	1.034	0.196
Sex (female = 1, male = 0)	0.739	0.680	0.803	<0.001	0.712	0.533	0.952	0.022
Operation (Yes = 1, No = 0)	3.260	2.772	3.834	<0.001	0.409	0.304	0.551	<0.001
eFI≥0.15	3.215	2.886	3.580	<0.001	34.26	22.46	52.26	<0.001
Emergency department and ICUs (*n* = 2,458)								
Age	1.015	1.003	1.028	0.018	1.032	1.016	1.049	<0.001
Sex (female = 1, male = 0)	0.854	0.720	1.012	0.068	0.745	0.601	0.924	0.007
Operation (Yes = 1, No = 0)	0.628	0.518	0.761	<0.001	0.411	0.311	0.542	<0.001
eFI≥0.15	4.750	3.427	6.585	<0.001	22.79	7.224	71.90	<0.001

eFI, electronic frailty index; CI, confidence interval; OR, odds ratio; ICUs, intensive care units.

costs for patients with colorectal surgery (6), cardiac surgery (13), or transcatheter aortic value implantation (35). In china, studies also showed similar results in annual healthcare costs (12, 14). However, one study showed that there was no significant difference in hospitalized costs between frail and non-frail groups with elective non-cardiac surgeries (36), which is contrary to our results. These inconsistencies might have been due to the small sample size.

To our knowledge, previous studies did not simultaneously analyze the correlation between hospitalized costs and frailty in different departments. Our results showed that the increases in hospitalized costs in the department of orthopedics were smaller than those in other subgroups, especially in terms of material costs. There are several possible reasons to explain this phenomenon. Firstly, the cost of medical consumable materials is a large part of the total hospitalized cost in the department of orthopedics, whether for frail or non-frail inpatients. Secondly, the cost of medical consumable materials in China depends not only on the patient's condition but also on the patient's own choice. For example, patients with low income or without medical insurance may be more likely to choose the less expensive of similar products. Thirdly, the frailty assessment was influenced by patient braking, which may have led to an overestimation of the degree of frailty in many patients with fracture. However, even so, hospitalized costs are positively related to the degree of frailty for older adult inpatients in the department of orthopedics, after adjusting for age, sex, and operation.

Overall, considering that in-hospital interventions on frailty have been effective for older adult inpatients to reverse the degree of frailty (37), timely recognition of frailty is important to guide

TABLE 4 | Association between eFI and hospitalized costs of elderly inpatients by generalized liner regression models.

Variable	Beta-coefficients (95%CI) for eFI (per 0.1)					
	Total costs	Examination costs	Treatment costs	Nursing costs	Pharmacy costs	Material costs
All patients (n = 42,821)						
eFI (per 0.1)	0.453 (0.441–0.465)**	0.269 (0.260, 0.278)**	0.414 (0.396, 0.432)**	0.381 (0.369, 0.394)**	0.524 (0.508, 0.540)**	0.578 (0.561, 0.594)**
Department of cardiology (n = 7,541)						
eFI (per 0.1)	0.330 (0.297, 0.364)**	0.193 (0.172, 0.213)**	0.502 (0.465, 0.539)**	0.410 (0.369, 0.450)**	0.592 (0.517, 0.667)**	0.516 (0.453, 0.578)**
Departments of internal medicine (except cardiology) (n = 13,683)						
eFI (per 0.1)	0.368 (0.348, 0.388)**	0.212 (0.198, 0.225)**	0.409 (0.368, 0.450)**	0.323 (0.303, 0.344)**	0.436 (0.410, 0.462)**	0.482 (0.450, 0.514)**
Department of orthopedics (n = 5,193)						
eFI (per 0.1)	0.072 (0.046, 0.097)**	0.193 (0.172, 0.215)**	0.108 (0.077, 0.139)**	0.165 (0.128, 0.202)**	0.287 (0.254, 0.319)**	0.047 (0.015, 0.078)*
Surgical departments (except orthopedics) (n = 13,946)						
eFI (per 0.1)	0.523 (0.497, 0.549)**	0.414 (0.391, 0.437)**	0.419 (0.378, 0.460)**	0.448 (0.420, 0.476)**	0.616 (0.582, 0.650)**	0.557 (0.521, 0.592)**
Emergency department and ICUs (n = 2,458)						
eFI (per 0.1)	0.382 (0.349, 0.415)**	0.327 (0.299, 0.355)**	0.433 (0.392, 0.474)**	0.332 (0.293, 0.372)**	0.530 (0.481, 0.579)**	0.397 (0.353, 0.441)**

The beta coefficients of eFI (per 0.1) on hospitalized costs were calculated by generalized linear regression models with log-linked gamma-distribution, after adjusting for age, sex, and operation.

eFI, electronic frailty index; CI, confidence interval; ICUs, intensive care units.

**P < 0.01 in the generalized liner regression model.*

***P < 0.001 in the generalized liner regression model.*

interventions on frailty and even reduce hospitalized costs to some degree for older adult inpatients.

LIMITATIONS

There are three main limitations in this study. First, there was no follow-up data after discharge. We could not verify the long-term predictive value of the eFI for adverse events in the older adult inpatients because it is difficult to link our hospital EHR with national resident death records or EHR from other hospitals. Second, we used discharge but not admit diagnoses when building eFI. In our hospital, discharge diagnoses were inspected and coded in a variation of ICD-10 by specialists, which are the best source we can find representing the disease burden of patients at present. One of our targets in the future research is to build eFI based on the information gathered in first 24 h after admission, and to verify the value in prediction of outcomes. Third, despite its relatively large size, the EHR data in this study were from a single general hospital, which may not represent all hospitals in China. Multicenter studies with follow-up data are warranted in the future.

CONCLUSION

In summary, we successfully developed an effective eFI using routine EHR for older adult inpatients from a general hospital in China. With good agreement with the CGA-FI, the eFI can be a useful and convenient tool to clinicians for detecting frailty in older adult inpatients. The prevalence of frailty varied obviously among different departments, but frailty was an independent risk factor for long hospital stay and death in hospital. As the degree of frailty increased, the hospitalized costs for older adult inpatients increased accordingly.

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 Ethics Committee of Beijing Hospital (No. 2019BJYYEC-131-01). The Ethics Committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

Y-DL, JS, J-FY, and HW contributed conception and design of the study. Y-BX performed data collection, preparation, and cleansing. Y-DL and M-HD performed the statistical analysis and wrote the draft of the manuscript. 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.2021.731445/full#supplementary-material

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frontiers in Medicine

REVIEW
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Helicobacter pylori Infection in Geriatric Patients: Current Situation and Treatment Regimens

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Helicobacter pylori (*H. pylori*) has so far infected more than half the global population. It is the most important and controllable risk factor for gastric cancer. The elderly, who are at a higher incidence of the infection, are also commonly found to develop antibiotic resistance. The symptoms, diagnosis, clinical features (of gastric or extra-digestive diseases), and treatment of *H. pylori* infection in the elderly, are different from that in the non-elderly. Health conditions, including comorbidities and combined medication have limited the use of regular therapies in elderly patients. However, they can still benefit from eradication therapy, thus preventing gastric mucosal lesions and gastric cancer. In addition, new approaches, such as dual therapy and complementary therapy, have the potential to treat older patients with *H. pylori* infection.

Keywords: *Helicobacter pylori*, eradication therapy, stomach cancer, dual therapy, complementary therapy, elderly

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INTRODUCTION

Aging is an inexorable process in the human life cycle. According to the World Health Organization, population aging is an evident phenomenon in all developed countries and some developing countries (1). Poor health of the elderly and the increasing disease burden have led to a great demand for medical care and social services (2, 3). Aging widely affects the functioning of various organs. Disrupted functioning of the digestive organs can lead to indigestion symptoms. A survey in Italy involving over 3,000 outpatients aged ≥60 years showed that over 40% of them had experienced gastrointestinal symptoms (4). Aging-related changes in the upper digestive system is mainly reflected in anatomical and physiological changes, such as gastric mucosa atrophy, decreased motility of the esophagus and stomach, reduced secretion of gastric acid and bile, decreased mucosal blood flow, and reduced digestive enzyme activity. Moreover, depending on factors such as infections, comorbidities, nutrition, and medications [e.g., non-steroidal anti-inflammatory drugs (NSAIDs)], aging can cause digestive disorders or further progression of diseases acquired in youth.

Among aged people, *Helicobacter pylori* (*H. pylori*), the most common infectious pathogen in the stomach, is the main risk factor for gastric cancer (5). Although *H. pylori* affects individuals of different age groups, the elderly have a higher prevalence of *H. pylori* infection, and risk of developing atrophic gastritis, and stomach cancer (6–8). As per a previous study, the effect of *H. pylori* eradication therapy in decreasing gastric cancer deaths varied among different age groups (failing in patients aged ≥80 years), but most of the aged patients with *H. pylori* infection could still benefit from the treatment (9). The eradication of *H. pylori* in elderly patients could be tricky due to decline in bodily functions, complications of other disease like renal failure, drug combinations, etc. (10). The use of mainstream therapies have to face more competing situations in older patients. The

Fifth Chinese National Consensus Report on *H. pylori* infection has focused on geriatric patients, but it lacks information and treatment strategies specific to such patients (11). There is substantial scope to improve health care for elderly patients with *H. pylori*-related diseases. Therefore, this article aims to review the current knowledge on *H. pylori* infection in the geriatric population and the promising new approaches in this regard (**Figure 1**).

EPIDEMIOLOGY

Approximately 50% of the global population is infected with *H. pylori*. The infection rate varies with age, socioeconomic class, and geographic area. *H. pylori* infection is usually acquired during childhood, and chronic infection lasts a lifetime if untreated. Due to improvement in sanitary conditions, the prevalence of *H. pylori* infection has gradually decreased in recent years, especially among the younger generation in the developed countries (12). However, in poor and developing countries and regions, the prevalence *of H. pylori* infection remains high in children. Decades later, these children might get affected by *H. pylori*-related diseases when they age (13, 14). The total *H. pylori* infection rate among the elderly in Beijing, China, according to a seroepidemiological investigation 15 years ago, was 83.4% (15), while in a recent study using the ^{13}C-urea breath test, it was found to be 46.5% (16). Our previous study retrospectively collected the results of the ^{13}C-urea breath test performed in our department from 2013 to 2019, in which the prevalence of *H. pylori* infection in people aged <20 years was 22.0%, and in those aged >60 years, it was 39.4% (17). The geriatric population in developing countries such as China is still facing the challenge of a high incidence of *H. pylori* infection. In addition, antibiotic

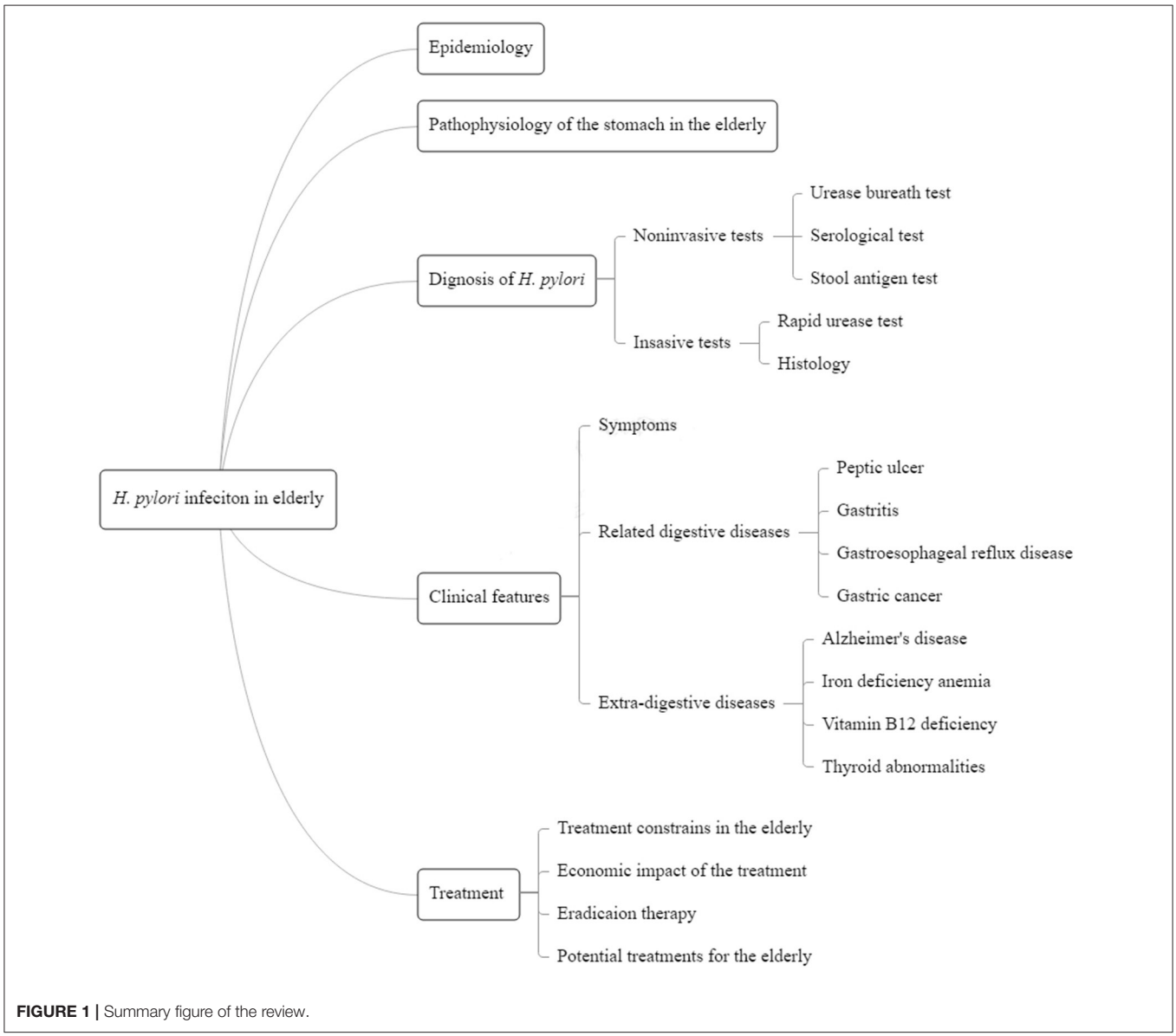


FIGURE 1 | Summary figure of the review.

resistance is more severe in the elderly population. A study conducted in China revealed that the antibiotic resistance rates to clarithromycin, levofloxacin, and metronidazole were 17.76, 19.66, and 95.5%, respectively in the entire patients; the highest antibiotic resistance rate was observed in patients aged 71–80 years (18). A larger study found that younger patients exhibited lower antibiotic resistance rates compared to patients aged ≥40 years (19). Thus, the epidemiology of *H. pylori* infection in elderly patients is characterized by high prevalence and drug resistance.

CHARACTERISTICS OF AGING STOMACH

Compared with normal stomach, the stomach of the elderly exhibits functional and structural abnormalities, which lead to a series of biological responses, including impaired nuclear-mitochondrial communication (20), hypoxia (21), apoptosis (22), and increased levels of reactive oxygen species. The common characteristics of aging stomachs include slowing of gastric emptying, and dyspepsia (23). It also results in 'anorexia of aging' (24) and post-prandial hypotension (25). Further, aging also contributed to a decrease in microbial diversity in stomach. In *H. pylori*-uninfected gastric corpus mucosa, the abundance and the microbial diversity of Firmicutes (*Streptococcus*, and *Veillonella*), Fusobacteria (*Fusobacterium*), Actinobacteria (*Rothia*), and Bacteroidetes (*Prevotella*) both decreased with age (26). In addition, atrophy of the gastric glands and the decrease in gastric mucosal blood flow weaken the gastric mucosal defense. The atrophy of the gastric glands induces the reduction of bicarbonate and prostaglandin production in the stomach and impairs the mucosal barrier. Gastric blood vessels are important for facilitating blood flow and preserving gastric mucosal morphology (27). They maintain the mucosal barrier, provide nutrients and oxygen, and defend the gastric mucosa against injury (28). As reported in a study, in elderly people, the mucosal blood flow decreases by >60%, causing profound hypoxia in all mucosal cells (29). The fundamental process of angiogenesis is impaired in aging gastric mucosa (30). These changes lead to increased susceptibility to injuries, such as the NSAID. *H. pylori* infection induces overproduction of nitric oxide, upregulates endothelial nitric oxide synthase expression, and induces angiogenesis (31), thus leading to obstruction of oxygen and blood flow.

H. pylori infection causes stomach mucosal lesions, atrophy, and microcirculation dysfunction in older people. Eradication therapy for *H. pylori* infection in geriatric patients can potentially prevent gastric cancer (32). The testing for *H. pylori* should be performed in aspirin and NSAID users (33). *H. pylori* eradication can prevent gastric mucosal injury induced by antiplatelet drugs (34). However, due to the complicated comorbidities, history of medications, and poor adherence to eradication therapy among the older patients, further efforts are required to develop appropriate treatment strategies for them.

DIAGNOSIS

Non-invasive Tests

Non-invasive tests include the urea breath test (UBT), *H. pylori* stool antigen test, and serological tests (35, 36). UBT is considered the gold standard of non-invasive methods for *H. pylori* diagnosis (37). It is the first choice for treating outpatients because of its wide availability and high accuracy (96%). In a previous study, the mean UBT values were found to significantly increase with age (38). The manufacturer-recommended cut-off values for UBT are not applicable in every setting. The ^{13}C-UBT might have higher threshold values in subjects aged >60 years due to impairment in gastric emptying or lower endogenous CO_2 production, compared to younger people (39). Severe gastric mucosal atrophy and intestinal metaplasia are independent risk factors for false positivity of UBT (40) because of the resultant lowered *H. pylori* density in the stomach (41). Thus, the UBT cut-off values should take age of the patient into account (42).

As per a study, the sensitivity, specificity, and diagnostic accuracy of serological tests in elderly patients were 74.4, 59, and 67%, respectively (43). The combined use of serological tests with UBT may further increase the sensitivity and specificity of *H. pylori* detection. However, the *H. pylori* antibody test may often yield false negative results because of spontaneous disappearance of *H. pylori* with advanced gastric mucosal atrophy, particularly in individuals aged ≥65 years (44).

H. pylori stool antigen test can effectively compensate for the drawbacks of UBT in the elderly. Detection of bacterial antigens was not affected by atrophic gastritis, ulceration, or intestinal metaplasia. In a study that evaluated the diagnostic efficiency of *H. pylori* stool antigen test in elderly subjects (≥65 years old), the accuracy (91.5%) and specificity (97.6%) were both high for all participants. However, the sensitivity was only 68.7%. Further, it was found that constipation and colorectal polyps were negatively and positively associated with its sensitivity, respectively (45).

Invasive Tests

Rapid urease test (RUT) is the preferred method for invasive detection of *H. pylori*, with a sensitivity of up to 95% and specificity of 85–95% (46). The sensitivity of RUT performed on antral biopsies of patients aged ≥60 years (57%) was lower than that performed on younger patients (75%) (47). Histological diagnosis of *H. pylori* can be performed at the same time as the pathological diagnosis in the gastric mucosa. For patients with high risk of gastric cancer, histological detection is recommended, which is of great significance for the evaluation of prognosis and the formulation of treatment measures. Upper gastrointestinal endoscopy is often necessary for the diagnosis of *H. pylori* infection in older adults with varying abdominal symptoms because of the high prevalence of severe stomach disorders in this age group (48). Bacterial culture performed on gastric biopsy specimens is mainly used for scientific research and is not a routine method for *H. pylori* detection. It showed low sensitivity (53.3%) and high specificity (100%) (49).

CLINICAL PRESENTATION

Symptoms

H. pylori infection is associated with the occurrence of peptic ulcers, chronic atrophic gastritis, gastric cancer etc. (50). With increasing age, the incidence and severity of most upper gastrointestinal diseases increase. The clinical features of *H. pylori* infection range from asymptomatic gastritis to

gastrointestinal malignancy (51). Symptoms such as nausea, vomiting, epigastric pain, and belching are also common in acute *H. pylori* infection. However, most symptoms improve or disappear gradually in persistent chronic infection. In case of old patients, long-term *H. pylori* infection usually has no or mild digestive symptoms. These non-specific symptoms are often confused with those of other diseases, especially in case of *H. pylori*-induced gastritis. Patients with treatment-resistant *H. pylori* infections show more severe gastrointestinal symptoms (52). Further, older people with a history of treatment failure and excessive antibiotic exposure might also have more prominent symptoms.

Peptic Ulcer Disease

H. pylori infection is strongly associated with peptic ulcer disease (PUD) (53). As the population ages, the incidence of cardiovascular and musculoskeletal diseases increases, as does the use of aspirin and NSAIDs. Aspirin, NSAIDs, and *H. pylori* are independent risk factors for PUD and its complications (54–56). The incidence of PUD increases with age, with most ulcers occurring between the ages of 25 and 64 (57). The most common and serious complication of PUD is bleeding, and people aged >60 years are at the highest risk of suffering from it (58). Treatment for *H. pylori*-associated PUD is mainly directed toward the eradication of infection. In cases of NSAID-induced ulcers, *H. pylori* eradication alone did not impair ulcer healing; and the use of proton pump inhibitors (PPI), H_2 receptor antagonists, and misoprostol are recommended before using NSAIDs, in order to protect the gastric mucosa and prevent PUD and its complications (33, 55, 58). Early eradication of *H. pylori* in patients with PUD can reduce the risk of gastric cancer (59).

Chronic Atrophic Gastritis

Chronic atrophic gastritis (CAG) is a disease characterized by atrophy of the gastric glands and/or intestinal metaplasia, which is mainly caused by prolonged persistence of *H. pylori* infection. Studies on the prevalence of CAG in different parts of the world have found that CAG is relatively common among the elderly (7). A study from Germany found that the prevalence of chronic atrophic gastritis increased from 4.8% in the 50–54 age group to 8.7% in the 70–74 age group (6). CAG is also a precancerous lesion of gastric cancer, especially when accompanied by intestinal metaplasia. All *H. pylori*-positive individuals should receive eradication therapy unless there are competing considerations (60). The eradication of *H. pylori* can reverse the atrophy of the gastric antrum and gastric body to a certain extent, but it has no observable effect on intestinal metaplasia (61). In the elderly, however, eradication of *H. pylori* may improve gastric atrophy and prevent the progression of intestinal metaplasia (8). Further, it can also delay the progression of CAG in the elderly, which is of great significance for the prevention of gastric cancer (62).

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) is a multifactorial disease that causes reflux of acidic stomach contents into the esophagus, causing tissue damage. Under normal conditions, gastric acid secretion does not decrease with age, but factors that cause atrophic gastritis, such as *H. pylori* infection, reduce gastric acid secretion (36). A case-control study found that compared with young and middle-aged GERD patients, atypical symptoms, low upper esophageal sphincter resting pressure, increased incidence of ineffective esophageal motility, and acid exposure were more significant in the elderly (63). A meta-analysis indicated that the prevalence of GERD was significantly higher in patients with *H. pylori* eradication than in those without it (64). However, eradication of *H. pylori* may not affect the healing rates or relapse rates of preexisting GERD (65). For patients with GERD, their condition should be comprehensively evaluated before carefully initiating *H. pylori* eradication therapy.

Gastric Cancer

Gastric cancer is the fifth most common cancer and the third most common cause of cancer-related deaths worldwide (66). More than 1 million new cases of gastric cancer were reported in 2018, with an estimated 783,000 deaths (equivalent to 1 in 12 deaths worldwide). East Asian countries have a high incidence of gastric cancer (67). *H. pylori* is the main risk factor for gastric cancer apart from diet, alcohol, and smoking (67). *H. pylori* eradication may reduce the risk of gastric cancer in healthy, asymptomatic, and gastrointestinal patients (68). Among the high-incidence- and high-risk-population of gastric cancer, screening and eradication of *H. pylori* are recommended before the development of atrophic gastritis and intestinal metaplasia to prevent gastric cancer (14, 69). Due to the high incidence of gastric mucosal atrophy and intestinal epithelial metaplasia in elderly patients, it was thought in the past that the benefit of *H. pylori* eradication might be limited to treating gastric cancer. However, a long-term cohort study demonstrated that the risk of gastric cancer was significantly lower in people aged ≥60 years than that in the general population aged ≥10 years, after eradication of *H. pylori* (32). Moreover, patients at early stages of gastric cancer who received *H. pylori* eradication therapy had lower rates of metachronous gastric cancer than those who did not (70).

Extra-Digestive Diseases

Although the relationship between *H. pylori* infection and gastric pathology has been established, the effect of this bacterium on the host body as a whole remains to be studied. It is well-known that some pathogens exist locally and may cause systemic pathological effects (71). Studies have found that *H. pylori* is associated with blood disorders such as vitamin B12 deficiency, iron-deficiency anemia (IDA), primary immune thrombocytopenia, as well as a number of dermatological, eye, metabolic, neurological, and allergic diseases (71). Among these diseases, we will only elaborate on diseases that have a greater impact on the elderly.

Approximately 46.8 million people live with dementia worldwide in 2015 (72). Alzheimer's disease (AD) is the single biggest cause of dementia, and is doubling in prevalence every 5 years after age 65 (73). Epidemiological studies have shown an association between *H. pylori* infection, mild cognitive impairment, and AD (74). *H. pylori* may affect the pathophysiology of AD in various ways (74, 75). Selective

eradication of potentially curative *H. pylori* infection is recommended for *H. pylori*-infected patients with AD, and those who might fulfill the criteria of clinicians (for example, poor response to conventional drugs and complicated gastrointestinal symptoms) (74).

Iron deficiency is a common cause of anemia in the elderly. Many studies have shown a strong link between *H. pylori* infection and IDA. Compared with uninfected individuals, the prevalence of IDA was higher, and iron levels were significantly lower in those infected with *H. pylori* (76, 77). Hemorrhage (i.e., bleeding from ulcers) resulting from blood loss and the reduced iron absorption are the main causes of IDA (71). The Maastricht V/Florence Consensus Report recommends that patients with IDA of unknown cause should be diagnosed and treated for *H. pylori* (33). *H. pylori* eradication therapy combined with iron supplementation may help improve ferritin and hemoglobin levels (76).

Vitamin B12 deficiency is common in the elderly, and its prevalence increases with age (78, 79). Chronic atrophic gastritis, ingestion of drugs that affect gastric acid secretion or acid (i.e., proton pump inhibitors and antacids), *H. pylori* infection, overgrowth of intestinal bacteria, inadequate food intake, alcohol abuse, and smoking can all lead to B12 deficiency (79, 80). The clinical manifestations of B12 deficiency are heterogeneous; generally, there are no visible clinical symptoms. Its classical manifestations include Hunter's glossitis, megaloblastic anemia, and subacute combined degeneration of the spinal cord, and are associated with atherosclerotic vascular disease and neuropsychiatric disorders (78). B12 deficiency is particularly difficult to diagnose in elderly individuals. The Maastricht V/Florence Consensus Report recommends that all patients with vitamin B12 deficiency be screened for *H. pylori* infection, and treated if necessary (33).

Persistent active inflammation induced by *H. pylori* infection can lead to autoimmune immunopathological reactivity in affected patients, including thyroid abnormalities. The prevalence of anti-thyroid peroxidase antibody positivity is more frequent in subjects with *H. pylori* infection, and the association was still significant after adjusting other confounding factors (81). *H. pylori*-mediated chronic inflammation has also been shown to increase the expression of proinflammatory cytokines. And non-thyroidal-illness syndrome may develop on this background of chronic inflammation. A positive association between chronic active *H. pylori* infection and non-thyroidal-illness syndrome prevalence in elderly male cohort was found (82).

TREATMENT

Several clinical guidelines are available for treating *H. pylori* infection in adults (11, 33, 83–86), children, and adolescents (87, 88). In general, the regimens recommended for adults are effective for older patients. However, a comprehensive benefit/risk assessment should be performed and individualized treatment be given to eradicate *H. pylori* in elderly patients (11, 34), due to their declining physical conditions, serious comorbidities, side effects and ongoing medications (89). A retrospective study indicated that clinicians might be reluctant to treat very old patients, possibly due to concerns about complications (90). Age, physical health condition, and history of medications are the determining factors for performing *H. pylori* eradication therapy.

Constraints in Treatment

The elderly population is more likely to be resistant to antibiotics because of excessive use in the past (91, 92). A multicenter cohort study showed that people aged >40 years were particularly at risk of developing dual drug resistance to levofloxacin and metronidazole (93). In case of chronic infectious bronchial pneumonia in the elderly, it is important to be wary of levofloxacin resistance, as they may have already been treated with quinolones or fluoroquinolones (94). It is recommended to select antibiotics according to the results of antibiotic susceptibility test. If eradication treatment fails, multidrug resistance may develop, making antibiotic selection more difficult (95, 96).

Aging stomachs are less defensive and more sensitive to stimuli, and the side effects of medications may be more pronounced, which may lead to less compliance to the regimen. Progressive aging of the human body can also change the ecological flora. The core microflora, such as Bacteroidetes, decreases in number, while the colony abundance of subdominant microflora such as Firmicutes, Actinobacteria, and Proteobacteria increases (97). The intestinal flora of the elderly population is more likely to be affected by antibiotic treatment as compared to that of the general population. Using probiotics during or after eradicating *H. pylori* may prevent or reduce microecological imbalance in elderly patients, thus reducing the occurrence of adverse effects (98, 99).

In addition to physiological senility, elderly people often suffer from a variety of diseases, such as hypertension, diabetes, liver and kidney dysfunction, etc. These diseases limit the use of certain drugs. For instance, the doses of amoxicillin and clarithromycin may have to be adjusted in patients with renal insufficiency or severe liver impairment. Further, comorbidities in the elderly patients result in drug interactions that can cause serious side effects (100). Some PPIs such as omeprazole can easily interact with cardiovascular drugs such as clopidogrel, which are commonly used in the geriatric population (101, 102). Amoxicillin, clarithromycin, metronidazole, and tetracycline may also interact with cardiovascular medications, such as statins, antiarrhythmic drugs, and warfarin (101).

Economic Impact

Some economic analyses suggest that *H. pylori* screening and eradication are cost-effective for preventing gastric cancer, especially in high-risk areas (103–111). A study in Japan found that from 2013 to 2019, *H. pylori* eradication was economical and reduced the incidence of and mortality caused by gastric cancer in patients aged 20–80 years compared to those not having undergone eradication. Among the patients that had

TABLE 1 | Current mainstream regimens.

First line/rescue therapy	Eradication regimens	Definition	Duration
Restricted option[a]/–	Classic triple therapy	PPI+AMO+CLA PPI+AMO+MTZ PPI+CLA+MTZ	14 d
Recommended/recommended	Bismuth quadruple therapy	PPI+B+TET+MTZ	10–14 d
Recommended/undetermined	Concomitant (non-bismuth quadruple) therapy	PPI+AMO+CLA+MTZ	10–14 d
Not recommended/not recommended	Sequential (non-bismuth quadruple) therapy	PPI+AMO followed by PPI+CLA+MTZ	5–7 d 5–7 d
Conditional recommended by ACG/–	Hybrid therapy	PPI+AMO followed by PPI+CLA+MTZ	7 d
Not recommended/recommended	Levofloxacin triple therapy	PPI+AMO+LFX	10–14 d
Conditional recommended by ACG/–	Levofloxacin sequential therapy	PPI+AMO followed by PPI+AMO+LFX+MTZ	5–7 d 5–7 d
Conditional recommended by ACG/–	LOAD therapy	PPI+LFX+MTZ+ doxycycline	
–/restricted option[b]	Rifabutin triple therapy	PPI+AMO+RFB	10 d
–/Recommended	Modified (high-dose) dual therapy	PPI+AMO	14 d

The table is developed according to the Toronto Consensus guidelines, Maastricht V /Florence Consensus and American College of Gastroenterology Clinical Guideline.
[a]*Restricted to areas with low clarithromycin resistance (<15%).*
[b]*Restricted to cases in whom at least 3 recommended options have failed.*
ACG, American College of Gastroenterology Clinical Guideline; AMO, amoxicillin; B, bismuth; CLA, clarithromycin; LFX, levofloxacin; LOAD, levofloxacin, omeprazole, alinia and doxycycline; MTZ, metronidazole; PPI, proton pump inhibitor; RFB, rifabutin.

received eradication therapy, those aged 60 years had the highest cost benefits and best health outcomes (110). The use of *H. pylori* eradication as a strategy for the prevention of gastric cancer can not only save lives, but also greatly reduce the healthcare-related economic burden on the national budget (110).

Eradication Regimens

Triple therapy has been used worldwide for decades and is the standard first-line eradication regimen for *H. pylori* infection (112). However, increased antibiotic resistance, particularly to clarithromycin, metronidazole, and levofloxacin (113, 114), has reduced the eradication rate of triple therapy (115, 116). A case-control study assessed the efficacy of a standard *H. pylori* eradication therapy among elderly patients, and concluded that the elderly did not affect efficacy or safety of a clarithromycin-based triple therapy for *H. pylori* eradication (117). Triple therapy was only recommended in the areas with clarithromycin resistance rate of <15%. Bismuth-containing quadruple therapy, concomitant therapy, sequential therapy, hybrid therapy, levofloxacin triple therapy, and rifabutin triple therapy were developed to overcome the challenge of antibiotic resistance (**Table 1**). These regimens are recommended by different consensus and guidelines for certain cases of *H. pylori* infection (33, 83, 84). Few studies have evaluated the efficacy and safety of these therapies in elderly patients. Bismuth-containing quadruple therapy was successful for the initial eradication of *H. pylori* in elderly patients, but 28% of patients had mild to moderate side effects (118). The sequential treatment regimen achieved significantly higher eradication rates in comparison with standard triple therapy in elderly patients, and there were mild side effects (<12%) of both the regimens (119). A retrospective investigation of 1,271 cases of *H. pylori* infection in elderly patients indicated that the rate of side effects with both the first and second treatment using triple therapy was <10%, suggesting that clinicians need not withhold treatment strictly based on old age (90).

Potential Treatments

High-dose dual therapy consisting of amoxicillin and a PPI has drawn much attention recently because of the low resistance to amoxicillin and simpler drug composition as compared to the quadruple therapies. It has been recommended by the ACG Clinical Guidelines as a salvage regimen (84). A systematic review and meta-analysis indicated that the efficacy and compliance of modified dual therapy was comparable with the current mainstream first-line regimens for *H. pylori* infection, with a significantly lower incidence of adverse side effects (120, 121). A retrospective, real-life study demonstrated that modified dual therapy consisting of high-dose amoxicillin and rabeprazole was effective and safe for the first-line treatment of *H. pylori* infection in elderly patients (122). Although the dosage and frequency are increased in modified dual therapy, the total dose throughout the day remains within the safe range. Dual therapy reduces the use of antibiotics and bismuth, which is a promising new approach for the elderly. However, it must be used in patients not allergic to penicillin and those not having renal insufficiency. A randomized controlled clinical trial showed that the cost of medications in the modified dual therapy was lower than that in bismuth-containing quadruple therapy (123).

The development of new drugs has also widened the options for eradication therapy in the elderly population. Vonoprazan, a novel potassium-competitive acid blocker, is

more potent and long-acting than traditional PPIs (124, 125). According to a network meta-analysis, vonoprazan-based triple therapy achieved high eradication rates of more than 90% as a first-line empiric treatment. Vonoprazan-based triple therapy is highly effective and well-tolerated, regardless of clarithromycin susceptibility (126). A retrospective cohort study reported that a triple-drug blister-packaged medication with amoxicillin, clarithromycin, and vonoprazan improved the first-line eradication rate of *H. pylori* in elderly patients (127). Therefore, vonoprazan-based therapy can be a valuable and promising new approach for the treatment of *H. pylori* infection in elderly.

New treatment strategies, including complementary and alternative medicine, are also being considered. Phytomedicines such as traditional Chinese medicine (TCM) treatment can not only improve the eradication rate of *H. pylori*, but also alleviate clinical symptoms and reduce adverse effects (128). *H. pylori* is considered as an "evil qi" in TCM theory. TCM believes that while trying to get rid of the "evil qi," the "healthy qi" should be strengthened. In other words, it emphasizes on the protection of gastric mucosa and the promotion of immune regulation, which is of great significance in the prevention of *H. pylori*-related diseases. The Fifth Chinese National Consensus Report on the management of *H. pylori* infection suggests that the therapeutic effect of Chinese herbal medicines and Chinese patent medicines on *H. pylori* infection should be studied (11). To date, many studies have been conducted on the efficacy of classical ancient formulas [e.g., Banxia Xiexin decoction (129), Huangqi Jianzhong decoction (130), etc.], empirical prescriptions [Shengjiang Yiyou decoction (131), etc.], and proprietary Chinese medicines [Qingwei Qushi granules (132), Jinghua Weikang capsules (133), etc.] to treat *H. pylori* infection. For example, a randomized, double-blind, placebo-controlled clinical trial showed that the Burdock complex can ameliorate UBT, enhance antioxidant capacity, and reduce inflammatory response in asymptomatic patients with *H. pylori* infection (134). Some Chinese herbal medicines, such as Coptidis Rhizoma (Huang Lian) (135, 136), Scutellariae Radix (Huang Qin) (137), and Polygonum capitatum (Tou Hualiao) (138), also have anti-*H. pylori* effect. The studies have been in-depth and specific to the active components with clear chemical structure, among which berberine, the active component of Coptidis Rhizoma and many other traditional Chinese medicines, has been studied the most. Studies have indicated that berberine exerts antibacterial and anti-inflammatory effects by attenuating the Th17 response triggered by the B cell-activating factor, thus regulating macrophage polarization through the IL-4-STAT6 signaling pathway and suppressing proinflammatory genes and the IRF8-IFN-γ signaling axis (139–141). A meta-analysis has shown that the addition of berberine to standard triple therapy significantly improves *H. pylori* eradication, relieves clinical symptoms, accelerates ulcer healing, and has fewer side effects comparing to the standard triple therapy (142). As per a previous study, the combination of traditional Chinese and Western medicine may overcome the problem of antibiotic resistance, or be useful as a remedy after the failure of antibiotic-based eradication therapy (143). For elderly patients showing contraindications to the use of antibiotics, TCM may be an appropriate option to suppress gastric mucosal inflammation, delay lesion progression, and improve the quality of life.

DISCUSSIONS

H. pylori infection is considered the most common and controllable risk factor for gastric cancer. Screening and employing appropriate treatment strategies in areas with a high incidence of gastric cancer can effectively reduce its risk, ideally before the occurrence of gastric mucosal atrophy and intestinal metaplasia. Eradication therapy can reduce the risk of gastric cancer and prevent NSAID-induced ulcer in elderly patients. However, the degree of benefit depends on the degree of aging and life expectancy. Due to the decline in physical functions, comorbidities, and the presence of certain combined medications, many older adults have difficulty in following the standard treatment regimen recommended for adults.

Eradication therapy should be used to treat elderly patients only after an adequate risk-benefit assessment. The ideal regimen should be safe and effective, with minimal interaction with other drugs. However, the situation of continuous upgrade of the types and duration of eradication therapy, remains not ideal for the elderly patient. By optimizing the doses, reducing the use of antibiotics, or supplementing complementary drugs, the risk of adverse effects and drug interactions can be effectively reduced. The resurgence of dual therapy, especially the current hot topic, high-dose dual therapy, and vonoprazan, provided new directions. It successfully achieved satisfactory efficacy with fewer medications in normal patients. Further evaluation of its efficacy and safety in elderly patients should be conducted to gather more evidence (e.g., ChiCTR2100045059 in https://www.chictr.org.cn/).

Eradication therapy of *H. pylori* might not benefit all elderly patients. Patients aged >80 years, or those with severe organ function decline, and limited life expectancy, cannot tolerate full dosage and duration of eradication therapy. However, the possible benefits of eradication therapy should not be ignored in case of *H. pylori*-related diseases. Non-antibiotic treatment, typically involving probiotics and natural products that inhibit *H. pylori* activity, might be a complementary and alternative therapy. Several herbal medicines show remarkable anti-*H. pylori* properties (144); however, clinical trials are needed to confirm their effects. In China, integrative medicine is being considered as a new approach for *H. pylori* treatment in older patients, for which, clinical trials are being conducted (e.g., ChiCTR1900028373 in https://www.chictr.org.cn/).

Considering the progress toward an aging society and the high incidence of gastric cancer, more attention needs to be paid to the rational diagnosis and treatment of *H. pylori* infection in the elderly. Elderly patients also need to be finely stratified and

treated with appropriate individualized eradication regimens or non-antibiotic regimens.

AUTHOR CONTRIBUTIONS

QH and XJ studied the literature and drafted the articles. YC participated in writing. XZ and HY identified the topics, analyzed the literature, presented the outlines, reviewed, and approved the publication of the article. All authors read and approved the final version of the manuscript.

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Effect of Poor Nutritional Status and Comorbidities on the Occurrence and Outcome of Pneumonia in Elderly Adults

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Background: Malnutrition and comorbidity are two common geriatric syndromes. The pathology of pneumonia is multifactorial, making its diagnosis and management a great challenge. Hospital-acquired pneumonia (HAP) and community-acquired pneumonia (CAP) are two main types of pneumonia. However, the effect of geriatric syndromes on pneumonia and its prognosis have not been clearly explored.

Methods: We collected the relevant electronic data of inpatients aged over 65 years and diagnosed with pneumonia in the Geriatrics Department Building of the First Affiliated Hospital with Nanjing Medical University between December 2018 and December 2019, and further divided them into HAP group and CAP group. The correlations of age, age-adjusted Charlson Comorbidity Index (aCCI), basic diseases and nutritional indexes (i.e., albumin, electrolyte, hemoglobin) with pneumonia and prognosis were analyzed. We analyzed the associations between infection prognosis/infection level and age, nutritional status, aCCI and underlying diseases, using linear regression model. The box plot was applied to present infection outcome, and the nomogram was built for predicting infection outcomes. We utilized the heat map to show the associations between nutritional status and infection level/outcome in all infected patients, HAP, and CAP.

Results: The final study comprised samples of 669 pneumonia patients divided into HAP group ($n = 517$) and CAP group ($n = 152$). In all patients, the infection outcome was negatively correlated with age ($P = 0.013$). The level of albumin was negatively correlated with infection prognosis in all patients ($P = 0.03$), and negatively correlated with neutrophil count and CRP ($P = 0.008$, $P < 0.001$). ACCI was positively correlated with CRP ($P = 0.003$). The prognosis was negatively associated with age and albumin level. In the patients with basic dementia/Alzheimer's disease and chronic obstructive pulmonary disease/asthma, the prognosis was worse.

Conclusion: There was a correlation between poor nutritional status-related indexes and inflammatory indexes. A poor nutritional status might predict a high risk of pneumonia in elderly adults. Advanced age and comorbidities were risk factors for the occurrence and poor prognosis of pneumonia. Therefore, comorbidities should be well-treated in the elderly with pneumonia.

Keywords: pneumonia, poor nutritional status, comorbidity, outcome, elderly

INTRODUCTION

Around the world, people are living longer and it is estimated that by 2050, the proportion of the world's population over the age of 60 will nearly double, and the total number of elderly people aged 65 or older will reach 3.200 million (1, 2). The elderly, especially those aged over 80 years, are at high risk of chronic diseases. The mortality due to chronic diseases in China is 533/100,000, accounting for 86.6% of the total deaths, far higher than the global average level (3). Older people are more likely to suffer from comorbidities. The concept of the comorbidity (4) was first proposed by Professor Feinstein in the United States in 1970 (5). Comorbidities can be interrelated or concurrent (6). Especially in cases of infectious diseases, comorbidities act as a catalyst in the occurrence and progression of the disease.

Poor nutritional status is a poor health condition that mainly reflects an inadequate supply of nutrients to meet the physical needs of the body. With the increase of age, related psychological and physiological changes, such as comorbidity, loss of appetite, poor oral health, loss of autonomous eating ability, cognitive impairment, reduced organ function and loss of function, lead to insufficient food intake, as well as absorption and metabolism disorders in the elderly (7–9). As a result, poor nutritional status is particularly common among the elderly. A study using the Mini Nutritional Assessment (MNA) found that the prevalence of poor nutritional status was 20% worldwide, 5.8% in the community and 50.5% in clinical and long-term care facilities (10). Another study showed that 25% of older people in communities were at risk of poor nutritional status and 5% were malnourished, and confirmed that poor nutritional status was associated with increased long-term mortality over 10 years (11, 12).Under the condition of poor nutritional status, the body's resistance decreases and it is prone to infection-related diseases. Under the condition of infection, the body's higher nutrient consumption further leads to the aggravation of poor nutritional status, and the two are mutually causal.

Infectious diseases, especially pneumonia, are the most common cause of hospitalization and death among the elderly patients (13, 14). Compared with that in normal adults, the pneumonia in the elderly, especially those with the advanced ages, is more difficult to be diagnosed and treated. Because the clinical symptoms and the examination results are not typical in the elderly, the diagnosis is more likely to miss, false and delay. Infection prolongates the course and worsens the prognosis of disease. Most of the infected elderly people are accompanied by poor nutritional status and underlying diseases, suggesting that comorbidities are potentially related to the occurrence of infection.

Based on elderly patients with clinical symptoms not obvious, inspection and test results not typical, are more likely to happen in diagnosis and misdiagnosis, delay condition, once the merger or poor nutritional status and a variety of basic diseases increased the risk of elderly patients with lung infection, aggravating illness, extend the course of the disease, diagnosis and treatment for the disease cause more trouble, lead to irreversible consequences. At present, the diagnosis and treatment of pneumonia in elderly patients is still a great challenge. Therefore, based on the clinical data of 669 patients with confirmed pneumonia, this study aimed to reveal the correlation between pneumonia in the elderly and nutrition level, comorbidities and different age groups, so as to provide a reference for early active prevention and treatment of risk factors, effective reduction or avoidance of infection, and clinical comprehensive treatment for elderly patients with pneumonia.

METHODS

Study Design and Participants

Patients with pneumonia in the Department of Geriatrics, The First Affiliated Hospital of Nanjing Medical University from December 2018 to December 2019 were consecutively collected. Inclusion criteria: (1) age $\geq$65 years; (2) Clear diagnosis of pneumonia. Exclusion criteria: (1) age $<$65; (2) patients with hormone and immunosuppressive drugs; (3) patients undergoing radiotherapy and chemotherapy. This study was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University. In this retrospective study, we screened inpatients aged over 65 years and diagnosed with pneumonia through the electronic medical record system, and further divided them into HAP group and CAP group. HAP diagnostic criteria strictly followed the international ERS/ESICM/ESCMID/ALAT guidelines for the management of HAP and ventilator-associated pneumonia (VAP) and the Chinese Guidelines for the Diagnosis and Treatment of HAP/VAP in Adults (2018 Edition) (15, 16). The diagnosis of CAP was established according the Chinese Guidelines for Adult CAP (2016 Edition) (17).

Data Collection

The following indicators were collected in this study: white blood cell count (WBC, normal range, 4.0–10.0 $\times 10^9$/L), neutrophil count (normal range, 1.80–6.30 $\times 10^9$/L), neutrophil percentage (normal range, 40–75%), C-reactive protein (CRP, normal range,

TABLE 1 | Baseline infection outcome.

		≤7 days	8–14 days	15–21 days	≥22 days	Death	χ^2/F	*P*
Gender	Male	165 (64.71)	144 (68.9)	61 (64.21)	29 (69.05)	48 (70.59)	1.743	0.783
	Female	90 (35.29)	65 (31.1)	34 (35.79)	13 (30.95)	20 (29.41)		
Age (year)	65–79	71 (27.84)	42 (20.1)	27 (28.42)	12 (28.57)	21 (30.88)	15.257	0.054
	80–89	100 (39.22)	86 (41.15)	31 (32.63)	16 (38.1)	35 (51.47)		
	≥90	84 (32.94)	81 (38.76)	37 (38.95)	14 (33.33)	12 (17.65)		
Albumin (g/L)	<35	171 (67.06)	132 (63.16)	73 (76.84)	32 (76.19)	47 (69.12)	7.104	0.130
	≥35	84 (32.94)	77 (36.84)	22 (23.16)	10 (23.81)	21 (30.88)		
Lymphocyte count (10∧9/L)	<1.1	127 (49.8)	95 (45.45)	49 (51.58)	28 (66.67)	30 (44.12)	7.255	0.123
	≥1.1	128 (50.2)	114 (54.55)	46 (48.42)	14 (33.33)	38 (55.88)		
Hb (g/L)	<130	193 (75.69)	162 (77.51)	69 (72.63)	36 (85.71)	53 (77.94)	3.070	0.546
	≥130	62 (24.31)	47 (22.49)	26 (27.37)	6 (14.29)	15 (22.06)		
aCCI	≤3	16 (6.27)	10 (4.78)	3 (3.16)	0 (0)	4 (5.88)	5.647	0.227
	4	31 (12.16)	25 (11.96)	9 (9.47)	6 (14.29)	6 (8.82)		
	5	45 (17.65)	45 (21.53)	22 (23.16)	9 (21.43)	11 (16.18)		
	≥6	163 (63.92)	129 (61.72)		27 (64.29)	47 (69.12)		
Myocardial infarction	NO	227 (89.02)	199 (95.22)	86 (90.53)	35 (83.33)	58 (85.29)	10.638	**0.031**
	Yes	28 (10.98)	10 (4.78)	9 (9.47)	7 (16.67)	10 (14.71)		
peripheral vascular disease	NO	225 (88.24)	194 (92.82)	88 (92.63)	35 (83.33)	64 (94.12)	6.928	0.140
	Yes	30 (11.76)	15 (7.18)	7 (7.37)	7 (16.67)	4 (5.88)		
cerebrovascular disease/TIA	NO	100 (39.22)	87 (41.63)	27 (28.42)	19 (45.24)	30 (44.12)	6.470	0.167
	Yes	155 (60.78)	122 (58.37)	68 (71.58)	23 (54.76)	38 (55.88)		
Dementia/Alzheimer's disease	NO	183 (71.76)	161 (77.03)	66 (69.47)	28 (66.67)	40 (58.82)	9.174	0.057
	Yes	72 (28.24)	48 (22.97)	29 (30.53)	14 (33.33)	28 (41.18)		
Chronic obstructive pulmonary disease	NO	238 (93.33)	176 (84.21)	86 (90.53)	36 (85.71)	58 (85.29)	11.213	**0.024**
	Yes	17 (6.67)	33 (15.79)	9 (9.47)	6 (14.29)	10 (14.71)		
Diabetes	NO	173 (67.84)	141 (67.46)	61 (64.21)	28 (66.67)	46 (67.65)	Fisher	0.908
	Yes	76 (29.8)	59 (28.23)	29 (30.53)	13 (30.95)	21 (30.88)		
	With organ injuries	6 (2.35)	9 (4.31)	5 (5.26)	1 (2.38)	1 (1.47)		
Moderate/severe chronic kidney disease	NO	206 (80.78)	179 (85.65)	72 (75.79)	35 (83.33)	52 (76.47)	5.700	0.223
	Yes	49 (19.22)	30 (14.35)	23 (24.21)	7 (16.67)	16 (23.53)		
Solid tumors	NO	197 (77.25)	167 (79.9)	74 (77.89)	32 (76.19)	47 (69.12)	Fisher	0.236
	Yes	45 (17.65)	39 (18.66)	18 (18.95)	7 (16.67)	19 (27.94)		
	With multiple metastases	13 (5.1)	3 (1.44)	3 (3.16)	3 (7.14)	2 (2.94)		
Hypertension	NO	76 (29.8)	71 (33.97)	28 (29.47)	13 (30.95)	29 (42.65)	4.689	0.321
	Yes	179 (70.2)	138 (66.03)	67 (70.53)	29 (69.05)	39 (57.35)		
Coronary heart disease	NO	152 (59.61)	136 (65.07)	58 (61.05)	24 (57.14)	35 (51.47)	4.444	0.349
	Yes	103 (40.39)	73 (34.93)	37 (38.95)	18 (42.86)	33 (48.53)		

The bold values mean P < 0.05.

800–8,000 ug/L) and procalcitonin (PCT, normal range, <0.5 ug/L) as inflammatory markers; albumin (normal range, 3.5–5.0 g/dL), electrolyte (calcium, Ca, normal range 1.10–1.34 mmol/L; potassium, K, normal range 3.5–5.5 mmol/L; sodium, Na, normal range 135–145 mmol/L; chlorine, Cl, normal range 95–105 mmol/L), hemoglobin (Hb, 12.0–16.5 g/dL for males, 11.0–15.0 g/dL for females), lymphocyte (normal range, 20–40%) as nutrient related indicators. Blood tests were all taken before anti-infection treatment of pneumonia. And all patients were treated according to guidelines for anti-infective therapy. The outcome of infection was divided into two groups according to whether the infection resulted in death, the death group and the non-death group. The non-death group was further divided into four groups based on the duration of pneumonia control: ≤7 days, 8–14 days, 15–21 days, ≥22 days. Age-adjusted Charlson Comorbidity Index (aCCI) is more widely used than CCI in scoring comorbidities. It incorporates the age of the patient as a correction variable of the final score. It quantifies comorbidities based on the number and severity of diseases a patient can be used to predict the risk of death from the disease (18–20).

The above information was obtained from the Medical Record System of the First Affiliated Hospital of Nanjing Medical University.

Statistical Analyses

Pearson or Spearman correlation analysis was used to calculate the correlation coefficient. Quantitative data in normal distribution between groups was compared by ANOVA.

TABLE 2 | Aging-related risk factors (age, nutrition, and comorbidities) on the outcome of pneumonia in all infected patients.

Duration of infection	Coef	*t*	*P*	95%CI	
Age (year)	−0.21	−2.490	**0.013**	−0.37	−0.04
Albumin (g/L)	−0.29	−2.180	**0.030**	−0.55	−0.03
aCCI	0.08	2.490	**0.013**	0.02	0.15
Myocardial infarction	0.24	1.040	0.298	−0.21	0.70
Peripheral vascular disease	−0.07	−0.320	0.749	−0.51	0.37
Cerebrovascular disease/TIA	−0.06	−0.410	0.685	−0.32	0.21
Hemiplegia	2.12	1.770	0.077	−0.23	4.47
Dementia/Alzheimer's disease	0.33	2.270	**0.024**	0.04	0.61
Chronic obstructive pulmonary disease/Asthma	0.45	2.210	**0.028**	0.05	0.85
Rheumatoid/connective tissue disease	−0.13	−0.280	0.778	−1.00	0.75
Peptic ulcer	0.07	0.090	0.925	−1.41	1.56
Diabetes	−0.02	−0.150	0.882	−0.25	0.22
Moderate/severe chronic kidney disease	0.28	1.660	0.098	−0.05	0.61
Liver disease	0.11	0.280	0.777	−0.66	0.88
Solid tumor	0.12	0.980	0.327	−0.12	0.36
Lymphoma	0.50	1.280	0.200	−0.27	1.27
Hypertension	−0.17	−1.230	0.218	−0.44	0.10
Coronary heart disease	0.11	0.800	0.424	−0.16	0.38

The bold values mean P < 0.05.

TABLE 3 | Correlation of age-related risk factors (age, nutrition, and comorbidities) in Neutrophils count in all infected patients.

Neutrophils count (10^9/L)	Coef	*t*	*P*	95%CI	
Age (year)	0.02	0.120	0.907	−0.38	0.43
Albumin (g/L)	−0.89	−2.650	**0.008**	−1.55	−0.23
aCCI	0.19	2.340	**0.020**	0.03	0.35
Myocardial infarction	0.69	1.190	0.236	−0.45	1.83
Peripheral vascular disease	0.49	0.870	0.386	−0.62	1.60
Cerebrovascular disease/TIA	−0.16	−0.460	0.644	−0.83	0.51
Hemiplegia	5.35	1.780	0.075	−0.55	11.25
Dementia/Alzheimer's disease	0.35	0.950	0.343	−0.37	1.06
Chronic obstructive pulmonary disease/Asthma	0.15	0.300	0.766	−0.85	1.16
Rheumatoid/connective tissue disease	0.83	0.750	0.456	−1.35	3.01
Peptic ulcer	1.74	0.920	0.358	−1.98	5.47
Diabetes	0.14	0.470	0.636	−0.45	0.73
Moderate/severe chronic kidney disease	0.00	0.000	0.998	−0.83	0.83
Liver disease	1.09	1.100	0.270	−0.85	3.03
Solid tumor	0.47	1.500	0.133	−0.14	1.07
Lymphoma	−1.28	−1.230	0.218	−3.31	0.76
Hypertension	0.72	2.060	**0.040**	0.03	1.40
Coronary heart disease	−0.11	−0.310	0.754	−0.78	0.57

The bold values mean P < 0.05.

Kruskal-Wallis test was used to compare the quantitative data not in normal distribution. Pearson chi-square test or Fisher's exact probability method was used to compare the classification data between groups. Linear regression model was used to analyze the association between infection prognosis/infection level and age, nutritional status, aCCI and underlying diseases. Logistic regression model was used for prediction, and stepwise screening strategy was used for basic diseases, nutritional indexes and inflammatory indexes. We also calculated AUC and draw ROC curve and Nomogram for risk assessment.

All analyses were conducted using the Stata (13.0) and R (3.6.1), and $P < 0.05$ was set as statistically significant.

RESULTS

Baseline Clinical Characteristics

Among the 669 patients, 486 (72.65%) were men with the average age of 84.87 ± 8.49 years. Their average aCCI was 6.34 ± 1.97, and 42.60% received anti-infection treatment of ≤7 days, 28.91% of 8–14 days, 13.14% of 15–21 days, 5.81% of ≥22

TABLE 4 | Correlation of age-related risk factors (age, nutrition, and comorbidities) in CRP in all infected patients.

CRP	Coef	*t*	*P*	95%CI	
Age (year)	−1.95	−0.650	0.518	−7.89	3.98
Albumin (g/L)	−16.73	−3.550	**<0.001**	−25.99	−7.47
aCCI	3.28	2.940	**0.003**	1.09	5.48
Myocardial infarction	−2.91	−0.340	0.737	−19.93	14.11
Peripheral vascular disease	−4.46	−0.610	0.539	−18.72	9.80
Cerebrovascular disease/TIA	5.90	1.220	0.223	−3.60	15.41
Hemiplegia	23.88	0.750	0.456	−38.99	86.75
Dementia/Alzheimer's disease	−1.62	−0.320	0.752	−11.71	8.46
Chronic obstructive pulmonary disease/Asthma	4.89	0.710	0.481	−8.74	18.52
Rheumatoid/connective tissue disease	10.17	0.670	0.505	−19.80	40.13
Peptic ulcer	29.41	0.930	0.355	−33.06	91.88
Diabetes	2.22	0.530	0.597	−6.01	10.44
Moderate/severe chronic kidney disease	−1.50	−0.250	0.802	−13.24	10.25
Liver disease	4.52	0.280	0.780	−27.31	36.35
Solid tumor	15.45	3.560	**<0.001**	6.92	23.97
Lymphoma	25.45	1.850	0.065	−1.61	52.51
Hypertension	3.01	0.610	0.543	−6.71	12.72
Coronary heart disease	−6.87	−1.440	0.151	−16.26	2.52

The bold values mean P < 0.05.

days and 9.54% of death. There was no significant difference in sex, age, aCCI, and most underlying diseases between the two groups ($P > 0.05$). Patients with myocardial infarction had significantly escalated risks of negative outcomes compared with those without ($P = 0.031$). Chronic obstructive pulmonary disease is another important factor related to infection outcome ($P = 0.024$) (**Table 1**).

Correlations of Infection With Age and Nutritional Status

Among all patients, the infection outcome was negatively correlated with age ($P = 0.013$). The level of albumin was negatively correlated with infection prognosis in all patients ($P = 0.03$) (**Table 2**), and negatively correlated with neutrophil count and CRP ($P = 0.008$, $P < 0.001$) (**Tables 3**, **4**).

Correlations of Infection With aCCI and Underlying Diseases

Among all patients, the infection outcome was negatively correlated with aCCI ($P = 0.013$) (**Table 2**). aCCI was positively correlated with neutrophils count and CRP ($P = 0.02$, $P = 0.003$) (**Tables 3**, **4**).

Prognosis varies among patients with different underlying diseases. Among all patients, the severity of infection outcome was positively correlated with dementia/Alzheimer's disease ($P = 0.024$), chronic obstructive pulmonary disease/asthma ($P = 0.028$) (**Table 2**).

Figure 1 shows the correlation between underlying disease and infection outcome. Chronic obstructive pulmonary disease (correlation coefficient = 0.0868, $P < 0.05$) and dementia/Alzheimer's disease (correlation coefficient = 0.0589, $P < 0.05$) were positively associated with infection outcome.

Associations Between Nutritional Status, Infection Level, and Pneumonia

The correlation coefficient matrix was shown by the heat map (**Figure 2**). The red region denotes a high positive correlation, and the blue region indicates a negative correlation. In all infected patients, HAP, and CAP groups, there was an obvious correlation between nutrition-related indicators and inflammatory indicators.

To understand the correlations between the variables and infection, we used the correlation coefficient considering the whole population of interest (**Figure 3**).

In all infected patients, age was positively correlated with leukocyte level and neutrophil count ($P < 0.05$), but had no statistical significance with CRP, PCT, and neutrophil percentage.

In nutritional markers, albumin was negatively correlated with all inflammatory markers (CRP, PCT, leucocyte level, neutrophil percentage, and neutrophil count). Different types of electrolytes had different associations with specific inflammatory markers, especially Na and Ca. Na was negatively correlated with CRP and positively correlated with WBC and neutrophil count. Ca was negatively correlated with CRP and neutrophil percentage, and there was no statistically significant relationship between other electrolytes and inflammatory indicators ($P < 0.05$).

Indicators of the severity of comorbidity: aCCI was positively correlated with CRP, WBC, neutrophil count, and percentage of neutrophils ($P < 0.05$).

Predictive Model for the Infection Outcomes

Based on logistic, dichotomous and sequentially screened analyses, a nomogram incorporating the seven risk factors was

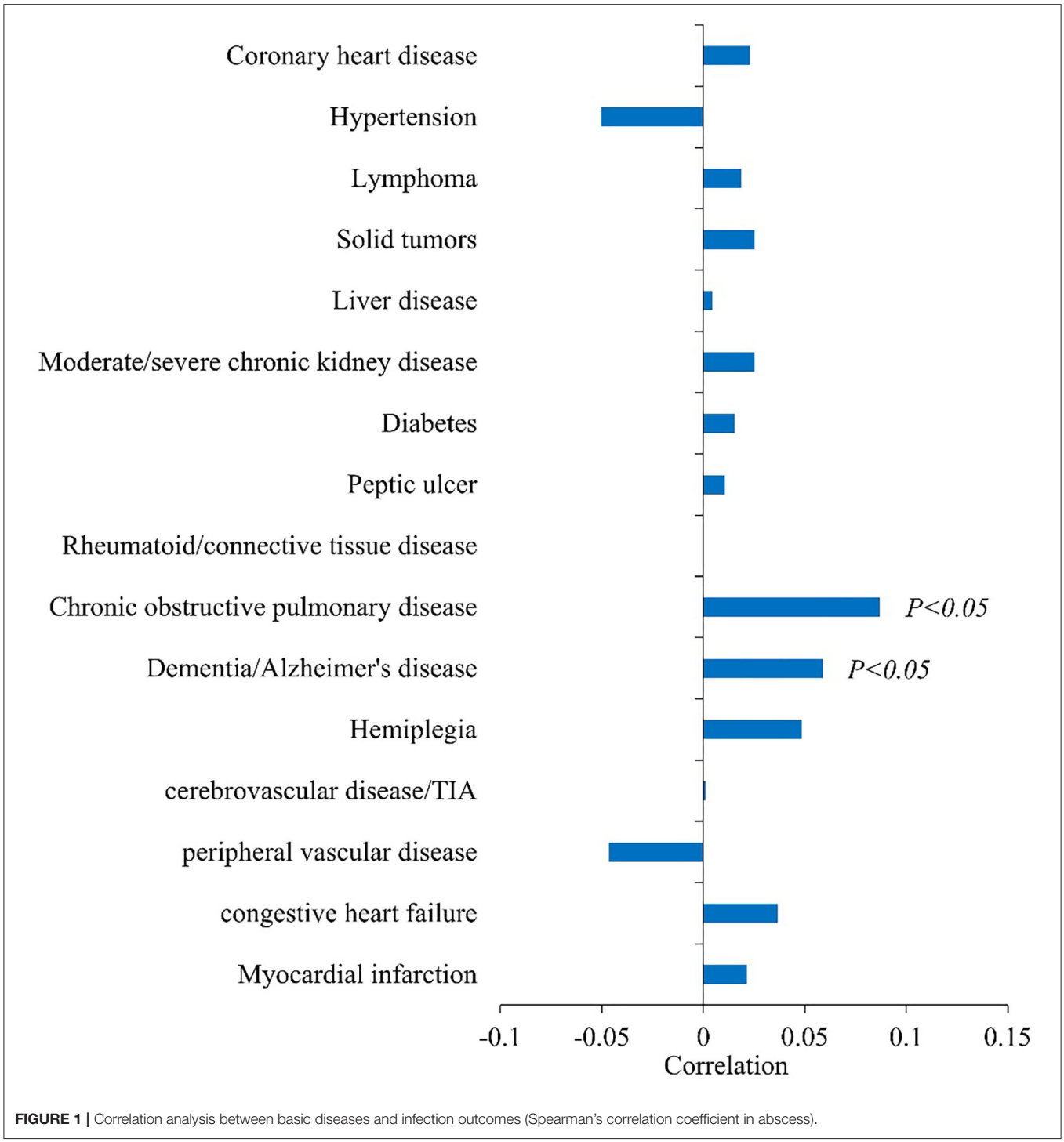


FIGURE 1 | Correlation analysis between basic diseases and infection outcomes (Spearman's correlation coefficient in abscess).

built for predicting infection outcome (**Figure 4**). Discrimination was performed by ROC curves.

Of all those infected, a total score was calculated with the use of lymphocyte percentage, lymphocyte count, albumin, Cl, and chronic obstructive pulmonary disease. The area under the curve (AUC) was 0.6300. In the HAP group, we selected myocardial infarction, albumin, Cl, and chronic obstructive pulmonary disease as risk factors that collaboratively achieved an AUC of 0.6219. In the CAP group, we used Ca, Cl, lymphocyte count and myocardial infarction to calculate the total score, achieving an AUC of 0.6066.

DISCUSSION

According to the World Health Organization, 450 million people, or 7 percent of the global population, are diagnosed with

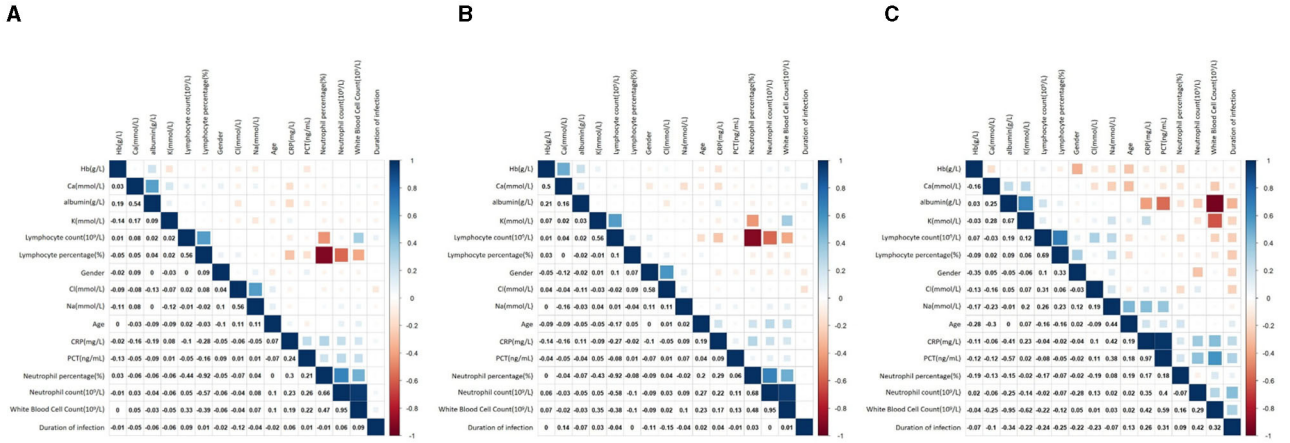


FIGURE 2 | Heat map of correlation analysis. **(A)** Associations between nutritional status, infection levels and pneumonia in all infected patients. **(B)** Associations between nutritional status, infection levels and pneumonia in HAP. **(C)** Associations between nutritional status, infection levels and pneumonia in CAP.

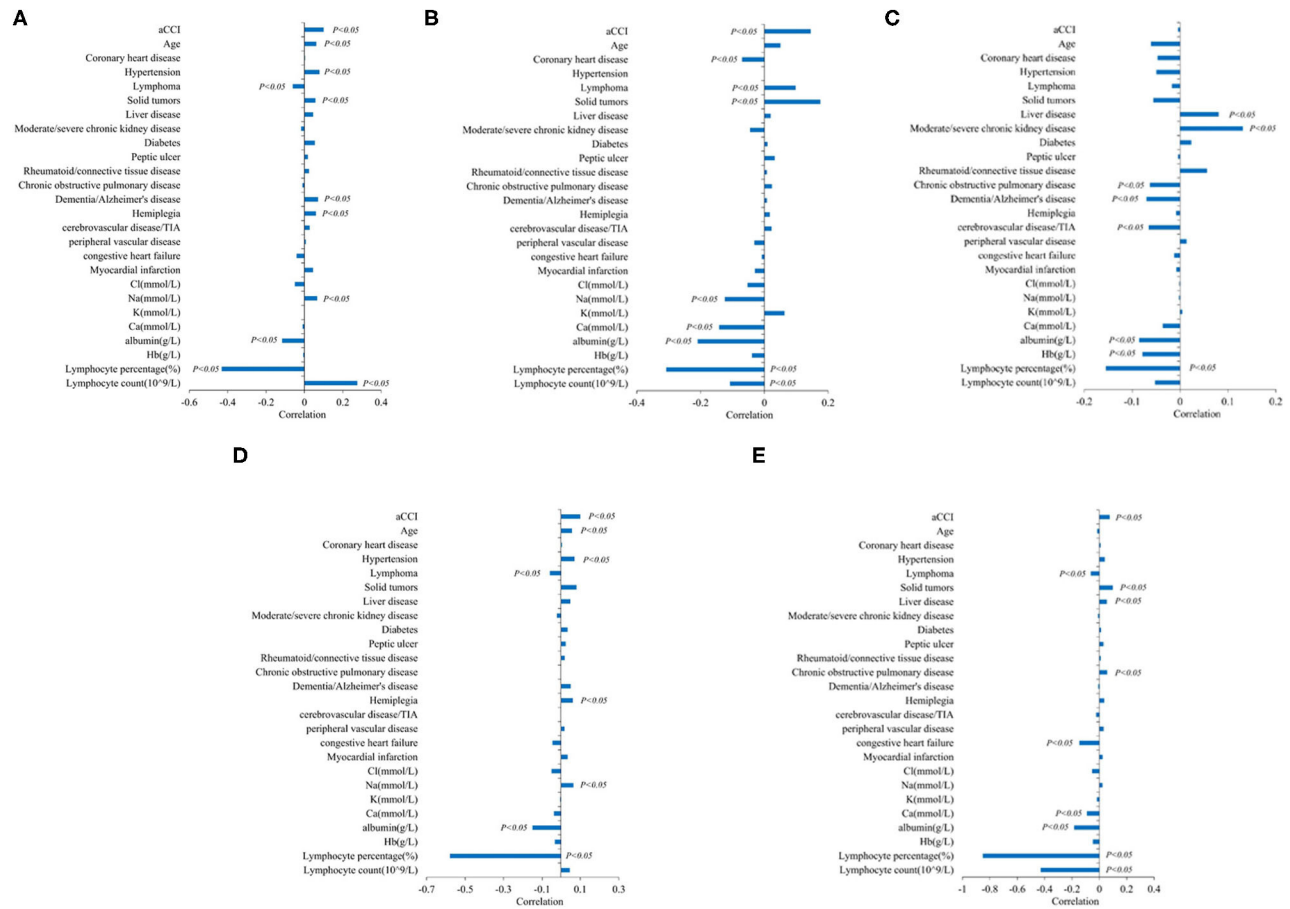


FIGURE 3 | Correlation analysis of aging-related risk factors and infection. **(A)** Correlation analysis of aging-related risk factors and white blood cell level. **(B)** Correlation analysis of aging-related risk factors and CRP. **(C)** Correlation analysis of aging-related risk factors and PCT. **(D)** Correlation analysis of aging-related risk factors and neutrophils count(10^9/L). **(E)** Correlation analysis of aging-related risk factors and neutrophils percentage (%).

pneumonia each year, and about 4 million people die from it (21). The elderly are more likely to suffer from this disease because of their declined organ function, aging immune system, basic diseases, poor nutrition and other abnormalities. In addition, compared with that in normal adults, pneumonia in the elderly brings higher medical costs and worse clinical outcomes. Severe

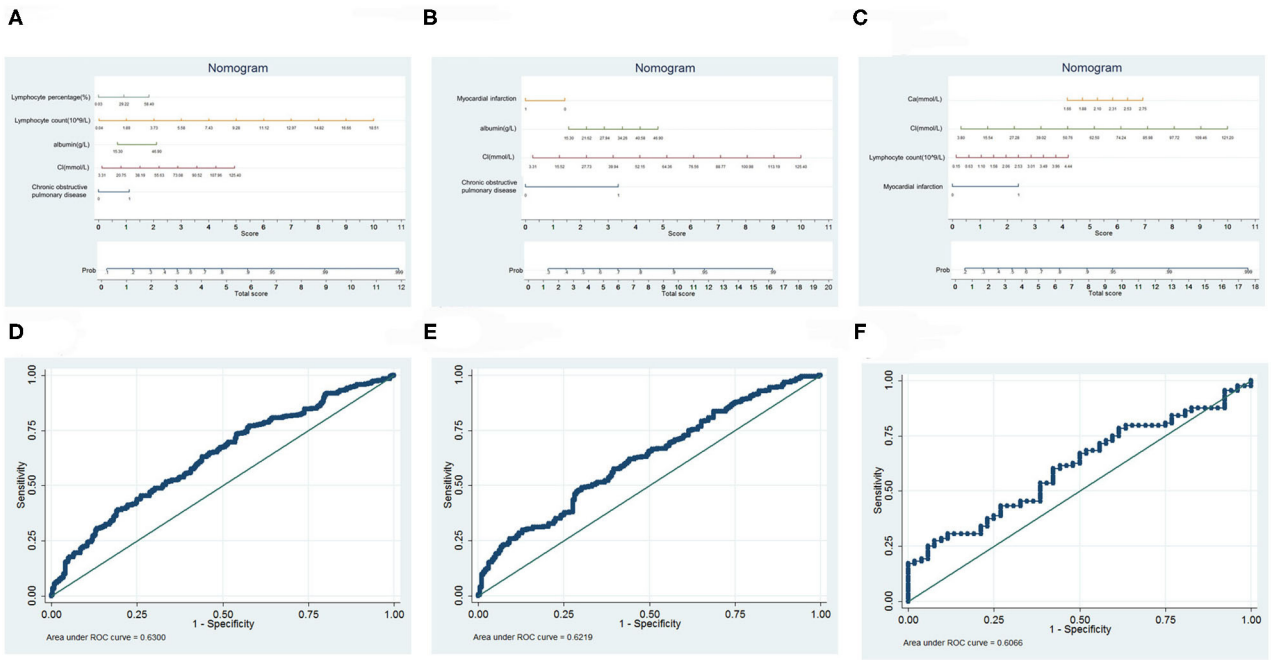


FIGURE 4 | Prediction model of infection outcome. **(A)** Nomogram of all infected patients. **(B)** Nomogram of HAP. **(C)** Nomogram of CAP. **(D)** ROC curves of all infected patients. **(E)** ROC curves of HAP. **(F)** ROC curves of CAP.

cases may demonstrate multiple organ dysfunction syndrome (MODS), respiratory and circulatory failure, even death (22, 23). Pneumonia has become one of the leading causes of death in the elderly (24). This study found that pneumonia in the elderly was correlated with nutrition status, basic diseases and age, providing a reference for clinical comprehensive treatment.

Some elderly patients with pneumonia show signs of loss of appetite, listlessness, etc. Reduced nutrient intake leads to poor nutritional status and aggravates infection in elderly patients (25). Poor nutritional status damages respiratory function, thus impairing immune function and increasing pneumonia (26, 27). Adequate nutrition can enhance respiratory muscle function and immune defense (28, 29). Therefore, nutritional intervention can control disease progression and improve respiratory function, thus reducing morbidity and mortality (30), hospitalization costs, and re-hospitalizations (31, 32). Albumin level below 3.5 mg/dL suggests a poor nutritional status and survival (33). There is a correlation between pneumonia and albumin level in elderly patients. Therefore, albumin level <3.5 mg/dL is a risk factor for the occurrence and poor prognosis of pneumonia in elderly patients.

Poor nutritional status is a common comorbidity of the elderly, and it interacts with other basic diseases. In this study, elderly patients with pneumonia were further divided into HAP and CAP groups. It was found that for both CAP and HAP patients, nutritional status was a risk factor for the occurrence and prognosis of pneumonia, compared with other underlying diseases. Common underlying diseases have an impact on nutrition include diabetes, COPD, cerebrovascular disease, hemiplegia, dementia, peptic ulcer, moderately severe chronic kidney disease, liver disease (34). Nutritional status differs across regions (35, 36). In addition to albumin and some others biochemical indicators, the Mini Nutritional Assessment Table (MNA) and MNA-SF (Short Form MNA) are fast and reliable methods for assessing the nutritional status of the elderly (37–42). Nutritional screening and targeted nutrition education should be carried out to reduce the incidence of poor nutritional status and pneumonia in the elderly.

Multiple underlying diseases also predispose the elderly to pneumonia, such as cerebral infarction, cerebral hemorrhage and other cerebrovascular diseases and left swallowing dysfunction. Esophageal tracheal fistula can also cause aspiration pneumonia, which is the most common pneumonia in the elderly (43). Patients with sequelae of cerebral infarction (such as hemiplegia) are prone to pneumonia, because of mobility difficulties and long-term bed rest. Patients with COPD have a higher susceptibility to respiratory infections (44, 45). In this study, the course of pneumonia was significantly prolonged in patients with COPD, dementia, cerebrovascular disease, and hemiplegia. Similarly, tumor was also identified as a risk factor for pneumonia in the elderly patients. It may be due to the decline of immunity after the use of hormones, immunosuppressants, or chemotherapy (46, 47).

At the end of the study, a model to predict the duration of pneumonia in elderly patients based on common nutritional indicators and basic diseases was obtained, which is feasible, simple and convenient, and suitable for the evaluation of clinical conditions of ordinary patients. The model can predict the course of disease and adjust the diagnosis and treatment plan in time to avoid increasing the burden of disease. However, due to the small

number of model parameters, the guiding significance to clinical needs to be further confirmed and strengthened.

This study is a retrospective study and has its limitations. A correlation analysis was performed only for the available outcomes in elderly patients with pneumonia during hospitalization. In the future, we will design and do more rigorous and scientific prospective study to investigate more relevant nutritional indicators, such as nutritional assessment scale, index of body examination and the clinical biochemistry, bioelectrical impedance analysis (BIA), and conduct long-term follow-up of patients' nutritional status, such as retreatment or readmission after discharge. Thus, we believe that our further results can provide a more intuitive and reliable reference for nutritional intervention of elderly patients with pneumonia.

CONCLUSIONS

Both for HAP and CAP patients, advanced age and comorbidities are risk factors for the occurrence and outcome of pneumonia in the elderly. Poor nutritional status and COPD have significant effects on the severity and course of pneumonia in the elderly, and can be used as risk factors to predict the risk and prognosis of pneumonia. The disease should be managed with anti-infection treatment, but also efforts to prevent poor nutritional status and comorbidities.

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BC designed the study and statistical analysis, interpreted the data, and drafted the manuscript. WL and YC collected the epidemiological and clinical data, interpreted the data, and drafted the manuscript. QS, ML, HZ, and WZ contributed to the data analysis and interpretation and revised the manuscript. JW and ZP designed the study, interpreted the data, and revised the manuscript. All authors approved the final version of the manuscript.

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Reliability and Validity of the Function Impairment Screening Tool in Chinese Older Adults

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Background: Physical function gradually decreases with age in older adults, affecting their independence and quality of life and leaving them prone to adverse outcomes. Despite the importance of assessing function for older adults, most studies have focused on disability and paid less attention to functional impairment. Thus, given the lack of valid and practical methods for evaluating functional impairment for older adults, we developed the function impairment screening tool (FIST) using the Delphi method.

Objective: This study aimed to evaluate the reliability and validity of the FIST in Chinese older adults.

Methods: A total of 489 participants aged 60 years or older, and who had completed the FIST were included. A subgroup of 50 participants completed the FIST a second time, 1 week after the first round, and the test–retest reliability was evaluated using the intraclass correlation coefficient (ICC). Reliability was tested using Cronbach's alpha. Validity was examined using exploratory factor analysis. Criterion-related validity was assessed using correlations between the FIST and the Barthel Index activities of daily living (ADL), Lawton, and Brody instrumental activities of daily living (LB-IADL).

Results: The Cronbach's alpha coefficient for the FIST was 0.930 ($P < 0.001$). The test–retest reliability was good, with an ICC of 0.928 (95% confidence interval [0.874, 0.960]). Exploratory factor analyses revealed one factor accounting for 60.14% of the scale's variance and the load values of every item were >0.4 (0.489–0.872). The correlation coefficient was 0.572 ($P < 0.001$) between the FIST score and ADL, and was 0.793 ($P < 0.001$) between the FIST score and IADL. The FIST score was positively correlated with walking speed ($r = 0.475$, $P < 0.001$) and grip strength ($r = 0.307$, $P < 0.001$), and negatively correlated with age ($r = -0.588$, $P < 0.001$) and Fried frailty phenotype ($r = -0.594$, $P < 0.001$).

Conclusion: The FIST is a reliable and valid instrument for assessing physical function impairment in older adults.

Keywords: functional impairment, reliability, validity, screen, older adults

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INTRODUCTION

Physical function gradually decreases with age in older adults, affecting their independence and quality of life, leaving older adults more vulnerable to adverse outcomes such as falls, hospitalization, and death (1–3). Declining function increases the cost of public healthcare systems and imposes the burden of additional care on families (4). In 2020, the Chinese population aged 60 or above was 264.02 million, accounting for 18.7% of the country's total population (5). Currently, China faces an enormous healthcare challenge. The World Health Organization (WHO) defined "healthy aging" as a process of maintaining functional ability to enable wellbeing in older age (6). The disease concept is increasingly being replaced by the concept of functional consequences in geriatric medicine (7). The original conceptual model on disability was proposed by Nagi. In his model, disability was defined as having problems in activities of daily life (ADL) (8). In 2001, WHO redefined disability by the International Classification of Functioning, Disability, and Health (ICF). Disability is an umbrella term, involving impairments, activity limitations, and participation restrictions (9). WHO developed Disability Assessment Schedule-3.6 for assessing disability which had very good psychometric properties (10). The frequently used tools for disability were Barthel Index (BI), Lawton and Brody instrumental activities of daily living (LB-IADL), and Katz Index (KI) (11). Physical function encompasses all body functions, activities, and participation (12). Physical function impairment is generally considered to occur earlier in the process of disability (13). Early identification and intervention are of great importance. Therefore, it is especially important to assess the functional status of older adults, as interventions for function impairment can prevent or delay the occurrence of disability and adverse events and promote healthy aging.

However, most previous studies have focused on disability (14–16), while paying less attention to the early stage of disability, that is, functional impairment. This may be attributable to the lack of valid tools to assess functional impairment in older adults. Though there were basic activities of daily living (BADL) and IADL for evaluating the performance in activities of daily living, but the BADL and IADL had low sensitivity for detecting mild function deficits. The advanced activities of daily living (AADL) can assess more complex functional performance, but some items of AADL were not suited to Chinese older adults; go to church, for example (17). We developed the function impairment screening tool (FIST) for Chinese older adults using the Delphi method (18, 19).

The FIST contains 16 items, divided into three domains: ability to perform activities of daily living, ability to engage in domestic life, and ability to engage in social activities (19). The FIST is a self-reported questionnaire, and it is low-cost and easy to use. Meanwhile, the FIST meets the definition of physical function, while avoiding the ceiling effect. However, there has been no formal psychometric evaluation of the FIST. This study aimed to evaluate the validity and reliability of the FIST in Chinese older adults.

METHODS

Participants

Participants aged 60 years or older were recruited from the inpatient department at the Department of Geriatrics at Xuanwu Hospital, Capital Medical University. Exclusion criteria included a Mini-Mental State Exam (MMSE) score <23 (20) and a BI score <40. Based on the criteria, 500 older adults were enrolled in the study. The study was approved by the Ethics Committee of Xuanwu Hospital Capital Medical University, and was registered, number: ChiCTR1900028382. All participants agreed to be included in the study and provided their written informed consent before participation.

Data Collection

Demographic characteristics and history of chronic diseases were collected for all participants by geriatricians or postgraduate students. All of the data gatherers were trained using standardized procedures on assessment a week before the study. ADL and IADL were assessed using the BI (21) and LB-IADL (22), respectively. Cognitive function was assessed *via* MMSE (20). We assessed frailty using the Fried frailty phenotype including weakness, slowness, exhaustion, inactivity, and weight loss (23). Weakness was assessed by measuring the dominant maximal grip strength according to standardized procedures. We used a hand dynamometer (EH101; Camry, Guangdong Province, China) to measure the grip strength. Participants sat in an upright position with the arm in adduction and the elbow flexed at 90 degrees (24). Two tests were carried out for the dominant hand, with a 1-min interval between two tests. We recorded the maximal grip strength of the two tests. Slowness was assessed by performing the 4-m walking test. A 4-m line was marked on the ground, and participants were asked to walk at their usual speed. Every participant was tested twice, and the shorter time was recorded (25). The cutoff values for grip strength and walking speed were derived from previous reports in Chinese older populations (26, 27). The total score of the Fried frailty phenotype is 5. Older adults with a score ≥ 3 were classified as "frail," those with 0 were considered "robust," and scores 1–2 indicated "prefrail."

Function Impairment Screening Tool

The FIST is a self-report questionnaire for assessing physical function in older adults. The FIST contains 16 items, divided into three domains: ability to perform activities of daily living (including eating, washing, going to toilet, dressing, moving in and out of bed, and bathing), ability to engage in domestic life (including housekeeping, handling finances, handing medications, lifting 5 kg of weight, and up and down stairs), and ability to engage in social activities (including using transportation, shopping, walking for 250 m, using telephone, and physical exercise) (19). Each item has three levels—independence, partial dependence, and complete dependence—and is scored as 1, 0.5, and 0, respectively. The total score range for all 16 questions is 0 to 16; higher score indicates better physical function (19).

Statistical Analysis

The data were analyzed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). The figures were drawn using GraphPad Prism version 7.0 software (GraphPad Software Inc., CA, USA). Quantitative variables were described as mean with standard deviation (±SD), and categorical variables were described as the number with percentages (%). The overall scale reliability was tested using Cronbach's alpha coefficient. Meanwhile, we also calculated item-to-total correlations (ITTC) the split-half coefficient, and the Guttman split-half coefficient. Internal Consistency Reliability and split-half testing measure reliability. The ITTC is a measure of the reliability of a multi-item scale and evaluates the correlation between an individual item and the total score without that item. An acceptable value should be >0.50 (28). Total score test–retest reliability was assessed by two-way random intraclass correlation coefficients (ICC) for absolute agreement. An indication of good reliability was values of ICC $\geq$ 0.7, and excellent reliability was indicated by ICC $\geq$ 0.9 (29). We also plotted the difference of scores between the test–retest measures using the Bland and Altman plot (30). The Bland and Altman plot is a graphical method to evaluate a bias and compare two measurements of the same variable. The construct validity was calculated by exploratory factor analysis (EFA). The EFA was run using the principal components analysis. The number of factors retained was based on the scree test (31, 32). An item was retained if its factor loading was >0.40. As the total score of FIST was non-normal distribution, the criteria validity of the FIST was measured using Spearman's correlation coefficient with the FIST and ADL, IADL scores. The absolute value of Spearman's correlation coefficient was used, for which <0.5, >0.7, and 0.5–0.7 mean weak correlation, strong correlation, and moderate correlation, respectively (33). Furthermore, we calculated the correlation between FIST score and age, physical performance, and physical frailty for exploring some related factors. All statistical tests were two-tailed, and a P of <0.05 was considered statistically significant.

We calculated sample size using subject-to-item ratios, allowing for a minimum of a 20:1 subject-to-item ratio (34). The minimum sample size was 320 subjects with a total of 16 items. The number of participants was greater than the number required (34, 35). We calculated the sample size of test–retest based on the COSMIN standards (36). We set an ICC value of 0.85 as a priori for the optimal target level of reliability. The minimal sample size was 35 and was calculated using two repeated measures with a confidence interval (CI) of 0.2. We evaluated the test–retest reliability with 50 older adults, which was greater than the above minimal sample size (37).

RESULTS

In total, 500 participants were enrolled from Jan 2020 to Mar 2021, 11 older adults declined to participate. A total of 489 older participants were included in the final analysis. The average age of participants was 74.01 (±9.60) years. Two hundred eighty-three (57.87%) of the participants were male. The mean FIST total score for all of the participants was 14.15 (±3.25). The mean ADL and IADL scores were 91.43 (±14.33) and 7.18 (±1.78), respectively. The mean values of grip strength and walking speed were 27.07 (±9.81) kg and 0.89 (±0.30) m/s, respectively. The demographic characteristics and chronic disease data of the participants are shown in **Table 1**.

TABLE 1 | Characteristics of study participants.

Characteristic	Total (N = 489)
Age, years	74.01 ± 9.60
Gender	
Male	283 (57.87)
Female	206 (42.13)
Marital status	
Never married	2 (0.41)
Married	391 (79.96)
Divorced/Separated	8 (1.63)
Widowed	88 (18.00)
Education level	
Illiteracy	13 (2.66)
Primary school	53 (10.84)
Middle school	178 (36.40)
Senior High school	126 (25.77)
University	105 (21.47)
Post-graduate	14 (2.86)
BMI, kg/m^2	25.37 ± 3.70
Chronic diseases	
Hypertension	372 (76.07)
Coronary heart disease	188 (38.45)
Diabetes mellitus	183 (37.42)
Cerebrovascular disease	108 (22.09)
Chronic kidney disease	59 (12.07)
Osteoarthropathy	141 (28.83)
SBP, mmHg	137.05 ± 18.02
DBP, mmHg	73.95 ± 11.48
FIST score	14.15 ± 3.25
IADL score	7.18 ± 1.78
ADL score	91.43 ± 14.33
MMSE score	27.64 ± 2.66
Grip strength, kg	27.07 ± 9.81
Walking speed, m/s	0.89 ± 0.30

Continuous variables are expressed as mean ± SD and categorical variables are expressed as frequency (%).
ADL, Activity of Daily Living; BMI, Body Mass Index; DBP, diastolic blood pressure; FIST, function impairment screening tool; IADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination; SBP, systolic blood pressure.

Reliability

We calculated the internal consistency reliability using the Cronbach coefficients. The Cronbach's alpha coefficient of the FIST total score was 0.930 (**Table 2**), and the split-half coefficient and Guttman split-half coefficient were 0.924 and 0.881, respectively (**Table 3**). A subgroup of 50 participants completed the FIST a second time after 1 week. The two-way random ICC test–retest reliability was 0.928 (P < 0.001; **Table 4**).

TABLE 2 | Scale overall reliability.

Items	Corrected item-to-total correlation (CITC)	Cronbach's alpha if item deleted
Ability of daily living		
Eating	0.541	0.931
Washing	0.655	0.928
Going to toilet	0.781	0.926
Dressing	0.707	0.927
Moving in and out of bed	0.778	0.926
Bathing	0.828	0.922
Ability of domestic life		
Housekeeping	0.751	0.923
Handling finances	0.805	0.921
Handling medications	0.745	0.923
Lifting 5 kg of weight	0.753	0.924
Up and down stairs	0.767	0.923
Ability of social activities		
Using transportation	0.851	0.920
Shopping	0.875	0.919
Walking for 250 m	0.463	0.943
Using telephone	0.642	0.928
Physical exercise	0.596	0.929

TABLE 3 | Internal consistency reliability and split-half reliability of the FIST scale and each factor.

	Internal consistency reliability coefficient	Split-half reliability coefficient	Guttman split-half coefficient
Total scale	0.930	0.924	0.881
Ability of daily living	0.929	0.952	0.945
Ability of domestic life	0.892	0.779	0.745
Ability of social activities	0.781	0.771	0.634

TABLE 4 | ICC coefficient for test–retest reliability of FIST total score.

	ICC	95%CI	*F*-test with true value 0			
			Value	df1	df2	*P*-value
Single measures	0.928	0.874–0.960	29.09	49	49	<0.001
Average measures	0.963	0.933–0.979	29.09	49	49	<0.001

CI, confidence interval; ICC, intraclass correlation coefficient.

The mean change of FIST scores and its 95% CI between test and retest were presented in the Bland–Altman plot (**Figure 1**).

Validity

Exploratory factor analysis was used to calculate construct validity. The Kaiser–Meyer–Olkin (KMO) measure of sampling adequacy was 0.917, and the Bartlett's test of sphericity (BTS) was 7,904.477 ($P < 0.001$), which indicated that the data were suitable for factor analysis. Exploratory factor analyses revealed one factor accounting for 60.14% of the scale's variance, and the load values of every item were >0.4 (0.489–0.872; **Table 5**).

Criterion-related validity was assessed by Spearman's correlation between the FIST and ADL, IADL. The correlation coefficient was 0.572 ($P < 0.001$) between the FIST scores with ADL and 0.793 ($P < 0.001$) between the FIST scores and IADL (**Figure 2**). Based on the absolute value of Spearman's correlation coefficient, the FIST had a moderate correlation with ADL and a strong correlation with IADL.

Figure 3 shows the correlation between the FIST score with age, physical performance, and physical frailty. The FIST score was positively correlated with walking speed ($r = 0.475$, $P < 0.001$) and grip strength ($r = 0.307$, $P < 0.001$) and negatively correlated with age ($r = -0.588$, $P < 0.001$) and the Fried frailty phenotype ($r = -0.594$, $P < 0.001$; **Figure 3**).

DISCUSSION

To evaluate the physical functional status in Chinese older adults, we developed the FIST using the Delphi method. The present study validated the new tool in Chinese older adults and showed that FIST was a reliable instrument to assess physical function impairment.

We previously developed a scale item pool based on a literature review and formed a preliminary scale through a two-round Delphi expert consultation (18). Next, the preliminary scale was used with older participants, and the FIST scale was developed using classical statistical methods (19). The FIST scale contains 16 items that belong to three domains of functional ability (ability to perform activities of daily living, ability to engage in domestic life, and ability to engage in social activities).

The instrument's reliability is the degree of measurement accuracy, and we evaluated the reliability of the FIST in three ways: internal consistency reliability, split-half reliability, and test–retest reliability. The internal consistency reliability and split-half reliability of the FIST were excellent. The Cronbach's alpha for the FIST was 0.930, and the split-half reliability was 0.924, meeting the recommended value range 0.70–0.95 (29, 38). These results were similar to those of other functional instruments. The internal consistency for the AADL overall scale was 0.80 in older adults in Brazil (17). The Cronbach's alpha coefficient of the Frenchay Activities Index was 0.83 in non-stroke older participants, 0.78 in pre-stroke participants, and 0.87 in post-stroke participants (39). Internal consistency reliabilities for the functional status questionnaire six subscales (basic ADL, intermediate ADL, mental health, work performance, social activity, quality of interaction) ranged from 0.64 to 0.82 in 1,153 outpatients (40). The test–retest reliability of the FIST scale was 0.928, which exceeded the recommendation (>0.75) (29, 41). The retest result was an ICC of 0.928, indicating that the FIST was stable. Thus, the FIST scale shows good reliability.

Exploratory factor analysis showed that FIST has good construct validity; the factor loading values of the 16 items were all >0.40, and the contribution rate of a common factor was 60.14%. In the exploratory factor analysis, according to the

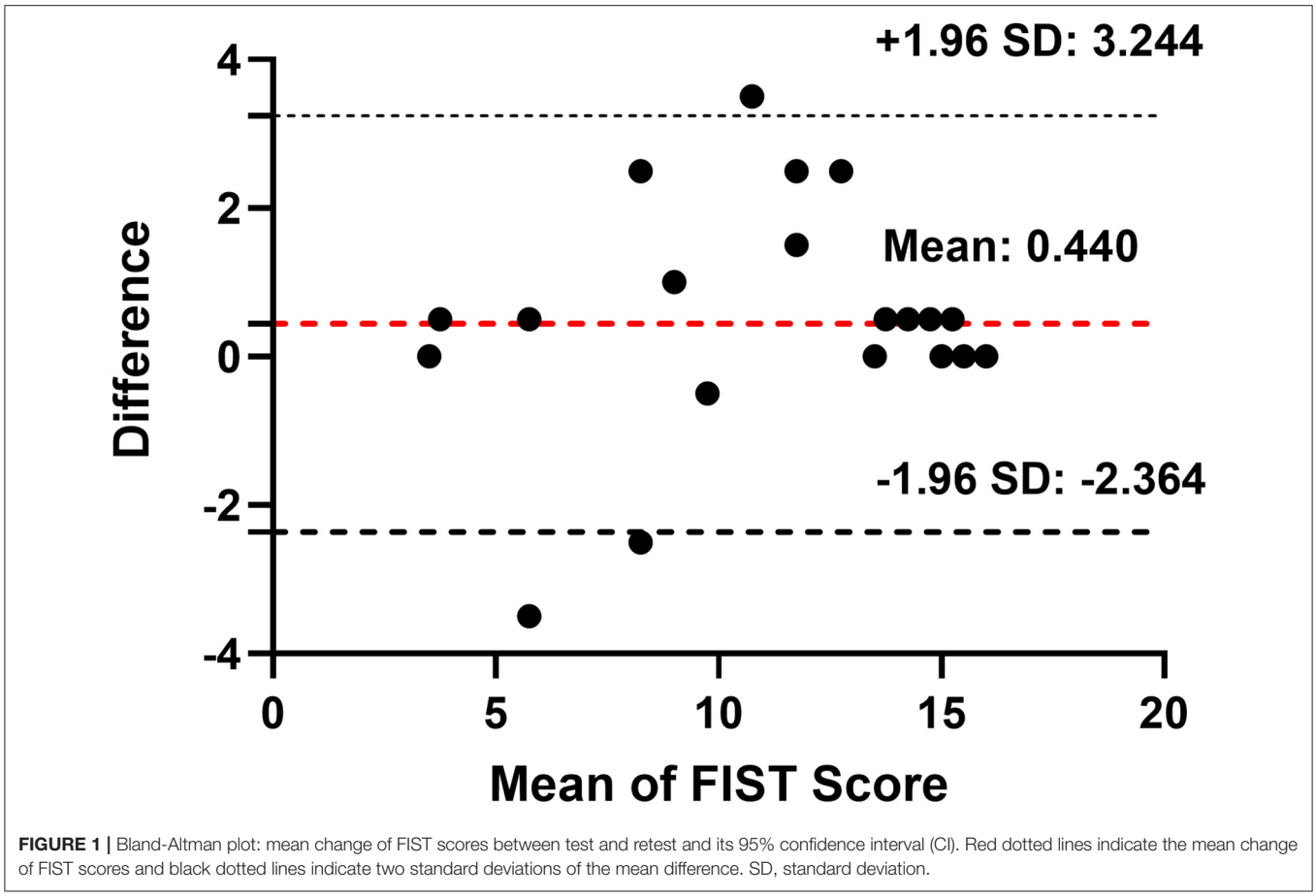


FIGURE 1 | Bland-Altman plot: mean change of FIST scores between test and retest and its 95% confidence interval (CI). Red dotted lines indicate the mean change of FIST scores and black dotted lines indicate two standard deviations of the mean difference. SD, standard deviation.

scree test, we retained one factor that variance contribution rate was 60.074% that was different from the three domains of the FIST. But the load values of each item were >0.4. No item was deleted according to the statistical analysis. As our participants were older inpatients, they had worse functional status than community-dwelling older adults. The FIST should be further refined in the future and verified in different populations, especially community-dwelling older adults. Meanwhile, we also evaluated the criterion validity. There is no gold standard for functional impairment, so we analyzed the correlation coefficients between the FIST and ADL, IADL, which showed that the FIST has a moderate correlation with ADL and a strong correlation with IADL.

A previous study showed that the Groningen activity restriction scale (GARS) and the modified Reintegration to Normal Living Index were reliable and valid tools for use in older adults both in hospital and community (42). GARS contained 11 ADL items and 7 IADL items (43). Compared with GARS, the FIST scale includes not only ADL and IADL items but also items regarding social activities.

With advancing age, physical function gradually deteriorates, age was a significant predictor of functional decline (44). Our results showed that the FIST score was negatively correlated with age. Frailty is a geriatric syndrome that increases vulnerability, and it is related to a series of adverse outcomes including falls, disability, and mortality (45, 46). Our results revealed that the FIST was negatively associated with frailty. However, the function impairment was different from frailty, although some items of FIST were similar to frailty. The FIST contains not

TABLE 5 | Load values of each item in the FIST.

Item	Factor 1
Eating	0.646
Washing	0.762
Going to toilet	0.860
Dressing	0.804
Moving in and out of bed	0.864
Bathing	0.872
Housekeeping	0.750
Handling finances	0.804
Handling medications	0.805
Lifting 5 kg of weight	0.811
Up and down stairs	0.771
Using transportation	0.846
Shopping	0.865
Walking for 250 m	0.489
Using telephone	0.729
Physical exercise	0.625

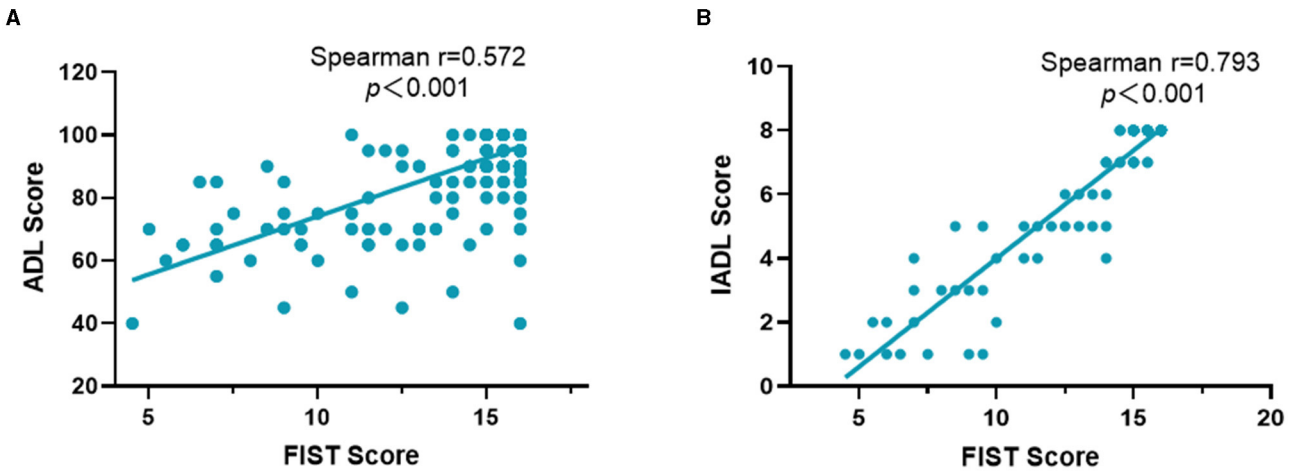


FIGURE 2 | The Spearman's correlation between the FIST and ADL **(A)**, IADL **(B)**. ADL, the activities of daily living; FIST, function impairment screening tool; IADL, instrumental activities of daily living.

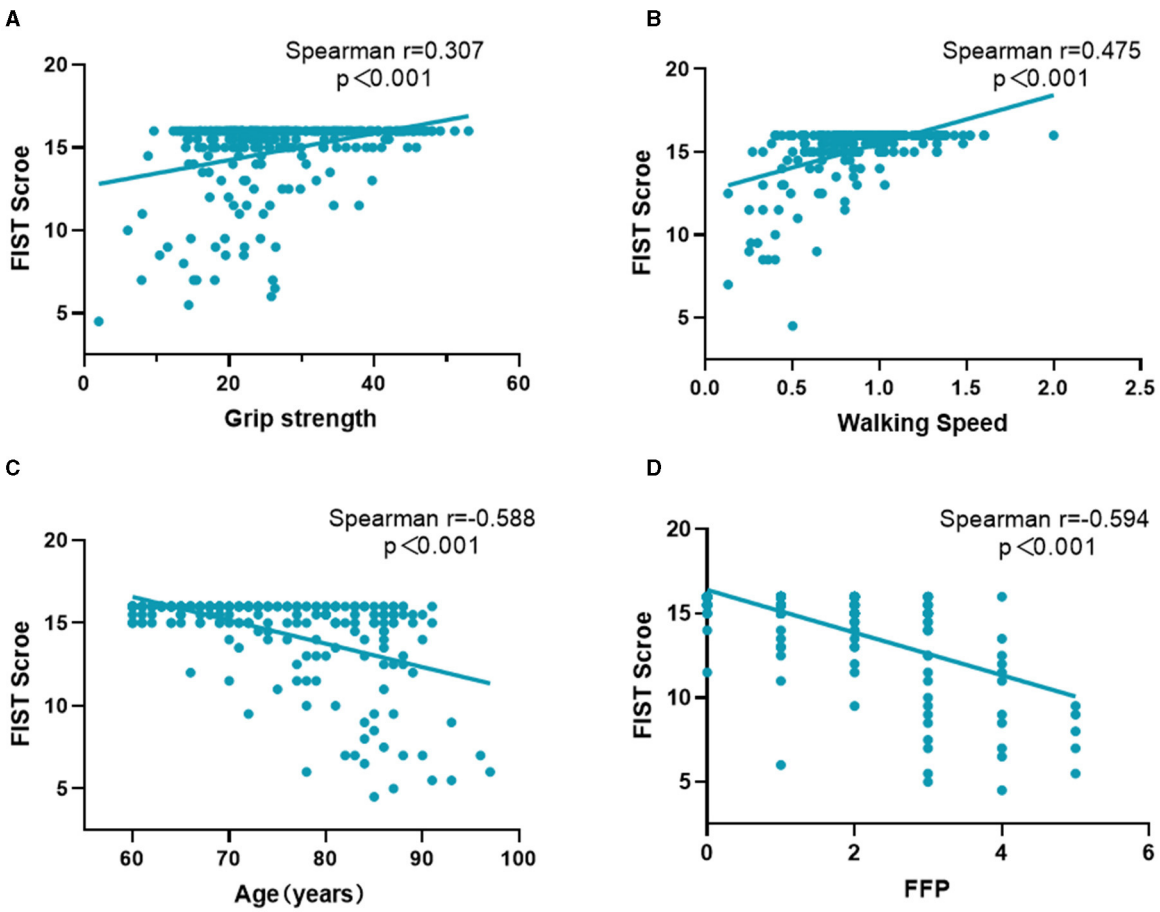


FIGURE 3 | The Spearman's correlation between the FIST score and age, physical performance, physical frailty. **(A)** Describes the correlation between the FIST score and grip strength; **(B)** Describes the correlation between the FIST score and walking speed; **(C)** Describes the correlation between the FIST score and age; **(D)** Describes the correlation between the FIST score and the Fried frailty phenotype. FFP, the Fried frailty phenotype; FIST, function impairment screening tool.

only ability in daily living but also ability in domestic life and social activities.

Both muscle mass and muscle strength decreased gradually with aging, and strength declined faster than mass (47). Muscle strength and mobility ability are important components of physical performance. Walking speed is an objective measure of physical performance. Our study showed the FIST score was positively correlated with walking speed and grip strength. Several studies have reported that walking speed was associated with risks of functional dependence and disability (48–52). Furthermore, a 6-year follow-up study found that walking speed can predict the onset of functional dependence in rural older adults (48). Another study with 4.4 years follow-up found that Japanese community-dwelling older adults with faster walking speed had decreased risks of disability (adjusted hazard ratio [HR]: 0.87, 95% CI: 0.82–0.93) (49). Furthermore, slow walking speed increased the risk of future disability in frail (adjusted HR: 4.68, 95% CI: 2.72–8.05) and prefrail older adults (adjusted HR: 3.62, 95% CI: 2.19–5.96) (50). Muscle strength is also important to maintain physical function. Greater handgrip strength was associated with decreasing onset of ADL disability and IADL disability (51, 52). Thus, the FIST may reflect physical function. The diagnosis of sarcopenia, a progressive and generalized skeletal muscle disorder, includes the assessment of muscle strength, muscle mass, and physical performance (53, 54). Although the FIST score is positively correlated with muscle strength in the present study, the functional impairment is different from sarcopenia. If muscle strength is below the reference values, sarcopenia would be suspected, and the next diagnosis procedure would include the measurement of muscle mass (55).

Limitations

This study has several limitations. First, the participants were from a single-center general hospital in Beijing and did not provide a broad representation of all older adults in China. Further multi-center studies are warranted. Second, this is a cross-sectional study, and therefore the predictive validity of the FIST was not determined. Third, the assessment was conducted by several staff members, so measurement bias may have occurred; however, all the staff were trained using the same procedures to minimize the bias.

CONCLUSION

This study provided the validity and reliability evidence of the FIST. The results showed that the FIST is a reliable and valid instrument for assessing physical functional impairment in Chinese older adults. In addition, the assessment of function impairment in the early stage of disease could reduce the adverse outcome and improve the quality of life among older adults.

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 Xuanwu Hospital Capital Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YuL and LM contributed to conception and design of the study. PL, YP, YiL, and LZ organized the database. YZ performed the statistical analysis and wrote the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Age-Related Hearing Loss With Tinnitus and Physical Frailty Influence the Overall and Domain-Specific Quality of Life of Chinese Community-Dwelling Older Adults

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Objective: To investigate the impact of the severity of age-related hearing loss (ARHL) and tinnitus, presence of ARHL and/or tinnitus, and physical frailty on the health-related quality of life (HRQoL) and domain-specific HRQoL in Chinese community-dwelling older adults.

Design: This was a cross-sectional study of a community-based cohort.

Participants: We evaluated Chinese older adults ($n = 429$, 183 men and 246 women) aged $\geq$ 58years.

Measurements: The severity of HL and tinnitus were measured using pure-tone audiometry and the Tinnitus Handicap Inventory (THI), respectively. Physical frailty was measured using the five-item Fried scale. HRQoL was assessed using the Assessment of Quality of Life-8-Dimension (AQoL-8D) multi-attribute utility instrument (35 HRQoL items and eight domain-specific HRQoL subcategories). Low HRQoL (HRQoL score or subscores in the highest quintile) was used as a dependent variable in logistic regression analyses adjusted for demographic (Model 1) and health-related (Model 2) and psychosocial (Model 3) confounders.

Results: Age-related hearing loss severity was an independent determinant of senses in the physical dimension of HRQoL after adjusting for all covariates. Tinnitus severity was significantly associated with HRQoL and with independent living, senses, and pain in the physical dimension after adjusting for demographic and health-related covariates and was still associated with independent living and senses after adjusting for all covariates. The presence of ARHL and/or tinnitus was significantly associated with independent living and senses in the physical dimension after adjusting for all the covariates. Physical frailty was an independent determinant of HRQoL, independent living, and pain in the physical dimension and with mental health, happiness, and coping in the

psychosocial dimension after adjusting for demographic and health-related covariates. The association with HRQoL, independent living, and pain in the physical dimension, and with happiness and coping in the psychosocial dimension remained significant after adjusting for the covariates. Depressive symptoms, social dysfunction, and a number of comorbidities were critical determinants of psychosocial HRQoL.

Conclusion: Physical frailty has a stronger and more profound effect on HRQoL, particularly on independent living and pain in the physical dimension and on happiness and coping in the psychosocial dimension. Domain-specific HRQoL should be considered in the management of patients with ARHL with tinnitus and physical frailty.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier: NCT2017K020.

Keywords: age-related hearing loss, tinnitus, physical frailty, health-related quality of life, age-related hearing loss with tinnitus

INTRODUCTION

Age-related hearing loss (ARHL) is the most common chronic disorder of the sensory system (1). Physical frailty, especially mobility frailty characterized by slowness and/or weakness, is a common geriatric syndrome associated with a decline in the functioning of multiple physiological systems (2, 3). Both ARHL and physical frailty are principal causes of chronic disability (2, 4) and are expected to increase with the rapid growth of the aging population. Hearing loss is projected to become one of the top 10 burdens of disease by 2030 (5). ARHL is associated with frailty, falls, poor psychosocial well-being (e.g., social isolation, loneliness, and depression), poor communication, and cognitive decline (3, 6–8). Chronic subjective tinnitus is another common disorder of the auditory system that occurs as a comorbidity of ARHL in older adults.

The severity of ARHL (9) and tinnitus (10), and the presence of ARHL and tinnitus (11) have been reported to be associated with poor health-related quality of life (HRQoL). Physical frailty is an emerging global health burden, affecting ∼11% of older community-dwelling adults in high-income countries and having an even higher prevalence in low-income countries (2, 12). Physical frailty could result in various adverse outcomes, such as disability, falls, cognitive decline, depression, lower HRQoL, hospitalization, and mortality (2, 13, 14). Although ARHL, tinnitus, and physical frailty are important determinants of HRQoL, differences in their effects on HRQoL and on specific physical and psychosocial dimensions of HRQoL remain poorly understood.

The negative effect of the severity of ARHL and tinnitus and the presence of ARHL and/or tinnitus on HRQoL varies according to the assessment instruments used (e.g., hearing-related QoL and generic QoL instruments) and confounders (15, 16). Overall, HRQoL with broader dimensions is more widely used than hearing-related QoL to assess the physical and mental health of patients with ARHL and tinnitus. A series of cross-sectional studies on a Korean adult population assessed HRQoL using the EuroQol five-dimensional (EQ-5D) questionnaire, and those with moderate to severe hearing loss had lower health status than those without hearing loss after adjusting for sociodemographic, health-related, and psychological factors, and comorbidities (9). Moreover, patients with hearing loss with tinnitus have lower mobility, usual activity, and anxiety/depression HRQoL than those with a normal hearing without tinnitus (17). In studies that assessed the overall HRQoL of patients with hearing loss and tinnitus using the Medical Outcomes Study 36-item Short-Form Health Survey (12-item) (10, 18), individuals with more severe tinnitus had worse physical, bodily pain, vitality, and mental health scores (18). Further, sex, depressive symptoms, anxiety, and somatization symptoms were found to regulate the effect of chronic tinnitus on the mental and physical dimensions of HRQoL (10).

The older population has more complex multimorbidity due to the overlap among physical frailty, comorbidity, and chronic physical and mental health diseases (19). Physical frailty is highly prevalent and usually coexists with ARHL and tinnitus in older adults. Importantly, physical frailty might be a potential mediator of the association between ARHL with tinnitus and HRQoL (6). The effect of ARHL on cognition is greater among individuals older than 75 years (20). Furthermore, the coexistence of physical frailty with ARHL has been confirmed to be associated with worse cognitive performance in the elderly (21). Many previous studies have shown that community-dwelling older people with physical frailty have worse HRQoL and specific HRQoL domains after adjusting for confounders (13, 14). Thus, the impact of the severity of ARHL and tinnitus, and the presence of ARHL and/or tinnitus and physical frailty on the low HRQoL and specific domains of HRQoL needs to be further investigated.

This study aimed to determine whether these associations were different and independent of demographic, health-related, and psychosocial factors. We hypothesized that the association of physical frailty with HRQoL and specific domains in community-dwelling older people is different from that of ARHL with tinnitus.

MATERIALS AND METHODS

Study Design

In total, 429 community-dwelling Chinese older adults (age ≥58 years) were recruited from our previous cross-sectional cohort

study on ARHL with tinnitus and general health (22). The number and characteristics of participants were the same as those in our recently published article describing the association of frailty phenotypes with age-related hearing loss and tinnitus (3).

Participants

All the participants underwent cognitive function, hearing and tinnitus severity, QoL, and comprehensive geriatric assessments. The inclusion criteria were: (1) permanent residence in the community, (2) age ≥58 years, and (3) willingness to participate in the project. The exclusion criteria were as follows: (1) handicap, (2) profound loss of hearing (including hearing aids) and vision, (3) dementia, (4) psychiatric/neurological disorders and dyslexia, and (5) taking medicines that affect cognitive performance. All participants provided informed consent prior to participation. This study was approved by the Ethics Committee of Huadong Hospital (Approval No. Ref 2018K055), and was conducted in accordance with the Declaration of Helsinki.

HRQoL Assessment

Health-related quality of life was assessed using the 35-item Assessment of Quality of Life (AQoL-8D) self-report questionnaire. The questionnaire covers three physical (independent living, pain, and senses) and five psychosocial dimensions (mental health, happiness, coping, relationships, and self-worth) (23). The senses domain was defined as a sensory system function. The respondents were asked to rate each item, and the HRQoL score was calculated by summing answers to the 35 QoL items (from 0 to 140). The unweighted total score and subscore of each specific domain were standardized, and the total HRQoL score ranged from 0 to 100, with lower scores indicating higher HRQoL. The highest quintile for the HRQoL score, as well as each domain-specific HRQoL subscore, was defined as 1 = low HRQoL, while scores below the highest quintile were defined as 0 = better HRQoL.

Assessment of ARHL, Tinnitus, Cognition, and Physical Frailty

The severity of ARHL and chronic subjective tinnitus (i.e., >3 months) was assessed using pure-tone audiometry and the Tinnitus Handicap Inventory (THI), respectively. The pure-tone average (PTA) in the better ear was calculated using the.5-, 1-, 2-, and 4-kHz thresholds. The participants were then divided into four groups based on their hearing levels (0 = normal hearing [PTA ≤ 15 dB]; 1 = subclinical hearing loss [PTA >15, ≤ 25 dB]; 2 = mild loss [PTA > 25, ≤ 40 dB]; and 3 = moderate to severe hearing loss [PTA > 40 dB]) (24).

Tinnitus was classified into three categories by severity [0 = without tinnitus, 1 = mild (THI score: 1–16 and 18–36); 2 = moderate (THI score: 38–56, 58–76), and 3 = severe (THI score: 78–100)]. The patients were also scored based on the presence of ARHL and/or tinnitus (0 = without ARHL and tinnitus; 1 = only ARHL; 2 = only tinnitus; and 3 = with ARHL and tinnitus).

Cognitive performance was assessed using the global cognitive screening test; Mini-Mental Status Exam (MMSE); and normative z-scores of the neuropsychological test battery, including executive or attention, language, and memory domains (3, 25). Physical frailty was evaluated using the five-item Fried scale (weakness, slowness, unexplained weight loss, fatigue, and low physical activity) with Chinese reference values (26, 27). The Fried scale score ranges from 0 to 5, with scores 3–5 and 1–2 indicating frail and prefrail, respectively.

Covariates

All the subjects underwent face-to-face interviews to collect demographic information and completed a standardized medical questionnaire. The demographic information included age, sex, education level, height, body weight, and body mass index (BMI, calculated as weight in kg divided by height in m^2). The medical questionnaire included self-reported smoking, alcohol intake, and chronic comorbidities (3). The number of comorbidities was categorized as 0, 1, 2, and >2. Chronic diseases, such as diabetes mellitus, cardiovascular disease (CVD), stroke, and non-skin malignancies were also considered as covariates. Depressive symptoms, neuropsychiatric symptoms, and social dysfunction were assessed using the 15-item short form of the Geriatric Depression Scale, a brief version of the self-report Neuropsychiatric Inventory Questionnaire (NPI), and the 21-item Social Dysfunction Rating Scale, respectively (3).

Statistical Analysis

Continuous variables were expressed as medians and quartiles, and non-normally distributed variables were tested using the Kolmogorov–Smirnov test. Meanwhile, categorical data were expressed as proportions and compared using the X^2 test. Differences in continuous and categorical variables between groups were analyzed using Spearman's test for bivariate correlation and one-way analysis of variance, respectively. A univariate correlation was analyzed using the test of homogeneity or the Mann–Whitney U test as appropriate. The association of the severity of ARHL, tinnitus, or the presence of ARHL with tinnitus and HRQoL and specific domains of HRQoL was assessed using multiple logistic regression analyses adjusted for age, sex, education level (Model 1); adjusted for covariates in Model 1 and other health covariates (Model 2); and adjusted for covariates in Model 2 and psychosocial factors, including social dysfunction, depression, and neuropsychiatric symptoms (Model 3). These models were run for low HRQoL scores and then separately for each low domain-specific subscore, which was used as a dependent variable. All the statistical analyses were performed using SPSS version 18.0, and $P < 0.05$ was considered statistically significant.

RESULTS

Influencing Factors of HRQoL and/or Tinnitus

Patient characteristics stratified by ARHL, tinnitus, and the presence of ARHL and tinnitus are shown in **Table 1**. Bivariate analysis showed that sex, tinnitus severity, physical frailty, comorbidity number, CVD, diabetes mellitus, social dysfunction, depressive symptoms, and NPI were significantly

TABLE 1 | Participant characteristics by severity of ARHL and tinnitus and the presence of ARHL and/or tinnitus.

		ARHL severity *N* = 425						Tinnitus severity N = 427					The presence of ARHL and/or tinnitus N = 424					
	Total sample	0	1	2	3	F/X^2value	p	0	1	2	F/X^2value	P	0	1	2	3	F/X^2value	p
	N = 429	*N* = 105	*N* = 78	*N* = 125	*N* = 117			*N* = 279	N = 108	N = 40			N = 77	N = 140	N = 31	N = 176		
Age	72.91 ± 7.014	71.30 ± 6.262	69.92 ± 6.279	73.50 ± 7.490	75.52 ± 6.488	13.456	<0.01	72.90 ± 6.672	72.94 ± 7.350	72.47 ± 8.290	0.071	0.932	72.12 ± 6.287	73.21 ± 6.683	69.32 ± 5.918	73.49 ± 7.476	3.609	0.013
Female	246 (57.30%)	63 (60.00%)	49 (62.82%)	74 (59.20%)	58 (49.57%)	4.325	0.228	161 (57.71%)	64 (59.26%)	20 (50.00%)	1.059	0.589	48 (62.34%)	78 (55.71%)	17 (54.84%)	101 (57.39%)	1.011	0.799
Education	12 (9, 15)	12.0 (9.0, 16.0)	11.5 (9.0, 15.0)	12.0 (9.0, 14.0)	12.0 (9.0, 15.0)	1.944	0.122	12.0 (9.0, 15.0)	11.0 (9.0, 14.0)	12.0 (9.0, 15.0)	0.752	0.472	12.0 (9.0, 16.0)	11.5 (9.0, 15.0)	12.0 (9.0, 16.0)	12.0 (9.0, 15.0)	2.298	0.077
BMI	23.2 (16.4, 25.7)	24.7 (21.7, 26.4)	23.300 (20.575, 25.625)	22.5 (13.0, 25.2)	19.95 (11.75, 25.30)	14.304	<0.01	23.30 (19.40, 25.70)	22.00 (12.00, 25.40)	21.35 (15.25, 26.25)	2.897	0.056	24.10 (21.45, 26.10)	22.60 (16.00, 25.25)	25.00 (23.30, 27.70)	22.00 (12.00, 25.30)	7.799	<0.01
Smoking (%)						5.136	0.526				2.396	0.662					5.407	0.482
Never smokers (0)	353 (82.3%)	90	65	106	89			235	85	32			68	114	24	144		
Ever smokers (1)	38 (8.9%)	9	5	10	13			21	11	5			6	13	4	13		
Current smokers (2)	31 (7.2%)	5	8	7	11			19	9	3			2	10	3	16		
Drinking (%)						2.132	0.922				3.752	0.411					9.405	0.119
Never drinkers (0)	378 (88.1%)	95	67	111	101			251	91	34			70	126	27	150		
Ever drinking (1)	14 (3.3%)	3	4	4	3			7	5	2			3	1	0	10		
Current drinking (2)	30 (7.0%)	6	7	8	9			17	9	4			3	11	4	12		
Comorbidity						5.380	0.800				4.024	0.676					2.523	0.112
0	49 (11.4%)	13	11	12	13			35	12	2			12	17	1	19		
1	127 (29.6%)	38	21	33	34			85	28	13			26	41	12	47		
2	124 (28.9%)	26	22	43	31			81	32	10			18	46	11	46		
>2	98 (22.8%)	24	15	31	27			59	27	12			18	26	6	47		
CVD						8.761	0.033				1.155	0.561					0.709	0.871
0	174 (40.6%)	45	37	37	53			109	45	19			34	54	12	72		
1	254 (59.2%)	60	41	87	64			170	62	21			43	86	19	103		
Diabetes mellitus						3.160	0.368				0.773	0.679					2.170	0.534
0	352 (82.1%)	87	69	99	93			232	88	31			62	119	27	139		
1	76 (17.7%)	18	9	25	24			47	19	9			15	21	4	36		
Stroke						1.305	0.728				1.453	0.510					2.295	0.507
0	386 (90%)	94	73	112	104			248	98	38			67	126	30	159		
1	42 (9.8%)	11	5	12	13			31	9	2			10	14	1	16		
Non-skin malignancy						1.244	0.743				2.401	0.301					0.628	0.920
0	397 (92.5%)	99	73	115	106			262	98	35			73	129	29	161		
1	31 (7.2%)	6	5	9	11			17	9	5			4	11	2	14		

(Continued)

TABLE 1 | Continued

		ARHL severity *N* = 425						Tinnitus severity N = 427					The presence of ARHL and/or tinnitus N = 424					
	Total sample *N* = 429	0 *N* = 105	1 *N* = 78	2 *N* = 125	3 *N* = 117	F/X^2value	p	0 *N* = 279	1 N = 108	2 N = 40	F/X^2value	P	0 N = 77	1 N = 140	2 N = 31	3 N = 176	F/X^2value	p
Physical frailty stratification						16.250	0.012				3.655	0.455					3.703	0.719
Robust (0)	176 (41%)	48	41	52	34			119	44	13			32	57	16	70		
Pre-physical frailty (1)	202 (47.1%)	50	32	54	64			126	54	20			40	62	13	84		
Physical frailty (2)	45 (10.5%)	7	4	17	17			29	9	7			5	17	2	21		
MMSE	28 (26, 29)	28.0 (27.0,29.0)	28.0 (26.0,29.0)	27.0 (26.0, 29.0)	27.0 (26.0, 28.0)	4.761	0.003	28.0 (26.0,29.0)	27.0 (26.0,28.0)	27.0 (26.0, 28.0)	0.979	0.377	28.0 (26.0, 29.0)	27.0 (26.0,29.0)	28.0 (27.0, 29.0)	27.0 (26.0, 29.0)	2.389	0.06
Cognitive stratification						47.692	<0.01				5.497	0.240					23.836	<0.001
Normal	215 (50.1%)	72	46	54	42			150	47	17			52	66	22	73		
Pre-MCI	111 (25.9%)	22	25	36	27			70	30	10			17	35	6	52		
MCI	103 (24%)	11	7	35	48			59	31	13			8	39	3	51		
Social dysfunction	28 (24,43)	27 (24,32)	26 (23,31.75)	29 (25,37)	30 (25,38)	4.102	0.007	27 (24,32)	29 (25,38)	35 (25,39.75)	6.456	0.002	26.5 (23.75,32)	27 (24,32)	28.5 (24,36.5)	30 (24.25,38)	3.888	0.009
GDS	3 (1,5)	2 (1,5)	3 (1,5)	3 (1.25,5.75)	3 (2,6)	2.725	0.044	2 (1,5)	4 (2,6)	5 (3,8)	14.922	<0.001	2 (1,4.75)	3 (1,5)	4 (1,6)	3 (2,6)	3.393	0.018
NPI	0 (0,2)	0 (0,1)	0 (0,2)	0 (0,1.77)	0 (0,2)	1.019	0.384	0 (0,1)	0 (0,3)	2 (0,3)	11.405	<0.001	0 (0,1)	0 (0,1)	0 (0,2)	0 (0,2.75)	3.603	0.014

ARHL, age-related hearing loss; BMI, body mass index; CVD, cardiovascular disease; MMSE, the Mini-Mental Status Exam; MCI, mild cognitive impairment; GDS, the Geriatric Depression Scale; NPI, self-report Neuropsychiatric Inventory Questionnaire. HL 0 = Normal hearing; HL 1 = subclinical hearing loss; HL 2 = mild HL; and HL 3 = moderate or severe HL. Tinnitus 0 = without tinnitus; tinnitus 1 = mild tinnitus; and tinnitus 3 = moderate or disaster tinnitus. The presence of ARHL and/or tinnitus 0 = without ARHL and tinnitus; the presence of ARHL and/or tinnitus 1 = with ARHL; the presence of ARHL and/or tinnitus 2 = with tinnitus; and the presence of ARHL and/or tinnitus 3 = with ARHL and tinnitus. Physical frailty 0 = robust; physical frailty 1 = pre-physical frailty; and physical frailty 2 = physical frailty.

associated with HRQoL. The severity of ARHL and tinnitus, the presence of ARHL and/or tinnitus, physical frailty, comorbidity number, CVD, stroke, social dysfunction, age, depressive symptoms, and NPI were significantly associated with the physical dimensions of HRQoL. Meanwhile, tinnitus severity, physical frailty, comorbidity number, CVD, diabetes mellitus, smoking, age, social dysfunction, depressive symptoms, and NPI were significantly associated with the psychosocial dimensions of HRQoL.

Association of ARHL Severity and Physical Frailty With HRQoL

The results of the multiple logistic regression models on the relationships between the severity of ARHL and high HRQoL (low scores) or low subscores in the physical dimensions of HRQoL are shown in **Table 2**. No significant association between ARHL severity and HRQoL was observed. Physical frailty was significantly associated with low HRQoL. In Model 1, female sex was associated with a significantly lower probability of high HRQoL (odds ratio [OR] = 0.585, 95% confidence interval [CI] = 0.354–0.966) (**Table 2**). In Model 2, no physical frailty (OR = 11.839, 95% CI = 3.554–39.436], pre-physical frailty (OR = 6.028, 95% CI = 1.724–21.08), and no CVD (OR = 2.007, 95% CI = 1.148–3.51) were associated with significantly higher probability of high HRQOL. In Model 3, lack of physical frailty (OR = 17.385, 95% CI = 2.272–133.058), pre-physical frailty (OR = 9.529, 95% CI = 1.191–76.241), and no CVD (OR = 2.24, 95% CI = 1.142–4.393) were associated with significantly higher probability of high HRQOL. Meanwhile, social dysfunction (OR = 0.893, 95% CI = 0.829–0.962) and depressive symptoms (OR =0.797, 95% CI =0.667–0.952) were associated with significantly lower probability of high HRQoL.

For the physical dimensions, after adjusting for all the covariates in Model 3, absence of ARHL (OR = 10.319, 95% CI = 4.944–21.536) and subclinical ARHL (OR = 5.303, 95% CI = 2.432–11.61) were significantly associated with a higher probability of better HRQoL in senses domain. Meanwhile, mild ARHL (OR = 1.818, 95% CI = 0.898–3.68) showed a marginal association. In Model 3, physical frailty had no effect on senses, while social dysfunction (OR = 0.922, 95% CI = 0.89–0.955) was associated with significantly worse senses. Lack of physical frailty (OR = 5.605, 2.904; 95% CI = 2.237–14.043, 1.400–6.021, respectively) and pre-physical frailty (OR = 1.623, 2.221; 95% CI = 0.582–4.529, 1.03–4.79, respectively) were associated with significantly higher probability of independence and less pain after adjusting for all the covariates (**Table 2**). Other independent determinants were social dysfunction for independent living and psychosocial variables and education levels for pain.

Age-related hearing loss severity showed no significant association with all the five psychosocial dimensions (**Table 3**). No physical frailty was associated with significantly higher happiness (OR = 2.510, 95% CI = 1.109–5.682) and coping (OR = 3.637; 95% CI: 1.032–12.821) in Model 3, and better mental health (OR = 2.581, 95% CI = 1.179–5.647) in Model 2, but not associated with self-worth and relationship. No comorbidity was associated with significantly higher probability of better mental health (OR = 5.082, 95% CI =1.84–14.042), coping (OR = 7.51, 95% CI = 1.937–29.112) in Model 2, and relationships in Models 2 (OR = 6.162, 95% CI = 2.414–15.732) and 3 (OR = 4.046, 95% CI = 1.323–12.374). Depressive symptoms were associated with a significantly lower probability of better functioning across psychosocial dimensions, while social dysfunction was associated with lower mental health, happiness, and relationships.

Association of Physical Frailty and Tinnitus Severity With HRQoL

The results of the multiple regression models on the relationships between tinnitus severity and HRQoL or physical dimensions of HRQoL are shown in **Table 4**. Absence of tinnitus (OR = 8.014, 95% CI = 1.04–61.722) and mild tinnitus (OR = 10.024, 95% CI = 1.25–80.384) were associated with significantly higher probability of high HRQoL in Model 2, but not in Model 3. Lack of physical frailty (OR = 16.437, 95% CI = 2.146–125.896) and pre-physical frailty (OR = 8.945, 95% CI = 1.118–71.593) were associated with significantly higher probability of high HRQoL in Model 3. Social dysfunction and depressive symptoms were also independent risk factors of high HRQoL. Absence of tinnitus and mild tinnitus were associated with significantly better independent living (OR = 11.904 and 5.354, 95% CI = 1.529–92.697 and 0.631–45.42, respectively) and senses (OR = 12.502 and 7.293, 95% CI = 2.765–56.528 and 1.529–34.797, respectively) in Model 3. Furthermore, absence of tinnitus was associated with significantly lower odds of pain in Models 1 (OR = 3.507, 95% CI = 1.494–8.230) and 2 (OR = 2.639, 95% CI = 1.082–6.434,), but not in Model 3 after adjusting for additional psychosocial covariates. Absence of physical frailty (OR = 6.999 and 3.343, 95% CI = 2.742–17.865 and 1.593–7.018, respectively) was associated with a significantly higher probability of better independent living and lower probability of pain in Model 3, and pre-physical frailty (OR = 2.539, CI = 1.169–5.513) was associated with significantly lower probability of pain in Model 3 after adjusting for all the covariates. CVD was an independent determinant of independent living; age and social dysfunction were independent determinants of senses; and education level, social dysfunction, and depressive symptoms were independent determinants of pain (**Table 4**).

Among the five psychosocial dimensions, depressive symptoms were independent risk factors for worse psychosocial dimensions, and social dysfunction was an independent risk factor for worse mental health, happiness, and relationship. Tinnitus severity was not directly associated with the psychosocial dimensions (**Table 5**). Absence of physical frailty was associated with significantly higher probability of better mental health (OR = 2.664, 95% CI = 1.212–5.856) and happiness (OR = 2.906, 95% CI = 1.558–5.42) in Model 2, and with happiness (OR = 2.427, 95% CI = 1.069–5.509) and coping (OR = 3.584, 95% CI = 1.016–12.638) in Model 3 (**Table 5**). A lack of or presence of one comorbidity was associated with a significantly higher probability of high HRQoL in the psychosocial dimensions, including mental health, coping,

TABLE 2 | Multiple logistic regression analysis of the association of ARHL severity with high quality of life (low score) and low subscores in domain-specific quality of life.

	Low quality of life score			Independent living			Senses			Pain		
	Model 1 OR (95% CI)	**Model 2 OR (95% CI)**	**Model 3 OR (95% CI)**	**Model 1 OR (95% CI)**	**Model 2 OR (95% CI)**	**Model 3 OR (95% CI)**	**Model 1 OR (95% CI)**	**Model 2 OR (95% CI)**	**Model 3 OR (95% CI)**	**Model 1 OR (95% CI)**	**Model 2 OR OR (95% CI)**	**Model 3 OR (95% CI)**
Stratification of ARHL severity (Ref: 3)												
0							8.423 (4.580, 15.489)***	9.438 (4.892, 18.210)***	10..319 (4.944, 21.536)***			
1							5.423 (2.881, 10.209)***	5.504 (2.733, 11.085)***	5..303 (2.423, 11.610)***			
2							1.308 (0.726, 2.355)	1.494 (0.794, 2.811)	**1.818 (0.898, 3.680)**			
Age				0.952 (0.920, 0.985)**								
Female (ref: male)	0.585 (0.354, 0.966)*			0.602 (0.375, 0.966)*								
Education level											0.926 (0.869, 0.986)*	0.888 (0.824, 0.957)**
Social dysfunction			0.893 (0.829, 0.962)**			0.950 (0.910, 0.991)*			0.922 (0.890, 0.955)***			0.949 (0.914, 0.986)**
GDS15			0.797 (0.667, 0.952)*									0.873 (0.778, 0.979)*
NPI												**0.835 (0.691, 1.008)**
Comorbidity (refer 3)												
0					4.497 (1.642, 12.314)**						2.579 (1.160, 5.732)*	
1					3.755 (1.549, 9.102)**						2.336 (1.221, 4.469)**	
2					2.887 (1.170, 7.122)*						2.029 (1.063, 3.873)*	
CVD (ref: 1)		2.007 (1.148, 3.510)*	2.240 (1.142, 4.393)*									
Physical frailty (ref:2)												
0		11.839 (3.554, 39.436)***	17..385 (2.272, 133.058)**		3.739 (1.763, 7.928)***	5.605 (2.237, 14.043)***		2.072 (1.165, 3.685)*			4.184 (2.217, 7.897)***	2.904 (1.400, 6.021)**
1		6.028 (1.724, 21.080)**	9.529 (1.191, 76.241)*		1.497 (0.653, 3.431)	1.623 (0.582, 4.529)		2.028 (1.099, 3.742)*			3.191 (1.652, 6.165)***	2.221 (1.030, 4.790)*

*OR = odds ratios; CI = confidence intervals; ARHL, age-related hearing loss; CVD, cardiovascular disease; GDS, the Geriatric Depression Scale; NPI, self-report Neuropsychiatric Inventory Questionnaire. Model 1 is adjusted for age, gender, education, and social dysfunction. Model 2 is adjusted for covariates in model 1 and health-related factors, including self-reported smoking, alcohol intake, BMI, chronic comorbidities, chronic diseases, physical frailty, cognition based on normative z-scores of neuropsychological test battery. Model 3 is adjusted for covariates in model 2 and GDS, NPI and social dysfunction. HL 0 = Normal hearing; HL 1 = subclinical hearing loss; HL 2 = mild HL; and HL 3 = moderate or severe HL. CVD 0 = without CVD; CVD 1 = with CVD. Physical frailty 0 = robust; physical frailty 1 = pre-physical frailty; and physical frailty 2 = physical frailty. *p < 0.05; **p < 0.01; and ***p < 0.001; bold values denote marginally statistical significance.*

TABLE 3 | Multiple logistic regression analysis of the association of ARHL severity and psychological dimension of HRQoL.

	Mental health			Happiness			Self-worth			Coping			Relationships		
	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Age		1.080 (1.035,1.126)***	1.097 (1.041, 1.156)**							0.945 (0.902, 0.990)*					
Education level		0.922 (0.857, 0.992)*	0.893 (0.812, 0.982)*												
Smoking (refer 2)															
0			0.181 (0.061, 0.539)**												
1			0.136 (0.024, 0.773)*												
Social dysfunction			0.836 (0.767, 0.910)***			0.937 (0.893, 0.984)**									0.877 (0.817, 0.941)***
GDS15			0.724 (0.594, 0.882)**			0.835 (0.731, 0.955)**			0.784 (0.673, 0.913)**			0.743 (0.603, 0.915)**			0.839 (0.717, 0.981)*
Comorbidity (refer 3)															
0		5.082 (1.840, 14.042)**									7.510 (1.937, 29.112)**			6.162 (2.414, 15.732)***	4.046 (1.323, 12.374)*
1		3.502 (1.466, 8.365)**									**3.231 (0.885, 11.795)**			2.610 (1.115, 6.108)*	1.375 (0.486, 3.889)
2		1.867 (0.760, 4.586)									1.634 (0.406, 6.585)			**2.175 (0.912, 5.185)**	1.725 (0.617, 4.828)
CVD (ref: 1)			2.139 (1.064, 4.299)*												
Physical frailty (ref: 2)															
0		2.581 (1.179, 5.647)*			3.164 (1.675, 5.977)***	2.510 (1.109, 5.682)*					3.206 (1.045, 9.835)*	3.637 (1.032, 12.821)*			
1		1.466 (0.649, 3.312)			1.393 (0.684, 2.835)	1.341 (0.552, 3.258)					1.435 (0.410, 5.023)	1.085 (0.247, 4.765)			

*OR, odds ratios; CI, confidence intervals; ARHL, age-related hearing loss; CVD, cardiovascular disease; GDS, the Geriatric Depression Scale. Model 1 is adjusted for mobility CF, non-mobility CF, cognitive decline, and age. Model 1 is adjusted for age, gender, education, and social dysfunction. Model 2 is adjusted for covariates in model 1 and health-related factors, including self-reported smoking, alcohol intake, BMI, chronic comorbidities, chronic diseases, physical frailty, cognition based on normative z-scores of neuropsychological test battery. Model 3 is adjusted for covariates in model 2 and GDS, NPI and social dysfunction. Smoking 0 = never smoking; smoking 1 = ever smoking; smoking 2 = current smoking. Comorbidity 0 = without chronic disease; comorbidity 1 = with 1 chronic disease; comorbidity 2 = with 2 chronic diseases; comorbidity 3 = with more than 2 chronic diseases. CVD 0 = without CVD; CVD 1 = with CVD. Physical frailty 0 = robust; physical frailty 1 = pre-physical frailty; and physical frailty 2 = physical frailty. *p < 0.05; **p < 0.01; and ***p < 0.001; bold values denote marginally statistical significance.*

TABLE 4 | Multiple logistic regression analysis of the association of tinnitus severity with high quality of life (low scores) and low subscores of domain-specific quality of life.

	Low quality of life			Independent living			Senses			Pain		
	Model 1 OR (95% CI)	**Model 2 OR (95% CI)**	**Model 3 OR (95% CI)**	**Model 1 OR (95% CI)**	**Model 2 OR (95% CI)**	**Model 3 OR (95% CI)**	**Model 1 OR (95% CI)**	**Model 2 OR (95% CI)**	**Model 3 OR (95% CI)**	**Model 1 OR (95% CI)**	**Model 2 OR (95% CI)**	**Model 3 OR (95% CI)**
Stratification of tinnitus (refer 2)												
0	10.754 (1.430, 80.889)*	8.014 (1.040, 61.722)*		17.312 (2.299, 130.367)**	14.287 (1.875, 108.853)**	11.904 (1.529, 92.697)*	10.432 (3.571, 30.480)***	11.992 (3.528, 40.761)***	12.502 (2.765, 56.528)***	3.507 (1.494, 8.230)**	2.639 (1.082, 6.434)*	
1	10.852 (1.394, 84.498)*	10.024 (1.250, 80.384)*		10.454 (1.335, 81.870)*	8.388 (1.048, 67.123)*	5.354 (0.631, 45.420)*	4.887 (1.596, 14.968)**	6.521 (1.830, 23.238)**	7.293 (1.529, 34.797)*	1.967 (0.786, 4.925)	1.489 (0.564, 3.930)	
Age	0.962 (0.926, 1.00)*			0.945 (0.911, 0.980)**			0.951 (0.923, 0.981)***	0.959 (0.929, 0.990)**	0.936 (0.903, 0.971)***			
Female (refer male)	0.523 (0.312, 0.877)*			0.575 (0.353, 0.937)*								
Education level										0.942 (0.890, 0.998)*	0.918 (0.862, 0.978)**	0.901 (0.838, 0.970)**
Social dysfunction			0.892 (0.828, 0.961)**						0.921 (0.890, 0.953)***			0.951 (0.916, 0.988)**
GDS15			0.797 (0.667, 0.953)*									0.849 (0.757, 0.951)**
Cognition (refer 2)												
0								2.468 (1.418, 4.295)***				
1								1.922 (1.030, 3.585)*				
CVD (ref: 1)		2.170 (1.232, 3. 821)**	2.236 (1.140, 4.384)*		1.987 (1.180, 3.345)**	1.964 (1.084, 3.557)*						
Physical frailty (refer 2)												
0		8.617 (2.957, 25.110)***	16.437 (2.146, 125.896)**		4.061 (1.978, 8.335)***	6.999 (2.742, 17.865)***					4.878 (2.612, 9.109)***	3.343 (1.593, 7.018)***
1		4.076 (1.317, 12.613)*	8.945 (1.118, 71.593)*		1.251 (0.553, 2.831)	1.698 (0.597, 4.826)					3.156 (1.631, 6.107)***	2.539 (1.169, 5.513)*

*Model 1 is adjusted for age, gender, education, and social dysfunction. Model 2 is adjusted for covariates in model 1 and health-related factors, including self-reported smoking, alcohol intake, BMI, chronic comorbidities, chronic diseases, physical frailty, cognition based on normative z-scores of neuropsychological test battery. Model 3 is adjusted for covariates in model 2 and GDS, NPI and social dysfunction. Tinnitus 0 = without tinnitus; tinnitus 1 = mild tinnitus; and tinnitus 3 = moderate or disaster tinnitus. CVD 0 = without CVD; CVD 1 = with CVD. Physical frailty 0 = robust; physical frailty 1 = pre-physical frailty; and physical frailty 2 = physical frailty. *$p < 0.05$; **$p < 0.01$; and ***$p < 0.001$.*

TABLE 5 | Multiple logistic regression analysis of the association of tinnitus severity and psychological dimension of HRQoL.

	Mental health			Happiness			Self-worth			Coping			Relationships		
	Model 1 OR (95% CI)	**Model 2 OR (95% CI)**	**Model 3 OR (95% CI)**	**Model 1 OR (95% CI)**	**Model 2 OR (95% CI)**	**Model 3 OR (95% CI)**	**Model 1 OR (95% CI)**	**Model 2 OR (95% CI)**	**Model 3 OR (95% CI)**	**Model 1 OR (95% CI)**	**Model 2 OR (95% CI)**	**Model 3 OR (95% CI)**	**Model 1 OR (95% CI)**	**Model 2 OR (95% CI)**	**Model 3 OR (95% CI)**
Age		1.083 (1.038, 1.129)***	1.095 (1.040, 1.154)***							0.953 (0.910, 0.997)*					
Education level		0.918 (0.853, 0.987)*	0.896 (0.814, 0.985)*												
Smoking (refer 2)															
0			0.179 (0.060, 0.533)**												
1			0.138 (0.024, 0.780)*												
Social dysfunction			0.839 (0.770, 0.914)***			0.936 (0.891, 0.982)**									0.880 (0.820, 0.944)***
GDS15			0.721 (0.591, 0.879)***			0.836 (0.731, 0.956)**			0.784 (0.673, 0.913)**			0.743 (0.603, 0.915)**			0.833 (0.711, 0.976)*
Comorbility (refer 3)															
0		5.263 (1.903, 14.554)***									10.629 (2.829, 39.927)***			5.871 (2.275, 15.150)***	4.058 (1.328, 12.403)*
1		3.488 (1.456, 8.359)**									4.636 (1.310, 16.408)*			2.553 (1.076, 6.053)*	1.295 (0.454, 3.690)
2		2.016 (0.826, 4.923)									2.195 (0.566, 8.508)			**2.107 (0.878, 5.058)**	1.721 (0.615, 4.811)
CVD (ref: 1)			2.062 (1.022, 4.161)*												
Physical frailty (refer 2)															
0		2.664 (1.212, 5.856)*			2.906 (1.558, 5.420)***	2.427 (1.069, 5.509)*						3.584 (1.016, 12.638)*			
1		1.514 (0.667, 3.438)			1.222 (0.604, 2.474)	1.287 (0.529, 3.133)						1.059 (0.241, 4.651)			

OR, odds ratios; CI, confidence intervals; CVD, cardiovascular disease; GDS, the Geriatric Depression Scale. Model 1 is adjusted for age, gender, education, and social dysfunction. Model 2 is adjusted for covariates in model 1 and health-related factors, including self-reported smoking, alcohol intake, BMI, chronic comorbidities, chronic diseases, physical frailty, cognition based on normative z-scores of neuropsychological test battery. Model 3 is adjusted for covariates in model 2 and GDS, NPI and social dysfunction. Comorbidity 0 = without chronic disease; comorbidity 1 = with 1 chronic disease; comorbidity 2 = with 2 chronic diseases; comorbidity 3 = with more than 2 chronic diseases. Smoking 0 = never smoking; smoking 1 = ever smoking; smoking 2 = current smoking. CVD 0 = without CVD; CVD 1 = with CVD. Physical frailty 0 = robust; physical frailty 1 = pre-physical frailty; and physical frailty 2 = physical frailty. $^{*}p < 0.05$; $^{**}p < 0.01$; and $^{***}p < 0.001$; bold values denote marginally statistical significance.

and relationships in Model 2, and no comorbidity was still associated with a significantly higher probability of high HRQoL in the domain of relationships.

Association of Physical Frailty and the Presence of ARHL and/or Tinnitus With HRQoL

The relationships of presence of ARHL and/or tinnitus with HRQoL or physical dimensions of HRQoL in the different multiple regression models are shown in **Table 6**. The presence of ARHL and/or tinnitus was not significantly associated with HRQoL or pain as a physical dimension. The lack of ARHL and tinnitus and the presence of ARHL and/or tinnitus were associated with significantly low HRQoL subscores of physical dimensions of independent living (OR = 2.372, 95% CI = 1.01–5.573; OR = 2.786, 95% CI = 1.337–5.804; and OR = 3.551, 95% CI = 1.132–11.14, respectively) and sense (OR = 11.843, 95% CI = 5.477–25.605; OR = 2.56, 95% CI = 1.404–4.667; OR = 4.712, 95% CI = 1.753–12.665, respectively) after adjusting for all the covariates. No physical frailty and pre-physical frailty were associated with significantly higher probability of low HRQoL scores (OR = 17.385, 95% CI = 2.272–133.058 and OR = 9.529, 95% CI = 1.191–76.241, respectively) and low pain (OR = 2.901, 95% CI = 1.4–6.021 and OR = 2.221, 95% CI = 1.03–4.79, respectively) in Model 3. Patients without physical frailty were significantly more likely to have better independent living (low subscores) (OR = 5.864, 95% CI = 2.297–14.97) in Model 3.

The presence of ARHL and/or tinnitus was not associated with any of the five psychosocial HRQoL domains (**Table 7**). Those without physical frailty showed a significantly higher probability of high HRQoL (low subscores) in mental health (OR = 2.595, 95% CI = 1.185–5.681) after adjusting for the covariates in Model 2 and in happiness (OR = 2.51, 95% CI = 1.109–5.682) and coping (OR = 3.637, 95% CI = 1.032–12.821) after adjusting for all the covariates in Model 3. No comorbidity or only one comorbidity was associated with a significantly higher probability of high HRQoL (low subscores) in mental health (OR = 5.1, 95% CI = 1.845–14.092; OR = 3.513, 95% CI = 1.471–8.392, respectively), coping (OR = 7.512, 95% CI = 1.938–29.114; OR = 3.233, 95% CI = 0.886–11.8, $p = 0.076$, respectively) and relationships (OR = 6.162, 95% CI = 2.414–15.732; OR = 2.61, 95% CI = 1.115–6.108, respectively) after adjusting for the covariates in Model 2 and in relationships (OR = 4.046, 95% CI = 1.323–12.374) after adjusting for all the covariates in Model 3. Depressive symptoms were the major determinant of all the five psychosocial dimensions, and social dysfunction was an important determinant of mental health, happiness, and relationships. Age, education level, smoking, and CVD were also independent risk factors for mental health after adjusting for all the covariates.

DISCUSSION

The impact of the presence and severity of ARHL and tinnitus, ARHL, tinnitus, and physical frailty on the HRQoL and its specific domains in community-dwelling older adults is yet to be clarified to date. This study found an association of ARHL severity with the senses domain of HRQoL, and the association remains significant after adjusting for demographic, health-related, and psychosocial covariates. Tinnitus severity is negatively associated with HRQoL and with three physical dimensions, but the association is no longer significant for HRQoL and pain after adjusting for all the covariates in Model 3. The presence of ARHL and/or tinnitus is only significantly associated with independent living and senses, and the association remains significant after adjusting for all the covariates. The severity of physical frailty is significantly associated with worse HRQoL (high scores) and independent living and pain (high subscores), and the associations remain significant after adjusting for all the confounders. Moreover, the severity of physical frailty is also significantly associated with the psychosocial domains of mental health, happiness, and coping, and the association is only decreased for mental health after adjusting for the psychosocial covariates in Model 3. The use of a multidimensional HRQoL questionnaire and the three models, with successive adjustments for different covariates, provided original information on these relationships.

These results extend our understanding of the association among the severity of ARHL (8, 9), tinnitus (10, 18), physical frailty (13, 14, 26), and the presence of ARHL and/or tinnitus (17) with HRQoL. Furthermore, these findings provide more evidence on the interaction among ARHL, tinnitus, and physical frailty in their relationship with HRQoL after adjusting for demographic, health-related, and psychosocial factors. Physical frailty coexisting with ARHL, tinnitus, and ARHL with tinnitus had a stronger effect on the overall HRQoL. Several previous studies have indicated that ARHL (8, 9, 28, 29) and/or tinnitus (10, 30) were negatively associated with HRQoL. However, we found no significant association among ARHL severity, the presence of ARHL and/or tinnitus, and HRQoL, and the association between tinnitus severity and HRQoL was also no longer significant after adjustment for psychosocial factors. The difference in our results, in comparison with previous findings, may be due to the different assessment tools used for HRQoL and various covariates. Physical frailty has been shown to be an important determinant of HRQoL in numerous studies (13, 14), and consistent findings were obtained in this study. Physical frailty remained significantly associated with HRQoL after adjusting for all the covariates, such as the severity of ARHL and tinnitus and the presence of ARHL and/or tinnitus. Moreover, those with physical frailty had a significantly higher probability of poor HRQoL than those with pre-physical frailty.

The effects of age-related auditory disorders (ARHL and tinnitus) on the specific domains of HRQoL were significantly different from those of physical frailty. Previous studies have indicated that ARHL, tinnitus, and the presence of ARHL and/or tinnitus were significantly associated with physical function (7), frailty phenotypes (3), cognition (31, 32), social dysfunction (33), and psychological disorders (e.g., depressive symptoms and anxiety) (10, 11, 24, 34). However, this study found no significant associations between these age-related auditory disorders and the psychosocial dimensions of HRQoL. Among the three physical dimensions, ARHL severity was only significantly associated with

TABLE 6 | Multiple logistic regression analysis of the association of the presence of ARHL and/or tinnitus with high quality of life (low scores) and low subscores of domain-specific quality of life.

	Low quality of life			Independent living			Senses			Pain		
	Model 1 OR (95% CI)	**Model 2 OR (95% CI)**	**Model 3 OR (95% CI)**	**Model 1 OR (95% CI)**	**Model 2 OR (95% CI)**	**Model 3 OR (95% CI)**	**Model 1 OR (95% CI)**	**Model 2 OR (95% CI)**	**Model 3 OR (95% CI)**	**Model 1 OR (95% CI)**	**Model 2 OR (95% CI)**	**Model 3 OR (95% CI)**
Stratification of ARHL and/or tinnitus (Ref: 3)												
0				1.945 (1.001, 3.780)*	2.249 (1.081, 4.679)*	2.372(1.010, 5.573)*	9.774 (5.174, 18.463)***	9.600 (4.908, 18.775)***	11.843 (5.477, 25.605)***			
1				2.146 (1.221, 3.773)**	2.495 (1.324, 4.701)**	2.786(1.337, 5.804)**	2.550 (1.568, 4.145)***	2.702 (1.604, 4.552)***	2.560 (1.404, 4.667)**			
2				1.963 (0.798, 4.827)	**2.607 (0.996, 6.824)**	3.551 (1.132, 11.140)*	3.457 (1.541, 7.803)**	3.598 (1.541, 8.405)**	4.712 (1.753, 12.665)**			
Age	0.962 (0.926, 0.998)*			0.948 (0.915, 0.983)**			0.958 (0.928, 0.988)**	0.965 (0.934, 0.997)*	0.941 (0.906, 0.977)**			
Female (Ref: male)	0.548 (0.328, 0.917)*			0.599 (0.370, 0.969)*								
Education level											0.923 (0.866, 0.984)*	0.888 (0.824, 0.957)**
Social dysfunction			0.893 (0.829, 0.962)**			**0.958 (0.918, 1.001)**			0.919 (0.886, 0.953)***			0.949 (0.914, 0.986)**
GDS15			0.797 (0.667, 0.952)*									0.873 (0.778, 0.979)*
NPI												**0.835 (0.691, 1.008)**
Cognition (Ref 2)												
0								2.100 (1.170, 3.771)*				
1								1.942 (1.012, 3.727)*				
Comorbidity (Ref 3)												
0											2.578 (1.159, 5.734)*	
1											2.332 (1.219, 4.463)*	
2											1.977 (1.034, 3.781)*	
CVD (Ref: 1) 0		2.080 (1.184, 3.652)*	2.240 (1.142, 4.393)*		1.928 (1.144, 3.250)*	1.961 (1.080, 3.562)*						
Physical frailty (Ref: 2)												
0		11.835 (3.552, 39.437)***	17.385 (2.272, 133.058)**		4.648 (2.215, 9.755)***	5.864 (2.297, 14.970)***					4.189 (2.218, 7.909)***	2.901 (1.400, 6.021)**
1		5.684 (1.617, 19.976)**	9.529 (1.191, 76.241)*		1.464 (0.631, 3.395)	1.620 (0.565, 4.644)					3.129 (1.617, 6.053)***	2.221 (1.030, 4.790)*

*OR, odds ratios; CI, confidence intervals; GDS, the Geriatric Depression Scale; NPI, self-report Neuropsychiatric Inventory Questionnaire. Model 1 is adjusted for age, gender, education, and social dysfunction. Model 2 is adjusted for covariates in model 1 and health-related factors, including self-reported smoking, alcohol intake, BMI, chronic comorbidities, chronic diseases, physical frailty, cognition based on normative z-scores of neuropsychological test battery. Model 3 is adjusted for covariates in model 2 and GDS, NPI and social dysfunction. The presence of ARHL and/or tinnitus 0 = without ARHL and tinnitus; the presence of ARHL and/or tinnitus 1 = with ARHL; the presence of ARHL and/or tinnitus 2 = with tinnitus; and the presence of ARHL and/or tinnitus 3 = with ARHL and tinnitus. Cognition 0 = normal cognition; cognition 1 = pre-MCI; cognition 2 = MCI. CVD 0 = without CVD; CVD 1 = with CVD. Physical frailty 0 = robust; physical frailty 1 = pre-physical frailty; and physical frailty 2 = physical frailty. *$p < 0.05$; **$p < 0.01$; and ***$p < 0.001$; bold values denote marginally statistical significance.*

TABLE 7 | Multiple logistic regression analysis of the association of the presence of ARHL and/or tinnitus and psychological dimension of HRQoL.

	Mental health			Happiness			Self-worth			Coping			Relationship		
	Model 1 OR (95% CI)	**Model 2 OR (95% CI)**	**Model 3 OR (95% CI)**	**Model 1 OR (95% CI)**	**Model 2 OR (95% CI)**	**Model 3 OR (95% CI)**	**Model 1 OR (95% CI)**	**Model 2 OR (95% CI)**	**Model 3 OR (95% CI)**	**Model 1 OR (95% CI)**	**Model 2 OR (95% CI)**	**Model 3 OR (95% CI)**	**Model 1 OR (95% CI)**	**Model 2 OR (95% CI)**	**Model 3 OR (95% CI)**
Age		1.081 (1.036, 1.128)***	1.097 (1.041, 1.156)***							0.945 (0.902, 0.991)*					
Education level		0.923 (0.858, 0.993)*	0.893 (0.812, 0.982)*												
Smoking (Ref 2)															
0			0.181 (0.061, 0.539)**												
1			0.136 (0.024, 0.773)*												
Social dysfunction			0.836 (0.767, 0.910)***			0.937 (0.893, 0.984)**									0.877 (0.817, 0.941)***
GDS15			0.724 (0.594,0.882)***			0.835 (0.731, 0.955)**			0.784 (0.673, 0.913)**			0.743 (0.603, 0.915)**			0.839 (0.717, 0.981)*
Comorbidity (Ref 3)															
0		5.100 (1.845, 14.092)**									7.512 (1.938, 29.114)**			6.162 (2.414, 15.732)***	4.046 (1.323, 12.374)*
1		3.513 (1.471, 8.392)**									**3.233 (0.886, 11.800)**			2.610 (1.115, 6.108)*	1.375(0.486, 3.889)
2		1.897 (0.772, 4.660)									1.646 (0.408, 6.631)			2.066 (0.862, 4.955)	1.725 (0.617, 4.828)
CVD (Ref: 1)			2.139(1.064, 4.299)*												
physical frailty (Ref: 2)															
0		2.595 (1.185, 5.681)*			3.164 (1.675, 5.977)***	2.510 (1.109, 5.682)*					3.208 (1.046, 9. 840)*	3.637 (1.032, 12.821)*			
1		1.489 (0.658, 3.368)			1.332 (0.651, 2.726)	1.341 (0.552, 3.258)					1.444 (0.413, 5.055)	1.085 (0.247, 4.765)			

*OR, odds ratios; CI, confidence intervals; GDS, the Geriatric Depression Scale; NPI, self-report Neuropsychiatric Inventory Questionnaire. Model 1 is adjusted for age, gender, education, and social dysfunction. Model 2 is adjusted for covariates in model 1 and health-related factors, including self-reported smoking, alcohol intake, BMI, chronic comorbidities, chronic diseases, physical frailty, cognition based on normative z-scores of neuropsychological test battery. Model 3 is adjusted for covariates in model 2 and GDS, NPI and social dysfunction. Smoking 0 = never smoking; smoking 1 = ever smoking; smoking 2 = current smoking. CVD 0 = without CVD; CVD 1 = with CVD. Physical frailty 0 = robust; physical frailty 1 = pre-physical frailty; and physical frailty 2 = physical frailty. *p < 0.05; **p < 0.01; and ***p < 0.001; bold values denote marginally statistical significance.*

senses. This is consistent with a previous finding that hearing loss is inversely associated with physical health scores after adjusting for sociodemographic and health-related factors (35). Furthermore, we found that tinnitus is significantly associated with independent living, senses, and pain after adjusting for the demographic and health-related factors. However, the association between tinnitus severity and pain was no longer significant after adjusting for the psychosocial factors. A large-scale population-based study reported that people with increasing tinnitus severity had worse physical, pain, vitality, and mental health HRQoL (18). In another study, depression-and anxiety-mediated chronic tinnitus caused impairments in mental and physical HRQoL in women and men, respectively (10).

Our study also showed that psychosocial factors, such as social dysfunction and depressive symptoms, were independent determinants of the psychosocial dimensions of HRQoL. In a large cross-sectional population-based study of individuals aged >19 years, hearing loss with tinnitus had a significant impact on all five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) of HRQoL (17). In contrast, our results showed that the presence of ARHL and/or tinnitus was significantly associated with independent living and senses in physical dimensions, but not with psychosocial dimensions after adjusting for all the covariates.

Several studies have shown that frailty, including physical frailty, is significantly associated with worse HRQoL in the community-dwelling older people (13, 14). Among Fried's frailty criteria, "slowness" had the strongest correlation with worse HRQoL after adjusting for the age, sex, and socioeconomic and health covariates (26). Our results revealed that physical frailty has different effects on the physical and psychosocial dimensions of HRQoL. It was not only significantly associated with independent living and pain in the physical dimensions, but also with happiness and coping in the psychosocial dimensions. Participants with physical frailty had worse HRQoL in these dimensions than those with pre-physical frailty. Given that gait and ARHL are important contributors to frailty and the importance of sensory and locomotion domains in intrinsic capacity (6, 36), the different effects of multiple sensory and functional mobility impairments on HRQoL and specific domains need to be further investigated in the future.

Aside from ARHL, tinnitus, physical frailty, education level, BMI, alcohol intake, disability in basic activities of daily living, multicomorbidity, chronic diseases, cognition, and depressive symptoms also influence HRQoL (9, 10, 17, 26, 35). In this study, age and education level were independent determinants of the senses and pain domains of the physical dimension, respectively. Social dysfunction was an independent risk factor for overall HRQoL; senses and pain in the physical dimension; and mental health, happiness, and relationships in the psychosocial dimension. Depressive symptoms were independent determinants of overall HRQoL, physical pain, and all the five psychosocial dimensions. CVD was a risk factor for worse HRQoL, independent living in the physical dimension, and mental health in the psychosocial dimension. In addition, the number of comorbidities was associated with mental health, coping, and relationships, especially relationships in the psychosocial dimension.

To our best knowledge, this cross-sectional study is the first to report the different effects of the severity of ARHL, tinnitus, and physical frailty, and the presence of ARHL and/or tinnitus on overall HRQoL and its specific domains. The use of a multidimensional HRQoL instrument, in combination with several self-report and objective covariates, in the assessment improved the robustness of the data collected. However, there are also some limitations to this study. First, participation was voluntary, which could have led to selection bias. Second, the cross-sectional design limited the analysis of causal relationships. For example, ARHL and tinnitus are associated with depressive symptoms (3, 9, 10, 16–18, 28, 29, 34) and social dysfunction (3, 16, 33), which are independent determinants of HRQoL and specific domains. However, we failed to identify a significant association between ARHL/tinnitus and HRQoL/psychosocial dimensions of HRQoL. Moreover, it is difficult to determine whether ARHL, tinnitus, and physical frailty are causes or consequences of poor HRQoL and its specific domains. Finally, senses in the physical HRQoL dimension included few parameters of auditory-related QoL, such as sound localization, hearing in noise, sound clarity, and pitches (16). However, these are crucial for assessing HRQoL after cochlear implant or hearing aid use. Longitudinal studies are needed to understand the causal relationships among ARHL, tinnitus, physical frailty, and HRQoL.

In conclusion, ARHL severity is an independent determinant of senses, while tinnitus severity is an independent determinant of independent living and senses in physical HRQoL. Physical frailty is an independent determinant of overall HRQoL, of independent living and pain in the physical dimension, and of happiness and coping in the psychosocial dimension.

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Huadong Hospital, Fudan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

QR, ZY, and ZH conceived and designed the study. QR wrote the article. WZ, JR, RZ, MZ, XH, and ZY conducted the investigation and data analysis. All authors contributed to the article and approved the submitted version.

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REVIEW
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The Therapeutic Intervention of Sex Steroid Hormones for Sarcopenia

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Sarcopenia, characterized by the excessive loss of skeletal muscle mass, strength, and function, is associated with the overall poor muscle performance status of the elderly, and occurs more frequently in those with chronic diseases. The causes of sarcopenia are multifactorial due to the inherent relationship between muscles and molecular mechanisms, such as mitochondrial function, inflammatory pathways, and circulating hormones. Age-related changes in sex steroid hormone concentrations, including testosterone, estrogen, progesterone, and their precursors and derivatives, are an important aspect of the pathogenesis of sarcopenia. In this review, we provide an understanding of the treatment of sarcopenia through the regulation of sex steroid hormones. The potential benefits and future research emphasis of each sex steroid hormone therapeutic intervention (testosterone, SARMs, estrogen, SERMs, DHEA, and progesterone) for sarcopenia are discussed. Enhanced understanding of the role of sex steroid hormones in the treatment for sarcopenia could lead to the development of hormone therapeutic approaches in combination with specific exercise and nutrition regimens.

Keywords: sarcopenia, aging, sex steroid hormones, androgen, estrogen, progesterone, dehydroepiandrosterone, drug

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INTRODUCTION

The term "sarcopenia," established based on the efforts of different groups, is typically defined as an age-related decline in skeletal muscle mass and muscle function (1–4). It is characterized by the progressive loss of muscle mass, strength, endurance, and reduced metabolic capacity of muscle fibers (5). The average sarcopenia incidence is 5–13% for people aged 60–70 years and 11–50% for those older than 80 years (6). It is associated with many age-related adverse events, such as an increase in the duration of hospitalization (7, 8), an impaired quality of life (9), reduced mobility (8), and a higher risk of hip or vertebral fractures (10, 11). In some instances, sarcopenia is secondary to some uncontrolled chronic diseases, such as malignant tumors, liver disease, or renal dysfunction. Moreover, progressive sarcopenia may worsen the primary disease, or even increase the rate of mortality (12, 13). Currently, the common ways to treat sarcopenia have been approved as follows: aerobic and resistance exercise, protein and energy intake, and vitamin D supplementation, but with limited therapeutic effects (14, 15). Over time, sarcopenia has become a vital public health issue and is now recognized as an independently reportable clinical disorder, and better treatments are urgently needed (16).

The pathophysiology of sarcopenia is both complex and multidirectional. Reduced muscle mass in the elderly can be ascribed to the lower rate of muscle protein synthesis when compared to the

rate of muscle proteolysis (17). Microscopically, atrophy of type II muscle fibers increases, and motor units within the muscle are lost and replaced by adipose and connective tissue (18). As a result, abnormal muscle metabolism, reduced muscle mass, and muscle strength capacity as well as increased muscle damage is observed (18).

The severity of sarcopenia can be measured using three parameters: muscle strength, muscle mass, and physical performance. Hand grip strength, leg muscle strength, and a chair stand test are applied to test muscle strength (19). Low muscle mass is estimated by the lumbar muscle cross-sectional area derived from computed tomography (CT) or magnetic resonance imaging (MRI) (20), or is assessed by clinical practice, such as the appendicular skeletal muscle mass (ASMM) (21, 22). Lean body mass (LBM) is often used to measure muscle mass, especially in the condition of sarcopenia obesity (1). Physical performance is a multidirectional concept involving muscle function and nervous system function, including the body balance (23). It can be variously measured by the timed-up and go test (TUG), the 6-min walk test, and the short physical performance battery (SPPB) (1).

Research exploring the inner mechanisms of sarcopenia is expanding and includes studies on muscle fiber composition and neuromuscular function, the potential of myo-satellite cell to proliferate and differentiate, inflammatory processes, mitochondrial dysfunction, as well as the age-related alterations of anabolic hormones in the endocrine system (24–27). Muscle mass is associated with a dynamic change in the anabolic and catabolic processes of skeletal muscle tissues (27). Anabolic hormones, such as sex steroid hormones, growth hormone, and insulin, are believed to play a major role in muscle tissue growth and remodeling (27).

Sex steroid hormones such as testosterone, estrogen, and progesterone, are important systemic anabolic hormones involved in maintenance of skeletal muscle mass and function, including hypertrophy and the regeneration of damaged muscles (28, 29). During aging, their levels become depleted, which is consistent with decreased muscle mass (29). Myo-satellite cells, myoblasts and myocytes both express androgen receptors and estrogen receptors, while progesterone receptors are found in myocytes. It has been found that the expression of the receptors in muscle cells plays an essential role in regulating the proliferation and differentiation of these cells (30–32). Moreover, these sex steroid hormones may participate in intracellular signaling pathways such as the IGF-1/Akt/mTOR pathway, MAPK pathway, Wnt and Notch signaling, among others, either positively or negatively, although the specific mechanism is still not well-understood (33–36). In addition, suppression of myostatin mRNA expression, activation of MyoD and myogenin, improved function of mitochondrial, and counteracting inflammation play roles in the physiological effects of sex steroid hormones in the skeletal muscle cells (**Table 1**, **Figure 1**) (29, 34, 37–39).

Decreased circulating levels of the sex steroids may lead to deterioration in muscle mass and function in elderly (40). Although sex hormone-derived drugs have not been widely used, it has been demonstrated that supplemental

TABLE 1 | Physiological effects of sex steroid hormones on receptors expression, signaling pathways, and metabolic alterations in the skeletal muscles.

	Receptors expression in muscle cells	IGF-1/Akt/mTOR pathway	MAPK pathway	Wnt and notch pathway	Myostatin	MyoD and myogenin	IGF-1	Inflammatory environment	Mitochondrial function
Testosetone	+	+	+	+	+	ND	+	+	+
Estrogen	+	+	+	ND	+	+	+	+	+
Progesterone	+	ND	ND	ND	ND	+	ND	ND	+
DHEA	ND	ND	ND	ND	ND	ND	+	ND	+

DHEA, Dehydroepiandrosterone; IGF-1, Insulin-like growth factor-1; ND, No available data.

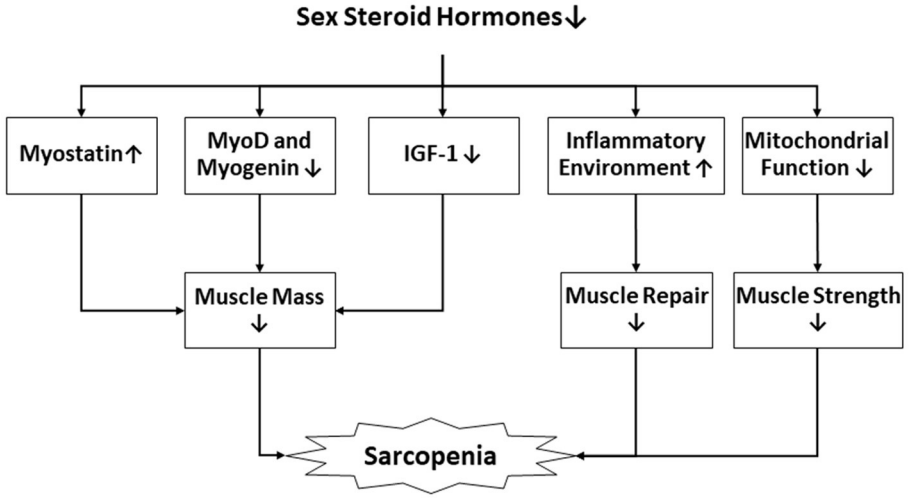


FIGURE 1 | The interactions between sex steroid hormones and sarcopenia. IGF-1, Insulin-like growth factor-1.

hormone intervention could be an effective approach to treat sarcopenia (41). In this review, we will outline the role of sex steroid hormones in the treatment of sarcopenia, focusing on recent findings.

TESTOSTERONE

Testosterone, a representative sex steroid hormone, is mainly produced by male Leydig cells and female ovarian thecal cells, and partly by adrenal gland (42). As the principal physiological anabolic hormone, testosterone increases protein synthesis in skeletal muscle, promotes muscle regeneration and repair by activation of myo-satellite cells, counteracts muscle proteolysis, and increases intramuscular insulin-like growth factor-1 (IGF-1) levels, etc. (43–45). During aging, testosterone levels in healthy men fall by 1% annually from the age of 30. For women, the testosterone levels at 40 years of age are about 50% of those at 20 years of age (46, 47). In some clinical conditions, the reductions in the testosterone levels may result in poorer clinical prognosis (48, 49).

Considering the significant physiological functions of testosterone, and its consistent benefits on muscle mass and strength in hypogonadal treatment, multiple randomized controlled trials (RCTs) have been conducted to explore the effects of testosterone replacement therapy (TRT) on the elderly since the 1990s. However, the effects observed on muscle performance and physical function were inconsistent due to the different treatment methods employed (47, 48, 50, 51). For healthy older men, TRT can help increase LBM, but muscle strength does not change (50, 52). Some other clinical trials showed that testosterone substitution results in an increase of both LBM and muscle strength (53–55). Previous trials were also limited by their relatively short duration, small sample sizes, and the heterogeneity of testosterone doses, regimens, and on-treatment testosterone levels (50–54). A meta-analysis conducted in 2018 showed that TRT may increase physical performance (measured by the Physical Activity Scale for the Elderly score and the 6-min walk test), but failed to increase muscle strength (measured by leg muscle strength and hand grip strength) (56).

The positive effects of exercise and physical training, including slowing down muscle loss and improving strength and performance in the elderly, have been substantiated (57, 58). Physical training, as the most effective intervention for sarcopenia, is often used in combination with pharmacological interventions to improve the effectiveness. Although, previous studies of TRT combined with exercise presented inconsistent results (55, 56, 59, 60), several clinical trials showed that the combination treatment can help increase the muscle mass or strength (59, 60). A prospective study demonstrated that TRT offers no benefit beyond resistance exercise alone (61). In 2021, a systematic review and meta-analysis on TRT of 21 RCTs for LBM and 15 RCTs for muscle strength concluded that both LBM and muscular strength were significantly improved by a combination regimen, which included physical exercise and testosterone-based interventions, when compared with physical exercise or testosterone-based interventions alone (62).

Several studies showed that patients with chronic diseases or injury can benefit from TRT (63, 64). Resistance training combined with TRT maximized improvements in muscle mass when compared with TRT alone for patients with spinal cord injury (63). In patients with advanced cancer, TRT improved LBM and physical activity, as well as their quality of life compared to placebo (64).

Recent studies in elderly women explored the anabolic effect of testosterone on sarcopenia (65, 66). Compared with placebo, low doses of TRT in women elevated the serum testosterone concentration and induced a significant increase in total LBM, and showed microscopic type II muscle fiber hypertrophy induced by testosterone (65). Another study showed

that short-term TRT in hysterectomized women with low circulating testosterone levels was related to increased trunk muscle area (66).

Nevertheless, TRT is still not widely recommended due to the adverse effects. TRT is associated with a higher risk of urogenital problems including benign prostatic hyperplasia and prostate cancer (67). Additionally, adverse cardiovascular events such as a significant increase in coronary artery non-calcified plaque volume (68) and menstrual changes in women and gynecomastia in men (69) are known to occur. A recent meta-analysis of testosterone did not indicate significant side effects and suggested that the adverse effects may be decreased by avoiding supraphysiological levels of plasma testosterone (62).

The strong anabolic effects of TRT, especially when combined with physical exercise, on muscle mass have been confirmed by a large body of evidence and the effects on muscle strength and function are supported by recent studies. Due to its inevitable side effects, TRT is still not recommended for wide use. Short term or intermittent TRT to maintain low serum testosterone levels in circulation may help lower incidence of adverse events. In the future, the risk-benefit balance between the adverse effects and effectiveness of TRT for sarcopenia needs to be explored. Furthermore, a specific TRT regimen (dosage for hormone therapy, in combination with exercise or nutrition) for older sarcopenic patients with different health conditions is worth exploring.

SELECTIVE ANDROGEN RECEPTOR MODULATORS (SARMS)

As an alternative to androgen replacement therapy, SARMs were created to provide a targeted therapeutic effect through the androgen receptors in different tissues. Binding of SARMS to androgen receptor in the prostate and seminal vesicles is partial agonistic, while in muscle and bone it is fully agonistic (70). Some SARMs have an anabolic/androgenic ratio of 20:1, in contrast to the ratio of 1:1 for testosterone (71).

The effects of highly selective drugs have been analyzed in several preclinical studies (72–75). Among them, one study demonstrated increased gastrocnemius muscle weight, bone biomechanical properties, and bone mineral density in ovariectomized female rats that were administered SARMs (72). On this basis, several clinical trials have found SARMs to benefit with body composition, exhibiting increased muscle mass, and decreased fat quality. However, its effects on muscle strength and function and its long-term efficacy remain inconclusive (70, 76–79). In a phase II clinical trial, Dalton JT showed that enobosarm (SARM) resulted in dose-dependent improvements in both LBM and physical performance as evaluated by the stair climbing test in healthy postmenopausal women and in aged men (80). Nevertheless, enobosarm failed to improve stair climb power in a separate phase III clinical trial, although LBM was increased significantly (81, 82).

According to various clinical trials, postmenopausal women could also take advantage of SARMs treatment. Neil D suggested that healthy postmenopausal women presented higher sensitivity to LBM improvement when treated with GSK2881078 (SARM) than healthy elderly men. Furthermore, the female cohort presented a better response at lower doses than males (73). In addition to postmenopausal women, patients suffering from any chronic disease, such as osteoporosis, non-small-cell lung cancer, stress urinary incontinence, and hip fractures, can also benefit from SARMs treatment with increased muscle mass (70, 81). Besides, the side effects of SARMs are much milder than TRT, such as the increases in alanine transaminase and aspartate transaminase, redeuctions in high density lipoprotein, and suppression of sex hormone binding globulin and total testosterone levels (76–78, 80).

Although SARMs have been shown to increase muscle mass, food and drug administration (FDA) still does not approve SARMs for the treatment of sarcopenia despite the fewer side effects when compared with testosterone. This may be a result of the inconsistent results of SARMs on muscle function. However, given the potential and safety of SARM therapy, future RCTs should be continued. It is recommended that SARMs be combined with nutritional supplements or exercise training, which will contribute to increased LBM and muscle function, especially for those with chronic diseases.

ESTROGEN

Estrogen, a common sex steroid hormone active in the reproductive organs, is also found in other organs and tissues, such as the skeletal muscle (83). In postmenopausal women or following bilateral oophorectomy, limited estrogen levels can cause osteoporosis, frailty, and sarcopenia (84–86). Estrogen deficiency is also related to decreased muscle strength (87), but the effects and function of estrogen on muscles remain unclear (88, 89). Estrogen may reduce the inflammation in the surrounding environment and thus prevent depletion of satellite cells, which help enhance skeletal muscle repair and growth if provided with necessary precursors (90).

Mice with low estrogen levels showed a decline in skeletal muscle strength, and this effect could be reversed by estrogen replacement therapy (ERT) (91, 92). Nevertheless, results concerning ERT in humans are conflicting (42). Although postmenopausal estrogen therapy is not as potent as testosterone, some studies revealed that it had a positive effect on muscle strength or muscle function (42, 93–97). However, other studies didn't support the hypothesis that ERT could work against sarcopenia (98–100). A meta-analysis of 24 studies showed that postmenopausal women treated with ERT had a significant impact on muscle strength compared with placebo (94). A subsequent meta-analysis in 2019, which included 12 studies, looked at the effects of hormones on muscle mass. No significant differences between an estrogen-based or an estrogen-progesterone-based hormone therapy and placebo were observed (101). Although the type and dosage of estrogen replacement administered varied among different trials, there were still no definitive conclusions.

Similar to TRT, ERT has been shown to enhance muscle function when combined with resistance training (94). In

a randomized placebo-controlled study in postmenopausal women, estrogen-progesterone-based hormone therapy combined with high-impact physical exercise showed significant increases in muscle strength as evaluated by knee extension torque and vertical jumping height when compared with the control group (99); more research is necessary to assess these findings.

Some severe complications have been reported when ERT is used in postmenopausal women with sarcopenia, including a higher risk of cardiovascular disease, breast cancer, endometrial cancer, and deep vein thrombosis (42, 102, 103). In a large-scale clinical trial (16,608 postmenopausal women aged 50–79 years), estrogen plus progestin increased total and invasive breast cancers compared with placebo during 5 years (104). Since ERT does not translate into improved physical function, and has potential risks, ERT is not recommended for healthy postmenopausal women to prevent or treat sarcopenia. Future clinical trials of estrogen as a therapeutic intervention for sarcopenia need to be conducted cautiously.

SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS)

SERMs are similar to estrogen in the observed drug effects but with fewer side effects. The highly selective drugs have estrogenic effects on the bone composition, blood vessels, and lipid metabolism but show anti-estrogenic effects on the breast and genital system (105, 106), leading to fewer side effects compared to estrogen. In a preclinical study, estradiol and SERMs influenced ER-α function in hSkM cells to promote muscle growth in postmenopausal women (107). Studies in ovariectomized rats have shown that raloxifene (SERM) modifies body composition by reducing body fat accumulation (108).

A RCT demonstrated that a 1-year raloxifene treatment could significantly increase the fat-free mass compared to placebo for postmenopausal women, without providing any significant advantage in muscle strength (109). In another randomized placebo-controlled trial, 1-year raloxifene treatment prevented enhanced body weight and abdominal adiposity (110). A study in 2016 consisting of 4,383 patients suggested that 5-year raloxifene treatment had significant effects on body composition achieved through maintaining body weight and increasing body mass index, with only minor side effects (111). Although it did not directly assess the roles of SERM on muscle mass or muscle strength, the 5-year trial revealed a preferential effect of SERM on the maintenance of muscle mass with fewer adverse effects. The side effects of SERMs were not significant compared with those of control groups, notably leg cramps and hot flashes (111).

Although there is still insufficient evidence on the effect of SERM on muscle mass and strength, it has been shown to maintain weight and increase fat-free mass over a long period of time in older postmenopausal women, with minor side effects. For this group, further research to explore the long-term effects of SERM on muscle mass and/or mass function may be useful, with consideration given to combining SERM with exercises, or for patients with chronic diseases who overtime, lose weight.

DEHYDROEPIANDROSTERONE (DHEA)

DHEA is mainly produced by the adrenal glands and can be converted to active androgens or estrogens in other tissues (112, 113). As a natural precursor to steroid hormone, DHEA exerts its anabolic effects when metabolized to active androgens or estrogens. DHEA also stimulates the production of IGF-1, which helps in muscle growth and repair, and increases its bioavailability in muscles by lowering the levels of IGF-1 binding protein-1 (114–116). In addition, DHEA improved insulin sensitivity, which directly affects the anabolic efficacy, by increasing the absorption rate of amino acids in the skeletal muscle (117). DHEA levels decline with age (118), and men in their 70–80s only have ∼20% of their peak value of DHEA, while similarly aged women have 30% of their peak value of DHEA (119). The decline in the level of DHEA is related to the loss of age-related muscle mass and strength (112, 113, 120, 121).

Thus far, the efficacy of DHEA replacement therapy for sarcopenia has not been consistently demonstrated. A randomized placebo-controlled trial showed that a daily oral dose of 100 mg was effective in maintaining body fat and muscle strength in elderly men, but not in elderly women (122). A decrease in body fat was observed in some studies (123, 124), while, other studies showed slight positive effects on muscle mass, strength, or function (125, 126). In 2011, a systematic review involving eight studies failed to confirm any efficacy of DHEA administration on muscle strength or physical performance (127). A meta-analysis in 2018, comprising four RCTs showed no positive effects of DHEA on muscles (128).

It is worth noting that some research found that when combined with exercise training, DHEA may play a better role in increasing muscle mass and strength in both rats and humans (129, 130). Elderly people in a RCT benefitted from a regimen with 50 mg DHEA daily and weightlifting exercise. This study showed a significant increase in muscular strength and mass in the combination group compared with individuals in the non-combination group (130). However, such a synergistic effect of DHEA was not confirmed by another combination trial (126). The differences between the results may be associated with the diversity of research designs, particularly the treatment time and dose, and the size of the sample population.

DHEA, which has fewer side effects than testosterone, is generally well-tolerated. Minor side effects including edema, facial hair growth, acne, and seborrhea have been observed in both men and women (131, 132). Unlike testosterone, no significant prostatic adverse events of DHEA were observed in elderly men. Most of these studies revealed no positive effects from DHEA supplementation alone. This was supported by a recent high quality meta-analysis (128). When DHEA was combined with exercises, muscle mass, and strength of elderly people was enhanced in some instances. As DHEA was observed to decrease the body fat in several trials, future RCT studies should explore an optimal formulation combining an exercise regimen with DHEA supplementation for senior patients with high body weight.

TABLE 2 | Summary of the main effects of sex steroid hormones.

	Muscle mass	Muscle strength	Physical performance	Adverse events	Effects when combined with exercises	Patients who may benefit	Future directions
Testosterone	Sufficient evidence in favor	Some evidence in favor	Some evidence in favor	Gynecomastia and prostatic diseases in men; menstrual changes in women; cardiovascular events	Sufficient evidence in favor	Hypogonadal men; short term or intermittent TRT for elderly men and postmenopausal women, including patients with chronic diseases or injury	Specific TRT formulation (dosage for hormone therapy, in combination with exercise or nutrition) for older sarcopenic people with different health conditions
SARMs	Sufficient evidence in favor	Insufficient evidence	Insufficient evidence	Increase in alanine transaminase and aspartate transaminase	No evidence	Elderly men and postmenopausal women, especially with chronic diseases	The long-term effects of SARMs combined with exercise training on muscle mass and/or mass function of elderly with chronic diseases
Estrogen	Insufficient evidence	Insufficient evidence	Insufficient evidence	Breast cancer, endometrial cancer, cardiovascular events, deep vein thrombosis	Some evidence in favor	Not recommended	Need to be conducted cautiously
SERMs	Some evidence in favor	Insufficient evidence	Insufficient evidence	Leg cramps, hot flashes	No evidence	Postmenopausal women who need long time administration to maintain their body weight and muscle mass	The long-term effects of SERMs on muscle mass and/or mass function of elderly with chronic diseases who are under normal weight over time
DHEA	Insufficient evidence	Insufficient evidence	Insufficient evidence	Edema, facial hair growth, acne, and seborrhea	Insufficient evidence	Not recommended	The optimal formulation of exercise and DHEA for specific high body weight seniors
Progesterone	Insufficient evidence	Insufficient evidence	Insufficient evidence	Venous thromboembolism, breast cancer	Insufficient evidence	Not recommended	The effects of bioidentical progesterone on postmenopausal women, especially with poor appetite or low body weight

DHEA, Dehydroepiandrosterone; SARMs, Selective androgen receptor modulators; SERM, Selective estrogen receptor modulators; TRT, testosterone replacement therapy.

PROGESTERONE

Progesterone, commonly produced by the adrenal gland as well as the ovaries or testes, has important functions in the female reproductive system and mammary gland. It also has functions involving several other tissues, including the cardiovascular system, the central nervous system, bones, and muscles (133). Progesterone receptors and estrogen receptors which are located and expressed in skeletal muscle tissue exert their direct effects on muscle tissue (134–136).

Progestogens have not been approved for use for sarcopenia, because of insufficient research on their direct therapeutic effect on muscle mass or function. In postmenopausal women, similar to testosterone, progesterone administration improved muscle protein fractional synthesis rate by ∼50% (33). The study also showed that progesterone has potent stimulatory impacts on myogenic differentiation 1 (MYOD1) mRNA expression, which is involved in muscle protein synthesis (33).

Megestrol is a synthetic progestin, which improves appetites and weight gain in patients with cancer, immunodeficiency syndrome, or other disabilities (137, 138). However, a RCT focusing on the elderly who do not have severe chronic illnesses, cancer, or immunodeficiency, showed negative results. The addition of megestrol did not seem to enhance the beneficial effects of resistance muscle training, leading to less muscle strength and function gains (139).

When combined with training and estrogen therapy, synthetic progesterone exerted a synergistic effect in increasing leg muscle cross-sectional area compared with the non-combination therapy group (140). Oral contraceptives (OC), which consists of synthetic estradiol and synthetic progesterone, are widely used by young females. A 2-year RCT indicated that young female runners receiving OC and resistance training increased LBM significantly compared to non-users (141). In contrast, another clinical study showed that OC impaired LBM gains in young women after resistant training, and this was connected to lower levels of anabolic hormones, such as DHEA and IGF-1, but higher catabolic hormone, like cortisol (142).

Adverse events including venous thromboembolism and breast cancer were observed during synthetic progesterone treatment. Compared with synthetic progestin, bioidentical progesterone is safer and more efficient. It has been shown that bioidentical progesterone can lower risk of breast cancer from estrogen (143), however, few studies have explored the effects of bioidentical progesterone on muscles.

The roles of progesterone on muscle mass or muscle function are controversial, even when combined with exercises. Based on this, we do not recommend progesterone supplementation for patients with muscle loss. Future research could focus on the use of bioidentical progesterone, especially in elderly patients with a poor appetite or low body weight.

OUTLOOK

Both positive and negative effects are observed in treatments using sex steroid supplementation for sarcopenia, namely testosterone, SARMs, estrogen, SERMs, DHEA, and progesterone. The main effects and our suggestions are shown in **Table 2**. It can be inferred that elderly with sarcopenia with different health conditions may benefit from different hormone treatments and future trials are needed to explore.

CONCLUSION

The decline of sex steroid hormones during aging influences the maintenance and development of skeletal muscles, resulting in sarcopenia. However, no sex steroid supplementation, including testosterone, estrogen, and progesterone, has been approved by the FDA for the management of sarcopenia, due to insufficient current evidence or low safety and effectiveness. In recent years, studies have explored better formulations of sex steroid hormones for sarcopenia, revealing more possibilities to treat this age-related disease. TRT is a promising treatment for sarcopenia, and we suggest that short term or intermittent TRT to maintain low serum testosterone levels may assist in optimizing its safety and effectiveness. Therefore, a specific TRT formulation for older sarcopenic patients with different health conditions is worth exploring. It is recommended that SARMs be combined with exercise training, especially for those with chronic diseases. Given the potential and safety of SARM therapy, future RCTs should be continued. SERMs can be used to maintain weight and increase fat-free mass over a long period of time in postmenopausal women with minor side effects. Estrogen is not recommended to treat sarcopenia or for further exploration due to its severe adverse effects. The role of progesterone and DHEA in the treatment of sarcopenia is still unclear. Large-scale clinical studies are necessary to investigate the promising drugs: testosterone, SARM and SERM. Considering the individual patient characteristics (sex, age, and chronic diseases), trials of different specific sex steroid interventions (combined with physical exercises or nutrition) for management of sarcopenia are urgently needed to determine their effectiveness and safety. Enhanced understanding of the role of sex steroid hormones in the treatment for sarcopenia could lead to the development of hormone therapeutic approaches, which could benefit patients with sarcopenia.

AUTHOR CONTRIBUTIONS

All authors contributed to the article and approved the submitted version.

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Associations of ADL Disability With Trunk Muscle Mass and Muscle Quality Indicators Measured by Opportunistic Chest Computed Tomography Imaging Among Older Inpatients

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Objectives: Sarcopenia is an important predictor of dependence in activities of daily living (ADL disability); however, the association between muscle quality and ADL disability has not been established. We aimed (1) to assess the feasibility of measuring trunk muscle mass and muscle quality by chest CT images; and (2) to explore the possible associations of ADL disability with these muscle mass and muscle quality indicators among older inpatients.

Methods: We included older patients in an acute care ward. ADL disability was defined as the Barthel Index (BI) score $\leq$ 60 points. Unenhanced chest CT images at the 12th thorax (T12) vertebral level were used to segment skeletal muscle area (SMA) and intermuscular adipose tissue (IMAT) and to measure the mean skeletal muscle radiodensity (SMD). Skeletal muscle index (SMI), the muscle mass indicator, was calculated by SMA (cm^2)/body height squared (m^2). The percentage of IMAT (IMAT%) was calculated using the equation: IMAT% = IMAT/(SMA+ IMAT) $\times$ 100%. Skeletal muscle radiodensity, IMAT, and IMAT% were the muscle quality indicators. Kendall's tau rank correlation coefficients (τ) were calculated to explore the correlations. Univariate and multivariate logistic regression models were performed to calculate odds ratios (OR) and 95% confidence interval (CI).

Results: We included 212 participants. Skeletal muscle index and SMD were positively and significantly associated with the BI score (τ = 0.14 and 0.31, respectively, both $P < 0.001$); whereas IMAT and IMAT% were negatively and significantly associated with the BI score ($\tau = -0.21$, $P < 0.001$; $\tau = -0.21$, $P < 0.012$). After adjusting for confounders, SMI (adjusted OR 1.03, 95% CI 0.97–1.09) was not independently associated with ADL disability; however, SMD (adjusted OR 0.94, 95% CI 0.88–0.99), IMAT (adjusted OR 1.11, 95% CI 1.03–1.20), and IMAT% (adjusted OR 1.09, 95% CI 1.02–1.16) were independently associated with ADL disability. Subgroup analysis found

similar results in men; however, none of these indicators were independently associated with ADL disability in women.

Conclusion: Trunk muscle quality indicators (SMD, IMAT, and IMAT%) measured by chest CT images, but not SMI, are independently associated with ADL disability in a single-center study population of older inpatients, especially in men. Further research is necessary to validate our findings.

Keywords: muscle depletion, muscle quality, muscle wasting, fat infiltration in muscle, myosteatosis

INTRODUCTION

Activities of daily livings (ADLs) are the basic tasks a person must perform to maintain their independence at home. Having difficulty performing ADLs, which is called ADL disability, is associated with an increased risk of morbidity and mortality (1). The prevalence of ADL disability increases with aging and has been reported highly prevalent in older adults, especially in older inpatients (2–4). Activities of daily living disability has become a public health issue in the aging world (5).

Skeletal muscle mass is essential for maintaining physical function and performing ADL (6). Sarcopenia, the loss of muscle mass and muscle function, has been associated with ADL disability (2). Recently, an updated version of the European Working Group on Sarcopenia in Older People (EWGSOP2) (7), the most widely used sarcopenia guideline (8), highlighted that muscle quality was as critically important as muscle mass. Muscle quality refers to "micro- and macroscopic changes in muscle architecture and composition" (9). The EWGSOP2 recommended highly-sensitive imaging tools, such as computed tomography (CT), to assess muscle quality, by measuring intermuscular adipose tissue (IMAT) and skeletal muscle radiodensity (SMD), indicating intramuscular adipose tissue (IntraMAT) (8).

Two recent studies reported that IntraMAT in quadriceps was strongly associated with ADL disability and the incidence of ADL disability in older inpatients (10, 11). However, both studies measured IntraMAT by ultrasound, which is not the "gold" method for measuring muscle quality. In contrast, IMAT measured by CT was not significantly associated with mobility disability and the risk of decline in gait speed in community-dwelling older adults (12). Moreover, most previous studies used abdominal or thigh CT images to assess muscle mass and muscle quality (13). In clinical practice, chest CT scans are far more common than abdominal imaging or thigh imaging, especially among hospitalized patients. Moreover, ADL disability is prevalent among older inpatients and correlates with poor health and financial outcomes among this population (14). Therefore, we aimed (1) to assess the feasibility of measuring trunk muscle mass and muscle quality by chest CT images; and (2) to explore the possible associations of ADL disability with these muscle mass and muscle quality indicators among older inpatients.

METHODS

Study Design and Participants

We conducted a cross-sectional study from January 2018 to December 2020. We consecutively invited older patients (aged 65 years and over) who were referred to the Center of Gerontology and Geriatrics, West China Hospital, to participate in this study. We excluded patients with any of the following conditions: (1) acute stroke; (2) New York Heart Association Classification Class IV heart failure; (3) severe respiratory failure (hypoxia with a PaO_2/FiO_2 ratio less than 300 mmHg) (15); (4) medical history of dementia, delirium, depression, anxiety, or hemodialysis; (5) trauma, surgery, or bone fracture within 3 months prior to enrollment; (6) refusal to sign the consent; (7) terminal diseases; (8) without chest CT images within 48 h after admission; (9) low-quality CT images or any anatomical distortion (e.g., chest wall edema or pleural effusion) or loss of any muscle mass area on CT images. All participants signed the informed consent form prior to participation. The study protocol was approved by the Biomedical Ethics Committee of West China Hospital, Sichuan University.

ADL Measurement

We applied the Barthel Index (BI) (16), a classic self-reported questionnaire, to assess ADL for each participant. The BI includes 10 items: bathing, toilet action, bowel continence, bladder continence, dressing, feeding, grooming, walking on a surface, going up and downstairs, and moving from a chair to a bed and from a bed to a chair. The BI score ranges from 0 points (total dependence) to 100 points (complete independence). The lower the BI score, the worse the ability to perform ADL tasks (16). As previously reported (16, 17), we defined ADL disability as the BI score $\leq$60 points.

Measurements of Muscle Mass and Muscle Quality Indicators

Each participant received chest CT scans within 48 h after admission for acute respiratory infection, chest pain, or other reasons. The CT scans were performed using a 16-slice spiral CT scanner (Brilliance; Philips Healthcare, Ohio, USA) with a 5-mm slice thickness. In this study, we applied a dedicated segmentation software (Mimics version 21.0; Materialise, Leuven, Belgium) to analyze unenhanced cross-sectional CT images at the 12^{th} thorax (T12) vertebral level.

Using a single CT image, skeletal muscle area (SMA) was segmented according to muscle tissue thresholds [−29 to 150 Hounsfield unit (HU)] (18). The HU scale reflects the density of tissue on a CT scan (19). In this study, SMA includes all skeletal muscle visible at the T12 vertebral level (i.e., *erector spinae, latissimus dorsi, rectus abdominis, obliquus externus, internus abdominis*, and *internal and external intercostal muscles*). According to previous studies (20, 21), we calculated skeletal muscle index (SMI) using the following equation: SMI = SMA (cm^2)/body height squared (m^2) to adjust for the impact of body size. A higher SMI indicates more skeletal muscle.

For muscle quality evaluation, we applied Mimics software to calculate the mean SMD of all skeletal muscles at the T12 vertebral level. In cases of lower SMD, there will be a larger percentage of IntraMAT (22), indicating the lower quality of skeletal muscle (23). Moreover, IMAT was assessed by identifying visible adipose tissue within muscle fascia at the T12 vertebral level according to fat tissue thresholds (−30 to−190 HU) (24, 25). Higher IMAT indicates poorer muscle quality. The percentage of IMAT (IMAT%) was calculated using the equation: IMAT% = IMAT (cm^2)/(SMA (cm^2) + IMAT (cm^2)) × 100% (26).

Measurements of Covariates

Trained staff assessed the nutrition status of the participants within 48 h after admission using the mini nutritional assessment short form (MNA-SF), a validated screening tool for identifying malnutrition in older adults (27). The score of MNA-SF ranges from 0 (best) to 14 points (worst). Moreover, the following information was obtained from the Hospital Information System: age, sex, body weight, height, body mass index, comorbidities (hypertension, cardiovascular disease, any type of cancer, diabetes, chronic obstructive pulmonary disease, chronic kidney disease, acute infection), albumin, and hemoglobin.

Statistical Analysis

The statistical analyses were performed in R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS software 26.0 (IBM SPSS Inc., New York, US). A p-value < 0.05 indicates statistical significance. The distribution of continuous data was evaluated using the Shapiro-Wilk test. Continuous data are presented as mean and standard deviation or median and interquartile range where appropriate. Categorical data are presented as numbers and percentages. Group differences were compared using independent samples t-test, Mann-Whitney U-test, or Chi-squared test. Kendall's tau rank correlation coefficients (τ) were calculated to explore the correlations of age, BMI, MNA-SF score, BI score, albumin, and hemoglobin with SMI, SMD, IMAT, and IMAT%. The correlation coefficients are considered as high, moderate, or low when τ is >0.5, 0.3–0.5, or <0.3, respectively (22). Univariate logistic regression was performed to explore the association of different variables with ADL disability. Multivariate logistic regression analysis was performed to assess the association of SMI, SMD, IMAT, and IMAT% with ADL disability with adjustment for age, sex, cardiovascular disease, diabetes, MNA-SF score, and albumin. The results of the logistic regression models are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Based on the significant differences regarding SMI, SMD, IMAT, and IMAT% between men and women found in data exploration using independent samples t-tests and Mann-Whitney U-tests, the main results were further stratified by sex.

TABLE 1 | Characteristics of the study population ($n = 212$).

	Men ($n = 162$)	Women ($n = 50$)	*P*-value
Age, years*	85.0 (11.3)	81.0 (10.8)	0.001
Weight, kg	60.5 (10.1)	55.0 (12.1)	0.001
Height, cm*	167.0 (9.0)	155.0 (9.0)	<0.001
Body mass index, kg/m^2	23.8 (3.9)	22.2 (7.6)	0.187
Comorbidities (%)			
Hypertension	77 (47.5)	24 (48.0)	0.954
Cardiovascular disease	53 (32.7)	15 (30.0)	0.719
Any type of cancer	53 (32.7)	11 (22.0)	0.149
Diabetes	95 (58.6)	36 (72.0)	0.089
Chronic obstructive pulmonary disease	16 (9.9)	8 (16.0)	0.232
Chronic kidney disease	23 (14.2)	11 (22.0)	0.189
Acute infection	68 (42.0)	13 (26.0)	0.042
MNA-SF score*	9.0 (5.0)	9.0 (6.0)	0.971
Barthel Index score*	85.0 (50.0)	80.0 (41.3)	0.698
Hemoglobin, g/L*	119.5 (31.0)	117.0 (32.0)	0.219
Albumin, g/L	36.3 (5.3)	39.3 (5.1)	<0.001
Body composition based on CT image			
SMI, cm^2/m^2	27.9 (7.0)	23.5 (6.3)	<0.001
SMD, HU*	33.4 (9.9)	31.6 (10.5)	0.244
IMAT, cm^{2*}	6.2 (6.3)	5.0 (6.0)	0.648
IMAT%, %*	8.1 (7.6)	9.4 (10.3)	0.050

Data presented as n (percentage) or mean (standard deviation) if not specified. IMAT, intermuscular adipose tissue; IMAT%, percentage of IMAT; MNA-SF: mini nutritional assessment short form; SMA, skeletal muscle area; SMD, skeletal muscle radiodensity, SMI, skeletal muscle index.

**Data presented as median and interquartile range.*

RESULTS

Patient Characteristics

Initially, 221 subjects were enrolled, but nine patients were excluded because we were unable to segment their CT images due to chest wall edema ($n = 2$), pleural effusion ($n = 6$), or loss of muscle mass on the CT image ($n = 1$). Thus, we successfully measured muscle mass and muscle quality indicators in 96% (212/221) participants.

We finally included 212 older inpatients (162 men and 50 women) in the analysis. The characteristics of the participants are presented in **Table 1**. Men were significantly older than women (median: 85.0 and 81.0 years of age, respectively, $P = 0.001$). Not surprisingly, men had more skeletal muscle than women (mean SMI: 27.9 and 23.5 cm^2/m^2, respectively, $P < 0.001$). However, there was no significant difference between men and women regarding skeletal muscle quality indicators (i.e., SMD, IMAT, and IMAT%). **Supplementary Table 1** shows the characteristics of the participants according to ADL disability.

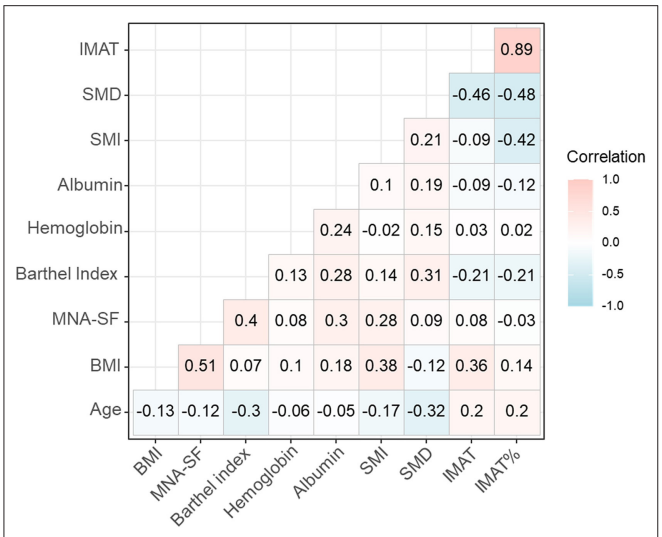


FIGURE 1 | The correlation coefficients of SMI, SMD, IMAT, and IMAT% with other variables. BMI, body mass index; IMAT, intermuscular adipose tissue; IMAT%, percentage of intermuscular adipose tissue; MNA-SF, mini nutritional assessment short form; SMD, skeletal muscle radiodensity; SMI, skeletal muscle index.

Patients with ADL disability were significantly older than those without (median: 87.0 and 82.0 years of age, respectively, $p < 0.001$). Moreover, patients with ADL disability were at higher risk of malnutrition than those without (median MNA-SF score: 7.0 vs. 10.0 points, $P < 0.001$; mean serum albumin: 34.9 vs. 38.7 g/L; $P < 0.001$).

Associations of Muscle Mass and Muscle Quality Indicates With Age and BI Score

Figure 1 shows the correlation coefficients of SMI, SMD, IMAT, and IMAT% with other variables. SMI was positively and significantly associated with the BI score ($\tau = 0.14$, $P < 0.001$), but negatively and significantly associated with age ($\tau = -0.17$, $P < 0.001$). Similarly, SMD was positively and significantly associated with the BI score ($\tau = 0.31$, $P < 0.001$), but negatively and significantly associated with age ($\tau = -0.17$, $P < 0.001$). In contrast, IMAT was negatively and significantly associated with the BI score ($\tau = -0.21$, $P < 0.001$), but positively and significantly associated with age ($\tau = 0.20$, $P = 0.001$). IMAT% was also negatively and significantly associated with the BI score ($\tau = -0.21$, $P = 0.012$), but positively and significantly associated with age ($\tau = 0.20$, $P = 0.011$).

Associations of Muscle Mass and Muscle Quality Indicates With ADL Disability

Figure 2 shows the violin plot and boxplot of SMI, SMD, IMAT, and IMAT% between patients with or without ADL disability. In both men and women, patients with ADL disability appeared to have higher SMI (indicating more muscle mass) than those without ADL disability but the group differences were not statistically significant (**Figure 2A**). Compared with their counterparts, men with ADL disability had significantly lower SMD but significantly higher IMAT and IMAT% (**Figures 2B–D**, all $p < 0.001$). Among women, there was no significant difference between groups regarding SMD, IMAT, and IMAT% (**Figures 2B–D**). Typical CT images of patients with or without ADL disability are shown in **Supplementary Figure 1**.

Table 2 shows the univariate logistic analyses to explore the association between ADL disability and different variables. As shown in **Table 2**, SMI was not associated with ADL disability (OR 0.97, 95% CI 0.93–1.01); however, muscle quality indicators were significantly associated with ADL disability (SMD: OR 0.91, 95% CI 0.87–0.96; IMAT: OR 1.08, 95% CI 1.02–1.15; and IMAT%: OR 1.05, 95% CI 1.01–1.10). Subgroup analyses indicated that SMI was not associated with ADL disability in both men and women (**Table 2**). Muscle quality indicators (SMD, IMAT, and IMAT%) were significantly associated with ADL disability in men but not in women (**Table 2**).

Table 3 shows the multivariate logistic analyses to explore the association of ADL disability with skeletal muscle mass and muscle quality indicators. After adjustment for potential confounders, SMI (adjusted OR 1.03, 95% CI 0.97–1.09) was not independently associated with ADL disability; however, SMD (adjusted OR 0.94, 95% CI 0.88–0.99), IMAT (adjusted OR 1.11, 95% CI 1.03–1.20), and IMAT% (adjusted OR 1.09, 95% CI 1.02–1.16) were independently associated with ADL disability. Subgroup analysis found similar results in men; however, none of these indicators were independently associated with ADL disability in women (**Table 3**).

DISCUSSION

Our study was the first to explore the associations of ADL disability with trunk muscle mass indicator (SMI) and muscle quality indicators (SMD, IMAT, and IMAT%) that were measured by opportunistic chest CT images among older patients in an acute care ward. We found that increased fat infiltration in trunk muscles at the T12 vertebral level was independently associated with ADL disability, especially in men. However, trunk muscle mass at the T12 vertebral level was not associated with ADL disability in either men or women.

Our study indicates that it is feasible to segment chest CT images to assess muscle mass and quality. We successfully extracted the relevant data from 96% CT images. Computed Tomography image analysis requires specialized software and trained personnel. In this study, we applied Mimics software, which has been successfully applied in other populations (28). In a previous study, segmentation software programs (FatSeg, OsiriX, ImageJ, and sliceOmatic) showed excellent agreement in measuring muscle mass indicators (29). However, the comparison of Mimics with other software programs that measure muscle mass and quality indicators needs to be further explored.

Only two previous studies addressed the associations of muscle mass and muscle quality with ADL in older inpatients (10, 11). Based on a cross-sectional study with 371 older inpatients, Akazawa et al. (11) reported that increased IntraMAT of the quadriceps was more strongly associated with declines in ADL

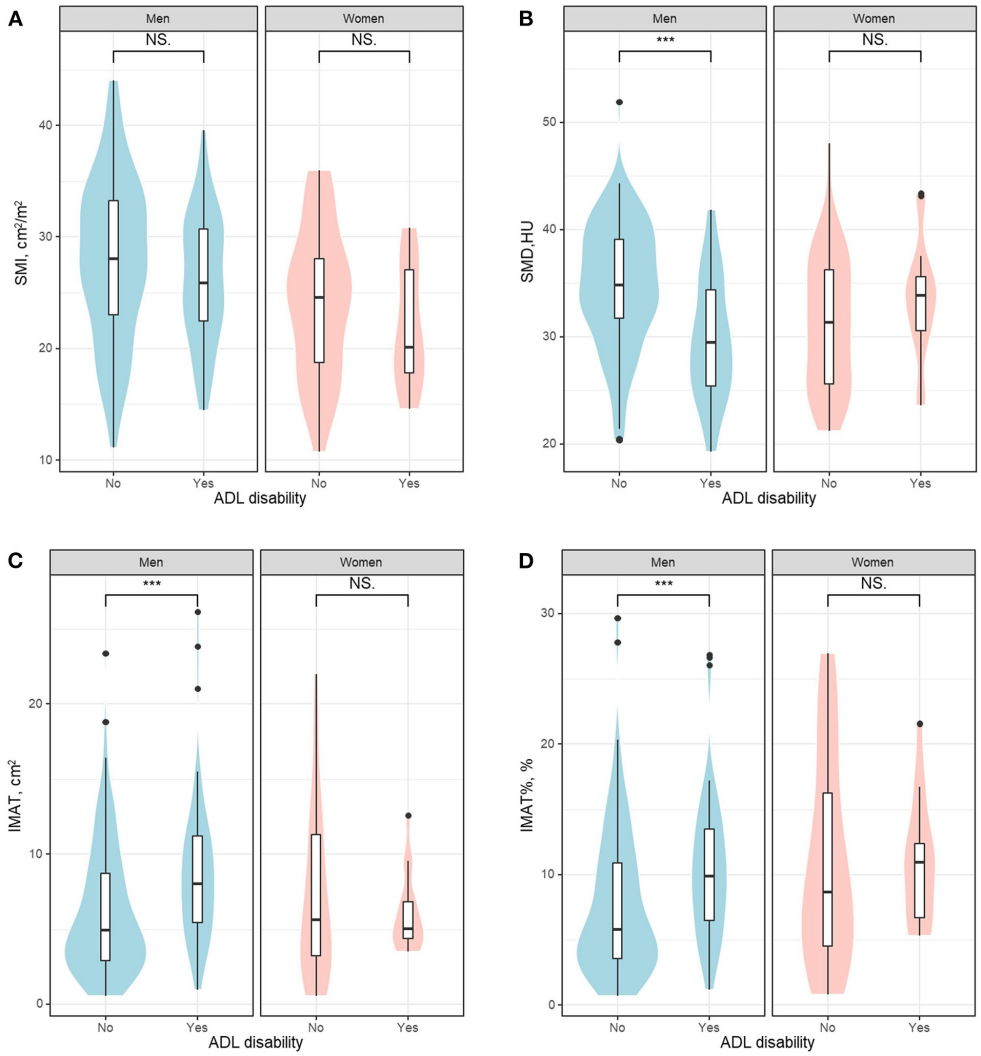


FIGURE 2 | The violin plot and boxplot of SMI **(A)**, SMD **(B)**, IMAT **(C)**, and IMAT% **(D)** between patients with or without ADL disability. ADL, activities of daily living; HU, Hounsfield unit; IMAT, intermuscular adipose tissue; IMAT%, percentage of intermuscular adipose tissue; NS, not significant; SMD, skeletal muscle radiodensity; SMI, skeletal muscle index. ***indicates $P < 0.001$.

than the loss of muscle mass. Most recently, the same team conducted a prospective cohort study with 404 older inpatients, and they found that increased IntraMAT of the quadriceps at admission was more strongly associated with worse recovery of ADL than the loss of muscle mass (10). Notably, both studies used ultrasound to measure muscle thickness and measured echo intensity as the surrogates of muscle mass and IntraMAT, respectively. Our results were in line with their findings, but we used chest CT images to assess muscle mass and muscle quality. Computed Tomography is one of the "gold" methods to measure muscle mass and fat infiltration in muscle, and it is supposed to be better than ultrasound in this field.

Unlike the two previous studies (10, 11), we measured trunk muscles at the T12 vertebral level instead of thigh muscles. Research on the relationship of muscle composition with physical function has focused primarily on the thigh muscle area (30). However, there was evidence that attenuation of trunk muscles (i.e., decreased SMD) explains a greater proportion of variance in lower extremity physical function than an attenuation of thigh muscles, highlighting the importance of trunk muscles for physical performance (31). These findings emphasized the importance of trunk muscle quality in physical function and ADL in older adults, implying that improving trunk muscle quality might improve functional status in older inpatients.

Sarcopenia has been proven as an important predictor of ADL among different study populations (2, 32–34). In these studies, sarcopenia was defined by the EWGOSP criteria, including both low muscle mass and decreased muscle function. However, there is controversy as to whether low muscle mass alone is associated with ADL impairments or not. For example, a recent

TABLE 2 | Univariate logistic analyses to explore the association between ADL disability and different variables.

	Total ($n = 212$)		Men ($n = 162$)		Women ($n = 50$)	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Age, years	1.09 (1.05–1.14)	<0.001	1.10 (1.05–1.16)	<0.001	1.07 (0.97–1.18)	0.158
Women	0.74 (0.37–1.48)	0.389	–	–	–	–
Body mass index, kg/m^2	0.95 (0.88–1.03)	0.187	1.00 (0.91–1.10)	0.945	0.86 (0.74–1.00)	0.051
Comorbidities						
Hypertension	1.49 (0.84–2.65)	0.175	1.45 (0.76–2.78)	0.264	1.67 (0.48–5.79)	0.422
Cardiovascular disease	1.70 (0.93–3.10)	0.084	1.77 (0.90–3.48)	0.101	1.44 (0.39–5.38)	0.583
Any type of cancer	1.21 (0.65–2.23)	0.553	1.23 (0.62–2.44)	0.555	0.96 (0.21–4.27)	0.951
Diabetes	1.71 (0.93–3.14)	0.086	2.05 (1.03–4.07)	0.040	0.96 (0.24–3.78)	0.955
Chronic obstructive pulmonary disease	1.52 (0.64–3.63)	0.341	1.54 (0.54–4.38)	0.419	1.69 (0.35–8.28)	0.517
Chronic kidney disease	1.31 (0.62–2.81)	0.481	1.26 (0.51–3.12)	0.620	1.66 (0.40–6.88)	0.487
Acute infection	1.46 (0.82–2.62)	0.202	1.48 (0.77–2.84)	0.243	1.20 (0.30–4.79)	0.796
MNA-SF score	0.72 (0.65–0.81)	<0.001	0.74 (0.65–0.84)	<0.001	0.66 (0.50–0.86)	0.003
Hemoglobin, g/L	0.99 (0.98–1.00)	0.202	0.99 (0.98–1.01)	0.346	0.98 (0.95–1.01)	0.980
Albumin, g/L	0.89 (0.84–0.94)	<0.001	0.90 (0.84–0.96)	0.002	0.82 (0.71–0.96)	0.013
Body composition based on CT image						
SMI, cm^2/m^2	0.97 (0.93–1.01)	0.121	0.97 (0.92–1.01)	0.140	0.94 (0.85–1.05)	0.269
SMD, HU	0.91 (0.87–0.96)	<0.001	0.87 (0.81–0.92)	<0.001	1.06 (0.96–1.18)	0.260
IMAT, cm^2	1.08 (1.02–1.15)	0.009	1.13 (1.05–1.22)	0.001	0.95 (0.84–1.09)	0.488
IMAT%, %	1.05 (1.01–1.10)	0.026	1.09 (1.03–1.16)	0.005	1.00 (0.92–1.09)	0.990

HU, Hounsfield unit; IMAT, intermuscular adipose tissue; IMAT%, percentage of IMAT; MNA-SF, mini nutritional assessment short form; SMA, skeletal muscle area; SMD, skeletal muscle radiodensity, SMI, skeletal muscle index.

TABLE 3 | Multivariate logistic analyses to explore the association of ADL disability with skeletal muscle mass and muscle quality indicators measured by chest CT image*.

	Total ($n = 212$)		Men ($n = 162$)		Women ($n = 50$)	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
SMI, cm^2/m^2	1.03 (0.97–1.09)	0.320	1.03 (0.97–1.10)	0.312	0.98 (0.83–1.15)	0.976
SMD, HU	0.94 (0.88–0.99)	0.035	0.89 (0.83–0.96)	0.002	1.01 (0.87–1.18)	0.916
IMAT, cm^2	1.11 (1.03–1.20)	0.007	1.15 (1.05–1.26)	0.003	1.14 (0.85–1.53)	0.387
IMAT%, %	1.09 (1.02–1.16)	0.005	1.10 (1.05–1.17)	0.001	1.07 (0.91–1.26)	0.412

CI, confidence interval; HU, Hounsfield unit; IMAT, intermuscular adipose tissue; IMAT%, percentage of IMAT; MNA-SF, mini nutritional assessment short form; OR, odds ratio; SMA, skeletal muscle area; SMD, skeletal muscle radiodensity; SMI, skeletal muscle index.

**These indicators were included in the multivariate logistic models independently, which adjusted for age, cardiovascular disease, diabetes, MNA-SF score, and albumin. In the whole sample, these multivariate logistic models further adjusted for sex.*

meta-analysis included nine relevant studies and summarized that low muscle mass was positively associated with ADL disability in five of the nine studies. Our study indicated that although SMI was positively and significantly associated with the BI score, it was no longer independently associated with ADL disability after adjustment for confounders. Similarly, in a recent cross-sectional study conducted in 316 community-dwelling volunteers, Wang et al. (35) reported that SMD, but not low muscle mass, correlated well with handgrip strength and physical performance. Moreover, Perez-Sousa et al. (36) reported that gait speed, a surrogate of physical performance, mediated the association between low muscle mass and ADL disability in 19,705 community-dwelling older adults. These findings highlighted the crucial role of muscle function in the definition of sarcopenia when exploring sarcopenia's relationship to ADL.

Myosteatosis (i.e., excessive fat infiltration in muscle) is now considered a different disease from sarcopenia. Both low SMD and high IMAT indicate myosteatosis. However, in this study, we did not report the association between myosteatosis and ADL disability. This is because there is currently neither a well-established diagnosis modality nor diagnostic cutoffs of SMD or IMAT to define myosteatosis. For example, a recent systematic review found that 32 different cutoffs of SMD were used to define myosteatosis across 73 included studies (37). Additionally, previous studies regarding myosteatosis primarily focus on malignant diseases (55 out of 73 studies), liver diseases (seven studies), and cardiovascular diseases (five studies) (37).

The prevalence of myosteatosis (either defined by increased IMAT or decreased SMD) was supposed to rise with advancing age; however, studies examining myosteatosis in older adults are relatively rare (38, 39). The opportunistic utility of chest CT images to diagnose myosteatosis may facilitate relevant studies in older populations.

LIMITATIONS

First, our study was of cross-sectional design. Thus, we could not determine the causal relationship of trunk muscle mass or muscle quality with ADL disability. Second, the sample size of our study was relatively small, especially for women. This might partly explain why the associations of SMI and IMAT with ADL disability were not statistically significant in women. Third, we did not assess some important confounders, such as depression and cognitive function. However, we excluded patients with medical records of dementia and depression. Fourth, this is a cross-sectional study conducted in a single center; therefore, the representation of our sample was limited. Fifth, we dichotomized the BI using the previously reported cutoff to define ADL disability, and statistical information might be lost in the process. Last, we did not test muscle strength and physical performance in this study, which are expected to be associated with both muscle mass and muscle quality.

CLINICAL IMPLICATIONS

The opportunistic utility of chest CT images has been increasing to identify other diseases, such as chronic obstructive pulmonary disease and osteoporosis (40, 41). Our study implies the potential value of opportunistic usage of chest CT images to assess loss of muscle mass (a key component of sarcopenia) and myosteatosis among older adults in both clinical practice and research. A recent systematic review demonstrated that most of the previous studies (66 out of 70) used abdominal CT to assess myosteatosis and only one study used chest CT (37). Nevertheless, chest CT is far more frequently used than abdominal CT in clinical practice and has been routinely used in health screening (13). Therefore, there would be a great opportunity to use chest CT images to analyze the quantity and quality of skeletal muscle in sarcopenia and myosteatosis research in the future.

Although muscle quality indicators were associated with ADL disability in our study population, they did not seem to be strong, and further study is necessary. Additionally, further research is needed to determine how these muscle quality indicators (and their combination with muscle function) correlate to diverse clinical outcomes (such as ADL disability and quality of life) among different populations.

CONCLUSION

Trunk muscle quality indicators (SMD, IMAT, and IMAT%) measured by chest CT images at the T12 vertebral level were independently associated with ADL disability in a single-center study population of older inpatients, especially in men. Despite the positive and significant association between the SMI and the BI score, the SMI was not independently associated with ADL disability after controlling for confounders. Our study supports the opportunistic utility of chest CT images for assessing muscle mass and muscle quality in older inpatients. More longitudinal studies with large sample sizes in different study populations are required to validate our findings and to determine the diagnostic cutoffs of SMI, SMD, IMAT, and IMAT% for defining low muscle mass and myosteatosis.

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 Biomedical Ethics Committee of West China Hospital, Sichuan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MY: conception and design of study and statistical analysis. LT: imaging data analysis. XJ and MY: drafting the manuscript. All authors: acquisition, analysis, and interpretation of data and critical revision of the manuscript for important intellectual content.

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SUPPLEMENTARY MATERIAL

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Proprioceptive Training for Knee Osteoarthritis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Background: There is increased interest in proprioceptive training for knee osteoarthritis (KOA). However, little consensus supports the effectiveness of this intervention.

Objective: This meta-analysis aimed to assess the effects of proprioceptive training on symptoms, function, and proprioception in people with KOA.

Methods: The PubMed, Cochrane Library, Web of Science, and EMBASE databases were systematically searched from the inception dates to April 16, 2021 for relevant randomized controlled trials (RCTs). Data were pooled by calculating the standardized mean differences (SMDs) and 95% confidence intervals (CIs). A random-effects model was used for the analyses.

Results: A total of 24 RCTs involving 1,275 participants were included in our analysis. This study indicated that compared to no intervention, proprioceptive training significantly improved pain, stiffness, physical function, joint position sense (JPS), muscle strength, mobility, and knee ROM ($P < 0.05$) in people with KOA. When compared to other non-proprioceptive training, proprioceptive training provided better results in terms of JPS (SMD = −1.28, 95%CI: [−1.64, −0.92], $I^2 = 0\%$, $P < 0.00001$) and mobility (timed walk over spongy surface) (SMD = −0.76, 95%CI: [−1.33, −0.18], $I^2 = 64\%$, $P = 0.01$), and other results are similar. When proprioceptive training plus other non-proprioceptive training compared to other non-proprioceptive training, the two groups showed similar outcomes, but there was a greater improvement for JPS (SMD = −1.54, 95%CI: [−2.74, −0.34], $I^2 = 79\%$, $P = 0.01$), physical function (SMD = −0.34, 95%CI: [−0.56, −0.12], $I^2 = 0\%$, $P = 0.003$), and knee ROM ($P < 0.05$) in the proprioceptive training plus other non-proprioceptive training group. When proprioceptive training plus conventional physiotherapy compared against conventional physiotherapy, the two groups demonstrated similar outcomes, but there was a significant improvement for JPS (SMD = −0.95, 95%CI: [−1.73, −0.18], $I^2 = 78\%$, $P = 0.02$) in the proprioceptive training plus conventional physiotherapy group.

Conclusions: Proprioceptive training is safe and effective in treating KOA. There is some evidence that proprioceptive training combined with general non-proprioceptive training

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or conventional physiotherapy appears to be more effective and should be considered as part of the rehabilitation program. However, given that the majority of current studies investigated the short-term effect of these proprioceptive training programs, more large-scale and well-designed studies with long-term follow up are needed to determine the long-term effects of these proprioceptive training regimes in KOA.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/#recordDetails, PROSPERO, identifier: CRD42021240587.

Keywords: proprioceptive training, knee osteoarthritis, rehabilitation, systematic review, meta-analysis

INTRODUCTION

Osteoarthritis (OA) is a chronic, degenerative joint disease that mainly affects weight-bearing joints (1). Knee osteoarthritis (KOA) is the most common form of OA and affects ∼265 million people worldwide (2). Additionally, it is one of the leading causes of disability (3). Due to population aging and the increasing incidence of obesity, the prevalence of KOA is rising (4), increasing the socioeconomic burden for affected individuals and healthcare systems (5, 6). KOA is clinically characterized by pain, joint stiffness, reduced joint motion, quadriceps weakness, and proprioceptive deficits (7, 8). Its pathology may be associated with degenerative lesions in cartilage secondary to inflammation linked to hyperplasia and chondrocyte apoptosis (9, 10). The treatment options for knee osteoarthritis include non-pharmacological, pharmacological, or surgical measures (11, 12). Current clinical guidelines recommend a multimodal, individualized non-pharmacological treatment program as first-line treatment for KOA (13, 14). The core treatment included therapeutic exercise (e.g., aerobic, resistance, strengthening, and proprioception), physical therapy (e.g., massage, ultrasound, and thermotherapy), lifestyle modifications, weight management, and education (11, 13, 15–17). These interventions aimed to relieve pain, improve physical function, and slow the progression of the disease (18–20).

Although the etiology of KOA remains largely undefined (21), some risk factors that have been proved to influence KOA susceptibility include age, sex, obesity, knee injury, muscle weakness, genetics, and ethnicity (22–26). Furthermore, many recent studies indicated that proprioceptive impairments could be an important risk factor for the incidence and progression of KOA (27–31). Proprioception mostly consists of several different biomechanical components, such as JPS, motion sense, velocity, and force (32). Proprioception derives from proprioceptors in skeletal muscles, tendons, ligaments, and joint capsule (33–35). With the progression of KOA, proprioception could also be decreased (30, 36). Additionally, proprioceptive impairments could be a cause of knee pain or activity limitations in KOA patients (29, 37).

The programs focused on improving or restoring proprioception have been referred to as proprioceptive trainings (38). Recently, although many studies have explored and analyzed the efficacy of proprioceptive training for KOA (39–41), several investigators have reported that there was insufficient clinical evidence of proprioceptive training for KOA, and the results of previous studies have been also inconsistent (35, 42). To our knowledge, two previous reviews have reported on the effects of proprioceptive training in KOA (35, 43). However, one of these is now about 10 years old, and the number of studies included is small (35), whereas the one recent review did not compare the efficacy of proprioceptive training with other general non-proprioceptive training for KOA (42). Besides, these two reviews did not assess the safety of proprioceptive training and investigate the effects of combinations of proprioceptive training with other interventions in KOA. Our interest in updating the current evidence has increased as the numerous renewals of high-quality studies on proprioceptive training in treating KOA (43–45). Therefore, we conducted this study to summarize all current high-quality evidence on the clinical efficacy and safety of proprioceptive training for KOA, and to provide a quantitative assessment. This will be very important and necessary, and the results of the study will provide evidence and guidance for the promotion and application of proprioceptive training in clinical practice.

METHODS

Methods and reporting of this systematic review and meta-analysis adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (46). The protocol for this meta-analysis was registered with PROSPERO (CRD 42021240587).

Search Strategy

We systematically searched the PubMed, Cochrane Library, Web of Science, and EMBASE databases from the inception dates to April, 16 2021. The following search string and MeSH terms were used to search: "Proprioceptive training," "Knee osteoarthritis," and "Randomized Controlled Trial." In addition, we also manually searched the reference lists of selected articles and reviews for additional relevant articles. Two independent reviewers (YW and ZW) screened eligible articles, all disagreements were resolved by independent third-party review and consensus. The search strategy is detailed in **Supplementary Table S1**.

Selection Criteria

We developed eligibility criteria for this study using the (PICOS) description model (47) of participants, interventions, comparisons, outcomes, and study design.

Participants

Inclusion criteria:

- Adult patients with KOA

Exclusion criteria:

- Participants who had suffered knee joint trauma or surgery
- Participants with other muscular, joint, or neurological conditions.

Intervention

- Proprioceptive training

Proprioceptive training includes proprioceptive, balance, and sensorimotor training. However, no restrictions were made in terms of the frequency, duration, or intensity of the intervention. Additionally, we excluded studies where the intervention was whole-body vibration or water training.

Comparators

- Proprioceptive training vs. no intervention
- Proprioceptive training vs. other non-proprioceptive training (e.g., resistance and strength training)
- Proprioceptive training with other non-proprioceptive training vs. other non-proprioceptive training
- Proprioceptive training with conventional physiotherapy vs. conventional physiotherapy.

Outcomes

Primary outcomes:

- Pain [visual analog scale (VAS), numeric rating scale (NRS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale, Knee Injury and Osteoarthritis Outcome Score (KOOS)]
- Stiffness (WOMAC, KOOS)
- Physical function (WOMAC, KOOS)

Secondary outcomes:

- Joint position sense (JPS)
- Muscle strength
- Mobility [walking-speed timed test (WST), Get up and go (GUG) test]
- Knee range of motion (ROM)
- Balance
- Adverse events.

Study Design

- Randomized controlled trials (RCTs)
- Published in English.

Data Extraction

Two independent reviewers (YW and ZW) used a standardized form extract the following information from each study in accordance with the pre-specified study protocol, including participant characteristics (e.g., age, gender, stage of KOA), study characteristics (e.g., lead author, publication year, country of origin, intervention frequency and duration, follow-up period), and main outcomes. Disagreements were resolved by discussion and consensus between the reviewers. If necessary, we will contact the corresponding authors to obtain the required information.

Quality Assessment

The methodological quality of each included studies was assessed independently by two reviewers (YW and ZW) using the Physiotherapy Evidence Database (PEDro) scale (46, 48). The PEDro scale (range, 0–10, with 10 indicating highest quality) is a reliable and valid appraisal tool to assess the quality of physiotherapy-based RCTs (48, 49). Furthermore, we also assessed the overall quality of the evidence for each outcome through the Grades of Recommendations, Assessment, Development, and Evaluation (GRADE) approach (47). Any inconsistency was resolved through independent third-party review and consensus.

Statistical Analysis

Data analyses were performed using Revman (version 5.3, Cochrane Collaboration) and Stata (version 13.0). We converted other forms of data (i.e., median, mean [95%CI], standard error and interquartile range) to means (SDs) based on the Cochrane Handbook for Systematic Reviews of Interventions (50). The standard mean differences (SMDs) with 95% confidence intervals (95% CIs) for pooled data were calculated. We pooled the data using a random-effects model and examined statistical heterogeneity by calculating the I^2 statistic. An I^2 statistic >50% was considered to be substantially heterogeneous (50, 51). We planned to perform subgroup analyses to identify potential determinants of efficacy. Sensitivity analysis was also used to explore potential sources of heterogeneity between studies and to assess whether the significant results were robust. Furthermore, we evaluated publication bias by examining funnel plots and statistical asymmetry tests (Begg's test and Egger's regression). $P < 0.05$ was considered statistically significant.

RESULTS

Study Selection

We retrieved 539 potentially relevant records through electronic and manual searching. EndNote X9 (Bld 12062) was used to screen eligible studies. Initially, 388 articles remained after removal of duplicates. Then we selected 40 articles for full-text review after screening their titles and abstracts. Fourteen articles were excluded since they did not meet inclusion criteria (e.g., non-randomization, no relevant outcome, ineligible intervention, non-English); two studies did not provide complete data for calculation of effect sizes. Ultimately, we selected 24 studies (39–41, 43–45, 52–69) for inclusion in our study (**Figure 1**).

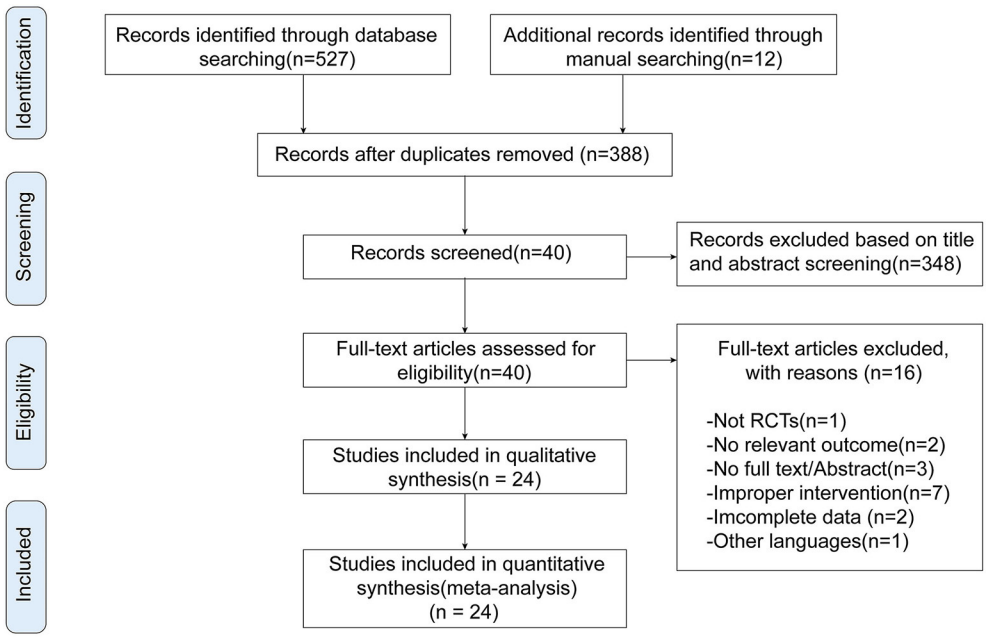


FIGURE 1 | Flowchart of study selection.

Study Characteristics

Twenty-four studies involving a total of 1,275 participants with KOA were included. The studies were from Brazil (52), Turkey (60, 64, 66, 69), Australia (58), Canada (59), Thailand (62), Egypt (55, 65), Iran (44), Malaysia (63), the United States (40, 41, 61), India (39, 43, 54, 68), and China (45, 53, 56, 57, 67). The publication intervals of 24 included articles were from 2005 to 2020, and the sample size ranging from 15 to 183 participants. Twenty-two studies reported the age of the participants. Their mean (SD) age ranged from 40.87 (4.91) to 72.4 (11.02) years. Except for three studies (39, 54, 61) that did not specify diagnostic criteria, all other studies used the Kellgren and Lawrence (70) radiological assessment scale or the American College of Rheumatologist's diagnostic classification (71) to diagnose KOA. Regarding the comparison of interventions, seven studies compared proprioceptive training to no intervention (40, 45, 56, 57, 59, 60, 67), eight studies compared proprioceptive training to other non-proprioceptive training (40, 52, 56, 57, 61, 62, 67, 68), seven studies compared proprioceptive training plus other non-proprioceptive training to other non-proprioceptive training (40, 41, 55, 58, 64–66), and seven studies compared proprioceptive training plus conventional physiotherapy to conventional physiotherapy (39, 43, 44, 53, 54, 63, 69).

The duration of the intervention ranges from 2 to 16 weeks. In addition, the shortest follow-up period was only 2 weeks (63) and the longest was 52 weeks (41, 66). The characteristics of the included studies are summarized in **Table 1**. And the detailed descriptions of interventions are presented in **Supplementary Table S2**.

Quality of Studies

The mean PEDro scale score for all studies was 6.25 (range, 4–8; **Table 2**), suggesting that the studies were of moderate quality. All 24 studies satisfied four of the PEDro criteria, namely "random allocation," "similar baseline," "between-group statistics," and "point measures," but only eight studies (40, 41, 52, 57–59, 61, 62) used concealed allocation to minimize allocation bias. However, except for two (29, 38), the remaining studies did not account for "the blinding of the subjects and therapists," 12 (39, 41, 44, 52, 53, 55, 57–59, 64, 66, 67) of the studies employed assessor blinding. In addition, six of the studies (40, 41, 43, 45, 53, 61) lost more than 15% participants during follow-up and the inconsistent use of "intention-to-treat" analyses were found to be consistent trial limitations in most of the studies.

Assessed Outcomes and Evidence Synthesis

Primary Outcomes

Pain

Nine studies (40, 44, 45, 53, 57, 58, 61, 66, 69) used the WOMAC pain subscale to assess pain. Subgroup analysis showed significant improvement in pain for proprioceptive training compared to no intervention (SMD = −1.07, 95%CI: [−1.46, −0.68], I^2 = 0%, $P < 0.00001$). When proprioceptive training compared against other non-proprioceptive training, the meta-analysis showed no statistically significant difference in alleviating pain (SMD = −0.02, 95%CI: [−0.74, 0.69], I^2 = 0%, $P = 0.95$). When proprioceptive training plus other non-proprioceptive training compared to other non-proprioceptive training, the meta-analysis revealed no significant difference (SMD = −0.17,

TABLE 1 | Characteristics of the included studies.

References: publication year, country	Study design	Participant characteristics	Diagnosis criteria/K-L grade	Intervention	Intervention characteristics, follow-up	Outcome measures	PEDro score
Gomiero et al. (52), 2018, Brazil	RCT	No. (M/F): 64 (3/61) IG: 32(2/30) CG: 32 (1/31) Dropout: 2 Mean Age ± SD, years: IG: 61.6 ± 6.8 CG: 61.8 ± 6.4	ACR/K-L I-IV	IG: Proprioceptive training CG: Resistance training	16 weeks, 2 sessions/week	VAS; WOMAC (total); Mobility; Balance	8
Tsauo et al. (53), 2008, Taiwan, China	RCT	No. (M/F):29 (5/24) IG: 15(1/14) CG: 14 (4/10) Dropout: 31 Mean Age ± SD, years: IG: 61.7 ± 6.6 CG: 60.1 ± 6.7	ACR/K-L II-III	IG: Proprioceptive training plus Conventional physiotherapy CG: Conventional physiotherapy	8 weeks, 3 sessions/week, 30 min/session	WOMAC (pain); WOMAC (stiffness); WOMAC (physical function); JPS	5
Kumar et al. (54), 2013, India	RCT	No. (M/F): 44 (19/25) IG: 22 CG: 22 Dropout: 0 Mean Age ± SD, years: IG: 53.18 ± 6.88 CG: 53.32 ± 5.36	NA	IG: Proprioceptive training plus Conventional physiotherapy CG: Conventional physiotherapy	4 weeks, 3 sessions/week	NRS; WOMAC (physical function); JPS	6
Fitzgerald et al. (41), 2011, USA	RCT	No. (M/F): 183 (61/122) IG: 91 (31/60) CG: 92 (30/62) Dropout: 38 Mean Age ± SD, years: IG: 63.3 ± 8.9 CG: 64.6 ± 8.4	ACR/K-L II-IV	IG: Proprioceptive training plus Strength training CG: Strength training	8, 26, and 52 weeks, 3 sessions/week, ≥30 min/session	NRS; WOMAC (physical function); WOMAC (total); Mobility	7
Rogers et al. (40), 2012, USA	RCT	No. (M/F):33 (13/20) IG (PT): 8 CG (RT): 8 CG (PT + RT): 9 CG: 8 Dropout: 11 Mean Age ± SD, years: IG (PT): 70.7 ± 10.7 CG (RT): 70.8 ± 6.5 CG (PT + RT): 68.8 ± 10.1 CG: 71.2 ± 10.9	ACR	IG (PT): Proprioceptive training CG (RT): Resistance training CG (PT + RT): Proprioceptive training plus Resistance training CG: Without intervention	8 weeks, 3 sessions/week, 30–40 min/session	WOMAC (pain); WOMAC (stiffness); WOMAC (physical function); WOMAC (total)	6

(Continued)

TABLE 1 | Continued

References: publication year, country	Study design	Participant characteristics	Diagnosis criteria/K-L grade	Intervention	Intervention characteristics, follow-up	Outcome measures	PEDro score
Ahmed et al. (55), 2011, Egypt	RCT	No. (M/F): 40 IG: 20 CG: 20 Dropout: 0 Mean Age ± SD, years: IG: 60 ± 3.6 CG: 62 ± 3.2	ACR/K-L II	IG: Proprioceptive training plus Traditional exercise CG: Traditional exercise	6 weeks, 3 sessions/week	VAS; JPS	7
Lin et al. (56), 2007, Taiwan, China	RCT	No. (M/F):81 (19/62) IG (PT): 29(9/20) CG (RT): 26(5/21) CG: 26(5/21) Dropout: 8 Mean Age ± SD, years: IG (PT): 61.6 ± 8.1 CG (RT): 61.0 ± 7.7 CG: 62.8 ± 6.3	ACR/K-L I-III	IG (PT): Proprioceptive training CG (RT): Resistance training CG: Without intervention	8 weeks, 3 sessions/week	Muscle strength	5
Jahanjoo et al. (44), 2019, Iran	RCT	No. (M/F):60 (13/47) IG: 30(8/22) CG: 30(5/25) Dropout: 0 Mean Age ± SD, years: IG: 57.53 ± 0.8 CG: 55.57 ± 1.6	ACR/K-L I-III	IG: Proprioceptive training plus Conventional physiotherapy CG: Conventional physiotherapy	5 weeks, 2 sessions/week	VAS; WOMAC (pain); WOMAC (stiffness); WOMAC (physical function); WOMAC (total); Mobility	7
Lin et al. (57), 2009, Taiwan, China	RCT	No. (M/F): 108 (33/75) IG (PT): 36 (11/25) CG (ST): 36 (12/24) CG: 36 (10/26) Dropout: 5 Mean Age ± SD, years: IG (PT): 63.7 ± 8.2 CG (ST): 61.6 ± 7.2 CG: 62.2 ± 6.7	K-L I-III	IG (PT): Proprioceptive training CG (ST): Strength training CG: Without intervention	8 weeks, 3 sessions/week	WOMAC (pain); WOMAC (physical function); JPS; Mobility	8
Gohil and Shukla (43), 2020, India	RCT	No. (M/F):22 IG: 11 CG:11 Dropout: 0	K-L II-III	IG: Proprioceptive training plus Conventional physiotherapy CG: Conventional physiotherapy	8 weeks, 3 sessions/week	NRS; WOMAC (physical function); JPS	4
Kirthika et al. (39), 2018, India	RCT	No. (M/F):40 IG: 20 CG:20 Dropout: 3 Mean Age ± SD, years: IG: 58.2 ± 5.7 CG: 58.8 ± 5.3	NA	IG: Proprioceptive training plus Conventional physiotherapy CG: Conventional physiotherapy	12 weeks, 5 sessions/week	VAS; WOMAC (total)	6

(Continued)

TABLE 1 | Continued

References: publication year, country	Study design	Participant characteristics	Diagnosis criteria/K-L grade	Intervention	Intervention characteristics, follow-up	Outcome measures	PEDro score
Pazit et al. (58), 2018, Australia	RCT	No. (M/F):19 (9/10) IG: 10(4/6) CG: 9(5/4) Dropout: 0 Mean Age ± SD, years: IG: 65.10 ± 4.77 CG: 67.78 ± 6.28	ACR	IG: Proprioceptive training plus Resistance training CG: Resistance training	8 weeks, 2 sessions/week	WOMAC (pain); WOMAC (stiffness); WOMAC (physical function); WOMAC (total); Mobility	8
Takacs et al. (59), 2017, Canada	RCT	No. (M/F):36(6/30) IG: 17(0/17) CG: 19(6/13) Dropout: 4 Mean Age ± SD, years: IG: 66.1 ± 8.7 CG: 67.1 ± 5.4	ACR/K-L II-IV	IG: Proprioceptive training CG: Without intervention	10 weeks, 4 sessions/week	NRS; WOMAC (physical function); Muscle strength	7
Sekir and Gür (60), 2005, Turkey	RCT	No. (M/F):22(6/16) IG: 12(3/9) CG: 10(3/7) Dropout: 0 Mean Age ± SD, years: IG: 59 ± 8.9 CG: 62 ± 8.1	ACR/K-L II-III	IG: Proprioceptive training CG: Without intervention	6 weeks, 2 sessions/week	VAS; JPS; Muscle strength	6
Rogers et al. (61), 2011, USA	RCT	No. (M/F):15 IG: 6 CG: 9 Dropout: 5 Mean Age ± SD, years: IG: 69.29 ± 11.36 CG: 72.4 ± 11.02	NA	IG: Proprioceptive training CG: Strength training	8 weeks, 3 sessions/week, 30 min/session	WOMAC (pain); WOMAC (stiffness); WOMAC (physical function); Mobility	5
Chaipinyo and Karoonsupcharoen (62), 2009, Thailand	RCT	No. (M/F):48(11/31) IG: 24(9/15) CG: 24(2/22) Dropout: 6 Mean Age ± SD, years: IG: 62 ± 6 CG: 70 ± 6	ACR	IG: Proprioceptive training CG: Strength training	4 weeks, 5 sessions/week	KOOS (pain); KOOS (symptoms); Muscle strength; Mobility	6
Mondam et al. (63), 2012, Malaysia	RCT	No. (M/F):50 IG: 25 CG:25 Dropout: 0	K-L I-II	IG: Proprioceptive training plus Conventional physiotherapy CG: Conventional physiotherapy	2 weeks, 7 sessions/week	VAS; WOMAC (total); Knee ROM	6
Diracoglu et al. (64), 2005, Turkey	RCT	No. (M/F):66(0/66) IG: 32 CG: 28 Dropout: 6 Mean Age ± SD, years: IG: 50.3 ± 6.5 CG: 50.8 ± 7.9	ACR/K-L I-II	IG: Proprioceptive training plus Strength training CG: Strength training	8 weeks, 3 sessions/week	WOMAC (physical function)	6

(Continued)

TABLE 1 | Continued

References: publication year, country	Study design	Participant characteristics	Diagnosis criteria/K-L grade	Intervention	Intervention characteristics, follow-up	Outcome measures	PEDro score
Elgendy et al. (65), 2005, Egypt	RCT	No. (M/F):30 IG: 15 CG:15 Dropout: 0	ACR	IG: Proprioceptive training plus Traditional exercise CG: Traditional exercise	8 weeks, 3 sessions/week	VAS; JPS	6
Song et al. (45), 2020, China	RCT	No. (M/F):29(11/18) IG: 13(5/8) CG: 16(6/10) Dropout: 7 Mean Age ± SD, years: IG: 68.5 ± 4.3 CG: 67.4 ± 3.4	K-L I-III	IG: Proprioceptive training CG: Without intervention	12 weeks, 3 sessions/week, 60 min/session	WOMAC (pain); Knee ROM	4
Diracoglu et al. (66), 2008, Turkey	RCT	No. (M/F):66(0/66) IG: 32 CG: 28 Dropout: 6 Mean Age ± SD, years: IG: 50.3 ± 6.5 CG: 50.8 ± 7.9	ACR/K-L I-II	IG: Proprioceptive training plus Strength training CG: Strength training	8.52 weeks, 3 sessions/week	WOMAC (pain); WOMAC (stiffness); WOMAC (physical function); WOMAC (total)	6
Jan et al. (67), 2009, Taiwan, China	RCT	No. (M/F):106(0/66) IG(PT): 36(12/24) CG(RT): 35(10/25) CG:35(11/24) Dropout: 6 Mean Age ± SD, years: IG(PT): 62.0 ± 6.7 CG(RT): 63.2 ± 6.8 CG:62.2 ± 6.7	ACR/K-L I-III	IG (PT): Proprioceptive training CG (RT): Resistance training CG: Without intervention	8 weeks, 3 sessions/week	WOMAC (physical function); JPS; Muscle strength; Mobility	7
Vamsidhar et al. (68), 2017, India	RCT	No. (M/F):30 IG: 15 CG: 15 Dropout: 0 Mean Age ± SD, years: IG: 40.87 ± 4.91 CG: 41.53 ± 6.28	K-L II-III	IG: Proprioceptive training CG: Strength training	3 weeks, 3 sessions/week	VAS; WOMAC (total)	6
Duman et al. (69), 2012, Turkey	RCT	No. (M/F): 54 (5/49) IG: 30 CG: 24 Dropout: 0 Mean Age ± SD, years: 64 ± 3.7	ACR/K-L III-IV	IG: Proprioceptive training plus Conventional physiotherapy plus NSAID meloxicam CG: Conventional physiotherapy plus NSAID meloxicam	3 weeks, 5 sessions/week	WOMAC (pain); WOMAC (stiffness); WOMAC (physical function); WOMAC (total); JPS	6

ACR, American College of Rheumatologists; CG, control group; CP, conventional physiotherapy; F, female; IG, intervention group; JPS, joint position sense; K-L, Kellgren and Lawrence radiological assessment scale; KOOS, Knee Injury and Osteoarthritis Outcome Score; M, male; NRS, numeric rating scale; NSAID, non-steroidal anti-inflammatory drug; PEDro, Physiotherapy Evidence Database; PT, proprioceptive training; RCT, Randomized Controlled Trials; ROM, range of motion; RT, resistance training; SD, Standard deviation; ST, strength exercise; TE, traditional exercise; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

TABLE 2 | PEDro scores of the included studies.

Study	Year	Eligibility criteria	Random allocation	Concealed allocation	Similar baseline	Blinding subjects	Blinding therapists	Blinding assessors	Dropout <15%	Intention to treat	Between-group statistics	Point measures	Total score
Gomiero et al. (52)	2018	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8
Tsauo et al. (53)	2008	Yes	Yes	No	Yes	No	No	Yes	No	No	Yes	Yes	5
Rogers et al. (40)	2012	Yes	Yes	Yes	Yes	Yes	No	No	No	No	Yes	Yes	6
Sekir and Gür (60)	2005	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	6
Rogers et al. (61)	2011	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	5
Pazit et al. (58)	2018	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8
Takacs et al. (59)	2017	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	7
Lin et al. (56)	2007	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	5
Lin et al. (57)	2009	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8
Jahanjoo et al. (44)	2019	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	7
Chaipinyo and Karoonsupcharoen (62)	2009	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes	6
Fitzgerald et al. (41)	2011	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	7
Duman et al. (69)	2012	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	6
Diracoglu et al. (64)	2005	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	6
Diracoglu et al. (66)	2008	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	6
Ahmed (55)	2011	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	7
Kumar et al. (54)	2013	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	6
Elgendy et al. (65)	2005	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	6
Gohil and Shukla (43)	2020	Yes	Yes	No	Yes	No	No	No	No	No	Yes	Yes	4
Song et al. (45)	2020	Yes	Yes	No	Yes	No	No	No	No	No	Yes	Yes	4
Kirthika et al. (39)	2018	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	8
Mondam et al. (63)	2012	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	6
Jan et al. (67)	2009	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	7
Vamsidhar et al. (68)	2017	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	6

PEDro, Physiotherapy Evidence Database scale.

95%CI: [−0.58, 0.23], $I^2 = 0\%$, $P = 0.40$). Additionally, the meta-analysis also showed no significant difference in relieving pain when proprioceptive training plus conventional physiotherapy compared against conventional physiotherapy (SMD = −0.39, 95%CI: [−0.99, 0.22], $I^2 = 68\%$, $P = 0.21$; **Figure 2**).

Stiffness

Seven studies (40, 44, 53, 58, 61, 66, 69) used the WOMAC stiffness subscale to assess stiffness. When proprioceptive training compared to no intervention, only one study reported WOMAC stiffness score, and demonstrated that proprioceptive training effectively improved stiffness ($P < 0.05$). When proprioceptive training compared to other non-proprioceptive training, the subgroup analysis showed no statistically significant difference in improving stiffness (SMD = −0.06, 95%CI: [−0.78, 0.65], $I^2 = 0\%$, $P = 0.86$). When proprioceptive training plus other non-proprioceptive training compared against other non-proprioceptive training, the meta-analysis revealed no significant difference (SMD = −0.09, 95%CI: [−0.69, 0.50], $I^2 = 43\%$, $P = 0.76$). Furthermore, the meta-analysis also showed no significant difference in improving stiffness when proprioceptive training plus conventional physiotherapy compared against conventional physiotherapy (SMD = 0.31, 95%CI: [−0.37, 0.99], $I^2 = 74\%$, $P = 0.37$; **Figure 3**).

Physical Function

Eighteen studies (39–41, 43, 44, 52–54, 57–59, 61, 63, 64, 66–69) used the WOMAC physical function subscale and WOMAC total score to assess physical function. When proprioceptive training compared to no intervention, the subgroup analysis showed significant improvement in physical function (SMD = −0.97, 95%CI: [−1.26, −0.67], $I^2 = 0\%$, $P < 0.00001$). Also, one study (40) showed statistically significant difference in WOMAC total score ($P < 0.05$). When proprioceptive training compared to other non-proprioceptive training, the meta-analysis showed no statistically significant difference in improving physical function (SMD = −0.03, 95%CI: [−0.75, 0.69], $I^2 = 3\%$, $P = 0.94$). With respect to WOMAC total score, the meta-analysis also revealed no significant difference (SMD = −0.86, 95%CI: [−2.68, 0.97], $I^2 = 93\%$, $P = 0.36$). When proprioceptive training plus other non-proprioceptive training compared against other non-proprioceptive training, the meta-analysis revealed significant improvement in physical function (SMD = −0.34, 95%CI: [−0.56, −0.12], $I^2 = 0\%$, $P = 0.003$). Similarly, the meta-analysis showed significant difference in WOMAC total score (SMD = −0.26, 95%CI: [−0.51, −0.01], $I^2 = 0\%$, $P = 0.04$). Furthermore, the meta-analysis showed no significant difference in improving physical function when proprioceptive training plus conventional physiotherapy compared against conventional physiotherapy (SMD = 0.01, 95%CI: [−0.57, 0.60], $I^2 = 77\%$, $P = 0.97$). Similarly, the meta-analysis also showed no significant difference in WOMAC total score (SMD = −0.57, 95%CI: [−1.69, 0.54], $I^2 = 93\%$, $P = 0.31$; **Figures 4**, **5**).

Secondary Outcomes

JPS

Nine studies (43, 53–55, 57, 60, 65, 67, 69) used the reposition error test to assess JPS. Subgroup analysis showed significant improvement in JPS for proprioceptive training compared to no intervention (SMD = −1.73, 95%CI: [−2.09, −1.37], $I^2 = 0\%$, $P < 0.00001$). When proprioceptive training compared to other non-proprioceptive training, the meta-analysis showed significant difference in improving JPS (SMD = −1.28, 95%CI: [−1.64, −0.92], $I^2 = 0\%$, $P < 0.00001$). When proprioceptive training plus other non-proprioceptive training compared against other non-proprioceptive training, the meta-analysis revealed statistically significant difference (SMD = −1.54, 95%CI: [−2.74, −0.34], $I^2 = 79\%$, $P = 0.01$). Additionally, the meta-analysis also showed significant improvement in JPS when proprioceptive training plus conventional physiotherapy compared against conventional physiotherapy (SMD = −0.95, 95%CI: [−1.73, −0.18], $I^2 = 78\%$, $P = 0.02$; **Figure 6**).

Muscle Strength

Three studies (56, 62, 67) assessed muscle strength by measuring knee flexion and extension torque. When proprioceptive training compared to no intervention, the subgroup analysis revealed that participants in the proprioceptive training group presented significantly increased knee flexion torque at the velocity of 60°/s (SMD = 0.65, 95%CI: [0.29, 1.01], $I^2 = 0\%$, $P = 0.0004$), but there was no significant difference at the velocity of 120 or 180°/s ($P > 0.05$; **Table 3**). Likewise, there was also significant greater improvement of knee extension torque in participants of the proprioceptive training group at the velocity of 60°/s (SMD = 0.42, 95%CI: [0.07, 0.78], $I^2 = 0\%$, $P = 0.02$), but no significant difference at the velocity of 120 or 180°/s ($P > 0.05$). When proprioceptive training compared against other non-proprioceptive training, the meta-analysis indicated that participants in the proprioceptive training group showed statistically significantly greater improvements in knee flexion torque at the velocity of 60°/s (SMD = 0.71, 95%CI: [0.30, 1.12], $I^2 = 0\%$, $P = 0.0008$; **Table 4**). Furthermore, Lin et al. (56) demonstrated that participants in the other non-proprioceptive training group presented significantly increased knee flexion torque at the velocity of 120 or 180°/s ($P < 0.05$). Nevertheless, the meta-analysis showed no statistically significant difference between the groups (SMD = 0.50, 95%CI: [−0.61, 1.61], $I^2 = 86\%$, $P = 0.38$) when knee extension torque was measured at the velocity of 60°/s. As in flexion, Lin et al. (56) indicated that participants in the other non-proprioceptive training group showed significantly higher knee flexion torque at the velocity of 120 or 180°/s ($P < 0.05$).

Mobility

Two studies (57, 67) used the WST test to assess mobility. When proprioceptive training compared to no intervention, the subgroup analysis demonstrated that participants in the proprioceptive training group showed greater mobility when assessed for timed walk over ground (SMD = −0.57, 95%CI: [−0.90, −0.24], $I^2 = 0\%$, $P = 0.0008$), timed stair ascent and descent (SMD = −1.15, 95%CI: [−1.50, −0.79], $I^2 = 0\%$, $P < 0.00001$), and timed walk over spongy surface (SMD = −1.66, 95%CI: [−2.05,−1.28], $I^2 = 0\%$, $P < 0.00001$; **Table 3**). When proprioceptive training compared against other non-proprioceptive training, the meta-analysis revealed that participants in the proprioceptive training group presented

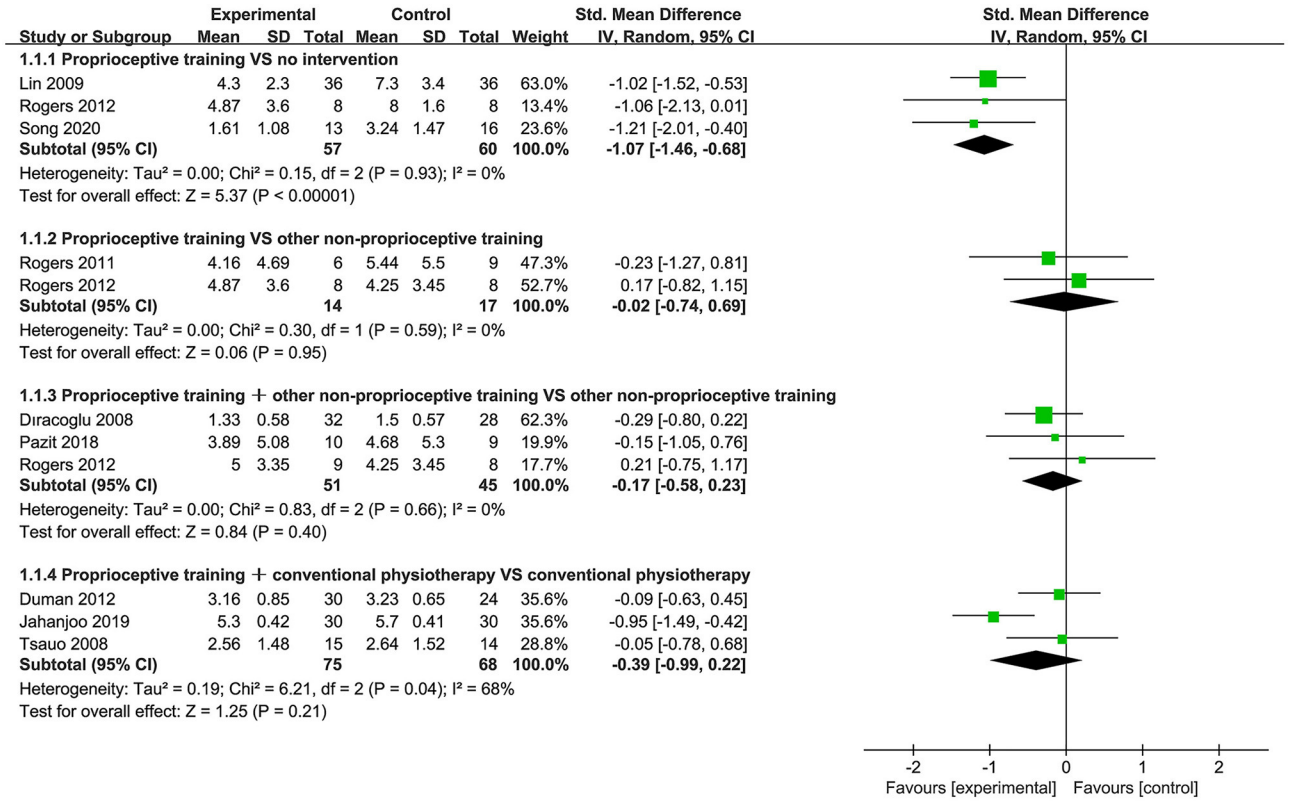


FIGURE 2 | Forest plot of meta-analysis on pain.

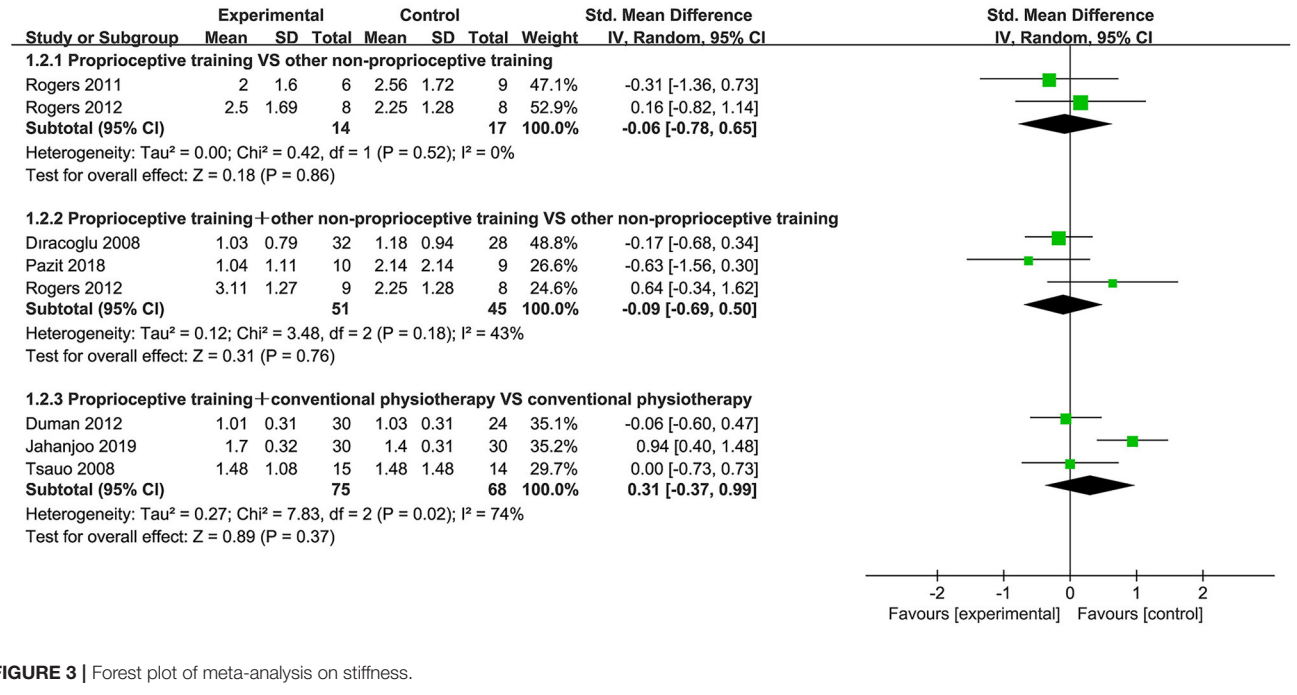


FIGURE 3 | Forest plot of meta-analysis on stiffness.

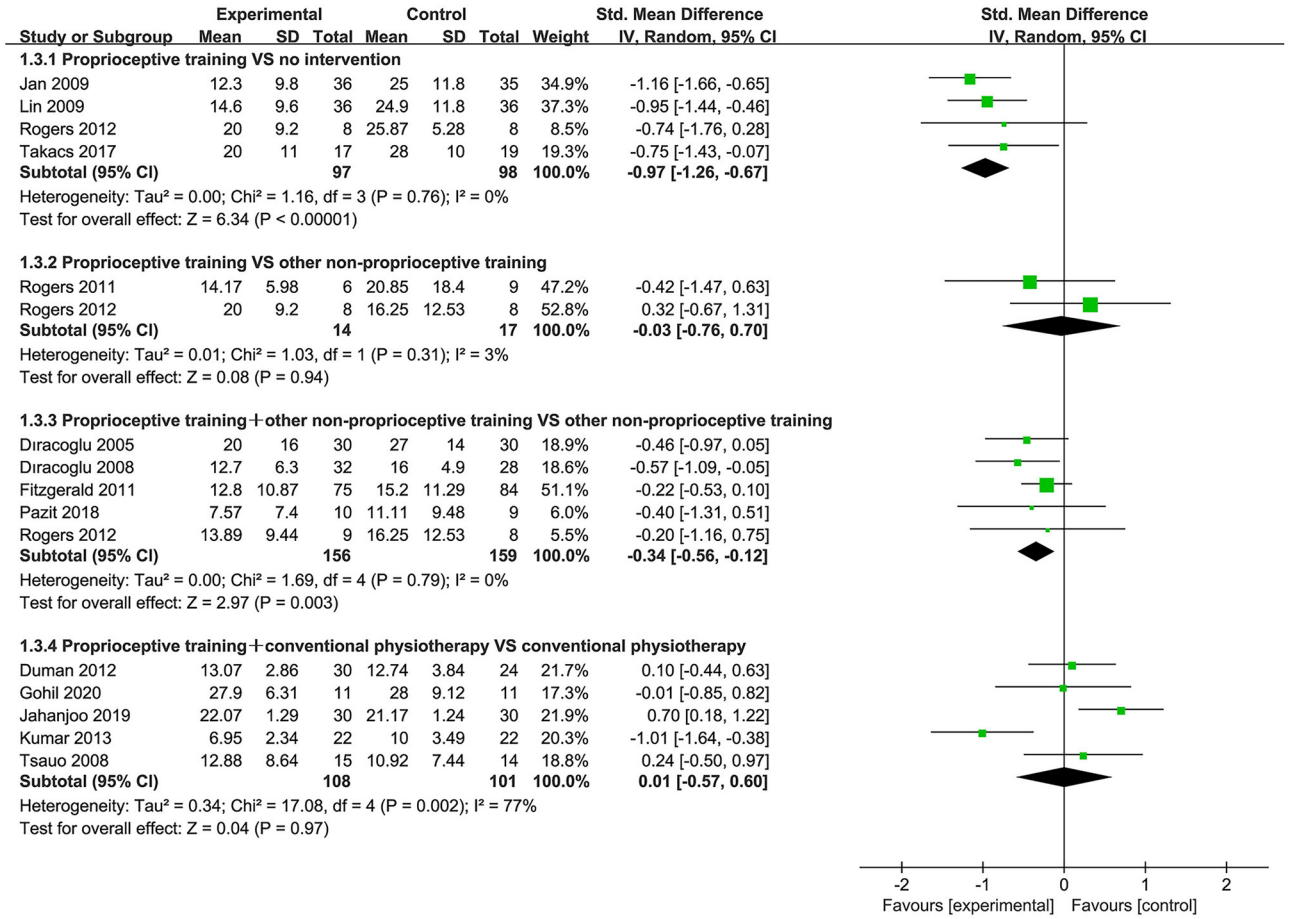


FIGURE 4 | Forest plot of meta-analysis on WOMAC (physical function) score.

increased mobility when assessed for timed walk over spongy surface (SMD = −0.76, 95%CI: [−1.33, −0.18], I^2 = 0%, P = 0.01), but no statistically significant difference in timed walk over ground and timed stair ascent and descent ($P > 0.05$; **Table 4**). Furthermore, four studies (41, 58, 61, 62) used the GUG test to assess mobility. Subgroup analysis showed no statistically significant difference between the groups when proprioceptive training compared against other non-proprioceptive training (SMD = −0.46, 95%CI: [−2.81, 1.89], I^2 = 92%, P = 0.70; **Table 4**). When proprioceptive training combined with other non-proprioceptive training compared against other non-proprioceptive training, the meta-analysis also revealed no significant difference in mobility (SMD = 0.05, 95%CI: [−0.55, 0.65], I^2 = 46%, P = 0.87; **Supplementary Figure S1**).

Knee ROM and Balance

One study (45) used standard goniometric procedures (72) to measure knee ROM and showed significant improvement in knee ROM for proprioceptive training compared to no intervention ($P < 0.05$). In addition, when proprioceptive training plus other non-proprioceptive training compared against other non-proprioceptive training, Mondam et al. (63) used the Goniometer to measure knee ROM and demonstrated that there was statistically significantly greater knee ROM for the proprioceptive training plus other non-proprioceptive training group ($P < 0.05$). For balance, Gomiero et al. (52) assessed balance using the Tinetti balance scale and demonstrated that there was significant difference between the proprioceptive training group and the non-proprioceptive training group ($P < 0.05$).

Adverse Events

Only eight studies (41, 45, 52, 56, 58, 59, 64, 66) reported safety-related data, however some trials stated that no adverse events were reported (41, 64, 66), no serious adverse events during the intervention occurred (58). In addition, from another four studies (45, 52, 56, 58) that provided data (n = 210), 12 participants (5.7%) reported adverse events, including post-exercise soreness, back pain, hip soreness, foot pain, and ankle injury.

Sensitivity Analysis

We used the leave-one-out method to conduct the sensitivity analyses for each of the evaluated outcomes (**Supplementary Tables S3–S8**). When proprioceptive training

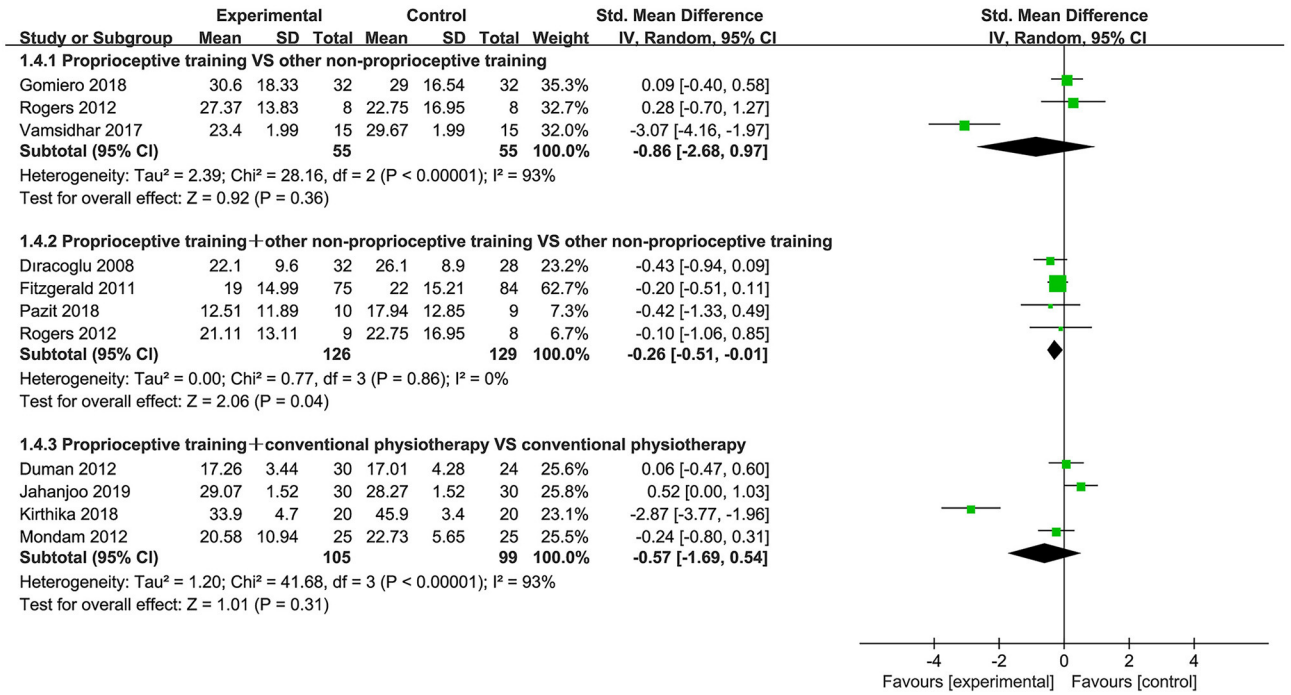


FIGURE 5 | Forest plot of meta-analysis on WOMAC (total) score.

compared to other general non-proprioceptive training, the sensitivity analyses for WOMAC (total) score showed that the heterogeneity decreased to 0 after removing the study conducted by Vamsidhar et al. (68). When proprioceptive training plus conventional physiotherapy compared against conventional physiotherapy, the sensitivity analyses for pain and stiffness revealed that the heterogeneity decreased to 0 after removing Jahanjoo et al.'s study (44). And the sensitivity analyses for WOMAC (physical function) score showed that the removal of study conducted by Kumar et al. (54) significantly reduced the heterogeneity. The sensitivity analyses for WOMAC (total) score demonstrated that the removal of study conducted by Kirthika et al. (39) significantly reduced the heterogeneity. Furthermore, the sensitivity analyses for JPS showed the significant impact of proprioceptive training combined with conventional physiotherapy on JPS was highly affected by the study by Duman et al. (69). In general, these results suggested that these studies conducted by Vamsidhar et al. (68), Jahanjoo et al. (44), Kumar et al. (54), Kirthika et al. (39), or Duman et al. (69) could be the potential source of heterogeneity.

Publication Bias

No obvious asymmetry was found by the visual inspection of funnel plots (**Figure 7**). There was no evidence for publication bias on the WOMAC (physical function) score (Begg's test, $P = 0.56$; Egger's regression, $P = 0.95$) and the WOMAC (total) score (Begg's test, $P = 0.28$; Egger's regression, $P = 0.15$).

Quality of Evidence

Based on the GRADE approach for evaluating quality of the evidence, the results showed that there is moderate evidence in pain, low to moderate evidence in stiffness, physical function, muscle strength and mobility, and very low to moderate evidence in JPS. The corresponding information are detailed in **Supplementary Table S3**.

DISCUSSION

Results of this meta-analysis indicated that compared to no intervention, proprioceptive training significantly improved pain, stiffness, physical function, JPS, muscle strength, mobility, and knee ROM in people with KOA. When compared to other non-proprioceptive training, proprioceptive training presented similar outcomes, only providing greater results in terms of JPS and mobility (timed walk over spongy surface). When proprioceptive training plus other non-proprioceptive training compared to other non-proprioceptive training, the two groups showed similar outcomes, but there was a greater improvement for JPS, physical function, and knee ROM in the proprioceptive training plus other non-proprioceptive training group. When proprioceptive training combined with conventional physiotherapy compared against conventional physiotherapy, the two groups demonstrated similar outcomes, but there was a significant improvement for JPS in the proprioceptive training combined with conventional physiotherapy group. In addition, although only eight studies reported safety-related data, considering the low rate of reported adverse events (5.7%)

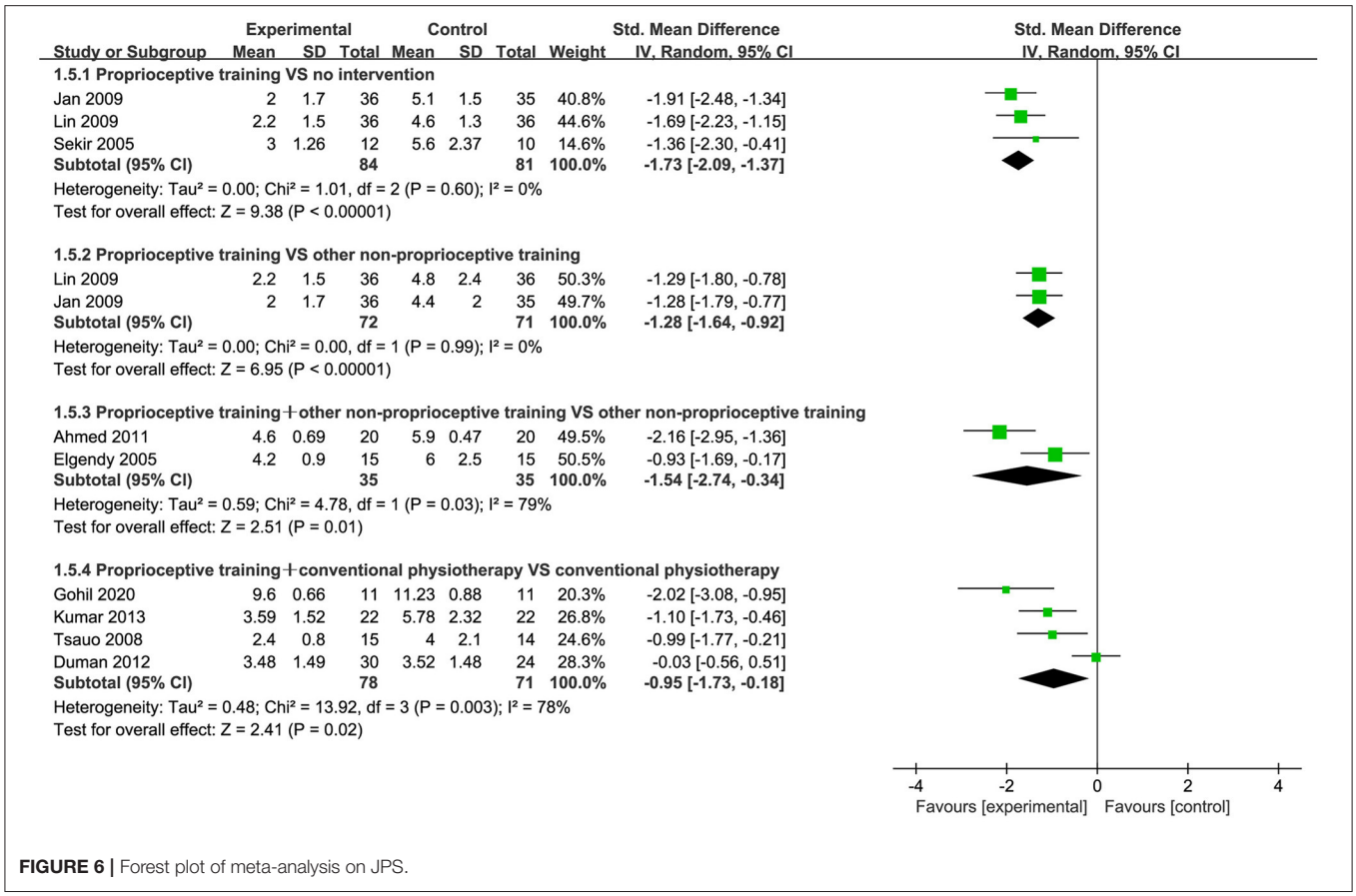


FIGURE 6 | Forest plot of meta-analysis on JPS.

TABLE 3 | Meta-analysis results of muscle strength and mobility when proprioceptive training compared to no intervention.

Outcomes	IG (sample size)	CG (sample size)	SMD (95% CI)	*P*-value	I^2 (%)
Knee flexion torque at 60°/s	65	61	0.65 (0.29, 1.01)	0.0004	0
Knee flexion torque at 120°/s	65	61	0.32 (−0.03, 0.67)	0.08	0
Knee flexion torque at 180°/s	65	61	0.25 (−0.10, 0.60)	0.17	0
Knee extension torque at 60°/s	65	61	0.42 (0.07, 0.78)	0.02	0
Knee extension torque at 120°/s	65	61	0.30 (−0.05, 0.65)	0.09	0
Knee extension torque at 180°/s	65	61	0.31 (−0.04, 0.66)	0.09	0
Timed walk over ground	72	71	−0.57 (−0.90, −0.24)	0.0008	0
Timed stair ascent and descent	72	71	−1.15 (−1.50, −0.79)	<0.00001	0
Timed walk over spongy surface	72	71	−1.66 (−2.05, −1.28)	<0.00001	0

CG, control group; CI, confidence interval; IG, intervention group; SMD, standard mean difference.

and about half of the reported adverse events ($n = 5$) were normal reactions after exercise, such as post-exercise soreness. Therefore, proprioceptive training could still be considered a relatively safe intervention for the treatment of KOA.

In this present study, the outcome measurements of JPS and walking speed over spongy surfaces were also specifically used to assess proprioception. When proprioceptive training compared to no intervention or other non-proprioceptive training, participants in proprioceptive training group showed greater improvement in the two outcomes. Similarly, when proprioceptive training plus other non-proprioceptive training compared against other non-proprioceptive training or proprioceptive training combined with conventional physiotherapy compared against conventional physiotherapy, participants in the groups that included proprioceptive training presented significantly improved JPS. This further demonstrated that the proprioceptive training could specifically improve knee proprioception in patients with KOA, thereby indicating the effectiveness of this intervention.

We found that the measurements of the muscle strength/torque were inconsistent. Previous studies have indicated that the improvement of proprioception could

TABLE 4 | Meta-analysis results of muscle strength and mobility when proprioceptive training compared to other non-proprioceptive training.

Outcomes	IG (sample size)	CG (sample size)	SMD (95% CI)	*P*-value	I^2 (%)
Knee flexion torque at 60°/s	53	44	0.71 (0.30, 1.12)	0.0008	0
Knee extension torque at 60°/s	53	44	0.50 (−0.61, 1.61)	0.38	86
Timed walk over ground	72	71	0.06 (−0.28, 0.40)	0.72	6
Timed stair ascent and descent	72	71	0.35 (−0.09, 0.80)	0.12	44
Timed walk over spongy surface	72	71	−0.76 (−1.33, −0.18)	0.01	64
GUG test	30	27	−0.46 (−2.81, 1.89)	0.70	92

CG, control group; CI, confidence interval; GUG, Get up and go; IG, intervention group; SMD, standard mean difference.

promote the increase of muscle strength (73–75). The results were partially consistent with our findings. When proprioceptive training compared to other non-proprioceptive training, the intervention in the other non-proprioceptive training group was knee extension exercises. This may account for the finding that the greater improvement of knee extensor torque was observed in the other non-proprioceptive training group with respect to muscle strength of the knee extensors. In addition, we also found that there was a greater improvement for physical function and knee ROM in the proprioceptive training plus other non-proprioceptive training group. This may be due to the greater training intensity and frequency of the combined intervention, as well as the greater variety of training method.

Comparison to Prior Reviews

To our knowledge, this is the first systematic review and meta-analysis to evaluate the safety of proprioceptive training for KOA and the effects of combinations of proprioceptive training with other interventions in KOA. In recent years, only a few studies have systematically investigated the effect of proprioceptive training on knee proprioception and function in KOA. Smith et al. (35) conducted a study to determine the effectiveness of proprioceptive training for KOA, the results indicated that significant improvement in functional outcomes (e.g., physical function, JPS, muscle strength, and mobility) for proprioceptive training compared to no intervention. When compared to other general non-proprioceptive training, proprioceptive training presented similar outcomes, only providing greater results in terms of JPS and mobility (timed walk over spongy surface). This is consistent with our review. In the most recent review (42), there is some evidence that proprioceptive training effectively improved pain and physical function in KOA, but stiffness and some other mobility measures (e.g., GUG) were unchanged after proprioceptive training. This is partially in line with our findings. The differences in the grouping of interventions may account for these inconsistent results.

Limitations

However, this present study had several following limitations. Firstly, methodologic limitations (e.g., inadequately concealed allocation, a small number of studies using therapists/subjects blinding or assessors blinding, high dropout rates, and inconsistent use of "intention-to-treat" analyses) could overestimate the overall effect size. Secondly, given the relatively small number of studies included in our review and the low number of participants per study, some results cannot be considered robust. Thirdly, since some of the included studies did not describe the race or age of the participants, we could not conduct a subgroup analysis based on race or age. Additionally, due to the relatively small number of included studies, subgroup analysis based on intervention characteristics (e.g., duration, dose or intensity) could not be carried out. Therefore, we could not determine the influence of these factors on the results. Fourthly, in our study, the components of the proprioceptive training programs in each study are different. We should perform the meta-analysis on each of the proprioceptive training separately, however, this is not possible given the few studies there are. These factors may also have a potential influence on our results. Furthermore, only two studies assessed outcomes after a year of follow-up. Accordingly, it is unable to determine the long-term effects of proprioceptive training in KOA.

Implications for Further Research and Practice

A larger and higher quality body of evidence is required before definite conclusions or recommendations could be made. Given that the main drawback of this review was the poor methodological quality of the included studies, future trials should use rigorous methodology to further ensure adequate concealed allocation, randomization, assessors blinding, and "intention-to-treat" analyses. Future researchers should improve the reporting in accordance with CONSORT guidelines (76). Future trials must also improve reporting of safety. Considering that this type of training may have potential therapeutic value, therefore it is necessary to further evaluate the optimal type of proprioceptive training. Additionally, the RCTs included in this review predominantly involved participants aged 50 years or over who presented early in their disease-stage. The majority of patients presented with moderate KOA (Kellgren-Lawrence grade II or III). Furthermore, the studies involving participants who had suffered knee joint trauma or surgery were also eliminated. Namely, this study only investigated patients with degenerative KOA. Given all this, the results of our study could only be applied to this KOA population. Therefore, it is still unclear whether the same clinical results would be obtained if proprioceptive

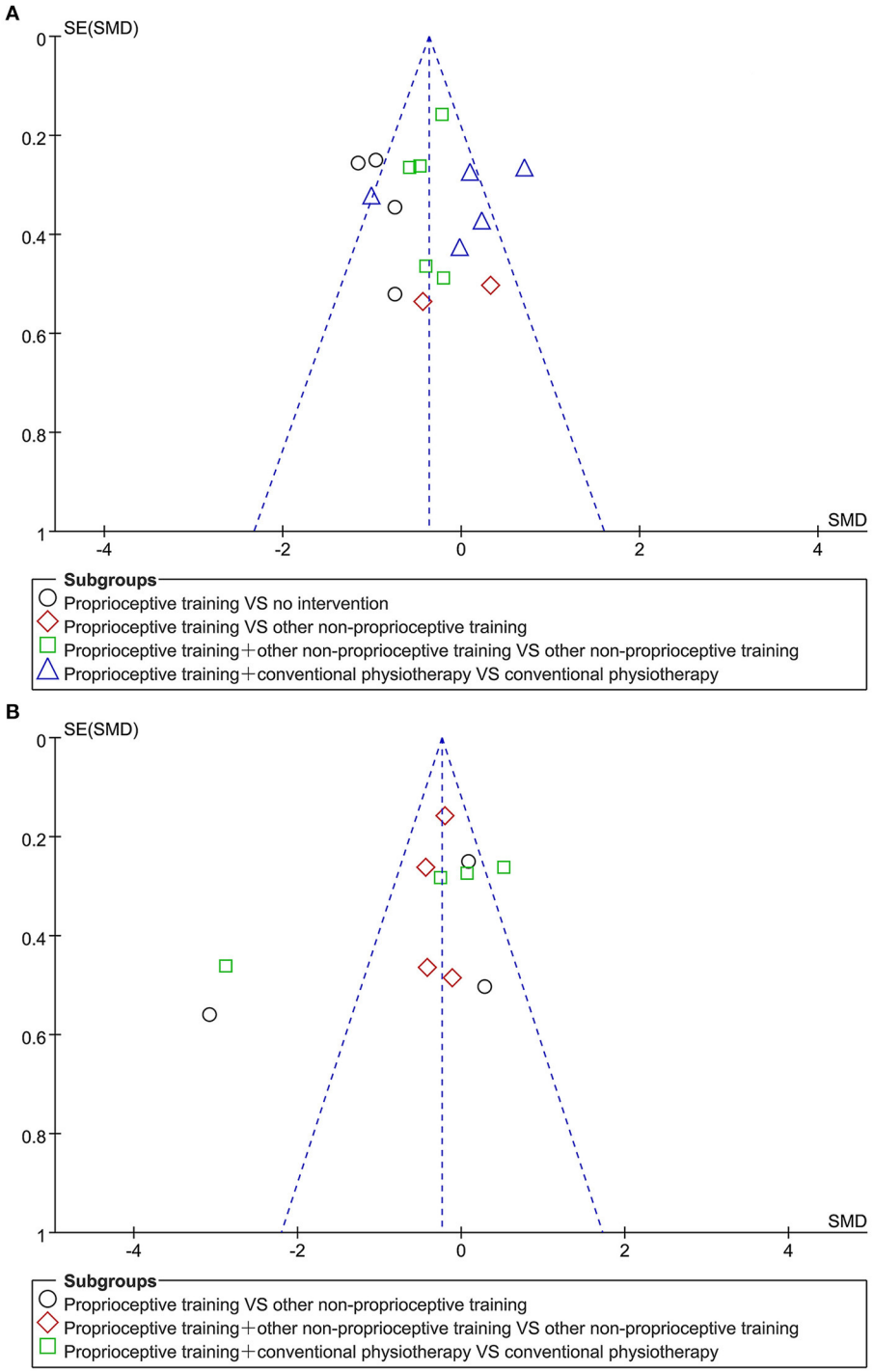


FIGURE 7 | Funnel plots for publication bias assessment on WOMAC (physical function) score **(A)** and WOMAC (total) score **(B)**.

training was prescribed for older people or those with more advanced KOA or those with KOA due to joint trauma or surgery. Further studies are needed to evaluate the clinical applicability of this exercise regime in different populations with knee OA.

CONCLUSIONS

In conclusion, this present study indicated that proprioceptive training is safe and effective in treating KOA. There is some evidence that proprioceptive training combined with general

non-proprioceptive training or conventional physiotherapy appears to be more effective and should be considered as part of the rehabilitation program. However, given that the majority of current studies investigated the short-term effect of these proprioceptive training program, more large-scale and well-designed studies with long-term follow up are needed to determine the long-term effects of these proprioceptive training regimes in KOA.

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

YW and XX came up with the initial study design. YW, ZW, ZC, XY, and JY reviewed all of the studies, extracted the data, analyzed and interpreted the data, and drafted the manuscript. YW, ZW, YG, JW, and GC were involved in quality assessment. PZ, FX, WC, and ZY checked the data extraction and analysis for accuracy. XX critically revised the manuscript for important intellectual content. All authors have reviewed and approved the final version of the 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.2021.699921/full#supplementary-material

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Association Between Sarcopenia and Depressive Symptoms in Chinese Older Adults: Evidence From the China Health and Retirement Longitudinal Study

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Background: Little is known about whether sarcopenia predicts incident depressive symptoms in older adults. Using the nationally representative data from the China Health and Retirement Longitudinal Study (CHARLS), we conducted cross-sectional and longitudinal analyses to estimate the association between sarcopenia and depressive symptoms among older adults.

Methods: The sample comprised 7,706 participants aged at least 60 years (50.6% women; mean age 68.0 ± 6.5) from the CHARLS 2015. Based on the Asian Working Group for Sarcopenia 2019 (AWGS 2019) criteria, sarcopenia status was classified into three types: no-sarcopenia, possible sarcopenia, and sarcopenia. Depressive symptoms were assessed using the validated 10-items of the Center for Epidemiologic Studies Depression Scale. A cross-sectional analysis was used to examine the relationship between sarcopenia status and depressive symptoms. A total of 4,652 participants without depressive symptoms were recruited from the same cohort in 2015 and were followed up in 2018. Cox proportional hazards regression models were conducted to examine the effect of sarcopenia status on subsequent depressive symptoms with the report of hazard ratio (HR).

Results: The prevalence of depressive symptoms in total populations, no-sarcopenia, possible sarcopenia, and sarcopenia individuals were 27.1% (2085/7706), 21.5% (927/4310), 33.6% (882/2627), and 35.9% (276/769), respectively. Both possible sarcopenia (OR: 1.75, 95% CI: 1.46–2.10) and sarcopenia (OR: 1.64, 95% CI: 1.23–2.19) were positively associated with higher odds of depressive symptoms (all $p < 0.01$). During the 3.7 years of follow-up, 956 cases (20.6%) with incident depressive symptoms were identified. In the longitudinal analysis, individuals with the diagnosed possible sarcopenia (HR: 1.27, 95% CI: 1.01–1.58) and sarcopenia participants (HR: 1.49, 95% CI: 1.06–2.09) were more likely to have new onset depressive symptoms than no-sarcopenia peers.

Conclusions: Both possible sarcopenia and sarcopenia, assessed using the AWGS 2019 criteria, were independent predictors for the occurrence of depressive symptoms among Chinese older adults. Our findings provided new evidence supporting the longitudinal connection between sarcopenia and mental health problems, it also provides further justification for timely identification and management of both possible sarcopenia and sarcopenia as part of comprehensive strategies to fight against depressive symptoms.

Keywords: sarcopenia, possible sarcopenia, depressive symptoms, low muscle mass, older adults

INTRODUCTION

Sarcopenia, a serious geriatric syndrome with a progressive skeletal muscle disorder, is a public health concern faced by aging societies (1, 2). In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) first recommended a diagnostic algorithm for sarcopenia (3). In 2014, the Asian Working Group for Sarcopenia (AWGS) consensus defined sarcopenia as "age-related loss of muscle mass, plus low muscle strength, and/or low physical performance" and specified cutoffs for each component (4). According to the AWGS 2014 criteria, the prevalence of sarcopenia among the elderly population ranges from 6.8 to 25.7% in Asian countries (5). Compelling evidence shows that sarcopenia is strongly associated with adverse outcomes, such as falls, fracture, frailty, morbidity, mortality, and increasing healthcare utilization (1, 6–9). To date, the clinical and research interest in sarcopenia has grown rapidly; however, the fields of sarcopenia and routine clinical practice are still largely separated. Most clinicians remain unaware of the condition and the diagnostic methods needed to identify it (1, 10). Therefore, developing and implementing comprehensive strategies to identify sarcopenia and its effects on mental and physical health is crucial.

Depression, a major mental health disorder, is closely linked to an increased likelihood of various health problems among older adults, such as disability, chronic illness (e.g., heart disease, diabetes mellitus, and hypertension), and all-cause mortality (11–14). Several previous studies have shown that sarcopenia was positively correlated with depression and depressive symptoms (15–18). A national survey in China reported that the prevalence of depressive symptoms among Chinese adults aged 45 years and older was 37% in 2015; only <5% of those with depressive symptoms were aware of their conditions and <2% sought care over time (19). Considering the various adverse outcomes associated with depressive symptoms in older people, it is important to understand its associations with sarcopenia. Recently, a growing body of literature has evaluated the relationship between sarcopenia and depressive symptoms (18, 20–22), but almost all studies were cross-sectional, with small sample sizes or using regional data. To date, there have not been large population-based perspective surveys on the causal relationship between sarcopenia and incident depressive symptoms in older adults. To promote healthy aging, the AWGS 2019 introduces "possible sarcopenia," defined by either low muscle strength or low physical performance only, to enable earlier lifestyle interventions (5). To our knowledge, no studies have evaluated the relationship between possible sarcopenia and depressive symptoms in Asia. Regarding sarcopenia components, in addition to muscle strength and physical performance, the impact of low muscle mass alone on mental health remains to be further studied.

At present, the contribution of individual sarcopenia status to depressive symptoms is still unknown, which gives us the impetus to investigate associations between possible sarcopenia, sarcopenia, and depressive symptoms among older adults in China. Using the nationally representative data from the China Health and Retirement Longitudinal Study (CHARLS) 2015 and 2018, we conducted cross-sectional and longitudinal analyses to estimate the association between sarcopenia status and depressive symptoms among Chinese community-dwelling older adults.

METHODS

Study Population

The CHARLS, established in 2011, is an ongoing nationally representative longitudinal survey in China. In short, CHARLS collects high-quality data through one-to-one interviews with a structured questionnaire, from a nationally representative sample of the Chinese middle-aged and older population, selected using multistage stratified probability-proportionate-to-size sampling. All participants underwent an assessment using a standardized questionnaire to collect data on sociodemographic and lifestyle factors and health-related information. In CHARLS 2011, a total of 17,708 participants in 10,257 households were recruited from 150 counties or districts and 450 villages within 28 provinces in China. The data included individual weighting variables to ensure that the survey sample was nationally representative. All participants were followed up with every 2 years after the baseline survey. Further details about the study design of the CHARLS have been previously reported (23).

In our study, we used data from the CHARLS 2015 and 2018. The inclusion criteria for the present study were (1) individuals aged at least 60 years old in CHARLS 2015; (2) having data regarding sarcopenia status. Exclusion criteria were (1) missing data of sarcopenia status; (2) no CES-D-10 scores; (3) no information about age; (4) persons aged <60 years old; and (5) no residence and body mass index data. This study was divided into two sections. (1) In the cross-sectional analysis,

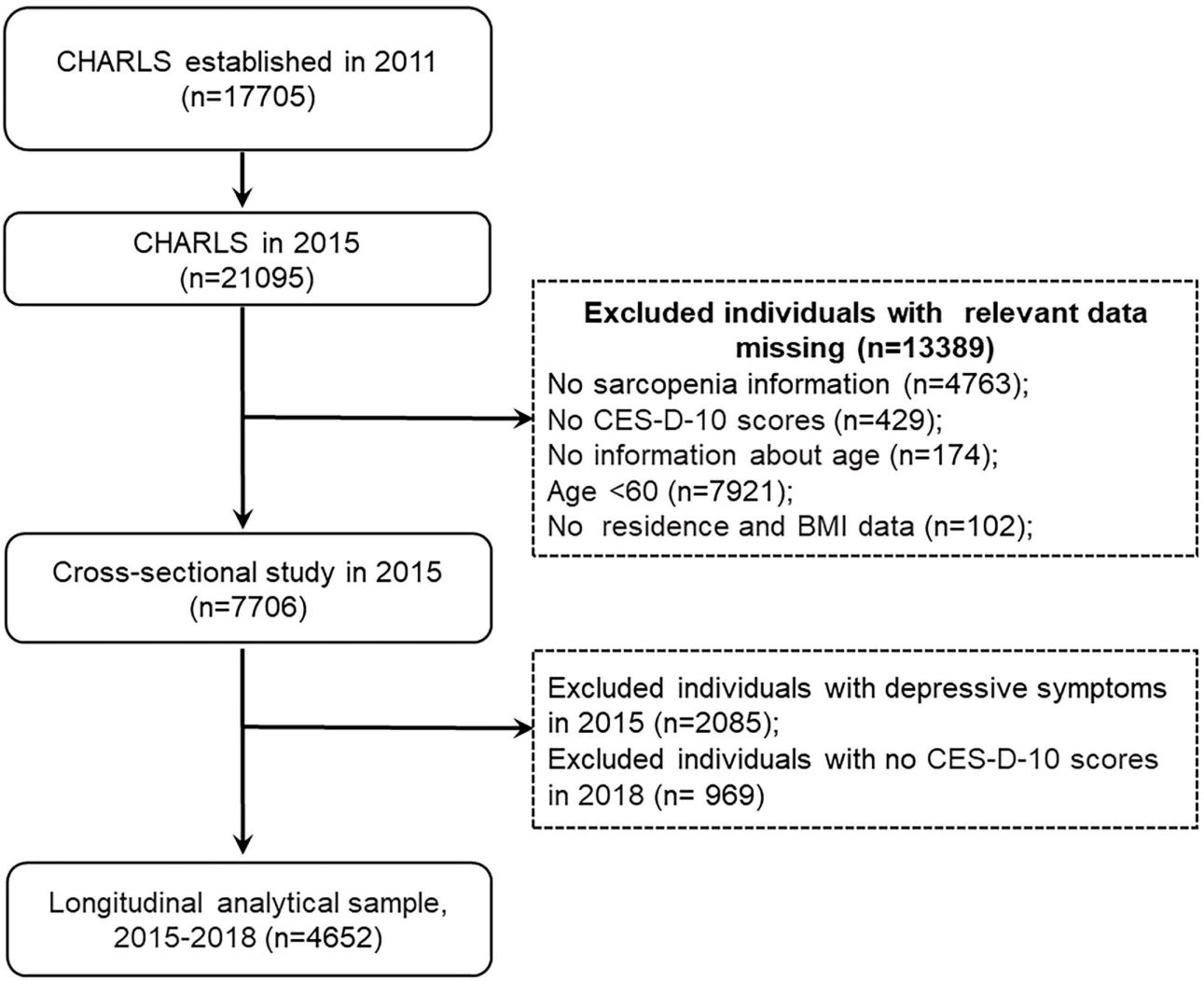


FIGURE 1 | Flow diagram for participants in a cross-sectional and longitudinal study. CES-D-10, the 10-item Center for Epidemiologic Studies Depression Scale; BMI, body mass index.

we used data from the large cohort that was followed up in 2015. A total of 21,095 participants were interviewed in CHARLS 2015, 13,389 individuals were excluded because of missing data of sarcopenia (n = 4,763), no CES-D-10 scores (n = 429), no information about age (n = 174), aged <60 years (n = 7,921), and no residence and body mass index (n = 102), leaving 7,706 participants for cross-sectional analysis. (2) In the longitudinal analysis, we further excluded 2,085 subjects with depressive symptoms in CHARLS 2015 and 969 participants without information of CES-D-10 scores in CHARLS 2018. Our final analytic sample included 4,652 participants, who had no depressive symptoms in CHARLS 2015 and followed up in 2018. The detailed selection process was shown in **Figure 1**.

The Biomedical Ethics Review Committee of Peking University approved CHARLS (approval number: IRB00001052-11015), and all participants were required to provide written informed consent.

Assessment of Sarcopenia Status

Sarcopenia status was assessed according to the AWGS 2019 algorithm, which is composed of three components: muscle strength, appendicular skeletal muscle mass (ASM), and physical performance (5). Handgrip strength (kg) was measured in the dominant hand and non-dominant hand, with the participant squeezing a YuejianTM WL-1,000 dynamometer (Nantong Yuejian Physical Measurement Instrument Co., Ltd., Nantong, China) as hard as possible (23). Every person was measured two times for both hands by holding the dynamometer at a right angle (90°). The cutoff points for low grip strength for men and women were <28 and <18 kg, respectively. The muscle mass was estimated by ASM using a previously validated anthropometric equation in Chinese residents (24, 25). Several studies have shown that the agreement of the ASM equation model and dual X-ray absorptiometry (DXA) was strong (24, 25). The cutoff for defining low muscle mass was based on the sex-specific lowest 20% of the height-adjusted muscle mass (ASM/Ht^2) among the

study population (25–27). Finally, the ASM/Ht^2 values of <5.69 kg/m^2 in women and <6.88 kg/m^2 in men were considered as low muscle mass. In terms of physical performance, the gait speed and the chair stand test were evaluated using the method described by Wu et al. (27). Using the cutoff points from the AWGS 2019 consensus, low physical performance was defined as a five-time chair stand test ≥12 s, or gait speed on a 6-m walk <1.0 m/s, or Short Physical Performance Battery (SPPB) score <9 (5). Further details about the definitions for sarcopenia components in the CHARLS have been previously published (27).

Sarcopenia is defined when low muscle mass plus low muscle strength or low physical performance are detected. Possible sarcopenia is diagnosed by low muscle strength with or without reduced physical performance. Individuals with all three components, including low muscle mass, low muscle strength, and low physical performance, are considered as having severe sarcopenia (5). In our study population, only 221 (2.9%) participants had severe sarcopenia. Therefore, we merged participants with severe sarcopenia into the sarcopenia group and divided all participants into three groups: no-sarcopenia, possible sarcopenia, and sarcopenia.

Assessment of Depressive Symptoms

In the CHARLS 2015 and 2018, depressive symptoms were measured using the 10-item short form of the Center for Epidemiologic Studies Depression Scale (CES-D-10) (28), which is a widely used self-report measure on depressive symptoms in population-based studies. The CES-D-10 has satisfactory validity and excellent psychometric properties among Chinese older individuals (29). The CES-D short form consists of 10 items: (1) bothered by little things, (2) had trouble concentrating, (3) felt depressed, (4) everything was an effort, (5) felt hopeful, (6) felt fearful, (7) sleep was restless, (8) felt happy, (9) felt lonely, and (10) could not get going. Each depressive symptom item in the past week was measured from 0 (rarely or none of the time [<1 day]) to three points (most or all of the time [5–7 days]). Individuals who had scores of at least 12 were classified as having depressive symptoms (29, 30).

Covariates

The study covariates included individual sociodemographic characteristics and health-related factors. Sociodemographic variables included age, sex, marital status (married and others), education (elementary school and below, secondary school, and college and above), residence (rural and urban), and socioeconomic status. We defined three socioeconomic groups on the basis of tertiles of per-capita household consumption expenditure (tertile 1, 0–4283 CNY; tertile 2, 4,284–9,550 CNY; tertile 3, 9,551 CNY or more). We used annual per-capita household consumption spending as a proxy for socioeconomic status (31). Health-related factors included body mass index (BMI), self-reported smoking and drinking status (yes or no), and 14 physician-diagnosed chronic conditions (hypertension, dyslipidemia, diabetes, cancer, chronic lung diseases, liver disease, heart disease, stroke, kidney disease, digestive disease, psychiatric disease, memory-related disease, arthritis or rheumatism, and asthma). BMI was divided into three categories according to the following WHO cutoff points for Chinese: underweight (BMI < 18.5 kg/m^2), normal weight (BMI = 18.5 to 24 kg/m^2), and overweight or obese (BMI ≥ 24 kg/m^2) (27). In addition, we also assessed the anemia status and cognitive function at baseline in 2015. Briefly, hemoglobin was measured at local county health centers, and the hemoglobin values of <13.0 g/dL in men and <12.0 g/dL in women are defined as anemia. Cognitive functioning was evaluated *via* a structured questionnaire in three dimensions: orientation and attention, episodic memory, and visuoconstruction. Scores on these three items were aggregated into a single score that ranged from 0 to 31, and higher scores indicate better cognitive function (32).

Statistical Analysis

Data are presented as means ± SD or median and interquartile range for continuous variables and percentages for categorical variables. First, baseline characteristics in the cross-sectional and longitudinal analytical sample are summarized based on sarcopenia status and compared between participants using the chi-squared test, Student's *t*-test, ANOVA, Mann–Whitney *U*-test, or the Kruskal–Wallis test, as appropriate. Second, logistic regression analysis was used to estimate associations between possible sarcopenia, sarcopenia, and depressive symptoms in cross-sectional analysis. To further examine the cross-sectional associations between possible sarcopenia, sarcopenia, and specific depressive symptoms, using the previously published method (30, 33), we coded the items as dichotomous variables by defining the responses as occasionally or a moderate amount of time (3–4 days) and all of the time (5–7 days) as having the specific depressive symptoms. Logistic regression analysis was used to calculate the odds ratio (OR) with a 95% CI.

In the longitudinal analysis, we calculated the incidence rates of depressive symptoms per 1,000 person-years in CHARLS 2018. We also measured the follow-up time as the time elapsed from the date of the last interview to either the date of diagnosis of depressive symptoms or the date of the latest interview (March 2019) in which the individual participated. To examine the association between baseline sarcopenia status and incident depressive symptoms in longitudinal analysis, Cox proportional hazards models were used to calculate the hazard ratio (HR) with 95%CI. Two models were estimated: in Model 1, age, sex, residence, marital status, educational level, smoking, drinking, socioeconomic status, and BMI were included; Model 2 was adjusted as for model 1 with further adjustment for 14 chronic comorbidities, anemia, and total cognitive score. In addition, we also evaluated the association between low muscle mass alone and depressive symptoms in the cross-sectional and longitudinal analytical sample. All statistical analyses were performed retrospectively with IBM SPSS (Version 25.0, IBM Corp., Armonk, NY, USA), and R version 3.5.1 (R Foundation for Statistical Computing). In all cases, $p < 0.05$ was considered significant.

RESULTS

Characteristics of Participants in the Cross-Sectional and Longitudinal Study

The baseline characteristics of the cross-sectional study participants are shown in **Table 1**. The mean (SD) age at baseline

TABLE 1 | Baseline characteristics of 7,706 participants by sarcopenia status in CHARLS 2015.

Characteristics	No sarcopenia (n = 4,310)	Possible sarcopenia (n = 2,627)	Sarcopenia (n = 769)	p
Age, years	66.2 ± 5.3	69.9 ± 7.0	72.0 ± 7.2	<0.001
Female, *n* (%)	2,004 (46.5)	1,537 (58.5)	358 (46.6)	<0.001
Married (vs. others)	3,678 (85.3)	1,935 (73.7)	557 (72.4)	<0.001
Urban (vs. rural)	638 (14.8)	306 (11.6)	50 (6.5)	<0.001
Smoking[a]	1,451 (35.3)	688 (27.6)	288 (39.0)	<0.001
Drinking[a]	1,361 (37.1)	603 (26.6)	201 (30.3)	<0.001
Educational level[a]				
Elementary school or below	2,965 (76.3)	2,047 (85.6)	630 (89.6)	<0.001
Secondary school	860 (22.1)	329 (13.8)	66 (9.4)	
College and above	63 (1.6)	16 (0.6)	7 (1.0)	
Socioeconomic status[a]				
Tertile 1 (the poorest)	780 (29.0)	627 (37.8)	206 (41.3)	<0.001
Tertile 2	950 (35.3)	507 (30.6)	158 (31.7)	
Tertile 3 (the richest)	959 (35.7)	523 (31.6)	135 (27.1)	
BMI category, *n* (%)				
Underweight	244 (5.7)	140 (5.3)	223 (29.0)	<0.001
Normal weight	2,232 (51.8)	1,314 (50.0)	417 (54.2)	
Overweight or obese	1,834 (42.5)	1,173 (44.7)	129 (16.8)	
Comorbidities, *n* (%)				
Hypertension	1,079 (25.0)	868 (33.0)	209 (27.2)	<0.001
Dyslipidemia	472 (11.0)	334 (12.7)	54 (7.0)	<0.001
Diabetes	279 (6.5)	218 (8.3)	41 (5.3)	0.003
Cancer	42 (1.0)	30 (1.1)	12 (1.6)	0.337
Chronic lung diseases	476 (11.0)	392 (14.9)	155 (20.2)	<0.001
Liver disease	204 (4.7)	99 (3.8)	34 (4.4)	0.162
Heart disease	560 (13.0)	454 (17.3)	126 (16.4)	<0.001
Stroke	69 (1.6)	121 (4.6)	26 (3.4)	<0.001
Kidney disease	301 (7.0)	202 (7.7)	55 (7.2)	0.543
Digestive disease	1,065 (24.7)	663 (25.2)	232 (30.2)	0.006
Psychiatric disease	51 (1.2)	45 (1.7)	14 (1.8)	0.123
Memory-related disease	62 (1.4)	83 (3.2)	14 (1.8)	<0.001
Arthritis or rheumatism	1,606 (37.3)	1,177 (44.8)	336 (43.7)	<0.001
Asthma	179 (4.2)	158 (6.0)	76 (9.9)	<0.001
Anemia[a]	679 (18.6)	479 (23)	214 (35.5)	<0.001
Handgrip strength (kg)	31.2 ± 8.6	21.1 ± 8.4	20.9 ± 7.2	<0.001
ASM/Ht^2 (kg/m^2)	7.1 ± 1.5	7.5 ± 1.0	5.5 ± 2.1	<0.001
Total cognitive score	14 (9, 18)	10 (6, 15)	9 (5, 14)	<0.001
CES-D score	6 (3, 10)	8 (4, 14)	8 (4, 15)	<0.001
Depressive symptoms[b]	927 (21.5)	882 (33.6)	276 (35.9)	<0.001

Data are shown as means ± SD median (interquartile range), or numbers (percentages).

[a]*Missing data: 362 for smoking, 1,103 for drinking, 722 for educational level, 2,860 for socioeconomic status, and 1,374 for anemia data.*

[b]*Defined as a score of 12 or greater on the 10-item Center for Epidemiologic Studies Depression Scale.*

ASM, appendicular skeletal muscle; BMI, body mass index; CES-D, the 10-item Center for Epidemiologic Studies Depression Scale.

was 68.0 (6.5) years; 3,807 (49.4%) of the participants were men and 3,899 (50.6%) were women. Among these 7,706 older adults, the prevalence of possible sarcopenia and sarcopenia was 34.1% (2,627/7,706) and 10.0% (769/7,706), respectively. Individuals with sarcopenia were older and not married, more likely to live in rural areas, had lower socioeconomic status and educational level, and had lower BMI and total cognitive score, and higher prevalence of chronic conditions (including hypertension, chronic lung diseases, stroke, heart disease, digestive disease, memory-related disease, arthritis or rheumatism, asthma, and anemia) than the no-sarcopenia individuals (all $p < 0.05$). A comparison of characteristics between individuals not included and those who were included in the longitudinal analysis is shown in **Supplementary Table 1**.

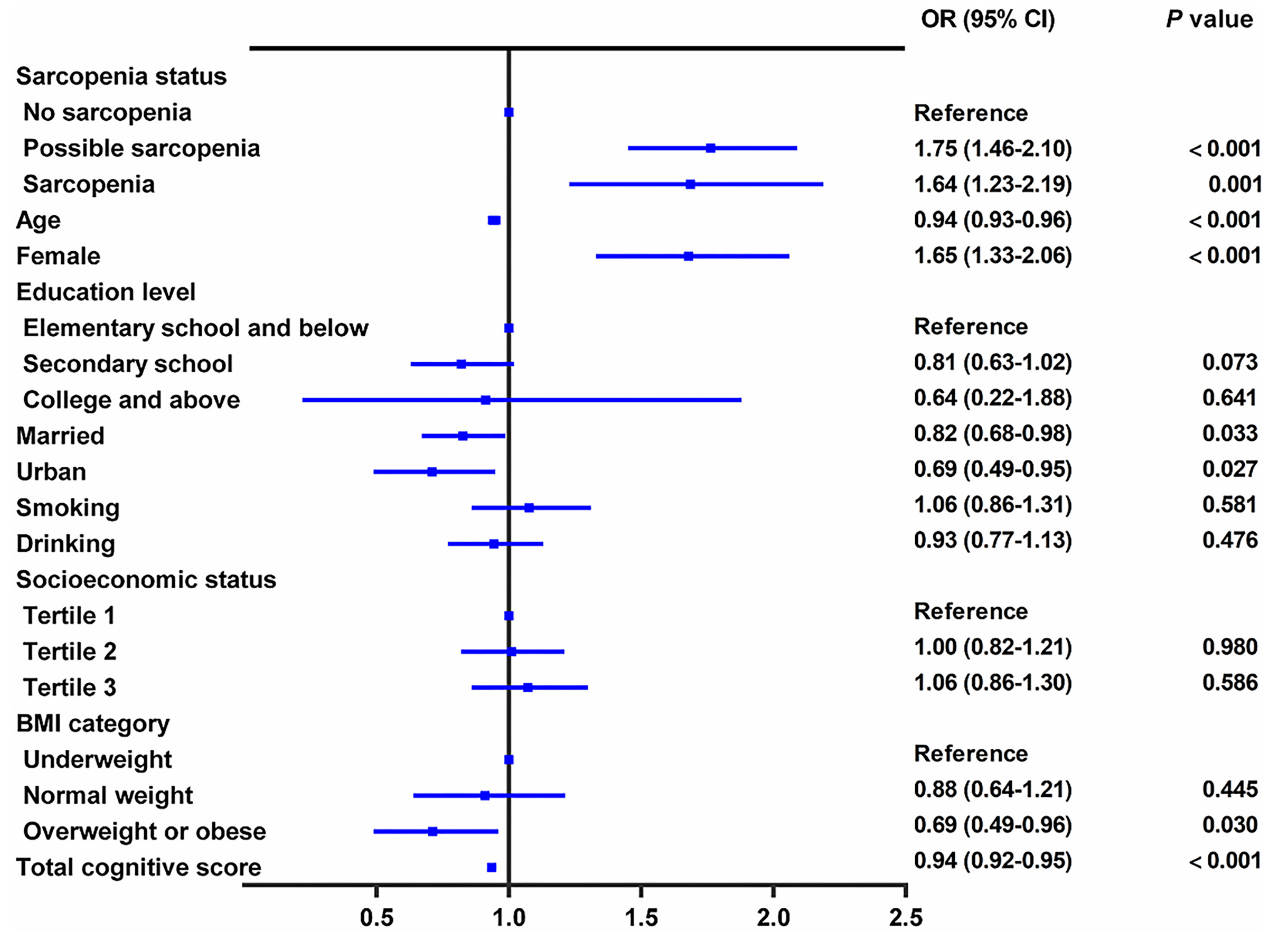


FIGURE 2 | Cross-sectional association between sarcopenia status and depressive symptoms. The graph shows odds ratio (OR) and 95% CI for depressive symptoms adjusted for age, sex, residence, marital status, educational level, smoking status, drinking status, socioeconomic status, body mass index, and comorbidities, including hypertension, dyslipidemia, diabetes, cancer, chronic lung diseases, liver disease, heart disease, stroke, kidney disease, digestive disease, psychiatric disease, memory-related disease, arthritis or rheumatism, asthma, anemia, and total cognitive score.

Supplementary Table 2 presents the baseline characteristics of 4,652 participants without depressive symptoms (46.4% women; mean age 67.4 ± 6.0) in the longitudinal study stratified by sarcopenia status. Except for gender, hypertension, digestive disease, and memory-related diseases, differences in baseline characteristics stratified by sarcopenia status were similar in the longitudinal analytical sample, as compared with the cross-sectional study.

Cross-Sectional Association of Sarcopenia Status With Depressive Symptoms in CHARLS 2015

In the cross-sectional study, persons with sarcopenia or possible sarcopenia had higher CES-D scores than no-sarcopenia individuals, and the prevalence of depressive symptoms in total populations, no-sarcopenia, possible sarcopenia, and sarcopenia individuals were 27.1% (2,085/7,706), 21.5% (927/4,310), 33.6% (882/2,627), and 35.9% (276/769), respectively (p for trend <0.001, **Table 1**). Compared with participants with no sarcopenia, both possible sarcopenia (OR: 1.75; 95% CI: 1.46–2.10, $p < 0.001$) and sarcopenia (OR: 1.64; 95% CI: 1.23–2.19, $p = 0.001$) were significantly associated with higher odds of depressive symptoms (**Figure 2**).

Table 2 shows the association between sarcopenia status and specific depressive symptoms after adjusting for confounders. Of the 10 individual depressive symptoms measured by the CES-D, sarcopenia was significantly associated with five symptoms, including had trouble concentrating (OR: 1.35; 95%CI: 1.01–1.79), felt depressed (OR: 1.54; 95% CI: 1.16–2.04), everything was an effort (OR: 1.88; 95% CI: 1.43–2.48), sleep was restless (OR: 1.48; 95% CI: 1.13–1.95), and could not get going (OR: 1.33; 95% CI: 1.02–1.74) (all $p < 0.05$). We also found that possible sarcopenia was significantly associated with higher odds of all the 10 individual depressive symptoms after adjusting for all covariates (all $p < 0.01$, **Table 2**).

TABLE 2 | The odds ratio of elevated specific depressive symptoms by sarcopenia status in 2015.

Items[a]	Symptomatic, *n*	No-sarcopenia	Adjusted OR (95% CI) for possible sarcopenia	Adjusted OR (95% CI) for sarcopenia
Bothered by little things	716 (15.4)	Reference	1.51 (1.26, 1.80)***	1.32 (0.99, 1.77)$^{+}$
Had trouble concentrating	832 (17.9)	Reference	1.35 (1.13, 1.61)**	1.35 (1.01, 1.79)*
Felt depressed	842 (18.1)	Reference	1.49 (1.25, 1.78)***	1.54 (1.16, 2.04)**
Everything was an effort	920 (19.8)	Reference	1.55 (1.30, 1.85)***	1.88 (1.43, 2.48)***
Did not feel hopeful	983 (21.1)	Reference	1.25 (1.06, 1.47)**	1.14 (0.87, 1.49)
Felt fearful	357 (7.7)	Reference	1.97 (1.51, 2.57)***	1.37 (0.90, 2.09)
Sleep was restless	825 (17.7)	Reference	1.35 (1.14, 1.60)**	1.48 (1.13, 1.95)**
Did not feel happy	1,158 (24.9)	Reference	1.52 (1.25, 1.85)***	1.16 (0.84, 1.58)
Felt lonely	659 (14.2)	Reference	1.50 (1.18, 1.90)**	0.99 (0.68, 1.45)
Could not get going	355 (7.6)	Reference	1.39 (1.17, 1.64)***	1.33 (1.02, 1.74)*

[a]*Measured by the 10-item Center for Epidemiologic Studies Depression Scale. Model was adjusted for age, sex, residence, marital status, educational level, smoking status, drinking status, socioeconomic status, body mass index, all comorbidities (hypertension, dyslipidemia, diabetes, cancer, chronic lung diseases, liver disease, heart disease, stroke, kidney disease, digestive disease, psychiatric disease, memory-related disease, arthritis or rheumatism, asthma), anemia, and total cognitive score.*

$^{+}p < 0.10$.

$^{*}p < 0.05$.

$^{**}p < 0.01$.

$^{***}p < 0.001$.

TABLE 3 | Incidence of depressive symptoms according to baseline sarcopenia status, 2015–2018.

Sarcopenia status	Cases, no.	Incidence rate, per 1,000 person-years	HR (95% CI)	
			Model 1[a]	Model 2[b]
No sarcopenia	531	47.09	Reference	Reference
Possible sarcopenia	326	69.56	1.44 (1.18, 1.76)***	1.27 (1.01, 1.58)*
Sarcopenia	99	69.62	1.53 (1.12, 2.09)**	1.49 (1.06, 2.09)*

HR, hazard ratio. [a]*Model 1 was adjusted for age, sex, residence, marital status, educational level, smoking status, drinking status, socioeconomic status, and body mass index.*

[b]*Model 2 was adjusted as for model 1 with further adjustment for comorbidities (hypertension, dyslipidemia, diabetes, cancer, chronic lung diseases, liver disease, heart disease, stroke, kidney disease, digestive disease, psychiatric disease, memory-related disease, arthritis, or rheumatism, asthma), anemia, and total cognitive score.*

$^{*}p < 0.05$.

$^{**}p < 0.01$.

$^{***}p < 0.001$.

Longitudinal Association Between Baseline Sarcopenia Status and Incident Depressive Symptoms at Follow-Up, 2015–2018

During the follow-up period between CHARLS 2015 and CHARLS 2018, 956 cases (20.6%) with incident depressive symptoms were identified (**Table 3**). During the 3.7 years of follow-up, the incidence rate of depressive symptoms was 47.09 per 1,000 person-years among participants with no-sarcopenia, 69.56 per 1,000 person-years among possible sarcopenia, and 69.62 per 1,000 person-years among participants with sarcopenia. **Table 3** shows the relation between baseline sarcopenia status and incident depressive symptoms in the longitudinal analysis. After adjusting for age, sex, residence, marital status, educational level, smoking status, drinking status, socioeconomic status, and BMI (in model 1), the presence of sarcopenia was independently associated with a 53.0% increased risk of depressive symptoms (adjusted HR:1.53; 95% CI: 1.12–2.09, $p < 0.01$). Individuals with possible sarcopenia had a 44.0% increased risk of incident depressive symptoms (adjusted HR: 1.44; 95% CI: 1.18–1.76, $p = 0.008$). The results did not significantly change after further adjusting for comorbidities, anemia, and total cognitive score (in model 2). Individuals with the diagnosed possible sarcopenia (adjusted HR: 1.27; 95% CI: 1.01–1.58, $p = 0.040$) and sarcopenia participants (adjusted HR: 1.49; 95% CI: 1.06–2.09, $p = 0.021$) were more likely to have incident depressive symptoms than no-sarcopenia peers (**Table 3** and **Figure 3**).

Cross-Sectional and Longitudinal Associations of Low Muscle Mass Alone With Depressive Symptoms

In the cross-sectional analysis, a total of 4,310 individuals (46.5% women; mean age 66.2 ± 5.3) were included, and 767 individuals (17.8%) had low muscle mass alone with neither low handgrip strength nor low physical performance. The prevalence of depressive symptoms was 20.8% (738/3,543) among individuals without any sarcopenia components and 24.6% (189/767) among individuals with low muscle mass alone (**Supplementary Table 3**). Individuals with low muscle mass alone were not significantly associated with higher odds of depressive symptoms (OR: 0.94; 95% CI: 0.69–1.29, $p = 0.700$). In the longitudinal analysis, a total of 2,949 participants (56.3% women; mean age 66.0 ± 5.1) were included, and 494 participants (16.8%) had low muscle mass alone with neither low handgrip strength nor low physical performance. The incidence rate of depressive symptoms was 44.77 per 1,000 person-years among participants without any sarcopenia components and 58.06 per 1,000 person-years among participants with low muscle mass alone (**Table 4**). Compared with the individuals without

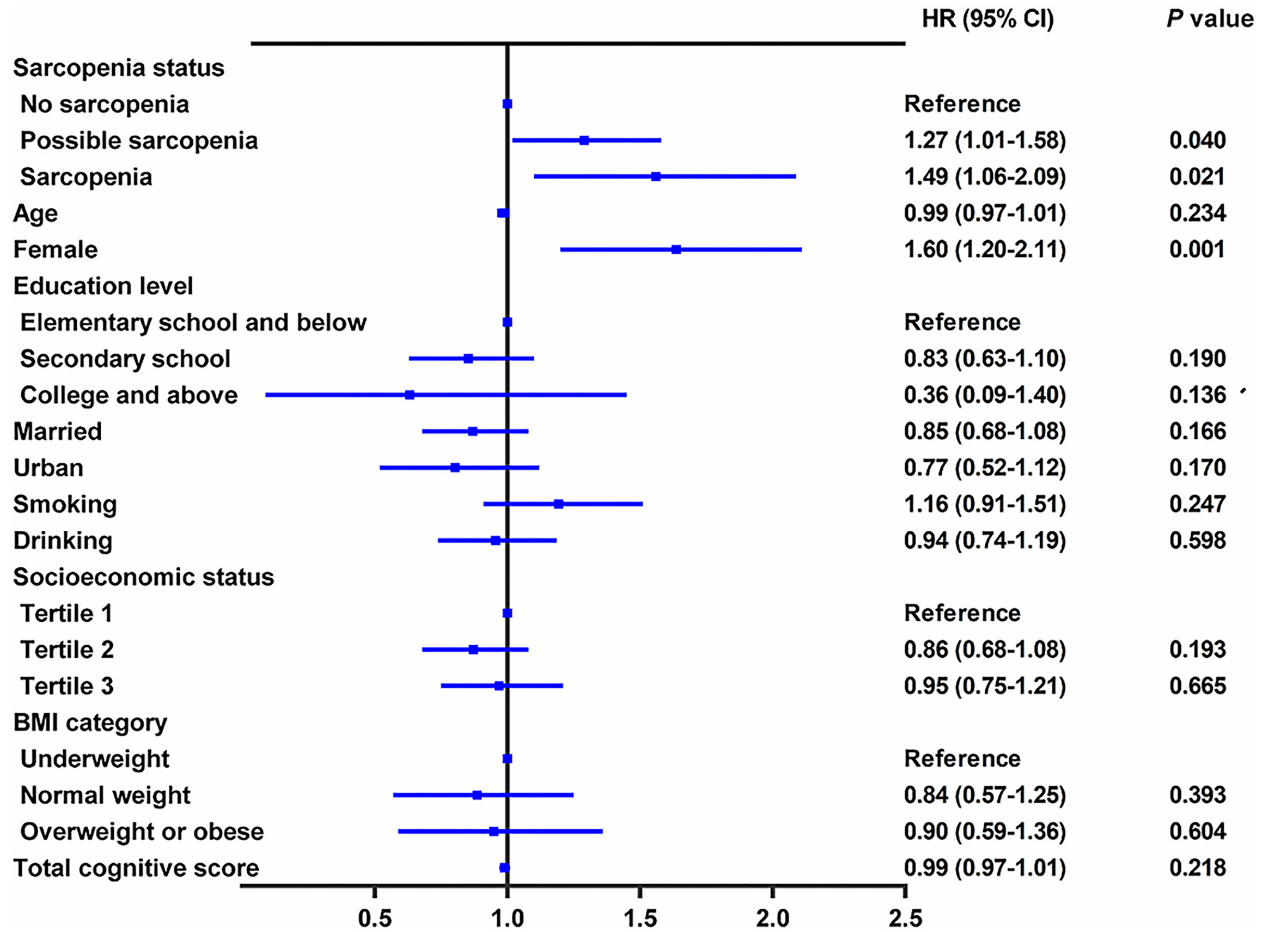


FIGURE 3 | Longitudinal association of baseline sarcopenia status with incident depressive symptoms, 2015–2018. The graph shows hazard ratio (HR) and 95% CI for depressive symptoms risk adjusted for age, sex, residence, marital status, educational level, smoking status, drinking status, socioeconomic status, body mass index, all comorbidities, anemia, and total cognitive score.

any sarcopenia components, those having low muscle mass alone in the absence of low grip strength and low physical performance were not significantly associated with an increased risk of incident depressive symptoms after adjusting for potential confounders (HR: 1.20; 95% CI: 0.85–1.69, $p = 0.311$).

DISCUSSION

To our knowledge, using a large nationally representative survey of the Chinese population, this study is the first attempt to investigate the cross-sectional associations between possible sarcopenia, sarcopenia, and depressive symptoms, and the effect of baseline sarcopenia status on the risk of subsequent depressive symptoms among Chinese older adults. We found that both possible sarcopenia and sarcopenia, assessed using the AWGS 2019 algorithm, were independently and positively associated with higher odds of depressive symptoms in the cross-sectional analysis. Importantly, individuals with diagnosed possible sarcopenia or sarcopenia were at higher risk of incident depressive symptoms among Chinese older adults. There was no significant increased risk of depressive symptoms for participants with low muscle mass alone in the absence of low grip strength and low physical performance.

In the cross-sectional study, we found that sarcopenia was independently associated with higher odds of depressive symptoms, and individuals with sarcopenia were more likely to report a higher CES-D score than no-sarcopenia peers. These findings are in line with several cross-sectional studies (16–18, 20, 21), suggesting that the presence of sarcopenia was closely correlated with higher odds of depressive symptoms and/or depression. A meta-analysis comprising of 15 observational studies conducted by Chang et al. (17) showed that sarcopenia demonstrated a significant positive association with depression after adjusting for potential confounders. Wang et al. (18), whose study focused on the elderly Asian population, demonstrated that sarcopenia was strongly associated with depressive symptoms among 865 elderly Chinese individuals. Moreover, the ELSA-Brasil Study (34) suggested that depression was associated

TABLE 4 | Longitudinal association of low muscle mass alone with incident depressive symptoms, 2015–2018.

	Cases, no.	Incidence rate, per 1,000 person-years	HR (95% CI)	
			Model 1[a]	Model 2[b]
Muscle mass (*n* = 2,949)				
Reference (*n* = 2,455)	411	44.77	1	1
Low muscle mass alone (*n* = 494)	107	58.06	1.54 (0.83, 1.60)	1.20 (0.85, 1.69)

HR, hazard ratio. Reference was a group of participants without any sarcopenia components. Low muscle mass alone, low muscle mass with neither low grip strength nor slow physical performance.

[a]*Model 1 was adjusted for age, sex, residence, marital status, educational level, smoking status, drinking status, socioeconomic status, and body mass index.*

[b]*Model 2 was adjusted as model 1 with further adjustment for comorbidities, anemia, and total cognitive score.*

with sarcopenia as defined by the National Institutes of Health criteria among 5,927 middle-aged and older Brazilian adults, and this association was mainly due to low muscle strength. However, there is a paucity of research on the causal relationship between sarcopenia and depressive symptoms in Asia. To our knowledge, this is the first large, population-based longitudinal study that has found sarcopenia is independently associated with an increased incidence of depressive symptoms among Chinese older adults. We found that individuals with sarcopenia had a 49% higher risk of new onset depressive symptoms compared with the no-sarcopenia group after the adjustment for the potential confounders. These results may indicate that assessment of sarcopenia in older adults might facilitate identification of those at greatest risk of incident depressive symptoms, who would benefit most from early intervention. The underlying mechanisms of the association between sarcopenia and depressive symptoms are multifactorial, involving common molecule-driven pathways (35, 36), including neurotrophins, chronic inflammation, and oxidative stress, and similar lifestyle factors (1, 2), such as malnutrition and physical inactivity. Exercise has been shown to ameliorate the process of sarcopenia and depression (1, 2, 37). Mounting evidence indicates that physical activity can diminish the blood-brain barrier permeability and function as it reinforces antioxidative capacity, reduce oxidative stress, alter neurotrophic factor status, and have anti-inflammatory effects (38–40). In particular, the muscle–brain endocrine loop mediated by myokine is also involved in the associations between sarcopenia and several health problems, such as depression, anxiety, and cognitive decline (40–43). In general, skeletal muscle can produce and secrete several cytokines and peptides, namely myokines that improve brain functions, including mood, cognitive, and neuronal injury protection, showing the existence of muscle–brain crosstalk (41, 42).

Based on the AWGS 2019 criteria, the diagnostic algorithm for sarcopenia consists of three components, namely muscle strength, skeletal muscle mass, and physical performance. The AWGS 2019 also recommended a new entity of "possible sarcopenia" to facilitate early lifestyle intervention in prevention settings (5). In addition to sarcopenia, the current study also demonstrated interesting findings regarding the effect of possible sarcopenia and low muscle mass alone on depressive symptoms. Compared with participants with no sarcopenia, possible sarcopenia was positively associated with higher odds of depressive symptoms in the cross-sectional analysis. As part of the results, we also found that participants with low muscle mass alone were not significantly associated with depressive symptoms. Consistent with our findings, the Toyota Prevention Intervention for Cognitive Decline and Sarcopenia study (20) reported that both low physical performance and low muscle strength were significantly associated with depressive mood among 432 Japanese older adults, but decreased muscle mass was not. In addition, the ELSA-Brasil Study also reported that depression was not associated with low muscle mass in the cross-sectional study with 5,927 middle-aged and older Brazilian adults (34). Furthermore, several studies have proven that low grip strength, a component of possible sarcopenia, was independently associated with depression (34, 44). In the current study, we tried to confirm the causal relationships between possible sarcopenia, low muscle mass alone, and depressive symptoms. In the longitudinal analysis, we first found that individuals with the diagnosed possible sarcopenia were associated with a significantly increased risk of incident depressive symptoms. But another component of sarcopenia, low muscle mass alone, did not show an increased risk of incident depressive symptoms. Our findings support the validity of current major criteria of possible sarcopenia by the AWGS 2019, and it also suggested that maintaining enough muscle strength and/or physical performance could be beneficial in the prevention of depressive symptoms for older adults. At the same time, early diagnosis, lifestyle interventions, and prevention of possible sarcopenia in routine clinical practice should be taken as a factor in fighting against depressive symptoms and promoting healthy aging.

Plenty of previous studies (16, 18, 20, 21) on the relationship of sarcopenia with depressive symptoms only regarded the presence of depressive symptoms as a binary variable. However, this schema discards data about specific symptom items, treating all as equivalent and interchangeable indicators of depressive symptoms (45). Moreover, two sarcopenic persons with equal CES-D scores may have different severity of clinical symptoms. To date, no studies have assessed the association between sarcopenia status and specific depressive symptoms of CES-D-10 among Chinese older adults. In this study, we found that sarcopenia was significantly associated with certain depressive symptoms, such as having trouble concentrating, feeling depressed, everything was an effort, sleep was restless, and could not get going. Our findings are consistent with evidence from the ELSA-Brasil Study (34) showing that several depressive symptom items, such as impaired concentration, sleep problems, and depressed mood, were associated with sarcopenia among middle-aged and older Brazilian adults. Our results suggest that elderly people who are at high risk of sarcopenia should be screened and intervened for specific depressive symptoms items.

There are several strengths to this study. First, we used a large and nationally representative sample, thereby allowing for broad generalizability of our findings to the Chinese older population. Second, unlike most previous cross-sectional studies, this is the first study to explore the longitudinal relationships between possible sarcopenia, sarcopenia, and depressive symptoms in Asia. In addition, the study was also the first one to examine the associations between sarcopenia status and specific depressive symptoms items of CES-D-10 among Chinese older adults. More importantly, our findings supported the validity of the current major algorithm of possible sarcopenia by the AWGS 2019 and suggested that preventing and/or improving both possible sarcopenia and sarcopenia may be beneficial in fighting against depressive symptoms and promoting healthy aging for Chinese older adults.

However, there are limitations to this study. First, in our study, individuals walked a 2.5-m course at their normal pace two times, rather than a 6-m walk. However, a systematic review comprising of 48 studies found that the "distance walked did not influence the recorded gait speed" among older adults (46). Moreover, Wu et al. (27) reported that the average gait speed among individuals with sarcopenia and without sarcopenia in CHARLS 2015 was consistent with the results of a previous Chinese study. Therefore, a 2.5-m walk might be appropriate for assessing the walking speed of Chinese older residents. Second, the information about the SPPB score are completely missing, so the estimates may have some degree of bias. Third, this study used observational data, which may have biased the observed relations by introducing confounding factors. To reduce such bias, we considered as many related factors as possible in the analysis; however, other potential confounding factors, such as nutritional status, hypoalbuminemia, food habits, physical inactivity, and sleep behavior, cannot be ruled out. Despite these limitations, our findings will provide essential clues for future research. Future studies are needed to pinpoint the role of depressive symptoms in the new onset of sarcopenia. With respect to the clinical implications of our findings, integration of both sarcopenia and depressive symptoms assessment should be introduced to community-based health checkups and routine clinical practice of older adults.

CONCLUSION

In conclusion, both possible sarcopenia and sarcopenia, assessed using the AWGS 2019 criteria, were independent predictors for the occurrence of depressive symptoms among Chinese older adults. Our findings provided new evidence supporting the longitudinal connection between sarcopenia and mental health problems in the context of aging, it also provides further justification for timely identification and management of both possible sarcopenia and sarcopenia as part of comprehensive strategies to fight against depressive symptoms in Chinese community-dwelling older adults.

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the protocol was approved by the Ethical Review Committee of Peking University (Approval No. IRB00001052-11015). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DZ and KG conceived the protocol. KG, DZ, TL, W-ZM, SH, B-LL, LZ, and JZ contributed to the analysis and interpretation of data. KG and DZ grafted the manuscript. W-ZM, TL, and SH critically revised the manuscript. All authors agree to be fully accountable for ensuring the integrity and accuracy of the work and 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.2021.755705/full#supplementary-material

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Association Between Overweight Sarcopenic Population and Acute Vertebral Osteoporotic Compression Fractures in Females: Retrospective, Cross-Sectional Study

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Background: This study aimed to determine whether the prevalence of acute vertebral osteoporotic compression fractures (VOCF) in the elderly population is related to the distribution of muscles and fat in the human body.

Methods: Data of acute VOCF and non-VOCF patients presenting at our institution between January 2018 and May 2020 were analyzed. Patients aged 65 years and older, who underwent body composition test and dual-energy X-ray absorptiometry at the same time were enrolled. After applying exclusion criteria, patients were divided into four groups: normal, sarcopenia without obesity, obesity without sarcopenia, and sarcopenic obesity. Body mass index $\geq$25 kg/m^2 was considered obesity, and sarcopenia was defined as skeletal muscle index lower than 7.0 kg/m^2 in males and 5.4 kg/m^2 in females. The VOCF rate was analyzed between the groups.

Discussion: A total of 461 patients were included, of whom 103 were males. Among them, 163 (35.36%) had normal body composition, 151 (32.75%) had sarcopenia without obesity, 110 (23.86%) had obesity without sarcopenia, and 37 (8.03%) had sarcopenic obesity. The sarcopenic obesity group had the highest rate of acute VOCF (37.8%), which was statistically significant. Specifically, females with sarcopenic obesity and sarcopenia without obesity had significantly higher acute VOCF rates compared to those with normal body compositions. Multivariate analysis showed that sarcopenic obesity was significantly associated with acute VOCF rate overall, as well as in females.

Conclusion: Sarcopenic obesity is strongly associated with acute VOCF, especially in females, and it could be an essential criterion for the prevention of acute VOCF.

Keywords: sarcopenic obesity, osteoporosis, vertebral compression fracture, bone mineral density, body composition test

INTRODUCTION

Vertebral osteoporotic compression fracture (VOCF) causes a reduction in vertebral body height and is most frequently seen in the thoracolumbar transition zone (1). Symptomatic fractures often lead to severe pain, deformity, decreased mobility, decreased pulmonary function, and increased risk of age-adjusted mortality. Therefore, evidence-based prevention and management are essential (2). However, with the increase in the senior population, VOCF has also been increasing. In the United States, 1.5 million fractures are attributed to osteoporosis every year; more than 700,000 Americans are annually diagnosed with vertebral fractures (3, 4). It is estimated that at least 25% of American women reaching menopause experience at least one VOCF in their lifetime (5).

Many risk factors associated with VOCF have been reported. Risk factors are categorized into not modifiable, such as age, gender, and race, and potentially modifiable factors such as alcohol use, osteoporosis, early menopause, and malnutrition (6). Recently, sarcopenia has been frequently studied as a risk factor for VOCF. Sarcopenia is a syndrome characterized by reduced muscle volume, muscle strength, and muscle activity. It has begun to attract attention in various medical fields. In addition to the vertebral compression fractures, multiple factors and diseases have been studied in relation to sarcopenia (7–9). Additionally, sarcopenia has been shown to be significantly associated with osteoporosis, and the decrease in muscle content, strength, and function substantially increased the risk of osteoporosis (10–12).

Sarcopenic obesity is a combination of two words: sarcopenia and obesity. Appendicular lean mass (see Diagnosis Criteria for Sarcopenia and Obesity section) is used to define sarcopenia. If sarcopenia coexists with excess body fat, it is called sarcopenic obesity (13). Numerous reports have been published regarding this syndrome, and several studies have evaluated its relationship with other diseases such as cardiovascular disease and solid tumors (14, 15). Furthermore, many disorders affecting metabolism, physical capacity, and quality of life have been linked to sarcopenic obesity, though whether sarcopenia and obesity act synergistically has yet to be determined (16). In particular, there are no previous studies on the relationship between sarcopenic obesity and VOCF.

In this cross-sectional study, we collected the data of patients who underwent dual-energy X-ray absorptiometry (DEXA), including body composition tests, and analyzed the rate of acute VOCF according to the groups divided by criteria of bone mineral density (BMD) and muscle volume. With the difference in the prevalence of acute VOCF and adequate statistical methods, we aimed to determine the relationship between body composition category and acute VOCF.

METHODS

Study Design and Patients

After institutional review board approval (No. 2021-02-019), we initially set up the range of the reference group. Informed consent for participants is waived. We included patients who were presented to the spine center and health promotion center at the CHA Bundang Medical Hospital between January 2018 and May 2020. For the patients who visited the spine center, those who were diagnosed with acute VOCF, based on history taking, physical examination, and spine radiography, was included in the experimental group (Acute VOCF group). We only assumed that the patient had the acute VOCF when the patient had the recent trauma history and the tenderness on the fracture site without callus formation on the spine radiography. Finally, we created a list of patients aged 65 years and over, who underwent DEXA with body composition tests at the same time. On the other hand, patients who visited the health promotion center were selected as a reference group. Since people over 65 can receive insurance coverage in our country. These patients took the same tests but did not have acute VOCF on spine radiography. As it was designed as a retrospective study, a total of 622 patients were enrolled initially. After detailed history taking and baseline evaluation, the patients were excluded based on the following exclusion criteria: 1. Patients with incomplete data ($n = 12$); 2. Patients with old VOCF history ($n = 95$) since we only focused on acute VOCF; 3. Patients with high-energy injury mechanisms, such as severe traffic accidents or falling from a tall height ($n = 14$) as most patients presented with mild back pain or other soft tissue injuries; 4. Patients who underwent body composition tests more than 2 weeks from the diagnosis of acute VOCF ($n = 36$) since the treatment of acute VOCF can influence the patient's nutrition and activity so that the body mass index and body composition can change; 5. Patients with possible secondary cause, such as bone metastasis and primary hyperparathyroidism ($n = 4$). Finally, a total of 461 patients were included in the statistical analyses (**Figure 1**).

Diagnosis Criteria for Sarcopenia and Obesity

Patients and healthy participants were divided into four groups: normal, sarcopenia without obesity, obesity without sarcopenia, and sarcopenic obesity. The primary anthropometric data, height and weight, were obtained. Body mass index (BMI) was calculated as body weight divided by squared height, and it was used as an index of obesity. Participants with BMI $\geq$ 25 kg/m^2 were considered obese according to the Korean cut-off values, since it is defined as standard guideline in Korea, related to clinical outcome (17, 18). Next, the body composition test results were analyzed to define and categorize the sarcopenic group. The sum of the muscle masses of the four limbs was defined as appendicular skeletal muscle mass (ASM), and skeletal muscle index (SMI) was defined as ASM/height (m)^2. To measure ASM, the results of 4 limbs from body composition test were used and [Sum of lean mass] (g) – [Sum of bone mineral content] (g) is the exact calculation method. Among various cut-off values from numerous studies, and especially for ASIA consensus, SMI lower than 7.0 kg/m^2 in males and 5.4 kg/m^2 in females were employed (19).

Variables

Age, gender, BMI, height and weight, body composition, and T-score at the lumbar vertebrae and hip were obtained. T-scores were measured using DEXA (GE Lunar Prodigy, Madison, WI,

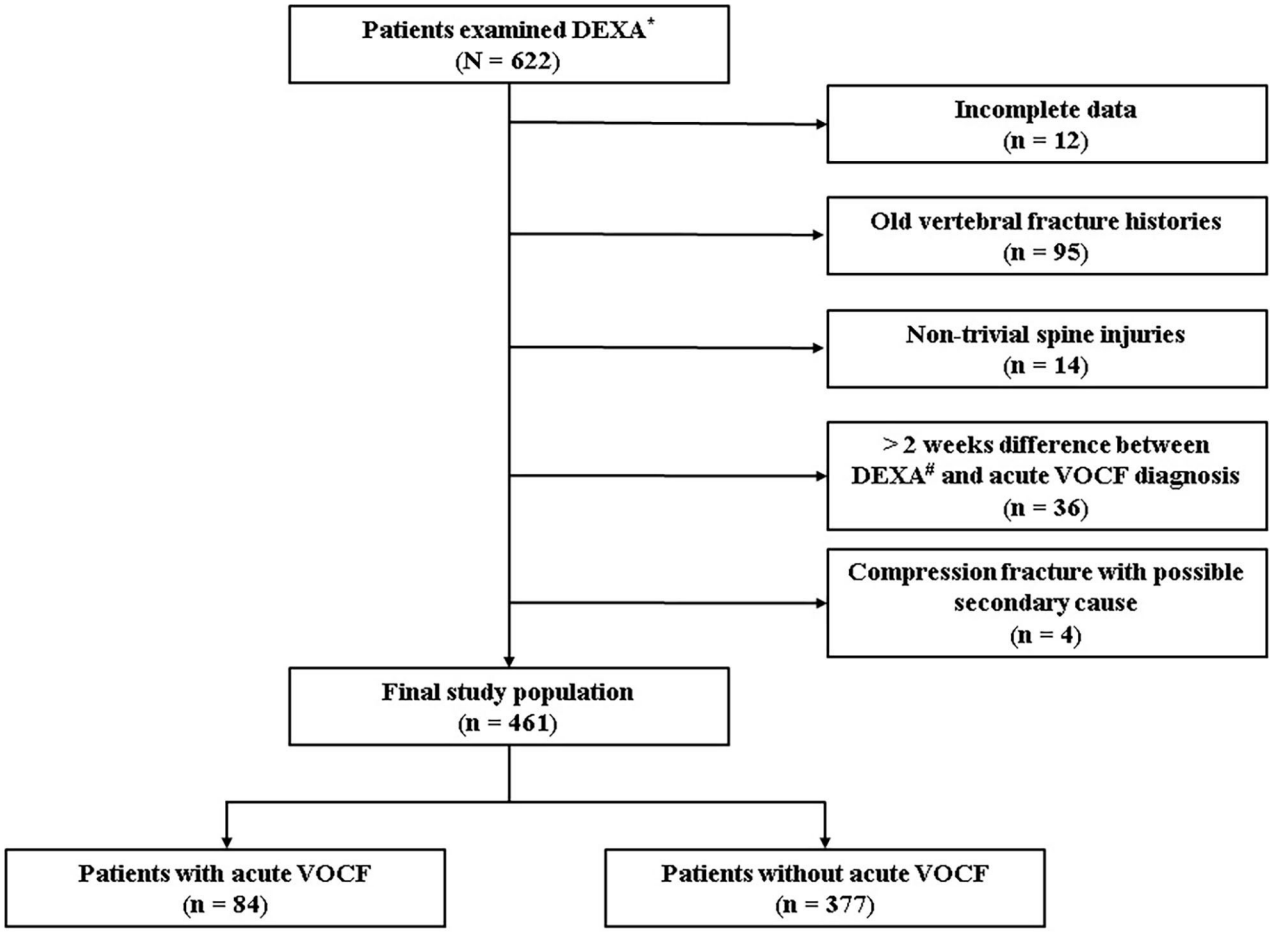


FIGURE 1 | Flowchart. *Dual energy X-ray absorptiometry, #vertebral osteoporotic compression fracture.

USA) and were calculated by taking the difference between a patient's measured BMD and the mean BMD in healthy young adults, matched for gender and ethnic group, and expressing the difference relative to the standard deviation (SD) of the young adult population (20). In addition, DEXA has become a method of choice for assessing body composition because of its unique ability to conveniently and efficiently measure distinct body compartments, including total and regional fat mass, lean tissue mass, bone mineral content, etc. (21). In addition, with the electronic medical record browsing, each participant's history, such as hypertension, diabetes mellitus, and cancer, was assessed. Laboratory results were also collected; reference levels and units are as follows. The detailed values of serum calcium (8.6–10.2 mg/dL), phosphorus (2.5–4.5 mg/dL), vitamin D (30–100 ng/ml), and parathyroid hormone (PTH) (15–65 pg/ml) were obtained. All samples are from the venous blood and each result is from specialized detection devices. Serum calcium and phosphorus levels were measured by Stat Profile® Critical Care Xpress analyzer (Nova Biomedical, Waltham, MA, USA). A 25(OH)D_3-specific kit (Cobra II Auto-γ Counting System, Packard Instruments, Downers Grove, IL, USA) was used for vitamin D measurement. Also, we measured Serum PTH levels by standard enzyme-linked immunosorbent assay-PTH immunoradiometric assay (IBL International GmbH, Hamburg, Germany) with 1.0 pg/ml as a minimal detection amount.

Statistical Analyses

The data manipulation and statistical analyses were performed using R software (version 3.6.3; The R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/). Continuous, normally distributed data are presented as mean and SD. Statistical significance was set at $p < 0.05$. We used the unpaired t-test and Pearson's chi-squared test to compare characteristics of subjects according to the gender. We also used Pearson's chi-squared test to confirm the difference between distributions of the body composition by gender. Univariate analysis was performed to determine the factors associated with acute VOCF. In addition, we performed *post hoc* analysis using Fisher's exact test, which is appropriate for handling small sample sizes, and compared the four body composition groups according to the presence or absence of acute VOCF. Multivariate logistic regression analysis was used, adjusting for factors and covariates

to confirm the simultaneous effect of multiple factors associated with acute VOCF in female. Normal body composition was used as the reference category. Results were presented as odds ratios (ORs) with 95% confidence intervals (CIs) and Akaike Information Criteria (AIC) values, which estimate the quality of each model.

RESULTS

Demographic Characteristics and Body Composition Categories Between Genders

Among 461 patients, 103 were males and 358 were females. Anthropometric factors such as height, weight, and ASM were significantly different between males and females. In addition, significant differences were observed in the T-scores for both the spine and hip between male and female groups. The females had the T-scores of -2.0 ± 1.2 in the spine and -1.9 ± 1.1 in the femur, and both were significantly lower compared to the males that are -1.1 ± 1.5 in the spine and -0.9 ± 1.4 in the femur ($p < 0.001$) (**Table 1**).

Regarding body composition category, ∼30–40% of the study population was in the normal body composition group, irrespective of gender. The proportion of subjects with obesity, with or without sarcopenia, was higher in the female group. In contrast, the rate of sarcopenia, with or without obesity, was higher in the male group. Consequently, among the total patients, 163 (35.36%) had a normal body composition, 151 (32.75%) had sarcopenia without obesity, 110 (23.86%) had obesity without sarcopenia, and 37 (8.03%) had sarcopenic obesity with $p < 0.001$ by Pearson's chi-squared test. The details of the proportions of subjects in each of the four body composition groups are summarized in **Table 2**.

TABLE 1 | Demographic characteristics between both genders.

Variable	Male ($n = 103$)	Female ($n = 358$)	p
Age	70.6 ± 8.6	70.5 ± 9.7	0.969*
Height (m)	1.66 ± 0.61	1.54 ± 0.06	<0.001*
Weight (kg)	63.9 ± 10.5	56.5 ± 9.5	<0.001*
BMI (kg/m^2)	23.1 ± 3.5	23.8 ± 3.6	0.102*
Exam date—Diagnostic date (days)	39.3 ± 90.0	30.7 ± 153.6	0.776*
ASM (kg)	19.5 ± 3.1	13.9 ± 2.3	<0.001*
SMI (kg/m^2)	7.1 ± 1.1	5.9 ± 0.8	<0.001*
T-score			
Spine	−1.1 ± 1.5	−2.0 ± 1.2	<0.001*
Hip	−0.9 ± 1.4	−1.9 ± 1.1	<0.001*
Lab			
Calcium (mg/dl)	9.0 ± 0.6	9.1 ± 0.6	0.145*
Phosphorus (mg/dl)	3.2 ± 0.6	3.5 ± 0.6	<0.001*
Vitamin D (ng/ml)	19.3 ± 8.9	23.8 ± 11.6	0.004*
PTH (pg/ml)	40.5 ± 19.5	45.6 ± 23.0	0.527*
Comorbidity			
Hypertension			0.574**
Yes	48 (46.6%)	153 (42.9%)	
No	55 (46.6%)	204 (57.1%)	
Dyslipidemia			0.108**
Yes	12 (11.7%)	68 (19.1%)	
No	91 (88.3%)	288 (80.9%)	
Diabetes mellitus			0.564**
Yes	22 (21.4%)	65 (18.2%)	
No	81 (78.6%)	292 (81.8%)	
Cancer			0.565**
Yes	8 (7.8%)	20 (5.6%)	
No	95 (92.2%)	337 (94.4%)	

** T-test, ** Pearson's chi-squared test.*

Differences Between Acute VOCF and the Healthy Controls

Among the 461 patients, 84 had acute VOCF and 377 did not. The average age was significantly higher in the acute VOCF group than in the healthy control group (74.7 vs. 69.6 years old, $p < 0.001$). The T-scores of the acute VOCF group were significantly lower than those of the healthy control group ($p = 0.002$ for the spine and $p < 0.001$ for the hip). In addition, calcium and phosphorus were also significantly different between the groups (8.7 vs. 9.2 mg/dL, $p < 0.001$ for calcium and 3.2 vs. 3.5 mg/dL, $p < 0.022$ for phosphorus). However, co-morbidities, such as hypertension and diabetes mellitus, were not significantly different between the two groups. In the normal group, 14.1% of the patients had acute VOCF. The sarcopenia without obesity group had a fracture rate of 22.5%. The obesity without sarcopenia group had the lowest fracture rate (11.8%). Finally, the sarcopenic obesity group had the highest fracture rate (37.8%). Pearson's chi-squared test demonstrated that the fracture rate was significantly different among these four groups ($p = 0.003$) (**Table 3**).

Next, a *post-hoc* analysis with Fisher's exact test was applied to assess fracture rate of each body composition group compared to that of the normal body composition group. In the entire study population, a significant difference was found only between normal and sarcopenic obesity ($p = 0.002$). Regarding the females, we observed that both sarcopenia without obesity and sarcopenic obesity groups had significantly higher rates of acute VOCF than the normal group ($p = 0.018$ and $p = 0.001$, respectively). However, in the male group, there were no statistically significant correlations in the *post hoc* analyses (**Table 4**).

Multivariate Logistic Regression Analysis of Factors Associated With Acute VOCF

Finally, we used multivariate logistic regression adjusting for factors and covariates such as age, BMI, four different body composition categories, T-score, laboratory results, and comorbidities. Models are divided into 4 ways, and Model 1 has only basic variables of the patients; other variables are gradually added to the other models and have roles as confounding factors

TABLE 2 | Distribution of the four body composition categories by gender.

	Normal *n* (%)	Sarcopenia without obesity *n* (%)	Obesity without sarcopenia *n* (%)	Sarcopenic obesity *n* (%)	Total	*p* *
Gender						0.037
Male	32 (31.07)	42 (40.78)	17 (16.50)	12 (11.65)	103 (100.0)	
Female	131 (36.59)	109 (30.45)	93 (25.98)	25 (6.98)	358 (100.0)	
Total	163 (35.36)	151 (32.75)	110 (23.86)	37 (8.03)	461 (100.0)	

** Pearson's chi-squared test.*

TABLE 3 | Univariate analysis of factors associated with VOCF.

Variable	Acute VOCF (*N* = 84)	Non-VOCF (*N* = 377)	*p*
Age	74.7 ± 9.9	69.6 ± 9.1	<0.001*
BMI (kg/m^2)	23.4 ± 3.6	23.6 ± 3.6	0.648*
Body composition category			<0.001**
Normal	23 (14.1%)	140 (85.9%)	
Sarcopenia without obesity	34 (22.5%)	117 (77.5%)	
Obesity without sarcopenia	13 (11.8%)	97 (88.2%)	
Sarcopenic obesity	14 (37.8%)	23 (62.2%)	
T-score			
Spine	−2.2 ± 1.3	−1.7 ± 1.3	0.002*
Hip	−2.2 ± 1.3	−1.6 ± 1.2	<0.001*
Lab			
Calcium (mg/dl)	8.7 ± 0.9	9.2 ± 0.5	<0.001*
Phosphorus (mg/dl)	3.2 ± 0.7	3.5 ± 0.6	0.022*
Vitamin D (ng/ml)	19.5 ± 11.1	23.4 ± 11.1	0.050*
PTH (pg/ml)	38.5 ± 15.4	48.7 ± 25.4	0.077*
Comorbidity			
Hypertension			0.301**
Yes	41 (49.4%)	160 (42.4%)	
No	42 (50.6%)	217 (57.6%)	
Dyslipidemia			0.757**
Yes	13 (15.7%)	67 (17.8%)	
No	70 (84.3%)	309 (82.2%)	
Diabetes mellitus			0.386**
Yes	19 (22.9%)	68 (18.0%)	
No	64 (77.1%)	309 (82.0%)	
Cancer			0.080**
Yes	9 (10.8%)	19 (5.0%)	
No	74 (89.2%)	358 (95.0%)	

** T-test, ** Pearson's chi-square test.*

so Model 4 has all variables included. In the *post hoc* analysis result, only female patients showed that sarcopenic obesity group has significant result compared to any other subgroups; we did this multivariate regression for the females. The results showed that the sarcopenic obesity, calcium, and PTH were significantly associated with acute VOCF ($p < 0.05$). Sarcopenic obesity was especially significant in all the models (**Table 5**). Forest plot was drawn for indicating the odds ratio of each variable (**Figure 2**).

DISCUSSION

In this cross-sectional study, we divided patients into four subgroups according to their body composition to evaluate the risk of acute VOCF. Patients with sarcopenia and obesity simultaneously (sarcopenic obesity) had a significantly higher fracture rate suggesting that both weight control and muscle gain may give a protective effect to the bone health, especially in vulnerable patients. Also, this result was prominent especially for the female patients. In addition, obesity may intensify sarcopenia by acting in concert with it, resulting in physical impairment, metabolic disorders, and mortality.

Previously, these important concepts have been broadly used in various studies, and their utilization is gradually increasing. Furthermore, several studies have already reported analyzed the association between body composition and VOCF and have not reached a conclusion yet. For instance, Hida et al. found a higher prevalence of sarcopenia and lower leg muscle mass among patients with acute VOCF compared to those without acute VOCF (22). On the other hand, Anand et al. concluded that sarcopenia was not an independent risk factor for fresh vertebral fragility fractures in the elderly (23). Based on these results, we concluded that sarcopenic obesity could be an independent factor for predicting vulnerability to acute VOCF.

We found some mechanisms and supporting reasons for the findings of the present study. The back muscles that protect the spine around us are huge, and when standing up, they have a significant impact on our stability, various exercises, and daily lives. Therefore, this reduction in muscle mass not only weakens the muscle strength but also contributes to body instability. Song et al. reported that lumbar disc degeneration was correlated with multifidus degeneration (24). According to Fried et al., reduced amount of muscle mass played an important etiologic role in the frailty process of elderly subjects, being a key player in its latent phase and illustrating certain aspects of the frailty status itself (25). Interestingly, in our research, more significant results were derived from sarcopenic obesity than from sarcopenia without obesity; in particular, the results were more meaningful in the female group. Another important implication is how much weight is applied to the fractured vertebrae. Since a person with sarcopenic obesity usually has a larger force on the vertebral body during injury, it could be a critical factor for the fracture rate.

In this study, the fracture rates among four body composition groups were not significantly different in

TABLE 4 | *Post hoc* analysis of the four groups by VOCF.

	Acute VOCF *n* (%)	Non-VOCF *n* (%)	*p* *		
Total	84 (18.2%)	377 (81.8%)			
Normal	23 (14.1%)	140 (85.9%)	Reference		
Sarcopenia without obesity	34 (22.5%)	117 (77.5%)	0.058	Reference	
Obesity without sarcopenia	13 (11.8%)	97 (88.2%)	0.716	0.033	Reference
Sarcopenic obesity	14 (37.8%)	23 (62.2%)	0.002	0.062	0.001
Male	15 (14.6%)	88 (85.4%)			
Normal	4 (12.5%)	28 (87.5%)	Reference		
Sarcopenia without obesity	6 (14.3%)	36 (85.7%)	1	Reference	
Obesity without sarcopenia	2 (11.8%)	15 (88.2%)	1	0.532	Reference
Sarcopenic obesity	3 (25.0%)	9 (75.0%)	0.391	0.735	0.193
Female	69 (19.3%)	289 (80.7%)			
Normal	19 (14.5%)	112 (85.5%)	Reference		
Sarcopenia without obesity	28 (25.7%)	81 (74.3%)	0.018	Reference	
Obesity without sarcopenia	11 (11.8%)	82 (88.2%)	0.703	0.042	Reference
Sarcopenic obesity	11 (44.0%)	14 (56.0%)	0.001	0.045	0.001

**Fisher's exact test.*

TABLE 5 | Multivariate logistic regression analysis of factors associated with acute VOCF for female.

Variable	Model 1		Model 2		Model 3		Model 4	
	AIC = 291.86		AIC = 288.13		AIC = 275.28		AIC = 283.03	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Diagnosed age	1.06 (1.02–1.09)	0.001	1.03 (0.99–1.07)	0.179	1.01 (0.97–1.05)	0.590	1.01 (0.97–1.05)	0.540
BMI	0.99 (0.86–1.12)	0.793	1.02 (0.89–1.18)	0.763	0.99 (0.86–1.15)	0.928	1.00 (0.86–1.16)	0.950
Body composition category								
Sarcopenia without obesity	2.01 (0.97–4.26)	0.063	2.01 (0.95–4.33)	0.069	2.09 (0.95–4.69)	0.069	2.08 (0.95–4.69)	0.072
Obesity without sarcopenia	0.82 (0.25–2.55)	0.741	0.81 (0.25–2.55)	0.727	1.00 (0.29–3.29)	1.000	1.00 (0.29–3.30)	1.000
Sarcopenic obesity	6.97 (2.04–24.33)	0.002	6.52 (1.88–23.13)	0.003	6.86 (1.85–26.35)	0.004	7.03 (1.88–27.32)	0.004
T-score								
Spine			0.82 (0.60–1.11)	0.203	0.834 (0.61–1.14)	0.260	0.84 (0.61–1.15)	0.277
Hip			0.71 (0.47–1.04)	0.084	0.77 (0.50–1.15)	0.203	0.76 (0.50–1.15)	0.206
Lab								
Calcium					0.36 (0.18–0.66)	0.003	0.36 (0.36–0.67)	0.004
Phosphorus					0.72 (0.41–1.25)	0.249	0.72 (0.41–1.25)	0.238
Vitamin D					0.98 (0.94–1.02)	0.302	0.98 (0.93–1.02)	0.270
PTH					0.96 (0.91–1.00)	0.041	0.96 (0.91–1.00)	0.046
Comorbidity								
Hypertension							0.84 (0.41–1.70)	0.626
Dyslipidemia							1.04 (0.41–2.42)	0.931
Diabetes mellitus							1.01 (0.42–2.30)	0.980
Cancer							1.06 (0.29–3.61)	0.923

males. It can be considered in conjunction with a higher BMD in males. In many previous studies, BMD has been proven numerically or biomechanically to be positively associated with osteoporotic fractures. Ehsanbakhsh et al. reported that vertebral fractures were observed in 43.6% of osteoporotic patients, 37.5% of osteopenic patients, and 22% of patients with a normal T-score (26). Jager et al. reported that vertebral fracture prevalence was 14% in patients with normal BMD, 21% in those with osteopenia, and 33% in those with osteoporosis (27). In addition, a relatively higher muscle mass compared to that of females may also be a contributing factor.

This study has some limitations. First, as mentioned above, the number of male patients is less than the female patients

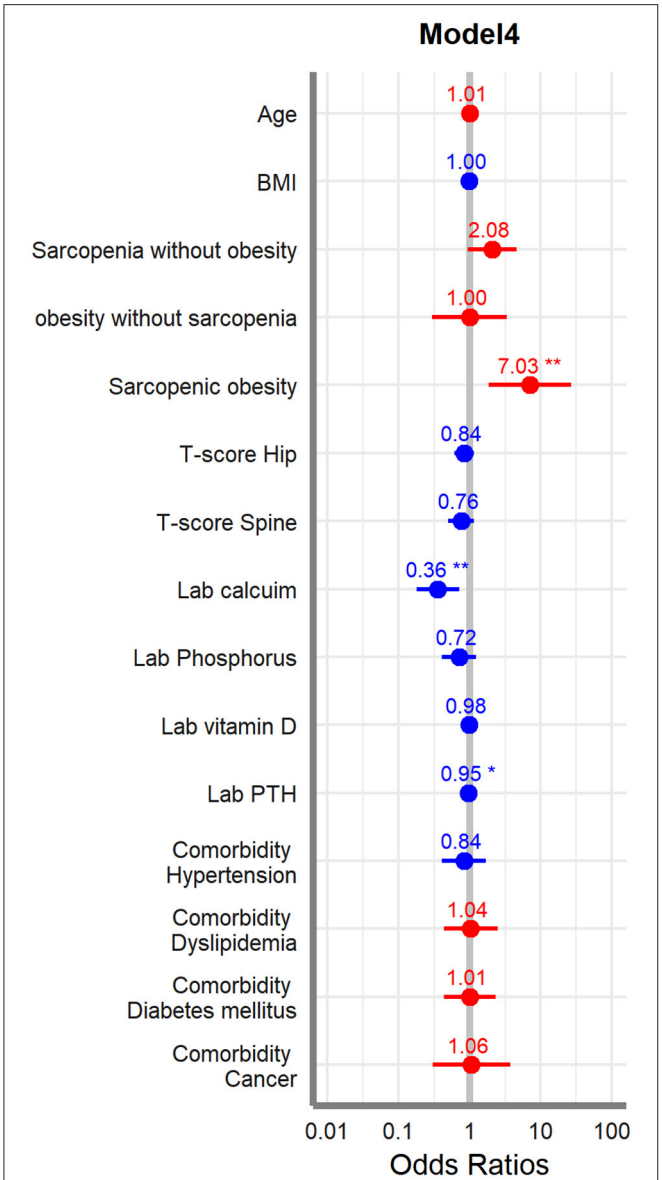


FIGURE 2 | Forest plot of multivariate regression analysis (female).

and the ratio of fracture was also lower. In the further study, more male patients would be collected and we hope to find some other meaningful result regardless of gender. Second, because of the characteristics of a cross-sectional study, it was impossible to establish a real cause-and-effect relationship. It is expected that prospective research will be needed in the future to identify the causes and results throughout the periodic examination and analyses. Third, while the T-score of the spine was meaningful in the univariate study, it was not in the multivariate study, although we measured the BMD clearly according to the criteria, such as the exclusion of the vertebra with fractures. We think that this is because of the sclerotic change in the spinal body with aging. Also, unlike hip, abdominal fats in obese group could also influence the result of spine T-score (28). Finally, although the definitions of sarcopenia are various and are composed of muscle strength or function as well as muscle mass index, we used only body composition of the definition. It would be better to investigate other criteria together, but due to the limitation of the retrospective study, there was a limitation of data collection. Also, in the definition of obesity, BMI is more than 30 worldwide, but Asian countries including Korea, use 25 as a cut-off value due to differences in race and lifestyle. In order to meet the global standard, we would like to overcome those limitations above in the future study.

CONCLUSION

Sarcopenic obesity can be one of the expectation factors of the acute VOCF. It could be an essential criterion for the prevention of fracture, thus finally could also be used as an fracture fragility indicator.

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 Institutional Review Board Approval (No. 2021-02-019). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

YL: manuscript writing and data curation. H-JL: conceptualization, investigation, manuscript review, and editing. SY: data curation and methodology. JS and K-CP: data curation. S-yL: project administration and funding acquisition. SL: project administration, funding acquisition, and formal analysis. All authors have read and approved the 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.2021.790135/full#supplementary-material

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Transcutaneous Electrical Acupoint Stimulation for the Prevention of Postoperative Cognitive Dysfunction: A Systematic Review and Meta-Analysis

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Background: No specific treatment is available for postoperative cognitive dysfunction (POCD). Recently, interest in the prevention of POCD during the perioperative period has increased. Although some studies suggest that transcutaneous electrical acupoint stimulation (TEAS) may be beneficial, the relevant evidence remains uncertain.

Objective: To evaluate the preventive effects of TEAS on POCD.

Methods: Seven databases including PubMed, EMBASE, CENTRAL, China National Knowledge Infrastructure (CNKI), Chinese Scientific Journal Database (VIP), Wanfang Database, and Chinese Biomedical Literature Database (CBM) were electronically searched up to April 2021. Two reviewers independently selected the studies, collected data, and assessed the risks of bias and grading of recommendations, assessment, development, and evaluations certainty of the evidence. A meta-analysis of the incidence of POCD, cognitive function score, pain, adverse reactions, and length of hospital stay after surgery was also performed.

Results: Twenty-nine randomized controlled trials with 1,994 participants were included. The results of the meta-analysis showed that the TEAS group has a significantly lower incidence of POCD compared with the control group on postoperative days 1 [OR = 0.33 (95%CI: 0.23, 0.47); $p < 0.001$, $I^2 = 0\%$, moderate certainty], 3 [OR = 0.38 (95%CI: 0.29, 0.50); $p < 0.001$, $I^2 = 0\%$, low certainty], and 7 [OR = 0.51 (95%CI: 0.32, 0.81); $p = 0.005$, $I^2 = 0\%$, low certainty] but not on day 5 ($p > 0.05$, low certainty). Moreover, TEAS improved the Mini-Mental State Examination scores on postoperative days 1, 3, and 7 [MD = 2.44 (95%CI: 1.61, 3.27); $p < 0.001$, $I^2 = 93\%$, low certainty]; [MD = 2.07 (95%CI: 1.53, 2.62); $p < 0.001$, $I^2 = 87\%$, low certainty]; and [MD = 0.49 (95%CI: 0.18, 0.79); $p = 0.002$, $I^2 = 21\%$, low certainty], respectively, but not on day 5 ($p > 0.05$, very low certainty). TEAS promoted a postoperative analgesic effect within 24 h after surgery. Furthermore, patients receiving TEAS showed a lower incidence of postoperative nausea and vomiting and a shorter hospital stay.

Conclusions: Limited evidence suggests that the application of TEAS in the perioperative period is associated with a reduced POCD rate and a protected early postoperative cognitive function.

Keywords: transcutaneous electrical acupoint stimulation, postoperative cognitive dysfunction, prevention, cognitive function, systematic review, meta-analysis

INTRODUCTION

Postoperative cognitive dysfunction (POCD) is a syndrome with prolonged cognitive impairment, which is characterized by limitations in memory, intellectual ability, and executive function after surgery. This condition is distinct from delirium and dementia (1). An estimated 312.9 million surgical procedures were performed worldwide in 2012, displaying an increase of 38% over the previous 8 years (2). Furthermore, with growing populations and increasing lifespan, the number of surgeries performed annually is likely to continue to increase (3). Cognitive dysfunction following a surgical procedure is one of the most common complications in the elderly, with estimated incidence rates of 20–50% at 3 months post-cardiac surgery and 5–55% after other major surgeries (4, 5). A higher 1-year mortality rate increased length of stay and cost, and premature withdrawal from the workforce have been observed in patients who experienced POCD. POCD is also associated with an increased risk of dementia and may lead to chronic neurodegeneration, particularly in the case of repeated surgery (6–8). Age, education level, infection, and preexisting cognitive disorders have been associated with cognitive decline after surgical procedures (4, 7, 9, 10). To date, there remains no available strategy for the treatment of POCD. Therefore, anesthesiologists and surgeons have sought to develop an approach to reduce the morbidity of POCD. As the occurrence of POCD may be multifactorial, the prevention methods are correspondingly multidisciplinary (8, 11, 12).

Acupuncture, as traditional alternative medicine, has been used to treat diseases and relieve pain for thousands of years in Asia. Transcutaneous electrical acupoint stimulation (TEAS) is a combination of transcutaneous electrical nerve stimulation (TENS) and traditional Chinese acupuncture that has been widely accepted and applied worldwide (13). Previous studies have shown the beneficial effects of TEAS for various aspects, such as reducing intraoperative opioid use and postoperative nausea and vomiting (PONV), relieving pain, and improving postoperative cognitive function (14–17). To our knowledge, few studies have systematically examined the efficacy and safety of TEAS for the prevention of POCD based on the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines. Therefore, we evaluated the preventive effect of TEAS on POCD to provide evidence for clinical practice by reviewing all currently available randomized controlled trials (RCTs).

METHODS

This systematic review and meta-analysis are reported in accordance with the PRISMA guidelines (18) and registered on the Open Science Framework (https://osf.io/bq4v2, doi: 10.17605/OSF.IO/BQ4V2).

Databases and Search Strategy

We searched PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), China National Knowledge Infrastructure (CNKI), Chinese Scientific Journal Database (VIP), Wanfang Database, and Chinese Biomedical Literature Database (CBM) from the dates of inception of the databases until April 2021 without any language restrictions. The search strategy used medical subject's headings (MeSH) terms in combination with free-text, such as "Cognitive Function," "Cognitive Dysfunction," "Cognition," "Cognitive Impairments," "Postoperative Cognitive Complications," "Transcutaneous Electrical Acupoint Stimulation," "Acupuncture Points," and "Electric Stimulation," etc. The detailed search strategy is described in **Supplementary File 1**.

Selection Criteria

This review focused on RCTs that were less prone to confounding bias by indication (19, 20). The eligibility criteria for study selection were as follows: ① Participants aged 18 years and above who underwent surgery and anesthesia and showed no abnormal cognitive function in preoperative assessment; ② the intervention group was treated with TEAS, alone or combined with other therapies; ③ the control group (CG) was treated with a sham intervention, with no treatment, or other therapies; and ④ no limit to the type of operation. We excluded studies with ① participants diagnosed with POCD, ② trials that used needles, such as electroacupuncture, body needle, auricular needle, etc., and ③ articles published using the same data sets.

Outcome Measures

The primary outcomes were the incidence of POCD and cognitive function scores assessed by any definition given in the original study. The secondary outcomes included postoperative pain, adverse reactions, and length of hospital stay.

Data Extraction and Quality Assessment

Two investigators (JML and YS) independently extracted data from eligible studies and inputted the outcome data into a predesigned spreadsheet. Any disagreements in the crosschecking process were resolved through discussion. Otherwise, a third investigator (LO) arbitrated the dispute. The main information extracted from the included articles included study design, populations studied, type of operation, type of anesthesia, intervention, outcomes, and postoperative test time. The Cochrane risk of bias tool was used to assess the methodological quality and the risks of bias of the individual studies (21). The certainty of the evidence for each outcome was

evaluated using the grading of recommendations, assessment, development, and evaluations framework (22).

Data Synthesis and Analysis

Data were synthesized using RevMan version 5.4. For dichotomous outcomes, such as the incidence of POCD, we calculated the odds ratio (OR) and 95% CI. For continuous outcomes, such as cognitive function scores, we pooled the mean difference (MD) and 95% CI. Statistical significance was set at $p < 0.05$.

Subgroup Analyses and Investigation of Heterogeneity

When sufficient studies reported relevant characteristics, we performed subgroup analyses for postoperative test time, anesthesia method, type of operation, and acupoint combination. We also conducted subgroup analyses to explore the impact of small sample-sized studies by grouping their sample size by quarter (from quarter 1, which includes 25% of the smallest trials, to quarter 4, which includes 25% of the largest trials) (23). The heterogeneity among the studies was assessed using Cochran Q tests (χ^2 tests for heterogeneity), and significant statistical heterogeneity was defined as a Q test with $p < 0.10$ or $I^2 > 50\%$. We used the random-effects model to calculate the effect size, allowing for differences between the studies (24).

Publication Bias and Sensitivity Analyses

We tested for publication bias when sufficient studies were available ($n \geq 10$). Asymmetric funnel and Harbord tests were applied to assess for potential publication bias when OR was used as an effect estimate, and the results showed there was no substantial heterogeneity between the studies. Moreover, when MD was regarded as an effect estimate, we adopted an asymmetric funnel and Egger's test to assess for potential publication bias (25). We also used the trim-and-fill method to identify and correct funnel plot asymmetries caused by publication bias (26). We conducted a sensitivity analysis to explore the source of heterogeneity by removing 1 study in each turn, and to examine the stability of the main outcome by excluding poor-quality trials with high risks of bias.

RESULTS

Study Selection and Characteristics

The database search identified a total of 371 articles. According to the inclusion and exclusion criteria, 29 RCTs (27–55) with 1,994 participants were eligible for data extraction. A flow diagram of the screening of the trials is shown in **Figure 1**. In the present review, all trials were conducted in China and published in Chinese and English. The average age of the participants in 11 trails (27, 28, 35, 36, 39, 40, 43, 44, 46, 47, 51) was 18–65 years and was > 65 years in the other studies. Of the 29 reported interventions, 3 trails (28, 32, 50) were treated with a combination of TEAS and controlled hypotension, and 1 (52) received TEAS combined with dexmedetomidine. Of 29 RCTs, 2 trials (27, 39) reported patients who underwent craniocerebral surgery, and 2 other studies (48, 53) involved patients undergoing cardiac surgery. Participants from the remaining 25 trails underwent non-cardiac surgery. The time points for evaluation in the included studies ranged from 0 to 7 days after surgery (**Table 1**).

Quality Assessments

All included studies were described as randomized. Among them, 22 studies (27–29, 31, 32, 34, 37–39, 41–45, 48–55) (76%) were performed using a random number table, and 1 (47) adopted drawing lots. Four studies (51–53, 55) (13%) described the proper way to complete allocation concealment. Seventeen studies (27, 29–31, 34–40, 42, 43, 46–48, 50) (57%) were at high risk of bias for failing to blind participants and personnel, whereas the others were at low risk of bias. Fourteen studies (29, 31, 32, 34–38, 40, 45, 49, 51, 53, 55) (48%) were blinded to the outcome assessment. All studies (100%) showed low risks for incomplete outcome data. In this review, most of the research protocols (93%) were not available on record, and so selective reporting was difficult to judge. The methodological quality of the included trials is shown in **Figure 2**.

Primary Outcomes

Incidence of POCD

Twenty-three studies (28–43, 45, 47, 49, 50, 53–55) reported the incidence of POCD. Overall, the results of the meta-analysis suggested a significantly lower incidence of POCD in the TEAS group than that in the CG [OR = 0.40 (95%CI: 0.33, 0.48); $p < 0.001$, $I^2 = 0\%$]. Subgroup analyses by evaluation time points (postoperative days 1, 3, 5, and 7) showed that the TEAS group had a significantly lower incidence of POCD compared with that in the CG on postoperative days 1 [OR = 0.33 (95%CI: 0.23, 0.47); $p < 0.001$, $I^2 = 0\%$, moderate certainty], 3 [OR = 0.38 (95%CI: 0.29, 0.50); $p < 0.001$, $I^2 = 0\%$, low certainty], and 7 [OR = 0.51 (95%CI: 0.32, 0.81); $p = 0.005$, $I^2 = 0\%$, low certainty]. On postoperative day 5, no significant difference was observed between the TEAS group and the CG for the incidence of POCD [OR = 0.70 (95%CI: 0.36, 1.36); $p = 0.29$, $I^2 = 0\%$, low certainty] (**Figure 3** and **Table 2**). Subgroup analysis of the operation type showed that compared with the CG, TEAS significantly reduced the incidence of POCD in patients undergoing non-cardiac and noncraniocerebral surgery [OR = 0.40 (95%CI: 0.33, 0.49); $p < 0.001$, $I^2 = 0\%$, moderate certainty]. There was no significant difference in the incidence of POCD between the TEAS group and the CG, either for patients receiving craniocerebral surgery [only 1 study (39) reported, OR = 0.32 (95%CI: 0.03, 3.18); $p = 0.33$, I^2 not applicable, low certainty] or cardiac surgery [only 1 study (53) reported, OR = 0.37 (95%CI: 0.14, 0.99); $p = 0.05$, I^2 not applicable, moderate certainty]. Furthermore, a subgroup analysis based on the different anesthesia techniques suggested a significant reduction of POCD-related morbidity in the TEAS group, regardless of using intravenous anesthesia [OR = 0.44 (95%CI: 0.34, 0.56); $p < 0.001$, $I^2 = 0\%$, low certainty], intravenous-inhalation anesthesia [OR = 0.38 (95%CI: 0.27, 0.52); $p < 0.001$, $I^2 = 0\%$, low certainty], or combined spinal epidural anesthesia (CSEA) [OR = 0.35 (95%CI: 0.19, 0.62); $p < 0.001$, $I^2 = 0\%$, low certainty] (**Supplementary Table 1**).

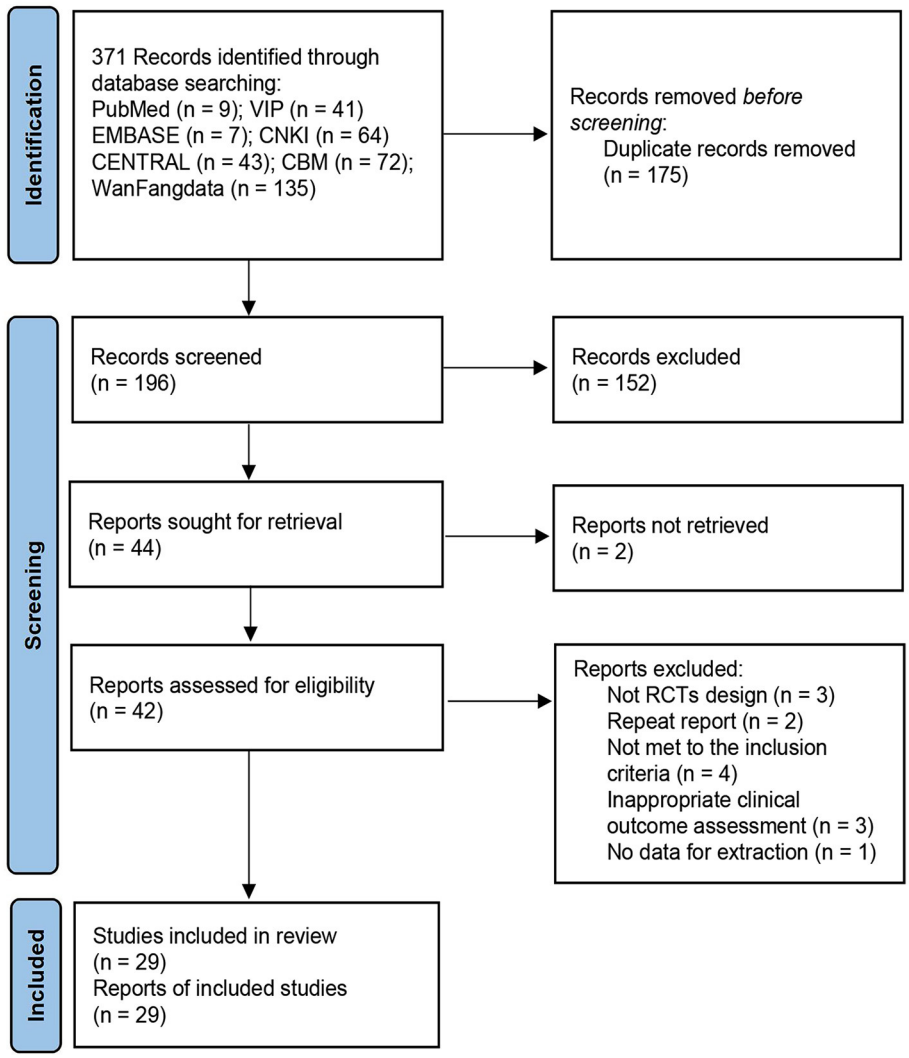


FIGURE 1 | Flowchart of study selection.

In the subgroup analysis of acupoint selection, we observed the efficacy of 6 kinds of acupoint combinations that were used more than 2 times in the included studies. Our metaanalysis showed that TEAS significantly reduced the incidence of POCD in 5 of the 6 combinations compared with CG. The acupoint combinations arranged in descending order of effect size were LI4, LI11, ST36, SP6 [OR = 0.33 (95%CI: 0.14, 0.77); $p = 0.01$, $I^2 = 0\%$, low certainty]; GV20, PC6, ST36, SP6 [OR = 0.37 (95%CI: 0.26, 0.54); $p < 0.001$, $I^2 = 0\%$, low certainty]; GV20, PC6, GB20 [OR = 0.38 (95%CI: 0.21, 0.71); $p = 0.002$, $I^2 = 0\%$, low certainty]; PC6, ST36 [OR = 0.40 (95%CI: 0.23, 0.69); $p < 0.001$, $I^2 = 0\%$, low certainty]; and LI4, PC6 [OR = 0.49 (95%CI: 0.31, 0.77); $p = 0.002$, $I^2 = 0\%$, low certainty]. Nevertheless, acupoint combination containing GV20, PC6, and ST36 in the TEAS group had no advantage in preventing POCD [OR = 0.53 (95%CI: 0.27, 1.04); $p = 0.07$, $I^2 = 0\%$, low certainty] (**Supplementary Table 1**).

The funnel plot of the above analysis showed no significant asymmetry (**Supplementary Figure 1**); moreover, the Harbord test showed no publication bias ($p = 0.647$; **Supplementary Figures 2**, **3**). Additionally, the trim-and-fill method revealed that publication bias had little effect on the combined results and that the results were stable (**Supplementary Figures 4**, **5**). Further sensitivity analysis by excluding low-quality studies showed that the pooled analysis results were stable (**Supplementary Table 2**).

Cognitive Function Score

The included articles applied 5 types of cognitive function scoring methods (including MMSE, MoCA, and QoR-15/40) used in the included articles. We eventually selected MMSE scores ($n = 24$ studies) to extract data for analysis (27, 29, 31–38, 40–42, 44–46, 48–55). One study (51) reported data in a figure, which was excluded from this analysis because of the absence of

TABLE 1 | Characteristics of the included randomized clinical trials.

First author	Age (years) EG/CG	Sample size	Type of operation/ anesthesia	Intervention			Outcomes	Postoperative test time
				EG	CG	Acupoints/Stimulation frequency/time		
Ren (27)	52 ± 9/ 54 ± 10	50	Craniotomy/ Intravenous-inhalation	TEAS	No treatment	LI4, LI11, ST36, SP6; 2∼100 Hz; from 30 min before anesthesia to the completion of operation	MMSE	1, 24, 48 h
Zhou et al. (28)	45∼65	75	Single spinal surgery/Intravenous-inhalation	TEAS+ Controlled hypotension	Controlled hypotension	LI4, LI11, ST36, SP6; 2∼100 Hz; from 30 min before anesthesia to the completion of operation	incidence of POCD	1, 3, 5d
Lin et al. (29)	68.5 ± 2.8/ 67.3 ± 2.7	49	Abdominal surgery/ Intravenous	TEAS	No treatment	GV20, GV29, PC6; 2∼100 Hz; from 30 min before anesthesia to the completion of operation	incidence of POCD, MMSE	3d
Wu et al. (30)	62∼76	100	Laparoscopic cholecystectomy/ Intravenous-inhalation	TEAS	No treatment	GV20, PC6, ST36; 2∼15 Hz; from 30 min before anesthesia to the completion of operation	incidence of POCD and PONV	3, 7d
Ni et al. (31)	65∼78	60	Laparoscopic resection of rectal cancer/Intravenous	TEAS	No treatment	GV20, PC6, ST36, SP6; 2∼100 Hz; from 30 min before anesthesia to the completion of operation	incidence of POCD, MMSE	1, 3, 5, 7d
Yin et al. (32)	78.3 ± 5.5/ 77.5 ± 5.2	53	Hip-replacement surgery/ Intravenous	TEAS+ Controlled hypotension	Sham stimulation+ Controlled hypotension	GV20, PC6, GB20; 2∼100 Hz; from 30 min before anesthesia to the completion of operation	incidence of POCD, MMSE	72 h
Yang et al. (33)	65∼80	60	Gynecological laparoscopic surgery/Intravenous	TEAS	Sham stimulation	PC6, ST36; 2∼100 Hz; from 30 min before anesthesia to the completion of operation	incidence of POCD, MMSE	1, 3, 5d
Wang(a) et al. (34)	69.9 ± 4.2/ 69.3 ± 4.1	60	Artificial femoral head replacement/CSEA	TEAS	No treatment	GV20, PC6, ST36, SP6; 2∼100 Hz; after anesthesia to the end of operation	incidence of POCD, MMSE, VAS	1, 3, 7d
Zhu et al. (35)	34.2 ± 9.7/ 34.6 ± 8.4	60	Gynecological laparoscopic surgery/Intravenous-inhalation	TEAS	No treatment	PC6, ST36; 2∼100 Hz; from 30 min before anesthesia to the completion of operation	incidence of POCD, MMSE	1d
Wei et al. (36)	55.2 ± 6.1/ 56.5 ± 4.6	40	Gynecological laparoscopic surgery/Intravenous-inhalation	TEAS	No treatment	GV20, PC6, GB20; 2∼100 Hz; 30 min before anesthesia	incidence of POCD, MMSE	1, 3d
Li et al. (37)	65.7 ± 6.1/ 66.5 ± 4.0	60	Radical thoracoscopic lung cancer operation/ Intravenous-inhalation	TEAS	No treatment	PC6, ST36; 2∼100 Hz; from 30 min before anesthesia to the completion of operation	incidence of POCD, MMSE	1, 3d
Wang(b) et al. (38)	70.3 ± 4.2/ 69.5 ± 4.4	60	Laparoscopic radical gastrectomy for cancer/ Intravenous	TEAS	No treatment	GV20, PC6, ST36, SP6; 2∼100 Hz; after anesthesia to the end of operation	incidence of POCD, MMSE, VAS	1, 3, 7d
Zhao et al. (39)	37.0 ± 11.7/ 37.9 ± 11.9	80	Transsphenoidal surgery/ Intravenous-inhalation	TEAS	No treatment	LI4, TE5, EX-HN4; 2∼100 Hz; from 30 min before anesthesia to the completion of operation	incidence of POCD, neuropsychological tests	3d

(Continued)

TABLE 1 | Continued

First author	Age (years) EG/CG	Sample size	Type of operation/ anesthesia	Intervention			Outcomes	Postoperative test time
				EG	CG	Acupoints/Stimulation frequency/time		
Wei et al. (40)	57.9 ± 3.9/ 57.6 ± 4.1	40	Gynecological laparoscopic surgery/ Intravenous-inhalation	TEAS	No treatment	GV20, PC6, GB20; 2∼100 Hz; 30 min before anesthesia, stimulation for 1 h	incidence of POCD, MMSE	1, 3d
Tan et al. (41)	67.1 ± 6.2/ 66.4 ± 5.5	70	Laparoscopic cholecystectomy/ NR	TEAS	Sham stimulation	GV20, PC6, ST36, SP6; 2∼100 Hz; 30 min/d from the first day before operation to the 7 day after operation	incidence of POCD, MMSE	3, 7d
Tang et al. (42)	69.6 ± 5.8/ 70.1 ± 6.3	90	Colorectal cancer surgery/ intravenous	TEAS	No treatment	GV20, GV24; 2∼100 Hz; from 30 min before anesthesia to the completion of operation	incidence of POCD, MMSE	1, 3, 5, 7d
Fan et al. (43)	54 ± 7/ 54 ± 8	56	Laparoscopic resection of colorectal cancer/ Intravenous-inhalation	TEAS	No treatment	PC6, LI4, ST36, ST37, ST39; 2∼100 Hz; from 30 min before anesthesia to the completion of operation	incidence of POCD and PONV, QoR-15, length of hospital stay	3d
Mi et al. (44)	44 ± 6/ 45 ± 8	100	Laparoscopic cholecystectomy/ Intravenous-inhalation	TEAS	Sham stimulation	LI4, PC6, ST36; 2∼100 Hz; from 30 min before anesthesia to the completion of operation	QoR-40, MMSE, incidence of PONV	4, 8, 24, 48 h
Sun et al. (45)	86.3 ± 4.4/ 85.8 ± 4.2	40	Hip fracture surgery/CSEA	TEAS	Sham stimulation	GV20, GB20; 2∼100 Hz; (3 times/d, 30 min/time) since 2 days before operation until the operation finished	incidence of POCD, MMSE	24, 72 h
Mao et al. (46)	35∼55	80	Breast cancer surgery/ Intravenous	TEAS	No treatment	LI4, PC6; 2∼100 Hz; from 10 min before anesthesia to the completion of operation	MMSE, incidence of PONV	24, 48 h
Li and Yang (47)	39.0 ± 5.2/ 39.0 ± 5.3	90	Laparoscopic Myomectomy/ Intravenous-inhalation	TEAS	Dex	PC6, ST36; 2∼100 Hz; from 30 min before anesthesia to the completion of operation	incidence of POCD and PONV	3d
Wu and Chen (48)	72.3 ± 5.3/ 71.9 ± 5.1	84	Cardiac surgery/ Intravenous	TEAS	No treatment	GV20, PC6, ST36, SP6; 2∼100 Hz; from 30 min before anesthesia to the completion of operation	MMSE, VAS, incidence of PONV	3d
Duan et al. (49)	78 ± 10/ 76 ± 11	80	Hip replacement/ Intravenous-inhalation	TEAS	Sham stimulation	LI4, PC6; 2∼200 Hz; from 30 min before anesthesia to the completion of operation	incidence of POCD, MMSE, VAS	24, 72 h
Lu et al. (50)	72.1 ± 2.5/ 71.3 ± 2.3	91	Hip replacement/ Intravenous-inhalation	TEAS+ Controlled hypotension	Controlled hypotension	GV20, PC6, GB20; 2∼100 Hz; Before anesthesia induction to the end of operation	incidence of POCD and PONV, MMSE, VAS	72 h
Yu et al. (51)	48.5 ± 16.2/ 45.9 ± 17.5	60	Gynecological laparoscopic surgery/ Intravenous	TEAS	Sham stimulation	GV20, GV29, ST36, PC6; 2∼100 Hz; 30 min before anesthesia	QoR-40, MMSE, VAS, incidence of PONV	1, 2d

(Continued)

TABLE 1 | Continued

First author	Age (years) EG/CG	Sample size	Type of operation/ anesthesia	Intervention			Outcomes	Postoperative test time
				EG	CG	Acupoints/Stimulation frequency/time		
Yang (52)	71.1 ± 5.4/ 71.0 ± 5.6	60	Hip surgery/CSEA	TEAS+ Dex	Sham stimulation+ Dex	EX-HN3, GB20; 2~100 Hz; from 30 min before anesthesia to the completion of operation	MMSE	24h
Huang et al. (53)	65.3 ± 6.9/ 65.4 ± 5.2	82	Off-pump coronary artery bypass grafting/ Intravenous	TEAS	Sham stimulation	PC6, LI4, GV14; 2~100 Hz; from the beginning of operation to the completion of operation	incidence of POCD, MMSE	7d
Wu and Luo (54)	72 ± 10/ 72 ± 9	84	Non cardiac surgery/ Intravenous	TEAS	Sham stimulation	LI4, PC6; 2~60 Hz; before anesthesia to the completion of operation	incidence of POCD and PONV, MMSE, MoCA	1, 3, 7d
Duan et al. (55)	69.2 ± 7.7/ 70.4 ± 3.9	80	Total hip replacement/ Intravenous	TEAS	Sham stimulation	LI4, PC6; 30 min before anesthesia	incidence of POCD, MMSE, VAS	1, 3d

EG, experimental group; CG, control group; CSEA, combined spinal epidural anesthesia; TEAS, transcutaneous electrical acupoint stimulation; MMSE, mini-mental state examination; POCD, postoperative cognitive dysfunction; PONV, postoperative nausea and vomiting; VAS, visual analog scale; MoCA, montreal cognitive assessment; QoR-40/15, quality of recovery-40/15; LOTCA, loeweistein occupational therapy cognitive assessment; Dex, Dexmedetomidine; NR, not reported.

available data. The meta-analysis of different time points after surgery suggested that, compared with the CG, TEAS resulted in significantly improved MMSE scores on postoperative day 1 [MD = 2.44 (95%CI: 1.61, 3.27); $p < 0.001$, $I^2 = 93\%$, low certainty], 3 [MD = 2.07 (95%CI: 1.53, 2.62); $p < 0.001$, $I^2 = 87\%$, low certainty], and 7 [MD 0.49 = (95%CI: 0.18, 0.79); $p = 0.002$, $I^2 = 21\%$, low certainty] but not on day 5 [MD = 0.98 (95%CI: −0.03, 1.99); $P = 0.06$, $I^2 = 70\%$, very low certainty] (**Figure 4** and **Table 2**).

Based on the above analysis, visual inspection showed an asymmetrical funnel plot (**Supplementary Figure 6**); however, Egger's test did not detect publication bias ($p = 0.20$; **Supplementary Figures 7**, **8**). Therefore, we used the trim-and-fill method for further sensitivity analyses. After including the estimated missing studies, the imputed studies produced a symmetrical funnel plot, and the results after trimming and filling showed a significantly higher MMSE score in the TEAS group than that in the CG [MD = 1.48 (95%CI: 1.03, 1.93)] (**Supplementary Figures 9**, **10**). Considering the substantial heterogeneity, further sensitivity analysis by excluding individual studies or low-quality studies suggested that the pooled analysis results were stable and no significant source of heterogeneity was found (**Supplementary Table 2**, **Supplementary Figures 11–14**).

Secondary Outcomes

Seven studies (34, 38, 48–51, 55) reported postoperative visual analog scale scores. The results of the meta-analysis demonstrated that TEAS had a significantly greater pain reduction compared with the CG at 8 h [MD = −0.39 (95%CI: −0.73, −0.05); $p = 0.03$, $I^2 = 64\%$, low certainty], 12 h [MD = −0.31 (95%CI: −0.43, −0.20); $p < 0.001$, $I^2 = 0\%$, moderate certainty], and 24 h [MD = −0.46 (95%CI: −0.74, −0.17); $p = 0.002$, $I^2 = 85\%$, low certainty] postoperatively, but not at 48 h [MD = −0.36 (95%CI: −0.81, 0.10); $p = 0.12$, $I^2 = 84\%$, low certainty] (**Figure 5** and **Table 2**). Considering the significant heterogeneity between studies, we changed the pooled effect index to SMD. The heterogeneity was significantly reduced, and the pooled results remains statistically significant for 24 h after surgery (**Supplementary Figure 15**). Nine studies reported the incidence of PONV (30, 43, 44, 46–48, 50, 51, 54). Meta-analysis showed a significantly lower incidence of PONV in the TEAS group than in the CG [OR = 0.36 (95%CI: 0.22, 0.58); $p < 0.001$, $I^2 = 0\%$, low certainty] (**Figure 6** and **Table 2**). Only 1 trial (43) was included in the meta-analysis of the effect of TEAS on the length of hospital stay. As shown in **Figure 7** and **Table 2**, compared with the CG, the length of hospital stay in the TEAS group was significantly shorter [MD = −2.50 (95%CI: −3.91, −1.09); $p < 0.001$, low certainty].

DISCUSSION

Transcutaneous electrical acupoint stimulation has been widely used in clinical practice and has become an important part of perioperative management. TEAS provides many benefits in promoting rehabilitation after surgery from many aspects,

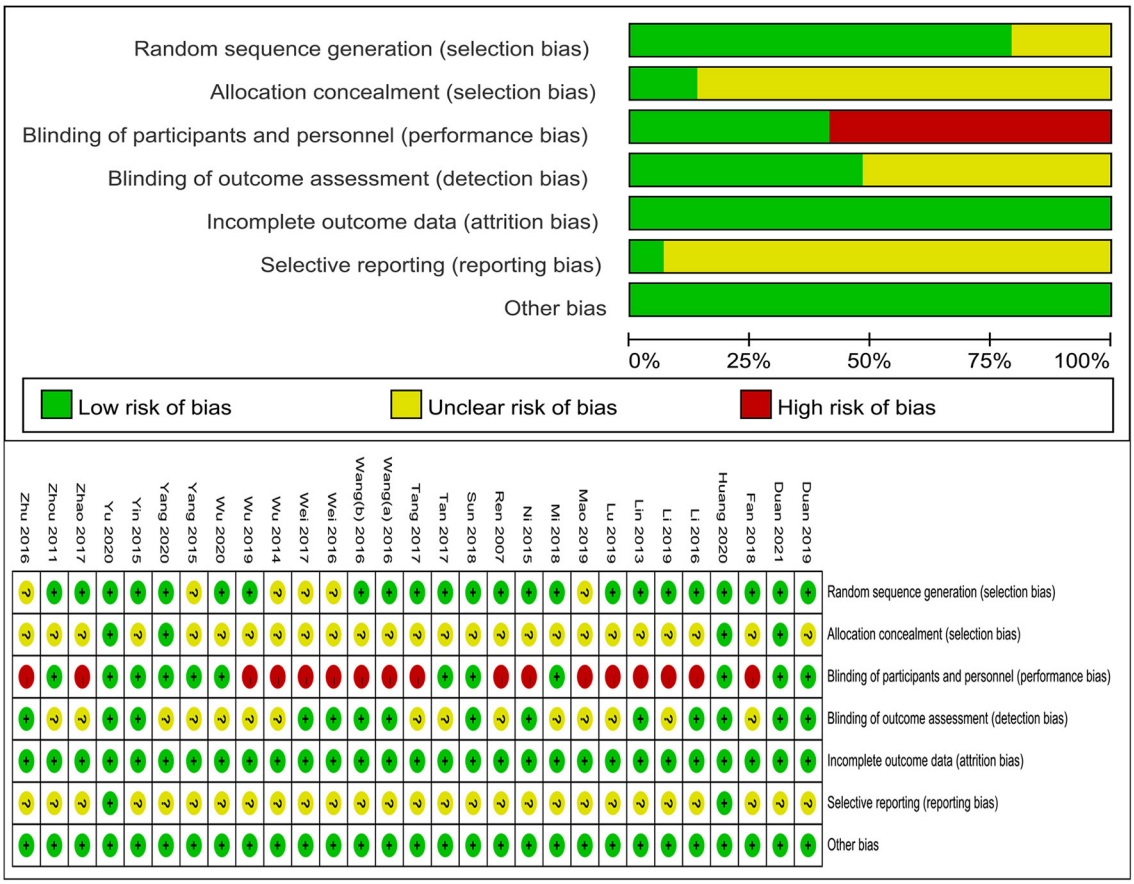


FIGURE 2 | Risk of bias graph.

including analgesia, gastrointestinal tract regulation, anti-inflammatory effects, stress response reduction, and POCD prevention (56). In this study, we examined the preventive effect of TEAS on postoperative short-term cognitive change. Our results showed that TEAS exerted a significant effect on increasing MMSE scores and lowering the incidence of POCD on postoperative days 1, 3, and 7. On a postoperative day 5, TEAS showed no significant therapeutic advantage in the primary outcomes, namely the incidence of POCD and MMSE scores. As reported in the literature, POCD, as a syndrome of prolonged impairment of cognitive function, occurs immediately to several years after surgery and usually persists for weeks or months (57). The effects of TEAS on medium- and long-term postoperative follow-up are still unclear. Anesthesia and surgery may be involved in the incidence of POCD. A previous meta-analysis showed that general anesthesia, compared to other forms, might increase the risk of developing POCD (58). A Cochrane systematic review suggested that, for elderly people undergoing non-cardiac surgery, maintenance with propofol-based total intravenous anesthesia might reduce the prevalence of POCD compared to maintenance with inhalational anesthesia (59). However, the effects of anesthesia and surgery on POCD remain controversial. A multicenter prospective cohort study indicated that exposure to surgery and general anesthesia were not significant risk factors for long-term cognitive impairment after major non-cardiac surgery associated with a critical illness (60). In this study, the subgroup analysis of anesthesia type showed that TEAS, compared with the CG, had a significant tendency toward a lower incidence of POCD, whether under general anesthesia (including intravenous and intravenous-inhalation) or non-general anesthesia. Furthermore, we found significantly reduced POCD in patients who underwent non-cardiac and noncraniocerebral surgery with TEAS. Of note, only one study involving cardiac surgery was included in this outcome. Based on the currently available data, there is insufficient evidence to recommend the use of TEAS in patients undergoing cardiac surgery.

The perioperative period is often accompanied by varying degrees of pain, which affects patient sleep, reduces the quality of life, and increases the length of hospital stay. TEAS do not only reduces pain and the incidence of complications caused by analgesics but also lessens the amount of anesthesia used in perioperative pain management (61). For postoperative pain, we found that TEAS enhanced the postoperative analgesic effect

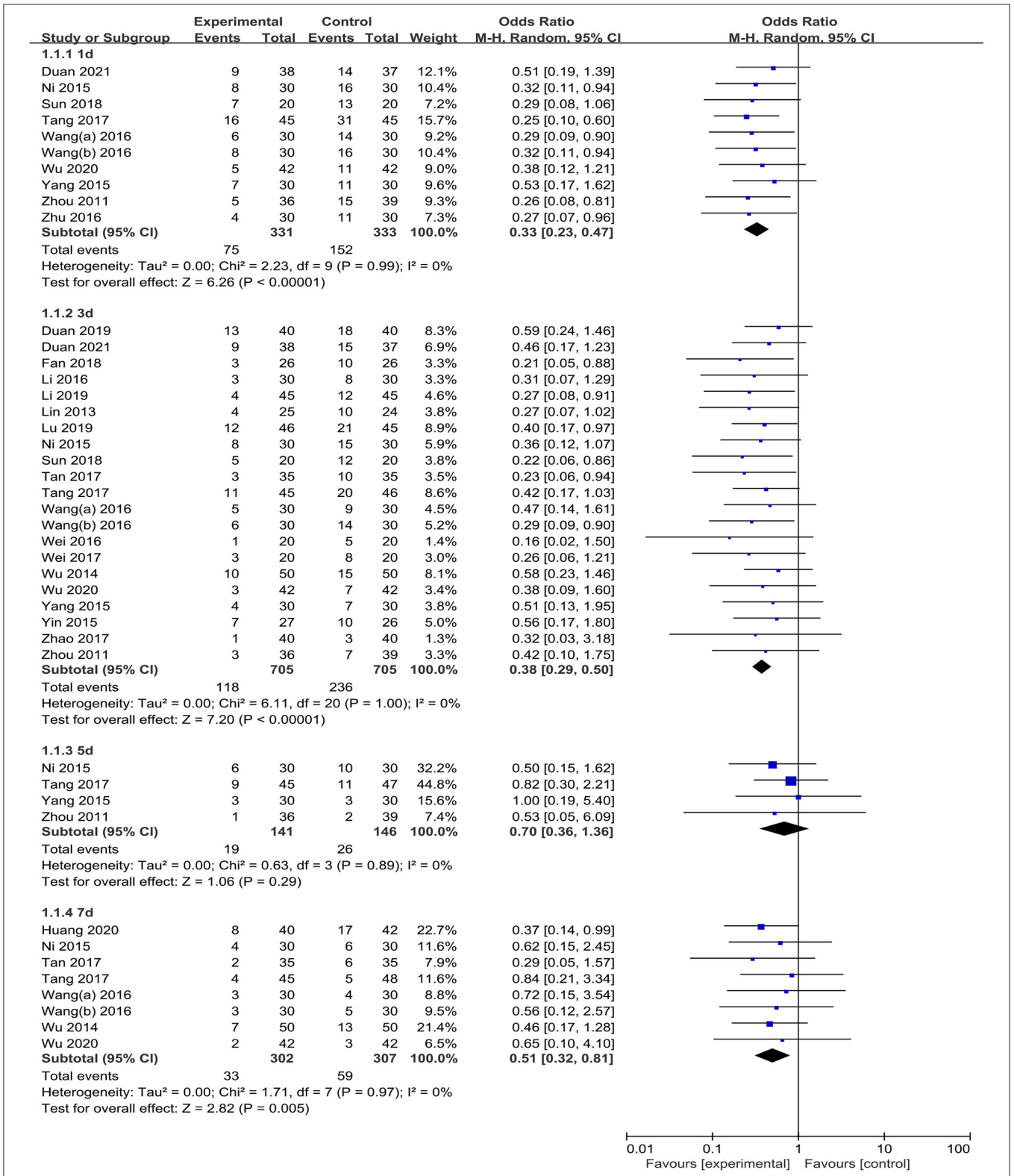


FIGURE 3 | Meta-analysis and forest plot for the incidence of POCD at different periods.

TABLE 2 | Main findings and evidence quality of the meta-analysis of TEAS for the prevention of POCD.

Outcomes	No of studies (Participants)	Quality assessment						Effect (95% CI)	Quality
		Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Incidence of POCD									
1d	10 studies (664)	RCT	Downgraded[a]	Not downgraded	Not downgraded	Not downgraded	Not downgraded	OR 0.33 (0.23, 0.47)	moderate
3d	21 studies (1410)	RCT	Downgraded[a]	Not downgraded	Not downgraded	Not downgraded	Downgraded[d]	OR 0.38 (0.29, 0.50)	low
5d	4 studies (287)	RCT	Downgraded[a]	Not downgraded	Not downgraded	Downgraded[c]	Not downgraded	OR 0.70 (0.36, 1.36)	low
7d	8 studies (609)	RCT	Downgraded[a]	Not downgraded	Not downgraded	Downgraded[c]	Not downgraded	OR 0.51 (0.32, 0.81)	low
MMSE scores									
1d	17 studies (1099)	RCT	Downgraded[a]	Downgraded[b]	Not downgraded	Not downgraded	Not downgraded	MD 2.44 (1.61, 3.27)	low
3d	17 studies (1096)	RCT	Downgraded[a]	Downgraded[b]	Not downgraded	Not downgraded	Not downgraded	MD 2.07 (1.53, 2.62)	low
5d	3 studies (210)	RCT	Downgraded[a]	Downgraded[b]	Not downgraded	Downgraded[c]	Not downgraded	MD 0.98 (−0.03, 1.99)	very low
7d	7 studies (506)	RCT	Downgraded[a]	Not downgraded	Not downgraded	Not downgraded	Downgraded[d]	MD 0.49 (0.18, 0.79)	low
VAS scores									
8 h	2 studies (175)	RCT	Downgraded[a]	Downgraded[b]	Not downgraded	Not downgraded	Not downgraded	MD−0.39 (−0.73, −0.05)	low
12 h	2 studies (164)	RCT	Downgraded[a]	Not downgraded	Not downgraded	Not downgraded	Not downgraded	MD−0.31 (−0.43, −0.20)	moderate
24 h	7 studies (510)	RCT	Downgraded[a]	Downgraded[b]	Not downgraded	Not downgraded	Not downgraded	MD−0.46 (−0.74, −0.17)	low
48 h	3 studies (226)	RCT	Downgraded[a]	Downgraded[b]	Not downgraded	Not downgraded	Not downgraded	MD−0.36 (−0.81, 0.10)	low
Incidence of PONV	9 studies (741)	RCT	Downgraded[a]	Not downgraded	Not downgraded	Downgraded[c]	Not downgraded	OR 0.36 (0.22, 0.58)	low
Length of hospital stay	1 study (52)	RCT	Downgraded[a]	Not downgraded	Not downgraded	Downgraded[c]	Not downgraded	MD−2.50 (−3.91, −1.09)	low

TEAS, transcutaneous electrical acupoint stimulation; POCD, postoperative cognitive dysfunction; MMSE, mini-mental state examination; PONV, postoperative nausea and vomiting; VAS, visual analog scale; RCT, randomized controlled trial; CI, confidence intervals; OR, odds ratio; MD, mean difference.

[a] *Downgraded by 1 level because unclear risk of bias was likely to lower confidence in the estimate of effect.*

[b] *Downgraded by 1 level because heterogeneity ($I^2 > 50\%$).*

[c] *Downgraded by 1 level because total (cumulative) sample size was lower than the calculated optimal information size (OIS) and/or 95% CI included a null effect.*

[d] *Downgraded by 1 level because reporting bias ($p < 0.1$).*

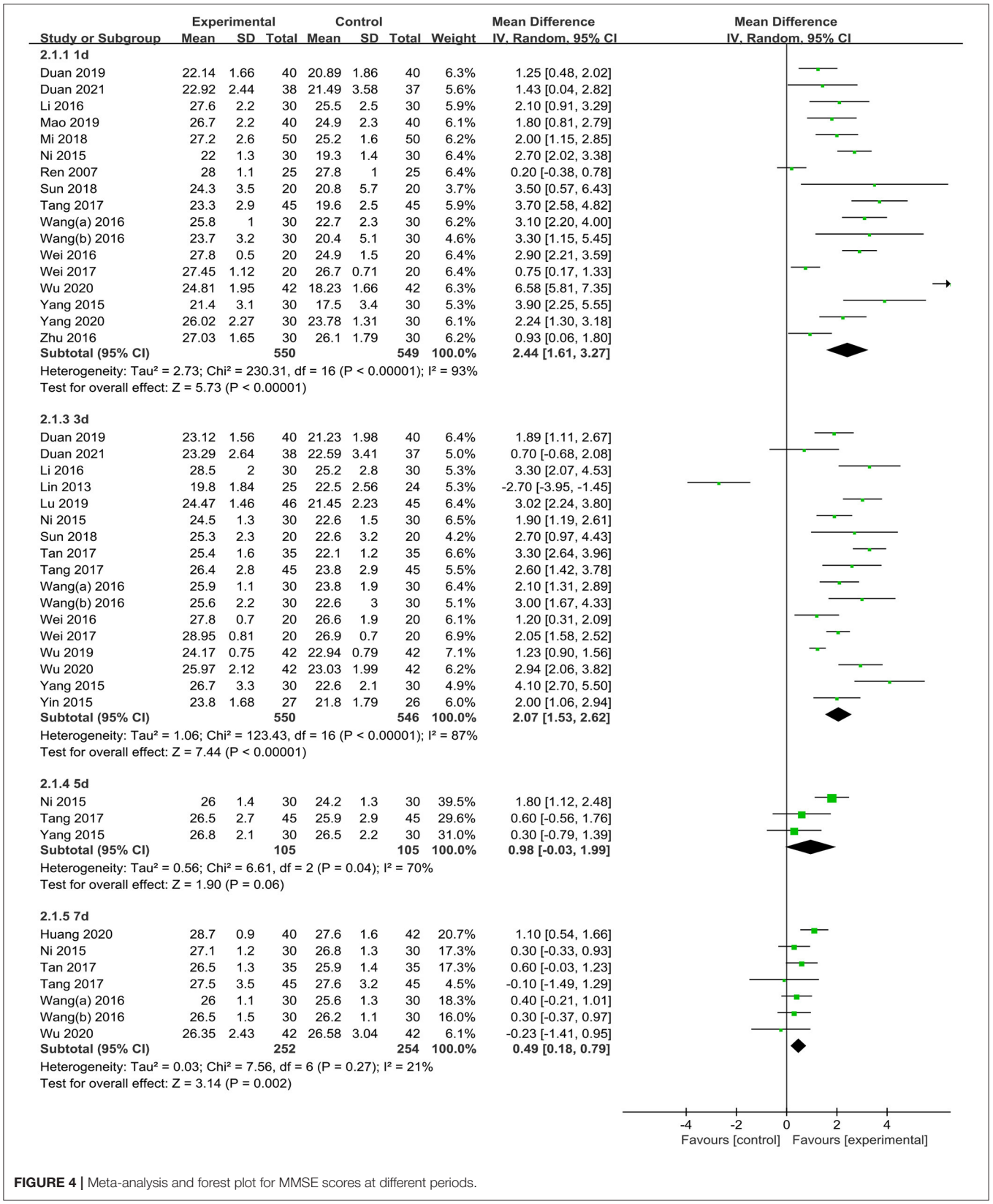


FIGURE 4 | Meta-analysis and forest plot for MMSE scores at different periods.

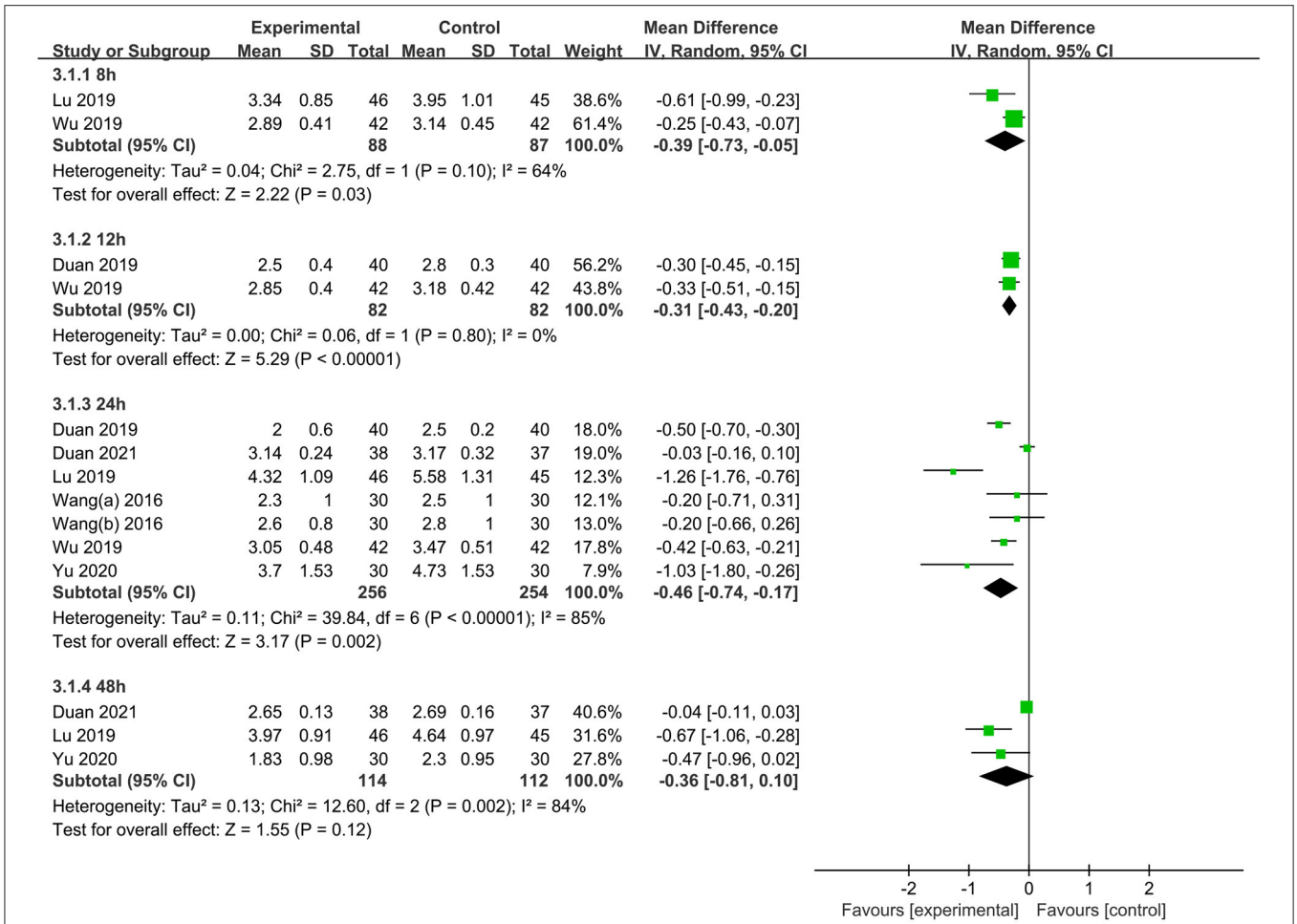


FIGURE 5 | Meta-analysis and forest plot for VAS scores at different periods.

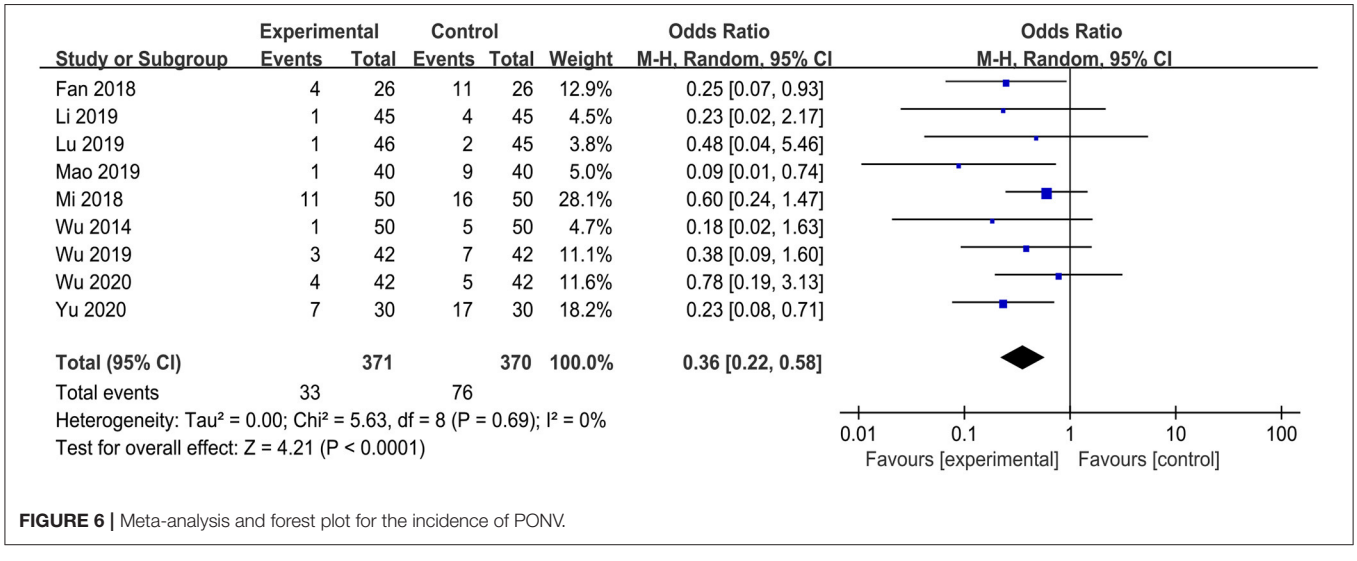


FIGURE 6 | Meta-analysis and forest plot for the incidence of PONV.

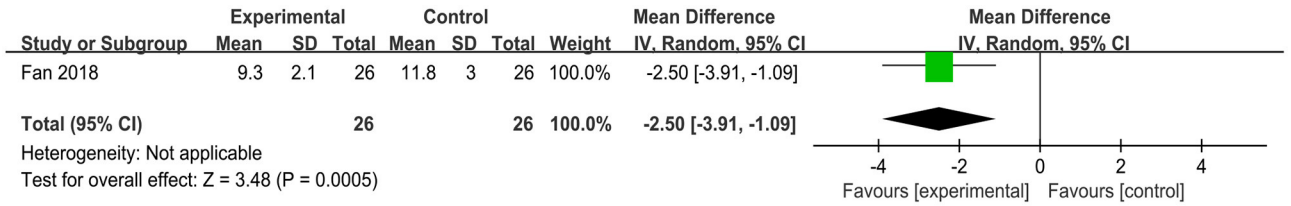


FIGURE 7 | Meta-analysis and forest plot for the length of hospital stay.

within 24 h after surgery. Furthermore, TEAS also effectively promoted the recovery of gastrointestinal function after surgery by increasing the level of plasma excitatory gastrointestinal hormone (62). A previous meta-analysis including 14 RCTs suggested that TEAS showed evidence of PONV prevention after general anesthesia (63), which was consistent with our findings. In general, POCD is associated with an increased length of hospital stay. Our review found that TEAS had advantages in shortening the postoperative hospital stay. Moreover, the selection of acupoints is an important factor in the TEAS treatment. The top 3 acupoints used in the included studies were PC6 (23 times), ST36 (15 times), and GV20 (14 times), which have the function of Kaiqiao Xingnao according to the theory of traditional Chinese medicine. As for the choice of acupoint combinations, we believe that the best combination is LI4, LI11, ST36, and SP6.

Transcutaneous electrical acupoint stimulation is "acupuncture-like TENS," which is an ideal combination of acupoints and bioelectricity. Compared with traditional acupuncture or electroacupuncture, TEAS is a non-invasive therapy. The potential mechanism of TEAS in preventing POCD may be explained by the following: first, TEAS alleviates postoperative inflammatory injury and reduces cytokine interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) levels in the central nervous system and peripheral circulation (32, 49, 53, 64); second, TEAS can reduce hippocampal neurons apoptosis by increasing the Bcl-2/Bax ratio and inhibiting activated caspase-3 expression (64); third, TEAS regulates serum neuron-specific enolase and S100-β protein (S100-β) levels (28, 36), or reduces the oxidative stress reaction (31); fourth, TEAS enhances the effect of postoperative analgesia and reduces the dosage of analgesics (65).

A recent expert consensus concluded that prevention was the best treatment for postoperative cognitive impairment and proposed some practical recommendations, such as pain control, cognitive screening, and minimizing psychoactive treatments (12, 66, 67). However, the recommended brain assessments and simple preventive measures were not routinely implemented and need further work to identify potential strategies with high therapy compliance (68). As a new type of acupuncture therapy, TEAS has attracted the attention of many researchers because of its multiple advantages, such as unified parameters, simple operation, and good patient compliance. The results of our review provided low to moderate certainty of evidence that TEAS was beneficial for the prevention of POCD in patients undergoing anesthesia and surgery, and it significantly reduced the incidence of PONV. We also observed the benefits of TEAS in improving neurological function scores, although the evidence level was downgraded to low due to statistical heterogeneity. Low to moderate certainties of evidence suggested that TEAS could enhance postoperative analgesia and shorten hospital stay. In general, these findings may provide new strategies for the management of perioperative brain health guidelines in the future.

LIMITATIONS

This review has several limitations. First, the long-term follow-up results are unknown because the observation time of the included studies was generally within 7 days after surgery. Second, all 29 included studies were conducted in China and most had small sample sizes ($\leq$100), which may have affected the reliability and extrapolation of the overall results. Due to the small sample size of the included studies, the estimated results were likely overestimated. Consequently, we performed a subgroup analysis to explore the impact of small sample sizes by grouping their sample size into quarters. The forest plot showed that the overall pooled results were not overestimated ($p > 0.05$) (**Supplementary Figure 16**). Generally speaking, the meta-analysis included no trials with large sample sizes; thus, the detection strength was also limited. Third, some of the studies had high risk and low quality, which downregulated the evidence strength of the research results. Therefore, future trials with higher-quality and larger sample sizes are needed to make more firm conclusions.

CONCLUSION

Our review systematically investigated and quantified the preventive effects of TEAS on POCD. Overall, our findings suggested that the application of TEAS in the perioperative period was associated with improved cognitive function scores and reduced POCD rates in the early postoperative period. Meanwhile, limited evidence suggested that TEAS could enhance the postoperative analgesic effect within 24 h after surgery, decrease PONV incidence, and reduce the length of hospital stay. Large RCTs are needed to determine the preventive effects of TEAS for POCD before recommending its routine use in surgical practice.

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

GH conceived the original study design. TZ and LO developed the search strategy and searched the literature database. JL and YS screened the eligible studies and extracted the data. JL and TZ evaluated the risk of bias. LO and ZC performed data analysis and evaluated the certainty of evidence. TZ drafted the first manuscript and GH revised the manuscript. All authors 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/fmed.2021.756366/full#supplementary-material

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Trajectory and Correlation of Intrinsic Capacity and Frailty in a Beijing Elderly Community

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Objectives: The World Health Organization proposed intrinsic capacity (IC) model to guide the implementation of person-centered care plan aimed at preserving or reserving functional ability, especially in frail older adults. We aimed to show the trajectory of IC and the overlap between IC impairment and frailty and investigate the correlation between IC domains and frailty status transitions.

Method: Longitudinal observational study covering 230 community-dwelling older adults (mean age 84.0 ± 4.5 years) at baseline, and transition information at 2-year follow-up (n = 196). IC was measured by five domains: locomotion, cognition, vitality, psychological, and sensory. Frailty was defined by FRAIL Scale. IC and frailty status transitions were assessed. Logistic regression, odds ratios (OR) and 95% confidence interval (CI) were used for the analysis.

Results: The prevalence of frailty was 23.0% and increased up to 41.8% over two years. Regarding frailty transitions, 38.3% of older adults progressed to more frailty status, and 8.6% regressed to lesser frailty status. The prevalence of IC impairment was 67.9% and increased to 81.6% over two years. Regarding IC transitions, 49.2% of adults with no IC impairment at baseline kept stable, and 50.8% developed new IC impairment. Among individuals with IC impairment at baseline, 57.9% worsened, and 13.5% improved. Importantly, IC impairment at baseline existed in 42.4% robust adults, 83.3% pre-frail adults, and 93.3% frail adults. 47.1% individuals who kept non-frail status within two years experienced IC worsened transition. Univariable analysis illustrated that new impaired locomotion, vitality, cognition, and sensory domains increased the risk of non-frail progressed to frail status. After adjusting for covariables, new impaired locomotion (OR = 3.625, 95% CI: 1.348–9.747) and vitality domains (OR = 3.034, 95% CI: 1.229–7.487) were associated with a higher possibility of non-frail progressed to frail status.

Conclusion: IC impairment and frailty overlap and co-exist in older adults. IC impairment, especially new impairment in locomotion and vitality are associated with the transitions from non-frail to frail status. It is important that geriatricians tightly monitor IC trajectory and find the new impaired domains to take early action to minimize the public health burden of frailty.

Keywords: frailty, intrinsic capacity, older adults, trajectory, transitions

INTRODUCTION

Population aging is accelerating rapidly worldwide, which brought a marked rise in the number of older adults with frailty (1). China is home to the largest population of older adults in the world (2), with the prevalence of frailty in older community-dwelling adults ranging from 5.9 to 17.4% (3). Previous relevant studies have revealed that higher age is related to higher frailty level (4). Frailty develops as the accumulated deficit in multiple physiological systems and is associated with an increased risk of poor outcomes like disability, falls, fracture, increased length of hospital stays, hospital readmission, hospital complications, morbidity, and mortality (5–7). According to several common frailty assessment tools, there is a universal description with three health statuses: robust, pre-frail, and frail. Based on these three statuses, much research exploring the trajectory of frailty demonstrates that it is a treatable and reversible clinical condition (8). Therefore, the detection of frailty should instead represent the entry point for more in-depth analysis with the aim of identifying the causes of an individual's increased vulnerability and implementing a person-centered care plan.

In order to overcome the weakness of frailty intervention and guide the implementation of health and social care plans in older community-dwelling adults, the World Health Organization (WHO) introduce intrinsic capacity (IC) to create a multidimensional construct related to individual's physical and mental ability (1, 9). IC can be evaluated by five domains: locomotion, cognition, vitality, psychological, and sensory capacities, reflecting the composite of all the physical and mental capacities (10, 11). Moreover, the WHO Healthy Aging model proposes that IC peaks in early adulthood and tends to decline from midlife onwards (12). Recent research demonstrated that IC can effectively predict adverse outcomes (e.g., falls and functional decline) in older community-dwelling adults (13, 14). Longitudinal studies over an extended period are needed to help us to investigate the extent to which the degree of IC changes as people age and guide person-centered care plan in older frail community-dwelling adults.

To our knowledge, the trajectory of IC with aging are still in its infancy and there are few studies to analyse the correlation between IC and frailty. In this study, we chose an elderly community with stable social support and a friendly living environment to show the natural trajectories of IC and frailty in order to avoid the interference of external factors. Moreover, we aimed to clarify the cross-sectional overlap between IC impairment and frailty and explore the impairment in IC domain and its correlation with frailty status transitions.

MATERIALS AND METHODS

Study Design and Participants

The data used in this longitudinal observational cohort study was collected from a Beijing continuing care retirement community (CCRC) (15–17), which could provide friendly living environment, convenient medical services, and strong social support for the residents. The independent residents were assessed by community physicians before living in the CCRC active area. All the participants were recruited consecutively from June to August in 2018. The inclusion criteria were: (1) aged over 75 years old and (2) lived in the CCRC active area. The exclusion criteria for the participants were as follows: (1) acute conditions including acute heart failure, acute coronary syndrome, acute exacerbation of chronic obstructive pulmonary disease, and acute pneumonia, and (2) severe cognitive impairment diagnosed by a neurologist. Sociodemographic and clinical variables, such as age, sex, marital status, educational level, polypharmacy, and comorbidities were included. Polypharmacy was the numerical definition of five or more medications daily. Number and severity of comorbidities were evaluated with the Charlson Comorbidity index (CCI) (18). The Comprehensive Geriatric Assessment (CGA), including unplanned return visits, and hospitalisations due to acute and chronic diseases, and changes in social status (death of the partner) (19), was carried out by the experienced geriatricians at baseline (from June to August in 2018) and at 2-year follow-up (from August to September in 2020). All the geriatricians were from Peking Union Medical College Hospital (PUMCH). The participants provided their written informed consent to participate in this study. This study was approved by the Research Ethics Committee of Peking Union Medical College Hospital (PUMCH, JS2002).

Measurements

Frailty and Frailty Status Transitions

Frailty status was defined based on FRAIL Scale (20) including five components: Fatigue (Do you feel tired at least 3 or 4 days per week?), Resistance (Can you climb one floor without assistance?), Ambulation (Can you walk one block or 100 m without assistance?), Illness (Do you suffer from more than five diseases?), and Loss of weight (Has your weight decreased by $\geq$4.5 kg or 5% of baseline in the previous 12 months?). Scores were assigned to each component (1 = Yes, 0 = No). Those who met 3–5 components were defined as frail, those with 1 or 2 components were deemed as pre-frail, and those without any were defined as robust. Participants who were robust or pre-frail were deemed as non-frail.

Frailty status transitions were classified into three categories: (1) Improved (adults who changed status from frail to non-frail), (2) Worsened (adults who changed status from non-frail to frail), and (3) Stable (adults with similar status at the follow-up period as the baseline status).

Intrinsic Capacity and IC Transitions

Intrinsic capacity (IC) was defined by five domains available from CGA Electronic Data Capture System. (1) Cognition was evaluated by Mini-Mental State Examination (MMSE) (21). Participants were cognitively impaired if they scored <25. (2) Psychological was assessed using the 15-item Geriatric Depression Scale (GDS-15) (22). The score ≥5 means psychological impairment. (3) Sensory (eye and hearing) was measured using two self-report questions. Do you have any difficulties in seeing far, reading, or eye diseases? Do you have any difficulties in hearing whisper? Both questions, if answered positively, means sensory dysfunction. (4) Vitality was evaluated with Mini Nutrition Assessment-Short form (MNA-SF) (23). The risk of malnutrition and malnutrition were deemed as vitality impairment. (5) Locomotion was measured by the Short Physical Performance Battery test (SPPB) (24). The sum score ≤9 means locomotion impairment. Each impaired domain is scored as 1 point, the total IC score is 5. An IC score ≥1 indicates IC impairment.

Intrinsic capacity (IC) transitions were defined based on changes of IC score at 2-year follow-up. Transitions were classified into three categories: (1) Improved (a decline of at least one point on IC score), (2) Worsened (an increase of at least one point on IC score), or (3) Stable (no change on IC score). Based on the 2-year difference in IC score (IC score at 2-year minus IC score at baseline), the 2-year change in number of impaired domains was identified.

Statistical Analysis

Data are presented using descriptive statistics. The clinical characteristics of participants at baseline were described as mean (standard deviation) or median (interquartile range) for continuous variables and numbers with percentages (*n*, %) for categorical variables. The Chi-square test was conducted to compare categorical variables. The student's *t*-test or Mann-Whitney *U*-test was used to compare continuous variables between different groups. The frailty status transitions after 2-year follow-up were described using a Sankey-diagram (https://www.highcharts.com.cn/demo/highcharts/Sankey-diagram).

Univariable and multivariable binary logistic regression analyses were used to evaluate the correlation between variables and frailty status transitions. For univariable analysis, each baseline characteristic was used as the independent variable and evaluated for its association with the dependent variable. We divided non-frail older adults into two groups according to the 2-year difference in IC score to identify statistically significant variables, as shown in the **Supplementary Table 1**. The covariables adjusted in multi-variable analysis were identified based on the statistically significant variables in univariable model. The odds ratios (OR) and 95% confidence intervals (CI) were reported. All statistical analysis was performed using SPSS (version 26.0; IBM SPSS Statistics for Windows, Armonk, NY: IBM Corporation). A p-value < 0.05 was deemed as statistically significant.

TABLE 1 | Comparison of baseline characteristics between total sample and participants who completed follow-up in a Beijing elderly community.

Baseline characteristics	Total participants ($n = 230$)	Participants who completed follow-up ($n = 196$)	*P*-value
Age, mean (SD)	84.0 (4.5)	83.7 (4.4)	0.572
Female, *n* (%)	133 (57.8)	116 (59.2)	0.777
Marital status, *n* (%)			0.648
Married	106 (46.1)	86 (43.9)	
Divorced or windowed	124 (53.9)	110 (56.1)	
Educational level, *n* (%)			0.843
Below senior high school	3 (1.3)	3 (1.5)	
Senior high school or higher	227 (98.7)	193 (98.5)	
Polypharmacy, *n* (%)	130 (56.5)	110 (56.1)	0.934
CCI, median (IQR)	1 (0.2)	1 (0.2)	0.679

CCI, Charlson Comorbidity Index; IQR, interquartile range; SD, standard deviation.

RESULTS

Baseline Characteristics of Study Population

Among 230 participants, 19 (8.3%) of them could not be contacted for follow-up due to moving back home, 15 participants were dead, and thus only 196 participants completed 2-year follow-up CGA. As shown in **Table 1**, there were no significant differences in age, sex, marital status, educational level, polypharmacy, and CCI between total participants ($n = 230$) and those who completed 2-year follow-up ($n = 196$). Among 196 participants, the mean age (SD) was 83.7 (4.4) years and 116 (59.2%) participants were female. The FRAIL Scale indicated a prevalence of pre-frail and frail of 33.7 and 23.0%, respectively. The median IC score was 1 (0–2). 133 (67.9%) participants were categorized as having IC impairment. The percentage of impairment in locomotion, cognition, vitality, psychological, and sensory domains were 58.2, 16.3, 14.3, 14.8, and 8.7%, respectively.

Frailty Status Transitions

The prevalence of frailty increased to 41.8% after two years, as shown in **Figure 1**. **Figure 2** shows the frailty status transitions from the baseline to 2-year follow-up. 104 (53.1%) individuals maintained baseline status, and 92 (46.9%) made bidirectional transitions (75, 38.3% progressed, and 17, 8.6% regressed). Among 85 robust older adults at baseline, 33.0% became pre-frail, and 12.9% became frail. 54.5% of pre-frail adults at baseline progressed to frail status, and 10.6% of them regressed to robust older adults. Importantly, 22.2% of frail older adults regressed to pre-frail status and 77.8% still maintained frail. No frail older adults directly regressed to robust status. Among 47 non-frail adults who progressed to frail status, 14 (29.8%) experienced

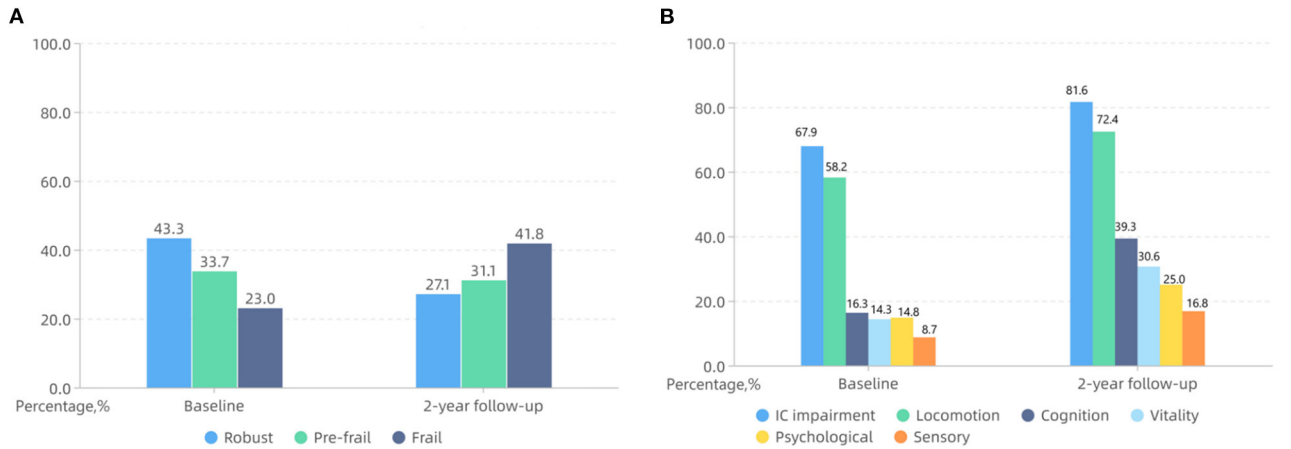


FIGURE 1 | The percentage of frailty status **(A)**, IC impairment and impaired intrinsic capacity (IC) domains **(B)** at baseline and 2-year follow-up in a Beijing elderly community.

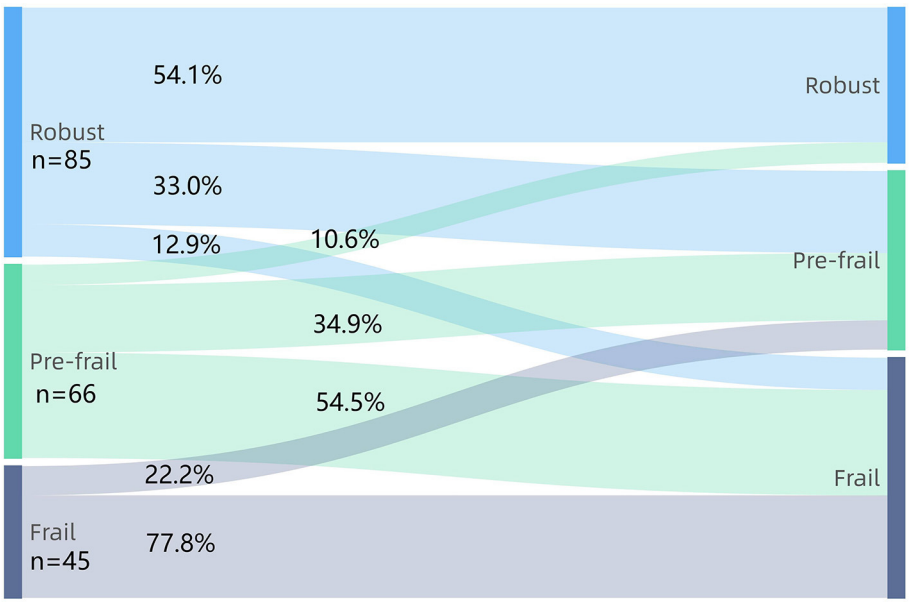


FIGURE 2 | The frailty status transitions between baseline and 2-year follow-up.

unplanned return visits, 19 (40.4%) experienced hospitalisations, and 4 (8.5%) had changes in social status (death of the partner). Lastly, only 15 (14.4%) experienced unplanned return visits, 25 (24.0%) suffered from hospitalisations, and none went through the death of partner among 104 adults who kept non-frail status during 2-year period.

Intrinsic Capacity Transitions

The percentage of IC impairment was 81.6% with a median score of 2 (1–3) over two years. Regarding IC transitions, 69 (35.2%) individuals kept stable, and 127 (64.8%) made bidirectional transitions (109, 55.6% worsened, and 18, 9.2% improved). The 2-year difference of IC score ranged from −1 to 4 and the median (interquartile range, IQR) was 2 (0, 3). In the adults who experienced IC-worsened transitions, there were 38 (34.9%) individuals had unplanned return visits, 42 (38.5%) experienced hospitalisations, and 4 (3.7%) suffered from the death of partner. Among 63 participants with no IC impairment at baseline, 31 (49.2%) kept stable, and 32 (50.8%) worsened. For 133 participants with IC impairment at baseline, 18 (13.5%) of them improved, 38 (28.6%) kept stable, and 77 (57.9%) worsened. As shown in **Figure 1**, the overall rate of impairment in locomotion, cognition, vitality, psychological, and sensory domains increased to 72.4, 39.3, 30.6, 25.0, and 16.8%, respectively. Importantly, 49 (25.0%) participants developed new impairment in cognition domain. 42 (21.4%) individuals experienced new impairment in

TABLE 2 | Comparison of characteristics among non-frail and frail participants according to frailty status transitions in a Beijing elderly community.

Characteristics	Non-frail ($n = 151$)			Frail ($n = 45$)		
	Worsened ($n = 47$)	Stable ($n = 104$)	*P*-value	Stable ($n = 35$)	Improved ($n = 10$)	*P*-value
Age, mean (SD)	84.7 (4.0)	82.4 (4.3)	0.002	85.8 (4.3)	85.4 (2.4)	0.838
Female, *n* (%)	26 (55.3)	58 (55.8)	0.959	25 (69.4)	8 (88.9)	0.238
Marital status, *n* (%)			0.382			
Married	19 (40.4)	50 (48.1)		14 (40.0)	3 (30.0)	0.565
Divorced or windowed	28 (59.6)	54 (51.9)		21 (60.0)	7 (70.0)	
Educational level, *n* (%)			NA			0.632
Below senior high school	0	0		2 (5.7)	1 (10.0)	
Senior high school or higher	47	104		33 (94.3)	9 (90.0)	
Polypharmacy, *n* (%)	32 (68.1)	45 (43.3)	0.005	26 (74.3)	7 (70.0)	0.787
CCI, median (IQR)	1 (0–2)	0 (0–1)	0.009	1 (1–2)	1 (1–3)	0.308
New impaired domains, *n* (%)						
Locomotion	13 (27.7)	13 (12.5)	0.022	4 (11.4)	0	0.263
Vitality	16 (34.0)	16 (15.4)	0.009	9 (25.7)	1 (10.0)	0.292
Cognition	19 (40.4)	24 (23.1)	0.029	5 (14.3)	1 (10.0)	0.725
Psychological	9 (19.1)	12 (11.5)	0.211	9 (25.7)	0	0.073
Sensory	8 (17.0)	5 (4.8)	0.013	5 (14.3)	1 (10.0)	0.725
IC transition, *n* (%)			0.000			0.269
Improved	0	11 (10.6)		5 (14.3)	2 (20.0)	
Stable	6 (12.8)	44 (42.3)		13 (37.1)	6 (60.0)	
Worsened	41 (87.2)	49 (47.1)		17 (48.6)	2 (20.0)	

BMI, body mass index; CCI, Charlson Comorbidity Index; IC, intrinsic capacity; IQR, interquartile range; NA, not available; SD, standard deviation.

vitality domain, 30 (15.3%) individuals had new locomotion and psychological impairment, and only 19 (9.7%) adults showed new impairment in sensory domain.

Correlation Between Intrinsic Capacity and Frailty Status Transitions

At baseline, IC impairment existed in 42.4% robust adults, 83.3% pre-frail adults, and 93.3% frail adults. After a 2-year period, IC impairment existed in 45.3% robust adults, 90.2% pre-frail adults, and 98.8% frail adults. According to frailty status transitions among non-frail adults, the comparison of characteristics between worsened and stable groups is shown in **Table 2**. Significant differences in age, polypharmacy, CCI, and new impairment in locomotion, vitality, cognition, and sensory domain were found between the two groups. No significant differences were reported about sex, marital status, and educational level between groups. Nearly half (47.1%) of adults who kept non-frail status within two years had experienced IC transitions worsened. Concerning non-frail older adults, the univariable analysis showed the 2-year change in the number of IC-impaired domains was correlated with frailty status transitions (OR = 2.125, 95% CI: 1.543–2.926, $P < 0.001$). The cut-off point of change in number of impaired domains for predicting frailty was 2. In multi-variables logistic regression analysis, the change in number of impaired domain (OR = 1.981, 95% CI: 1.424–2.756, $P < 0.001$) was also independently associated with frailty status transitions, after adjusting for age, polypharmacy, and CCI. Moreover, the univariable logistic regression analysis illustrated that age (OR = 1.142, 95% CI: 1.046–1.246), polypharmacy (OR = 2.797, 95% CI: 1.354–5.779), CCI (OR = 1.749, 95% CI: 1.237–2.471), and new impaired locomotion (OR = 2.676, 95% CI: 1.128–6.349), vitality (OR = 2.839, 95% CI: 1.269–6.348), cognition (OR = 2.262, 95% CI: 1.079–4.740), and sensory domain (OR = 4.062, 95% CI: 1.251–13.181) increased the risk of non-frail adults progressed to frail status ($P < 0.05$). After adjusting for age, polypharmacy, and CCI, the results showed that new impaired locomotion (OR = 3.625, 95% CI: 1.348–9.747) and vitality domain (OR = 3.034, 95% CI: 1.229–7.487) were associated with a higher probability of non-frail status progressed to frail status as given in **Table 3**.

TABLE 3 | Logistic regression analysis showing the correlation between new impaired domains and frailty status transitions in non-frail older adults.

New impaired domains	Uni-variable		Multi-variable[a]	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Locomotion	2.676 (1.128–6.349)	0.025	3.625 (1.348–9.747)	0.011
Cognition	2.262 (1.079–4.740)	0.031	1.960 (0.878–4.375)	0.101
Vitality	2.839 (1.269–6.348)	0.011	3.034 (1.229–7.487)	0.016
Psychological	1.816 (0.707–4.664)	0.215	1.650 (0.596–4.565)	0.335
Sensory	4.062 (1.251–13.181)	0.020	3.400 (0.922–12.537)	0.066

OR, odds ratio; CI, confidence interval; [a]including age, polypharmacy and Charlson Comorbidity Index.

For frail older adults at baseline, no differences of characteristics were observed between stable and improved

groups as shown in **Table 2**, neither in the univariable and multivariable analysis.

DISCUSSION

The present study investigated the natural trajectories of IC and frailty status, the main changes of IC domain, and its correlation with frailty status transitions in community-dwelling older adults. This is of clinical and public health interest since little is known regarding IC trajectories within 2-year period and the influence on frailty status transitions.

The Trajectory of Frailty Status and Intrinsic Capacity

We found that the prevalence of frailty according to FRAIL Scale was 23.0%. The result is consistent with the finding from a meta-analysis, which found that the prevalence of frailty among Chinese community-dwelling older adults aged over 80 years was 21.6% (25). Moreover, the prevalence of frailty at 2-year period was considerably higher than the baseline. This is in line with previous studies based on different frailty assessment tools wherein frailty is correlated with age (25, 26). This longitudinal observational study also proved that frailty is a dynamic process, which was comparable with previous research (27, 28). Half of older adults remained stable, with pre-frail adults being more likely to become frail than robust adults. Importantly, older adults can regress into lesser frailty status, although the probability is low. Thus, the early development and implementation of comprehensive person-centered care plan aimed at preserving or reserving frailty brook no delay.

Intrinsic capacity (IC) impairment was present in 67.9% of the community-dwelling older adults. The locomotion and cognition were the two most vulnerable domains in IC model. This result is in agreement with early findings which showed the percentage of IC impairment ranged from 69.1 to 75.3% (29, 30). It is almost certain that IC impairment is quite common among community-dwelling older adults. Another important finding was that the prevalence of IC impairment increased to 81.6% over two years, and the percentages of impaired domains also increased. This is also in accordance with the IC model that individuals' capacities will decline with aging (31). In addition, in IC trajectories, cognition and vitality were the two domains most prone to new impairment. At an individual level, while trajectories are continuous, they are rarely smooth. There is great variability in these trajectories and some components of capacity may remain stable, decrease, or even increase over the life course. Therefore, tracing IC trajectories can inform us to take action to reverse the trend and inform the effectiveness of the interventions implemented or the variation in one's needs.

Moreover, the occurrence of unplanned return visits and hospitalisations due to acute and chronic disease and changes in social status (death of the partner) were common in the older adults who experienced frailty status from non-frail or IC worsened transitions during 2-year period. There are two likely causes for the results. On one hand, frailty and IC decline can increase the risk of adverse health outcomes (e.g., hospitalisations, fall, and functional decline) in older adults. On the other hand, older adults may suffer from hospital-acquired complications, which cause the worsened transitions of frailty status or IC. Therefore, they may form a vicious circle, with each condition affecting the other.

IC Worsened Transition Occurs in Non-Frail Adults and New Impaired Locomotion and Vitality Predict Frail Status

The empirical results in this study provide a new understanding of IC impairment overlap with frailty status. Among robust older adults, nearly half of them existed IC impairment. The most interesting finding was that non-frail adults had experienced IC-worsened transition, even though they kept non-frail status over two years. Our study demonstrated that many individuals will experience a significant IC decline that is associated with frailty before death. In accordance with previous work, the WHO model of Healthy Aging proposes that this period of significant loss of IC is often preceded by earlier, more robust, health states (12, 32). Another cohort study from Gutierrez-Robledo and collaborators also demonstrate that IC is significantly associated in a cross-sectional way with frailty (33). We found that two or more impaired domain in 2-year follow-up period was associated with worsened frailty status among non-frail adults. Therefore, the monitoring of IC trajectories can support the detection of the individuals' fragilization. In the present study, there was no variability of educational level between stable and worsened groups among non-frail older adults. The reasons might be related to the selectivity of the study sample. All the participants lived in the CCRC active area with excellent living environment and social support, and most of them had good educational experience. In addition, significant differences in new impaired locomotion, vitality, cognition, and sensory domains were founded between stable and worsened groups. After adjusting for co-variables, new impairment in locomotion and vitality domains had the predictive value for frailty status among non-frail older adults over two years. Thus, from the perspective of IC, exercise and nutritional supplementation prevail as mainstays of person-centered care interventions. This study produced results that corroborate the findings of a great deal of the previous work in the frailty intervention field (34).

Surprisingly, no differences in IC domains were found between stable and improved groups among baseline frail older adults. The observed correlation might be explained in this way. Frailty is the long-term outcome of IC impairment in older age, and frail older adults are characterized by significant losses of IC. Previous study also described that frailty and IC were two distinct but related constructs, stemming from the same need of overcoming traditional medical paradigms (35, 36). Taking a more holistic life course approach, frailty is a state of reduced resilience to stressful events that occurs in response to physiological and/or psychosocial detriments (37, 38). Therefore, frail older adults have less reversibility

than non-frail adults. Frailty is potentially preventable up to a probable point of no return when it becomes a pre-death phase. It is challenging to improve IC to maintain less frailty status. Collectively, the interventions must be prioritized in ways that optimize trajectories of physical and mental capacities to avoid the onset and development of frailty, especially in non-frail adults.

The main strength of this research was the study was conducted in the CCRC, which is characterized by similar nutritional supplements and stable surrounding environment. Our results reflected the natural trajectories of IC and frailty within a two-year period in an elderly community. In addition, the changes of each IC domain and its relationship with frailty status transitions were shown in our study. However, there were some limitations in our study. First, our sample size was not big enough and further multi-center studies are needed to prove the results. Second, our study was not designed to measure IC in advance. All items were spared from CGA, but consistent with IC domains proposed by WHO. Third, FRAIL Scale used in our study was a self-report scale, which may affect the judgment of frailty status. Objective measurements may increase the accuracy of the results and reduced the overestimation or underestimation of frailty status. However, previous research has demonstrated that FRAIL Scale is a time and cost-effective screening tool with good validity and diagnostic test accuracy.

CONCLUSION

To the best of our knowledge, there were few longitudinal observational studies based on community-dwelling older adults to reveal the natural trajectories of IC and frailty simultaneously. Our results demonstrate the dynamics and diversity of IC with age and show IC impairment and frailty overlap and co-exist in older adults. It is important that geriatricians tightly monitor the natural IC trajectory and the new impairment in domains, to take early preventive and rehabilitative actions to minimize the public health burden of frailty.

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 Research Ethics Committee of Peking Union Medical College Hospital (PUMCH, JS2002). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SL, LK, and XL contributed to the design of the work, contributed to the analysis, and interpretation of data. SL, SZ, XW, JL, and SJ contributed to the data collection. SL drafted the manuscript. All authors contributed to writing the paper and revising it critically and gave final approval of this 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.2021.751586/full#supplementary-material

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Serum Uric Acid and Risk of Chronic Heart Failure: A Systematic Review and Meta-Analysis

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Objectives: A systematic review and meta-analysis was performed to evaluate the potential prognostic role of serum uric acid (SUA) in patients with chronic heart failure (CHF).

Methods: The Embase, PubMed, Web of Science and Cochrane Library databases were searched up to 5 April 2021 for relevant publications. Random effects model was used to pool data. STATA15.0 software was used to perform meta-analysis. Heterogeneity was assessed using the Cochran Q statistic (significance level of $P < 0.10$) and I^2 statistics (significance level of 50%).

Results: Ultimately, 18 publications reporting adverse events in CHF patients were included. The results indicate reveal associations between a high level of SUA and the risk of all-cause mortality (HR 2.24, 95% CI 1.49–3.37), cardiovascular mortality (HR 1.14, 95% CI 1.06–1.23), and the composite of death or cardiac events (HR 1.26, 95% CI 1.01–1.56) in CHF patients. A 1 mg/dL increase in serum uric acid led to 4% (HR 1.04, 95% CI 1.02–1.05) and 9% (HR 1.09, 95% CI 1.03–1.17) increases in the risk of all-cause mortality and the composite endpoint of death or cardiac events in CHF patients, respectively.

Conclusion: Serum uric acid is positively associated with the risk of adverse events in CHF patients. This study protocol has been registered at PROSPERO as CRD42021247084 (https://www.crd.york.ac.uk/PROSPERO).

Systematic Review Registration: https://www.crd.york.ac.uk/PROSPERO.

Keywords: chronic heart failure, serum uric acid, risk factor, systematic review, meta-analysis

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INTRODUCTION

Chronic heart failure (CHF) is one of the most significant public health problems, and its prevalence is increasing as the population ages (1). CHF leads to a deteriorating 5-year survival rate and poorer quality of life (2). The high rate of repeated hospitalizations and the high cost of hospitalization have severely increased the burden on the healthcare system (3). Gender, hypertension, valvular heart disease, coronary artery disease, and obesity were identified as risk factors for heart failure (4). Despite the improvement in patient management, the mortality of heart failure remains high, which calls for the need to identify other associated risk factors. Early identification of CHF patients with poor prognosis is of great significance for the treatment of CHF.

To predict the prognosis and progression of HF, several biomarkers have been used. Biomarkers (BNP and troponin), ejection fraction (EF), NYHA, etc., provide good predictive value for HF mortality. However, in the early stages of heart failure, their ability to discriminate is still uncertain. Serum uric acid (SUA), a byproduct of purine catabolism, which is well-known as a diagnostic indicator of gout. In recent years, many epidemiological studies have reported the relationship between SUA levels and a variety of cardiovascular and cerebrovascular diseases, including heart failure (5), hypertension (6), coronary artery disease (7), etc. The importance of these links, however, remains controversial. The Framingham Heart Study group, argued that uric acid is not a risk factor for cardiovascular disease and that clinicians should rely more on classic risk factors when evaluating patients (8). Major professional associations also do not consider SUA levels as a cardiovascular risk factor (9, 10). However, with the deepening of studies, several studies have found that the relationship between SUA level and the prognosis of cardiovascular diseases should be seriously considered. A meta-analysis (11) published in the European Journal of Heart Failure in 2014 linked uric acid levels to the occurrence and poor prognosis of heart failure. Since 2014, four original studies (12–15) with large samples have been published, which makes it urgent and necessary to conduct an updated meta-analysis to evaluate the relationship between serum uric acid and chronic heart failure comprehensively. Serum uric acid is a clinically readily available and low-cost test index. If serum uric acid can assess the prognosis of chronic heart failure, it will be very important for the early detection and prediction of CHF with poor prognosis. Several newly published studies have examined the significance of serum uric acid levels in the prognosis of CHF, so a focused meta-analysis of existing studies is necessary to further determine the value of SUA levels and better guide clinical practice. This systematic review and meta-analysis was designed to evaluate the potential prognostic role of SUA in patients with CHF.

METHODS

Systematic Literature Search

Based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines, a literature review and meta-analysis of the scientific peer-reviewed literature were carried out. We searched the PubMed, Web of Science, Embase, and Cochrane Library databases from the establishment of the database to 5 April 2021. The language was limited to English. The key search words used were ("left-sided heart failure" or "heart failure" or "congestive heart failure" or "cardiac failure" or "chronic heart failure") and "urate" or "uric acid" or "hyperuricemia"). Supplementary document (**Data Sheet 1**) describes the search strategies used in detail. Relevant publications found in the references were also included. Gray literature (unpublished literature) and conference abstracts were not included. All included references were imported into EndNote X8, and duplicate articles were filtered and deleted. Two independent reviewers independently screened and selected the literature. In the first round of screening, studies on irrelevant topics were excluded after reading the titles and abstracts. Next, full texts were examined to exclude ineligible articles.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: 1. observational studies or *post-hoc* analyses of randomized controlled trials; 2. studies reporting the prognostic value of adverse outcomes between SUA levels and CHF; 3. multivariate adjusted hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were published; 4. follow-up time more than 3 months. The exclusion criteria were as follows: 1. enrolment of AHF patients; 2. trial subjects were the same and did not report longer follow-up times; 3. letters, editorials, and review articles. 4. Studies of drug trials.

Data Extraction

The following data were extracted by two reviewers independently: first author's name, sample size, design, location of study, year of publication, baseline patient profiles, SUA cutoff value, event number, follow-up duration, and unadjusted or multivariate adjusted effect sizes [HRs] for outcomes.

Quality Evaluation

Quality assessments were independently conducted by two authors. Dispute was settled by further discussion. Should the dispute continue, a third party would be invited to the discussion for settlement. The Newcastle-Ottawa scale was used to assess quality of observational studies and cohort studies (16). The scores $\geq$7 points were considered as high quality.

Statistical Analysis

We used STATA15.0 software to perform meta-analysis. The definitions of "high" and "low" serum uric acid in the included studies. For the comparison between high and low SUA levels or per 1 mg/ml SUA increase, the most fully adjusted risk was used for analysis. Heterogeneity was assessed using the Cochran Q statistic (significance level of $P < 0.10$) and I^2 statistics (significance level of 50%). All combined effect sizes were analyzed by using the random effects model. Meta-regression analysis and subgroup analyses of the primary outcome were performed according to publication year, patient age, sample size, whether to adjust the confounding, quality score, and follow-up time. The subgroup differences were tested by the Z test (significance level at $p < 0.05$). When the number of analyzed studies exceeded 10, Begg's test (17) was used to assess publication bias. Publication bias will be adjusted by the method of trim and filling. To investigate the impact of any one study on the pooling summary, a sensitivity analysis was performed by deleting a single study in each round when the number of studies was 4 or more.

RESULTS

Literature Search

Figure 1 displays the study selection process. In total, 3,692 records were initially identified for screening from the PubMed, Embase, Web of Science, and Cochrane Library databases. By filtering the titles and abstracts, 452 duplicate articles were

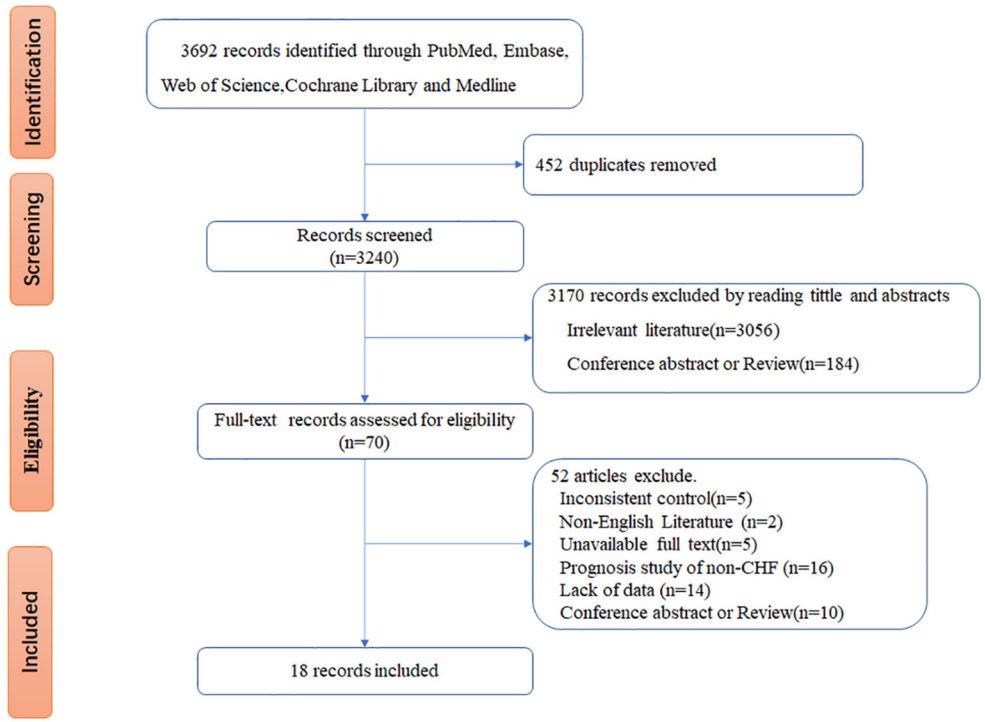


FIGURE 1 | The process of study selection.

excluded, and 3,170 records were excluded by reading the titles and abstracts (3,056 studies because of unrelated topics and 184 because of review or conference abstracts). A full-text review of 70 studies was conducted to determine the eligible studies. Fifty-two studies were further removed for the following reasons: inconsistent control ($n = 5$), non-English literature ($n = 2$), unavailable full text ($n = 5$), prognosis study of non-CHF ($n = 16$), lack of data ($n = 14$), conference abstract and review ($n = 10$). Thus, 18 studies (12–15, 18–31) were included for further analysis.

Study Characteristics

In **Table 1**, a description of baseline characteristics from the included studies is presented. A total of 32,303 patients were identified and analyzed. The mean/median age of the patients was 48 years and older. The sample sizes vary from 108 to 6,859. Follow-up time ranged from 1 to 5 years. These studies were conducted in Germany (22), Japan (19, 28, 29), Poland (14, 21, 27), the Czech Republic (31). Slovenia (26), South Korea (30), USA and Canada (20), the UK (23), Israel (18), Italy (12, 13, 24), additionally, there were two international multicenter studies (15, 25). Among them, 14 were cohort studies and 4 were case control studies. Of the 18 studies, 5 studies (14, 15, 18, 24, 31) diagnosed CHF according to the European Society of Cardiology (ESC) guidelines, while the rest studies diagnosed CHF according to clinical symptoms, physical signs, and treatment response. The laboratory measurement of serum acid uric was performed referring to enzymatic method. For methodological quality assessment, the NOS scores of these studies ranged from 5 to 9 points. Twelve of the studies had a quality score above 7, and the overall quality of the studies was high.

SUA and All-Cause Mortality of CHF Patients

A total of 15 studies (12–15, 18–27, 31) (16 data sets) reported the prognostic indication of SUA for overall mortality in patients with CHF. Two of the 14 publications defined their data as both categorical and continuous variables, 5 as only categorical variables, and 12 as continuous variables. Pooled data from 5 studies (18–22) (6 data sets) with estimates as categorical variables reported the association between hyperuricemia and the risk of all-cause mortality (HR: 2.24, 95% CI: 1.49–3.37); there was appreciable statistical heterogeneity among the studies ($I^2 = 89.9\%$, $P < 0.001$) (**Figure 2**). Twelve studies (12–15, 19, 22–27, 31) (13 data sets) reported the estimates as continuous variables. A 1 mg/dL serum uric acid rise increased the risk of all-cause mortality by 4% (HR: 1.04, 95% CI: 1.02–1.05). Heterogeneity was observed among HRs for all-cause mortality ($I^2 = 94.6\%$) (**Figure 2**). Publication bias was found by Begg's test ($P = 0.006$; $P = 0.001$) and funnel plot (**Figure 3**), and the trim and filling method was adopted for adjusted. The funnel plot after adjusted is shown in **Figures 4**, **5**. The combined effect between uric acid as a categorical variable and all-cause death has changed significantly after correction (the combined effect value before trimming: HR: 2.24, 95% CI: 1.49–3.37, $P = 0.000$;

TABLE 1 | Characteristics of included studies on the association between serum uric acid and the adverse outcomes of CHF.

References	Country	Study design	Age	Sample size (% male)	Definition of hyperuricemia	Follow-up (year)	Adjusted variables	Outcome	Quality score
Anker (22)	Germany	Cohort	59	294(85%)	10	4.3	Unadjusted	All-cause morality	6
Niizeki (28)	Japan	Case-control	77	123(48%)	7	1.2	Creatinine, NYHA functional class	Cardiac deaths and readmission	8
Jankowska (21)	Poland	Cohort	64	119(74%)	6.5	1.6	NYHA class, CrCl	All-cause morality	7
Koyama (29)	Japan	Case-control	66	141(62.4%)	Continuous	1.3	Pentosidine, BNP, eGFR, NYHA, creatinine, age, LV mass, ESV	Cardiac death, rehospitalization	7
Naruszewicz (27)	Poland	Cohort	66	108(72%)	Continuous	2.3	Unadjusted	All-cause mortality	5
Jindrich (31)	Czech Republic	Cohort	63.7	292(51%)	Continuous	5	Unadjusted	All-cause mortality	6
Lainscak (26)	Slovenia	Cohort	73	638(48%)	Continuous	2.9	COPD, age, sex, Hb, treatment with beta-blockers and furosemide	All-cause mortality	8
Kim (30)	South Korea	Case-control	61	122(62.3%)	8.7	2	Log NT-proBNP, SBP, EF, Hb, eGFR, PASP	Composite of cardiac death and readmission	6
Filippatos (20)	USA and Canada	Cohort	61.5	630(19%)	Men, 8; women, 6	2.1	Propensity score	All-cause mortality, HF hospitalization, Cardiovascular mortality	6
Hamaguchi (19)	Japan	Cohort	71.7	1,620 (60%)	7.4	2.1	Demographics, medical history, CABG, NYHA functional class, eGFR, BNP, LVEF, and medication use	All-cause death, Cardiac death, Rehospitalization, all-cause death or rehospitalization	7
Manzano (25)	Multicenter, international trial	cohort	≥70	2,128 (63%)	Continuous	1.8	Demographics, clinical, hemodynamics, laboratory, medical history, medications	Composite of all-cause mortality or cardiovascular hospital admission	7
Herrmann (23)	UK	Case–control	63	114	Continuous	1	sTNF-R1, NYHA class, cholesterol	All-cause mortality	7
Gotsman (18)	Israel	Cohort	75	6,204 (50%)	7.7	1.4	Age, sex, IHD, hypertension, AF, BMI, Hb, sodium, eGFR, urea, HF drug therapies	Mortality, Cardiac-related hospitalization	8
Baldasseroni (24)	Italy	Cohort	63	877(76%)	Continuous	1	Adjusted variables	All-cause mortality	6
Piepoli (13)	Italy	Cohort	62.7	4,577 (81%)	Continuous	3.4	Diuretic use		7
Romuk (14)	Poland	Cohort	48	774(85.8%)	Continuous	1	All demographic, clinical, echocardiography, laboratory variables, and medication data	All-cause mortality	8
Mantovani (15)	Multicenter, international trial	cohort	67	6,683 (78.3%)	Continuous	3.9	Age, sex, BMI, heart rate, total cholesterol, triglycerides, sodium, creatinine, fibrinogen, anemia, hypertension, atrial fibrillation/FL flutter, smoking, diabetes, chronic obstructive pulmonary disease (COPD), NYHA functional class, HF etiology, LV ejection fraction, and use of ACE-inhibitors/angiotensin receptor blockers (ARBs), allopurinol, statins (open/randomized) or any type of diuretic agents	All-cause death, Cardiovascular hospitalization, All-cause death or cardiovascular hospitalization (combined endpoint)	8
Canepa (12)	Italy	Cohort	67	6,859 (78.3%)	Continuous	3.5	Age, gender, BMI, heart rate, systolic blood pressure, hemoglobin, white blood cell count, total cholesterol, uricemia, glycemia, potassium, sodium, creatinine, years of HF, NYHA class, heart gallop, atrial fibrillation at ECG,	All-cause mortality	9

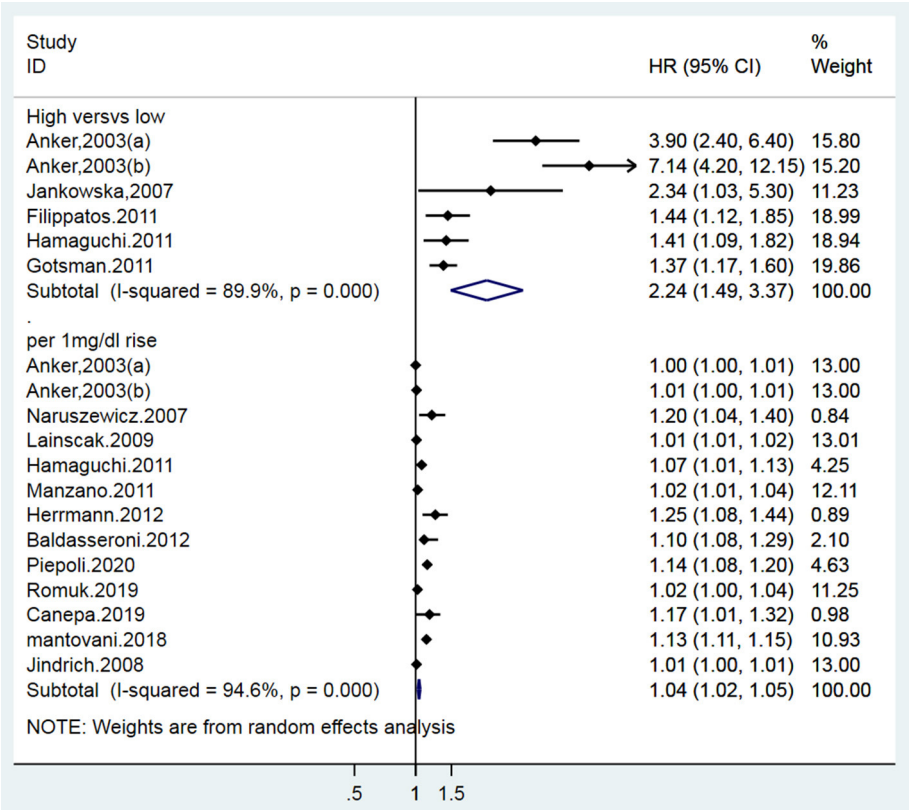


FIGURE 2 | Forest plot for the association of SUA and all-cause mortality of CHF.

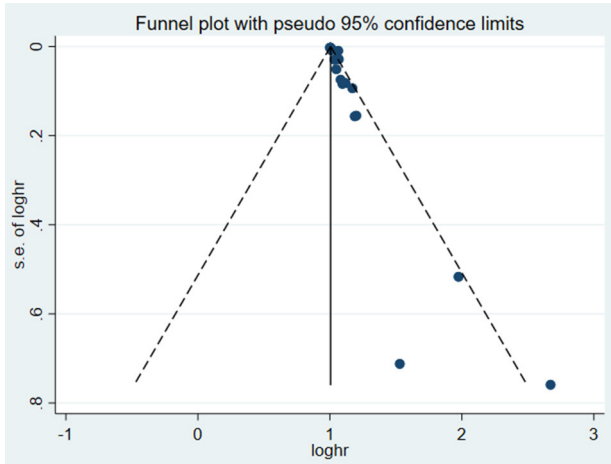


FIGURE 3 | Funnel plot for the association of SUA and all-cause mortality of CHF.

after trimming: HR:1.33, 95% CI: 0.93–1.88, $P = 0.116$), but the other result is stable (the combined effect value before trimming: HR: 1.03, 95% CI: 1.02 1.04, $P = 0.000$, after trimming: HR:1.02, 95% CI: 1.01–1.04, $P = 0.002$). The results of sensitivity analysis showed that there was no significant change in the effect size when we deleted any of the studies, which indicated that our results were stable and reliable (**Figures 6**, **7**).

SUA and Cardiovascular Mortality of CHF Patients

Four studies (13, 15, 19, 20) reported cardiovascular mortality. CHF patients with hyperuricemia were more susceptible to cardiovascular mortality (HR: 1.14, 95% CI: 1.06–1.23); there was statistical heterogeneity among the studies ($I^2 = 67.8\%$) (**Figure 8**). The sensitivity analysis results were consistent (**Figure 9**). Publication bias was found by funnel plot (**Figure 10**).

SUA and Death or Cardiac Events of CHF Patients

A total of eight studies reported incidents of death or cardiac events. After pooling data from 4 studies (18–20, 28) reporting the estimates as categorical variables, hyperuricemia was linked with a growing risk of the combined incidents of death or cardiac events in CHF patients (HR 1.26, 95% CI 1.01–1.56), but substantial statistical heterogeneity was found ($I^2 = 77.5\%$) (**Figure 11**). A 1 mg/dL serum uric acid rise significantly increased the risk of the composite endpoint of death or cardiac events by 9% after pooling the four studies reporting the estimates as continuous variables (HR 1.09, 95% CI 1.03–1.17) (15, 25, 28–30). In addition, a significant degree of heterogeneity was present ($I^2 = 93.4\%$) (**Figure 11**). The results of the sensitivity analysis

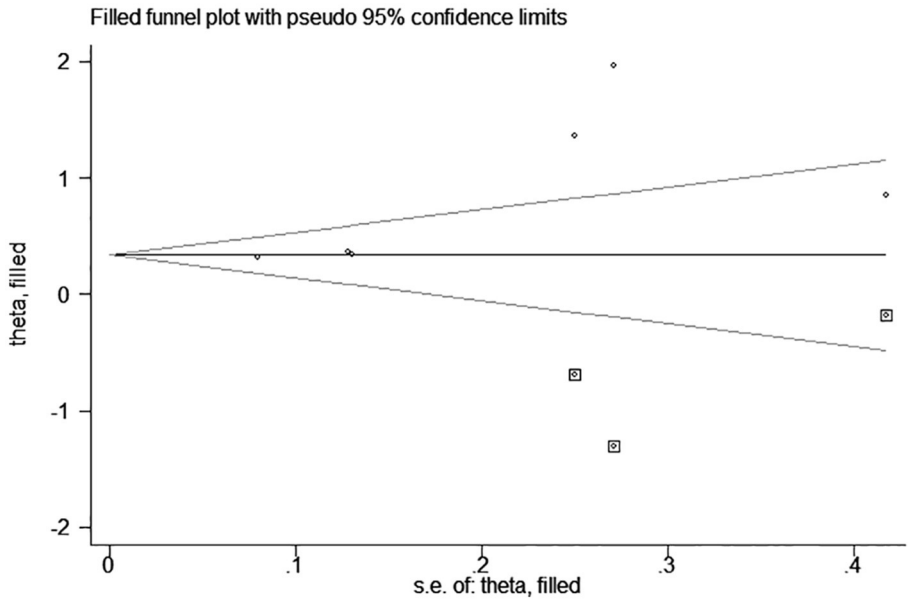


FIGURE 4 | Trim and filling method analysis of SUA and all-cause mortality of CHF (categorical variables).

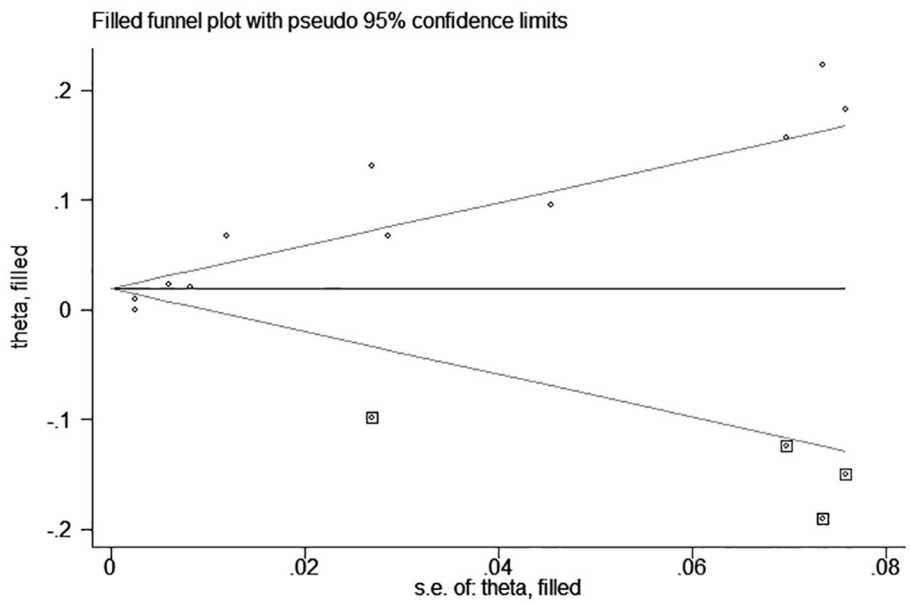


FIGURE 5 | Trim and filling method analysis of SUA and All-cause mortality of CHF (continuous variables).

were consistent (**Figures 12**, **13**). Publication bias was found by funnel plot (**Figure 14**).

Subgroup Analysis

To explore the heterogeneity of the study, we conducted a subgroup analysis of all-cause mortality based on publication year, patient age, sample size, quality score, and follow-up time. The results of subgroup analysis show that none of these factors are the main sources of heterogeneity. The test of differences between subgroups shows that the effect size of the results may be affected by the sample size, follow-up time, publication year, and whether to adjust factors (**Tables 2**, **3**).

Meta-Regression Analysis

To explore the source of heterogeneity, we conducted meta-regression analysis using mean age, gender, and mean follow-up time as covariables, and the results showed that age, gender and mean follow-up time had no statistical

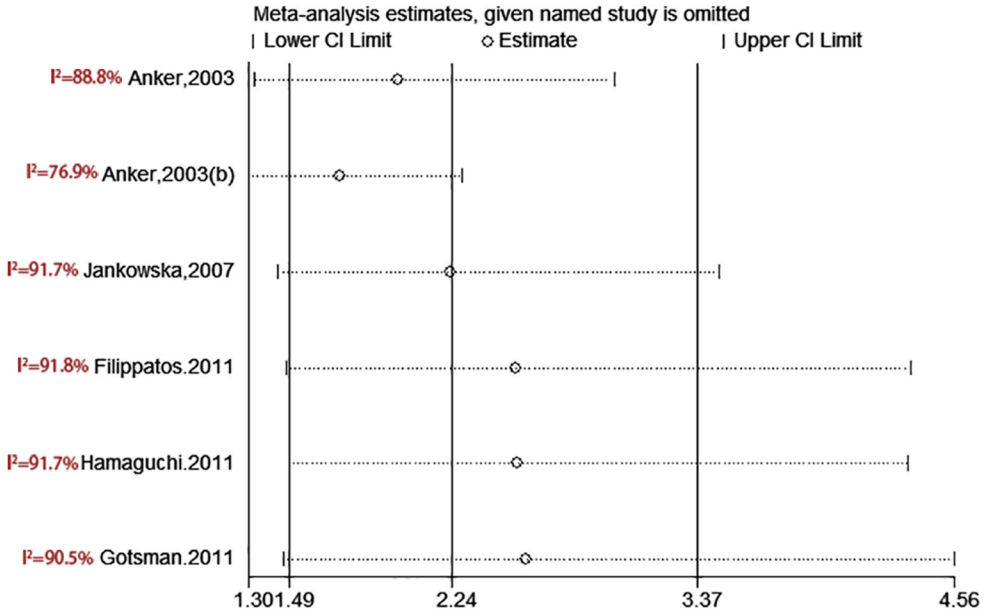


FIGURE 6 | Sensitivity analysis for SUA level and all-cause mortality of CHF (categorical variables).

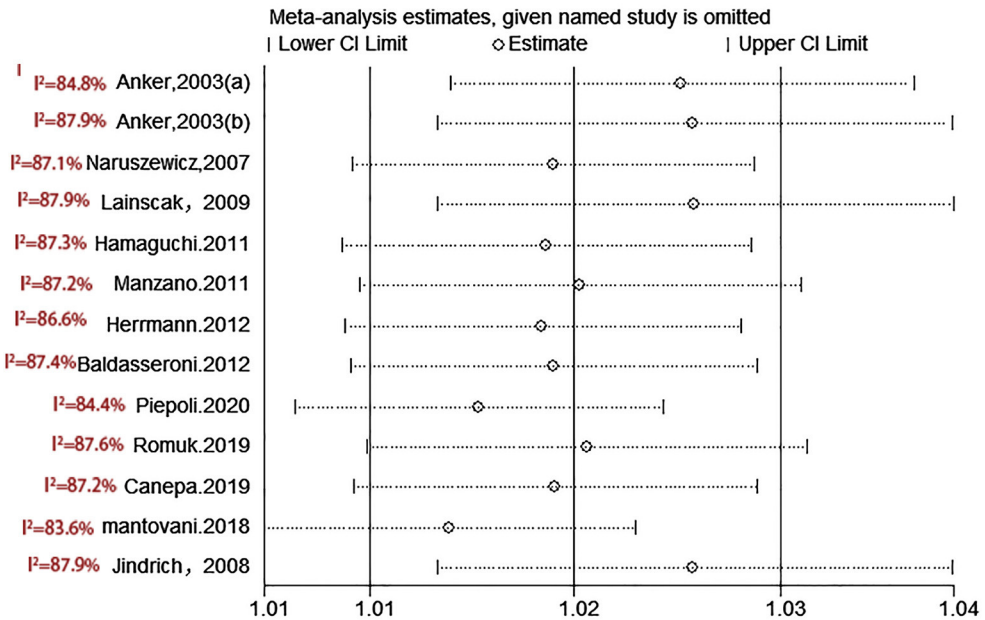


FIGURE 7 | Sensitivity analysis for SUA level and all-cause mortality of CHF (continuous variables).

significance ($p > 0.05$), so they were not the main sources of heterogeneity (**Tables 4**, **5**).

DISCUSSION

Our systematic review and meta-analysis of 18 studies with over 33,000 sample sizes suggested that a high level of SUA independently predicted the risk of all-cause mortality, cardiovascular death and combined death or cardiac events in CHF patients.

Three previous meta-analyses also examined the relationship between elevated SUA levels and the occurrence and prognosis of HF. A meta-analysis (11) of 33 studies published in 2013 by Huang et al. showed that elevated SUA levels are associated with

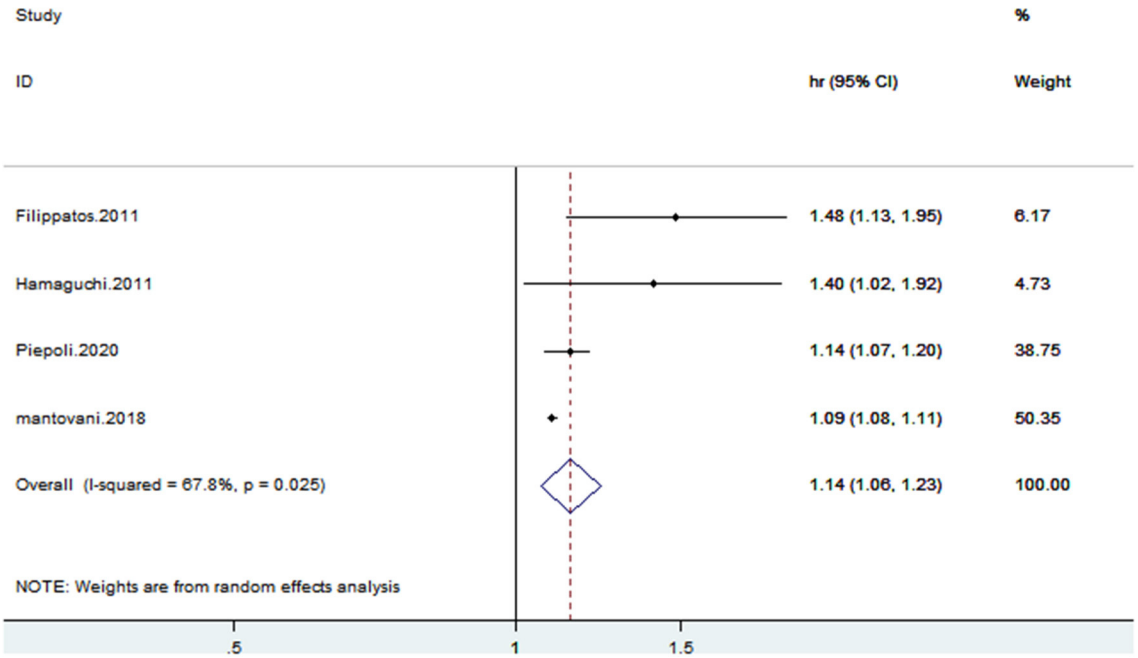


FIGURE 8 | Forest plot for the association of SUA and cardiovascular mortality of CHF.

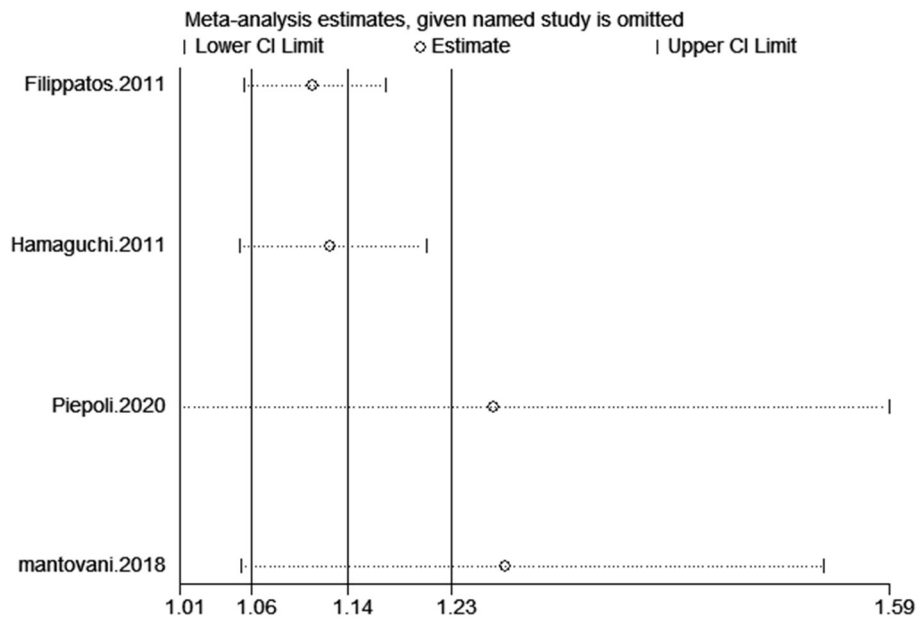


FIGURE 9 | Sensitivity analysis for SUA and cardiovascular mortality of CHF.

an increased risk of HF and adverse outcomes in patients with HF. Another meta-analysis (32) also identified a higher level of SUA as a strong independent predictor of all-cause mortality in patients with HF. However, the patients included in the above two studies were broadly defined. The relationship between different types of HF and SUA levels was not carefully analyzed. A meta-analysis (33) published in 2019 analyzed the relationship between serum uric acid level and the prognosis of AHF, and the results

showed that the elevated of SUA level independently predicted all-cause mortality and combined endpoint death or readmission in AHF patients. However, the association between SUA levels and CHF remains unclear Kazuhide Ogino et al. used the uric acid-lowering drug benzbromarone to observe the treatment effect of 14 CHF patients with hyperuricemia. The results of the study showed that benzbromarone significantly reduced SUA but brain natriuretic peptide, left ventricular ejection fraction and the size assessed by echocardiography did not change (34). Our study analyzed all the current studies on the relationship between SUA and the prognosis of CHF, and the results provided more proof information that a higher SUA level is a comprehensive risk factor for cardiac events, cardiovascular mortality and death, and all-cause mortality in patients with CHF.

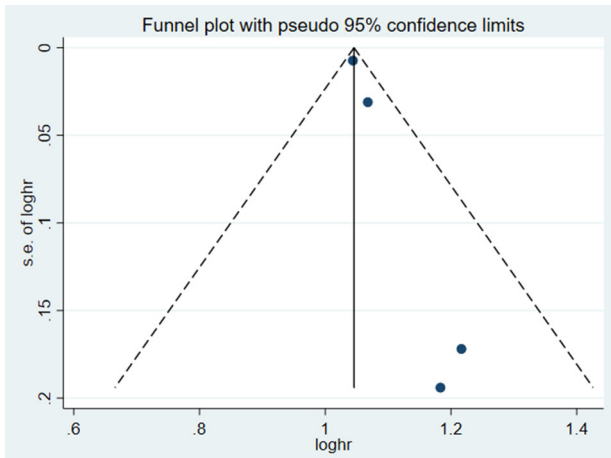


FIGURE 10 | Funnel plot for the association of SUA and cardiovascular mortality of CHF patients.

The clear pathophysiologic role of serum uric acid in CHF progression is not yet clear, it is speculated to be: (i) Functional upregulation of a key enzyme in purine metabolism, xanthine oxidase (XO), which derives reactive oxygen species that may be responsible for a series of harmful processes in the pathophysiology of CHF, such as cardiac hypertrophy, myocardial fibrosis, left ventricular remodeling and impaired contractility. (ii) Uric acid impairs vascular endothelial cells and causes poor prognosis (35). A previous randomized, placebo-controlled study reported that allopurinol can improve endothelial dysfunction in patients with CHF (36). (iii) Hyperuricemia is associated with worse hemodynamic measures (37). (iii) In patients with CHF, increased SUA levels demonstrated a significant association with diastolic dysfunction (38). In two placebo-controlled studies, allopurinol treatment improved blood flow and peripheral vasodilation in patients with CHF (39). In addition, sympathetic nerve excitement and the release of catecholamine neurotransmitters in patients with HF lead to the constriction of renal glomerular arterioles, a decrease

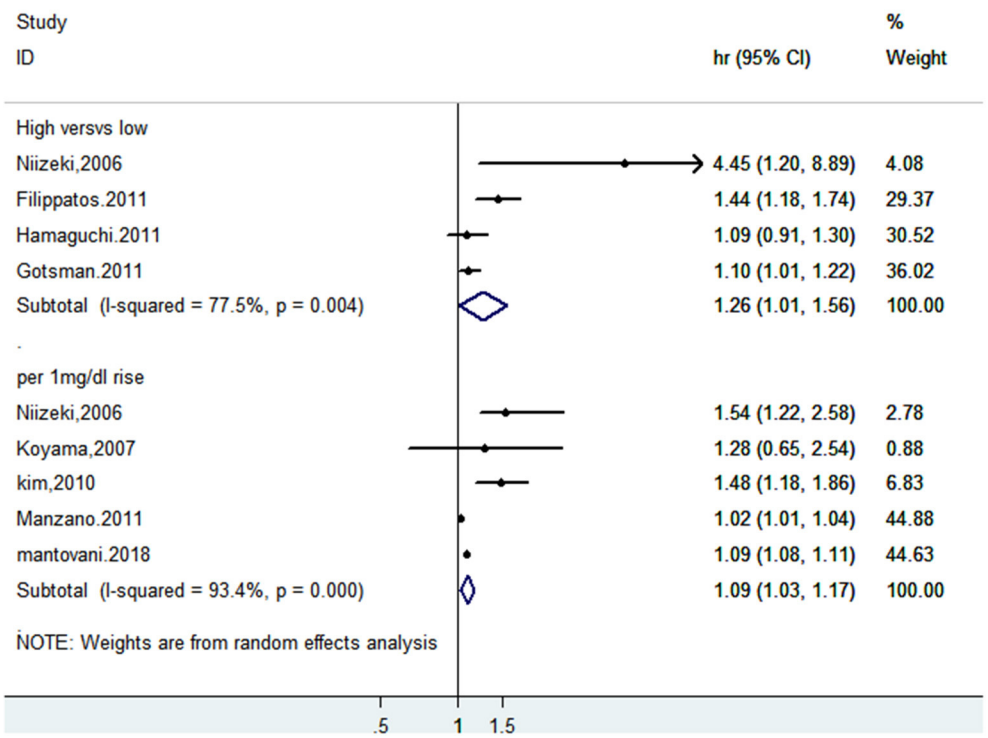


FIGURE 11 | Forest plot for the association of SUA and combined death or cardiac events of CHF.

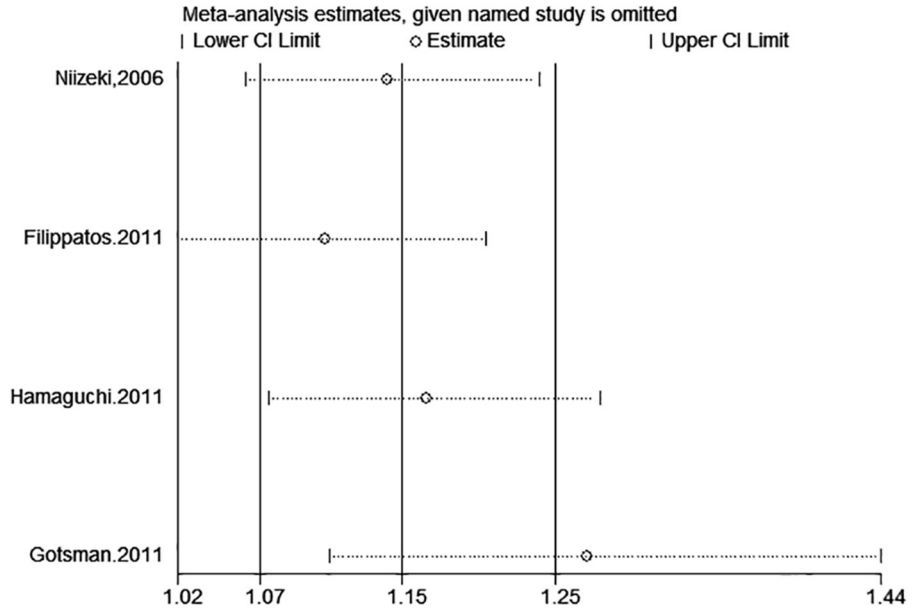


FIGURE 12 | Sensitivity analysis for SUA and combined death or cardiac events of CHF (categorical variables).

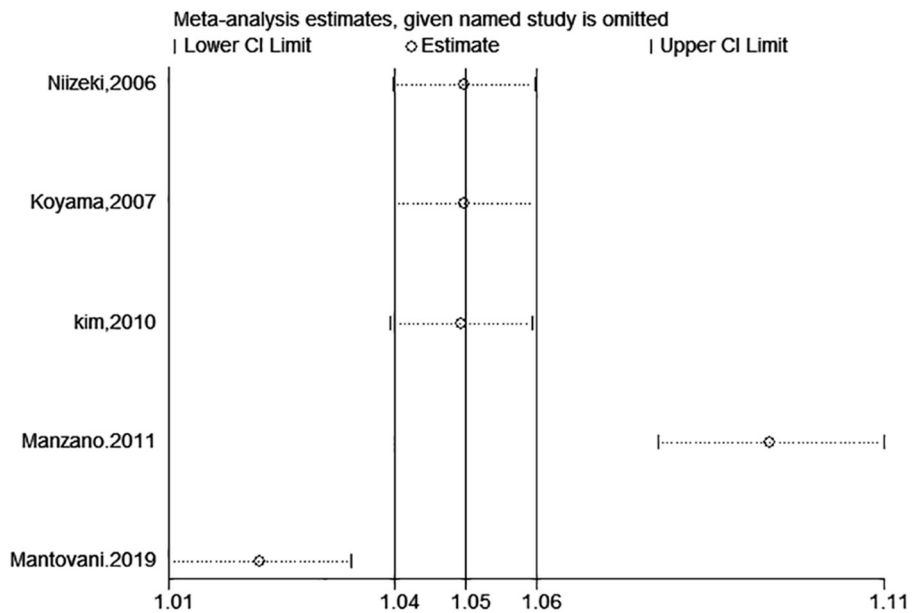


FIGURE 13 | Sensitivity analysis for SUA and combined death or cardiac events of CHF (continuous variables).

in the glomerular filtration rate, and a decrease in uric acid excretion, thus leading to an increase in uric acid. The increase in uric acid further activates the renin-angiotensin-aldosterone system, leading to ventricular remodeling and poor prognosis in patients with HF (40). Studies have also pointed out that the serum uric acid level of patients with chronic ischemic heart failure is related to left ventricular remodeling (41).

It is worth noting that the heterogeneity of the included studies was high. The potential sources of differences are age, sample size, variable adjustment, follow-up time, literature quality score and publication year. Based on the above factors, we conducted a subgroup analysis to explain the heterogeneity, but this did not find the source of heterogeneity. However, the results of our subgroup analysis did not change the conclusion

that elevated uric acid would increase the risk of all-cause death. In addition, according to the results of the subgroup analysis, we also found that the size of the effect may be affected by factors such as sample size, follow-up time, publication year, and age of the research subjects. The reason may be as follows: there is a significant difference between the research results before and after 2010. Combined with the subgroup analysis based on sample size, it can be inferred that the main reason may be related to the sample size. The sample size studied before 2010 was small, while the sample size studied after 2010 was larger. Subgroup analysis of studies with adjusted or unadjusted variables showed that unadjusted studies found that the risk of all-cause death in patients with heart failure was higher than that in adjusted studies. Although multivariate adjustments have been made in most observational studies, residual confounding factors still inevitably exist. Among them, the use of diuretics and the degree of renal damage may play a key role in variable factors. Uric acid is the final metabolite of purine and is catalyzed by xanthine oxidase. Under normal circumstances, the production and excretion of uric acid are in dynamic balance, and all factors that can affect the production or excretion of uric acid, such as the activation of xanthine oxidase, the use of diuretics, and the injury to renal function, can affect the concentration of uric acid in the body. Diuretics are the basic drugs for the treatment of HF. The extensive use of diuretics can not only increase uric acid, but also produce many adverse reactions, such as electrolyte disturbance, hemodynamic instability, and neuroendocrine activation. These adverse reactions can increase the risk of death and lead to poorer prognosis in patients with heart failure. Other factors that influence uric acid excretion, such as reduced glomerular filtration rate, hyperinsulinemia, renal vasoconstriction, and factors that increase uric acid production, such as tissue ischemia or oxidative stress, may influence the prognosis of uric acid and chronic heart failure.

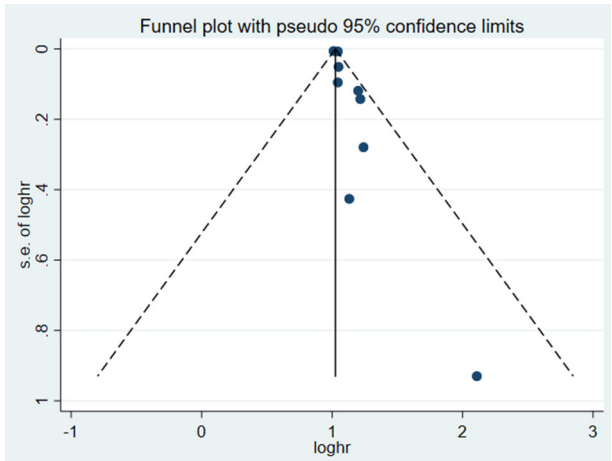


FIGURE 14 | Funnel plot for the association of SUA and death or cardiac events of CHF patients.

Although there have been many studies on the relationship between uric acid and cardiovascular disease, a crucial question about how to determine the cut-off of cardiovascular uric acid needs to be answered. The actual cut-off of hyperuricemia (>6 mg/dL in women and 7 mg/dL in men) is mainly based on the saturation point of uric acid, but previous evidence suggests that low levels of uric acid may also have a negative impact on the cardiovascular system. The recently published URRAH study reported the uric acid cut-off for total and cardiovascular mortality, which indicated that the optimal cut point for total mortality and cardiovascular mortality was 4.7 and 5.6 mg/dL, respectively (41). This research also proposes that the cut-off of uric acid may be different for various disease outcomes. For example, the research mentioned that uric acid cut-off for fatal myocardial Infarction is 5.70 mg/dL (41). Currently, a little data can be used to back up the critical point of uric acid for CHF, and our study merely incorporates the current mainstream uric acid critical point research. Thus, more studies are needed in the future to further determine the critical point of uric acid that

TABLE 2 | Subgroup analyses of the relationship between SUA and all-cause mortality in CHF patients (categorical variable).

Subgroup	Study	Heterogeneity		Meta-analysis		Number of study	*P*-value of
		I^2	*P*-value	Effect size	95% CI		Difference between subgroups
Sample size	<500	64.8%	0.059	HR 4.26	2.39–7.62	3	0.00
	≥500	0.0%	0.941	HR 1.39	1.24–1.57	3	
Adjustment	Adjusted	0.0%	0.653	HR 1.41	1.26–1.58	4	0.00
	Unadjusted	62.8%	0.101	HR 5.23	2.89–9.46	2	
Follow-up (year)	<2	36.8%	0.208	HR 1.53	1.00–2.34	2	0.58
	≥2	92.8%	0.000	HR 2.64	1.38–5.03	4	
Publication year	After 2010	0.0%	0.941	HR 1.39	1.24–1.57	3	0.00
	Before 2010	64.8%	0.059	HR 4.26	2.39–7.62	3	
Age	<70	62.8	0.101	HR 5.23	2.89–9.46	2	0.00
	≥70	0.0%	0.653	HR 1.41	1.26–1.58	4	
Quality score	<7	86.0%	0.000	HR 1.63	1.17–2.28	3	0.53
	≥7	0%	0.934	HR 1.43	1.19–1.71	3	

TABLE 3 | Subgroup analyses of the relationship between SUA and all-cause mortality in CHF patients (continuous variable).

Subgroup	Study	Heterogeneity		Meta-analysis		Number of study	*P*-value of difference
		I^2	*P*-value	Effect size	95% CI		between subgroups
Sample size	<500	86.3%	0.000	HR 1.01	0.99–1.03	4	0.01
	≥500	86.1%	0.000	HR 1.03	1.02–1.05	9	
Adjustment	Adjusted	80.7%	0.000	HR 1.05	1.03–1.08	4	0.00
	Unadjusted	87.2%	0.001	HR 1.01	1.00–1.01	9	
Follow-up(year)	<2	70.1%	0.018	HR 1.03	1.01–1.06	3	0.08
	≥2	88.8%	0.000	HR 1.02	1.01–1.03	7	
Publication year	After 2010	80.5%	0.000	HR 1.05	1.03–1.08	9	0.00
	Before 2010	80.8%	0.001	HR 1.01	1.00–1.01	4	
Age	<70	77.14%	0.004	HR 1.008	1.002–1.015	4	0.45
	≥70	88.19%	0.000	HR 1.069	1.040–1.099	9	
Quality score	<7	85.3%	0.000	HR 1.03	1.01–1.05	6	0.35
	≥7	83.8%	0.000	HR 1.04	1.02–1.06	7	

TABLE 4 | Meta regression analysis of SUA and All-cause mortality of CHF patients.

Concomitant variable	Coef.	Std. Err	z	*P* > |z|	[95% Conf. Interval]	
Mean Age	0.0007895	0.0004926	1.6	0.109	−0.0001761	0.001755
Mean follow up time	−0.0014168	0.0017655	−0.80	0.422	−0.0048772	0.0020436
Gender	0.026645	0.0183555	1.45	0.147	−0.009331	0.0626211
_cons	0.9443494	0.0442626	21.34	0.000	0.8575963	1.031102

TABLE 5 | Meta regression analysis of SUA and Death or cardiac events of CHF patients.

Concomitant variable	Coef.	Std. Err	z	*P* > |z|	[95% Conf. Interval]	
Mean age	−0.0032499	0.0077723	−0.42	0.676	−0.0184834	0.0119836
Mean follow-up time	0.0411667	0.022369	1.84	0.066	−0.0026758	0.0850092
Gender	−0.4208582	0.2307228	−1.82	0.068	−0.8730667	0.0313502
_cons	1.430657	0.5598989	2.56	0.011	0.3332758	2.528039

affects the prognosis of CHF, but our current study has already confirmed that the high uric acid will lead to the poor prognosis of CHF. In addition, attention should be paid to the influence of age and sex on the prognosis of uric acid and CHF. The study by Eugenio R. Cosentino et al. demonstrated that serum uric acid in male elderly patients with heart failure seems to be negatively correlated with EF%, and SUA has a severe effect on left ventricular function (41). A study from Norway also found that a high level of SUA was independently associated with lower 5-year survival rates of outpatient women rather than men (42). The Brisighella study revealed that vascular damage associated with high levels of SUA is age-dependent and reversible (43). Thus, stratification factors, including patients' population, age, sex, as well as the critical value of uric acid, need to be taken into consideration to better interpret serum uric acid and its correlation with CHF.

Strength and Limitation

To the best of our knowledge, this is the first meta-analysis focusing on the relationship between uric acid level and the prognosis of CHF. Our meta-analysis showed that uric acid level is an independent predictor of all-cause death, cardiovascular death and the composite end point of death or cardiovascular events in CHF patients. Moreover, included studies from different countries were included, and the sample size was large, so the results were relatively stable and reliable. All the quality of the included studies was relatively high. Although there was heterogeneity in the results, the results of our subgroup analysis and sensitivity analysis were stable.

However, our study also has limitations. First, the heterogeneity in our study was significant. Even though the sensitivity analysis and subgroup analysis were adopted, we still failed to explore the origin of heterogeneity. Second, the lack of repeated measurements of serum uric acid levels was a common limitation in the included studies. One time determination of serum uric acid levels may not accurately reflect the changes with time. Third, individual studies have different threshold for high and low uric acid, which would have an impact on our research results and may be a reason for the heterogeneity of outcome indicators. Four, considering the quality of the included research, we did not include some conference studies and gray literatures with small sample sizes, which may cause the publication bias. Finally, due to the insufficient of data, the relationship between serum uric acid levels and different stages of chronic heart failure cannot be evaluated in our meta-analysis.

Conclusion

High SUA levels independently predicted the risk of all-cause mortality, cardiovascular death and combined death or cardiac events in CHF patients.

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

JD and DS: conceptualization and supervision. LM and MG: data curation, formal analysis, investigation, and methodology. ZC: project administration. LM, YY, and PC: software and writing (original draft). MG and DS: writing (review and editing). LM, DP, and JG: modified the final version. 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.2021.785327/full#supplementary-material

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The Association of Sleep Duration With Vision Impairment in Middle-Aged and Elderly Adults: Evidence From the China Health and Retirement Longitudinal Study

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Objective: This study aims to investigate the association of sleep duration with vision impairment (VI) in middle-aged and elderly adults.

Methods: This cross-sectional study used the data from the baseline survey of the China Health and Retirement Longitudinal Study (CHARLS) 2011–2012, a national survey of adults aged 45 years or older. Weighted multilevel logistic regression models were used to evaluate the association between self-reported sleep duration and VI.

Results: Of the 13,959 survey respondents, a total of 4,776 (34.2%) reported VI. The prevalence of short (≤6 h/night) and long (>8 h/night) sleep durations was higher among respondents with VI than those without VI ($P < 0.001$). Multilevel logistic regression models showed that compared with a sleep duration of 6–8 h/night, a sleep duration of ≤6 h/night was associated with a 1.45-fold [95% confidence interval (CI) = 1.34–1.56] higher VI risk, and a sleep duration of >8 h/night was associated with a 1.18-fold (95% CI = 1.03–1.34) higher VI risk, after adjusting for sociodemographic data, lifestyle factors, and health conditions. Vision impairment was associated with short sleep duration in respondents from all age or gender categories. However, VI was associated with long sleep duration in respondents from the elderly or female categories. The association between VI and long sleep duration disappeared in respondents of middle-aged or male categories.

Conclusions: The potential impact of sleep on the risk of visual functions requires further attention. A more comprehensive and integrated health care and rehabilitation system covering vision and sleep is also needed.

Keywords: vision impairment, sleep duration, association, adults, China

INTRODUCTION

Vision impairment (VI) is a major global public health problem. According to a published report in Lancet Global Health, the number of people affected by VI has increased substantially, a situation attributable to population growth and aging (1). The combination of cataract and uncorrected refractive error contributed to 55% of the blindness and 77% of the VI in adults aged 50 years and older in 2015 (1). In China, the prevalence of low bilateral vision was 5.1%, and the prevalence of blindness was 1.0%, based on the World Health Organization (WHO) best corrected visual acuity (BCVA) criteria in the Taizhou Eye Study (2). Further analysis revealed that VI was associated with an increased rate of cognitive impairment and depression and a lowered quality of life (3–5). A few studies based on the US population have concluded that older adults with VI also experienced increased sleep disturbance (6, 7).

In terms of VI, sleep is one of the aspects of functioning that may be underestimated because attention is focused on establishing visual functions. Sleep is vital for optimal physical and mental health, and growing evidence now supports an association of both short- and long-duration sleep with adverse health outcomes (8–10). Several epidemiologic studies have reported an increased risk of all-cause mortality, as well as stroke and cardiovascular disease mortality, among those with self-reported short or long sleep durations (11–13). Recent findings have also uncovered differences in sleep health based on racial/ethnic and socioeconomic position differences. The underlying causes of disparities in sleep health are only beginning to emerge (14).

Recent studies have reported a statistically significant association between sleep disorders and ocular diseases, such as glaucoma, optic nerve dysfunction, and dry eye syndrome (15–17). However, sleep data have not yet been considered an essential element in many epidemiologic studies of VI. To our knowledge, few large-scale population-based studies have examined the potential association between sleep duration and VI in an Asian population. The aim of the present study was to evaluate the associations between sleep duration and the prevalence of VI in a nationally representative survey of the Chinese adult population aged 45 years or older, using data from the 2011 baseline survey of the China Health and Retirement Longitudinal Study (CHARLS).

MATERIALS AND METHODS

Data and Study Sampling

The CHARLS is a nationally representative survey of Chinese adults aged 45 years or older and their spouses. The national baseline survey for CHARLS was conducted between June 2011 and March 2012 and included 17,708 respondents in 150 counties or districts and 450 villages or urban communities throughout China (18). The CHARLS protocol followed the tenets of the Declaration of Helsinki (19) and received ethical approval from the institutional review board of Peking University (18). Informed consent was obtained from all participants when CHARLS was administered, consistent with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines (20).

Vision Impairment

Vision consisted of both distance vision and near vision. Distance vision was assessed by asking the participants: "How good is your eyesight for seeing things at a distance, like recognizing a friend from across the street (with glasses or corrective lenses if you wear them)?" Near vision was assessed by asking the participants: "How good is your eyesight for seeing things up close, like reading ordinary newspaper print (with glasses or corrective lenses if you wear them)?" Responses to these two questions were divided into a five-point scale (excellent, very good, good, fair, and poor). A response of "poor" in distance or near vision was categorized as VI, while a response of "fair" or above in distance and near vision was categorized as no VI (21).

Sleep Duration

Sleep duration was assessed by asking participants the following question: "During the past month, how many hours of actual sleep did you get at night (average hours for one night)? (This may be shorter than the number of hours you spend in bed)." The participant responses for sleep duration were categorized into three groups: (1) those reporting short sleep duration ($\leq$6 h), (2) those reporting long sleep duration (>8 h), and (3) those reporting 6–8 h of sleep (used as the reference group) (22, 23).

Covariates

Several potential confounding variables were taken into account, including participants' sociodemographic data, lifestyle factors, and health conditions. The sociodemographic data and lifestyle factors included in the analysis were as follows: age, sex (male or female), marital status (married or partnered vs. otherwise), smoking status (yes or no), drinking status (more than once a month, less than once a month, or none), and educational attainment (less than elementary school, elementary school, middle school, or high school or above).

Health conditions included in the analysis were hypertension (24, 25), dyslipidemia (26), diabetes (27), and chronic kidney disease (28–30), assessed by a combination of physical examination and self-report according to reference definition. In CHARLS, blood samples were collected and blood pressure was measured using a standard protocol by medically trained staff from the China Center for Disease Control and Prevention (31).

Statistical Analysis

Because CHARLS has a complex sampling design, sampling weights were considered in the analyses. Continuous variables were presented using mean ± SD. Categorical variables were presented using numbers. Characteristics of the study sample were compared using the χ^2-test for categorical variables and an independent-sample *t*-test for continuous variables. The subjects were divided into two groups according to gender or the median age: middle age and elderly. The prevalence of VI was calculated based on the complex survey design and non-response rate.

Abbreviations: VI, visual impairment; OR, odds ratio; CI, confidence interval; CHARLS, China Health and Retirement Longitudinal Study.

The PROC SURVEYFREQ procedure was used to calculate the overall age and gender-specific prevalence of VI using the inverse probability weighting method. Weighted multilevel logistic regression models were used to evaluate the odds ratio (OR) at a 95% confidence interval (CI). They modeled the association between self-reported sleep duration and VI, adjusting for sociodemographic data (age, sex), lifestyle factors (marital status, smoking status, drinking status, and education), and health conditions (hypertension, dyslipidemia, diabetes, and chronic kidney disease). Statistical analysis was carried out using the Statistical Analysis System (SAS) (version 9.4, SAS Institute, Cary, NC, USA) for Windows. All reported *P*-values were two-tailed, and values <0.05 were considered statistically significant.

RESULTS

After filtering, a total of 13,959 participants were deemed eligible for the current study. In total, 6,574 males and 7,385 females were included in the final analysis. The mean age was 59.97 (9.84) years. The characteristics of the included subjects in the CHARLS 2011–2012 are shown in **Table 1**. Of the study subjects, 4,776 reported VI, with a higher proportion of females than males reporting VI. Those who reported VI were older, less educated, and more likely to be unmarried or unpartnered. The subjects with VI were also more likely to have smoking history, hypertension, diabetes, and chronic kidney disease. Interestingly, sleep durations showed some relationships with VI. The prevalence of short (≤6 h/night) and long (>8 h/night) sleep durations was higher among respondents with VI than those without VI ($P < 0.001$).

The weighted VI prevalences in respondents, by age and sex, based on sleep durations are shown in **Table 2**. The prevalence of VI among the study respondents was 35.83%. More specifically, the prevalence of VI was higher among respondents with short (40.78%) or long (35.33%) sleep durations than those with sleep durations of 6–8 h (26.10%).

By age, the VI prevalence was higher in elderly respondents (40.98%) than in middle-aged respondents (31.08%). Separately, the VI prevalence was higher in elderly respondents with short (42.97%) or long (40.19%) sleep durations than with sleep durations of 6–8 h (31.68%). The VI prevalence was also higher in middle-aged respondents with short (35.78%) or long (25.80%) sleep durations than with sleep durations of 6–8 h/night (23.60%).

The VI prevalence was also higher in female respondents (38.47%) than in male respondents (32.89%). In the female participants, the VI prevalence was 45.84, 30.26, and 39.65% for subjects with sleep durations of ≤6, 6–8, and >8 h/night, respectively. In the male participants, the equivalent VI prevalence was 35.61, 26.88, and 30.82%, respectively. Overall, the VI prevalence was higher among respondents with short or long sleep durations than with normal sleep duration in all age and gender categories.

The associations between sleep duration and VI determined using multilevel logistic regression models are shown in **Table 3**. These associations had variations after covariate adjustments for age, sex, marital status, smoking status, drinking status, education, hypertension, dyslipidemia, diabetes, and chronic kidney disease. Even after adjusting for these factors, a sleep duration of ≤6 h/night was associated with a 1.45-fold (95% CI = 1.34–1.56) higher VI risk, while a sleep duration of >8 h/night was associated with a 1.18-fold (95% CI = 1.03–1.34) higher VI risk compared with 6–8 h/night of sleep.

A stratified analysis of age categories revealed that short (OR = 1.44, 95% CI: 1.29–1.60) and long (OR = 1.30, 95%

TABLE 1 | Demographic characteristics of middle-aged and elderly Chinese with and without suffering vision impairment (CHARLS 2011–2012).

Variables	Vision impairment	No vision impairment	*P*
Total	4,776	9,183	
Age, year	60.96 ± 9.87	59.09 ± 9.58	<0.001
Sex			<0.001
Male	1,980	4,594	
Female	2,796	4,589	
Marital status			<0.001
Married or partnered	4,055	8,191	
Otherwise	721	992	
Smoking status			0.002
Yes	1,760	3,633	
No	3,016	5,550	
Drinking status			0.126
Drink more than once a month	1,084	2,376	
Drink but less than once a month	313	765	
None	3,379	6,042	
Education			<0.001
Less than elementary school	3,591	5,697	
Elementary school	777	2,116	
Middle school	256	813	
High school or above	152	557	
Hypertension			<0.001
Yes	1,994	3,339	
No	2,782	5,844	
Dyslipidemia			0.060
Yes	1,624	2,977	
No	3,152	6,206	
Diabetes			<0.001
Yes	727	1,115	
No	4,049	8,068	
Chronic kidney disease			<0.001
Yes	407	495	
No	4,369	8,688	
Sleep duration			<0.001
≤6 h	2,718	4,252	
6–8 h	1,646	4,138	
>8 h	412	793	

TABLE 2 | Vision impairment prevalence in middle-aged and elderly Chinese according to sleep durations (CHARLS 2011–2012).

		Sleep duration groups (h/night)			*P*
	Overall	**≤6 h**	**6–8 h**	**>8 h**	
All	*n* = 13,959	*n* = 6,970	*n* = 5,784	*n* = 1,205	
Vision impairment, *n* (%)	4,776 (35.83)	2,718 (40.78)	1,646 (26.10)	412 (35.33)	<0.001
Age					
≥45 and ≤58 years	*n* = 7,239	*n* = 3,315	*n* = 3,320	*n* = 604	
Vision impairment, *n* (%)	2,101 (31.08)	1,125 (35.78)	813 (23.60)	163 (25.80)	<0.001
>58 years	*n* = 6,720	*n* = 3,655	*n* = 2,464	*n* = 601	
Vision impairment, *n* (%)	2,675 (40.98)	1,593 (42.97)	833 (31.68)	249 (40.19)	<0.001
Sex					
Male	*n* = 6,384	*n* = 3,172	*n* = 2,849	*n* = 553	
Vision impairment, *n* (%)	1,980 (32.89)	1,097 (35.61)	721 (26.88)	162 (30.82)	<0.001
Female	*n* = 7,385	*n* = 3798	*n* = 2,935	*n* = 652	
Vision impairment, *n* (%)	2,796 (38.47)	1,621 (45.84)	925 (30.26)	250 (39.65)	<0.001

CI: 1.08–1.57) sleep durations were associated with VI in elderly respondents. However, in middle-aged respondents, an association was only detected between short sleep duration and VI (OR = 1.45, 95% CI: 1.30–1.62). The association between long sleep duration and VI (OR = 1.11, 95% CI = 0.91–1.35) was absent among the middle-aged respondents.

A stratified analysis of gender categories revealed that short (OR = 1.45, 95% CI: 1.30–1.60) and long (OR = 1.24, 95% CI: 1.03–1.48) sleep durations were associated with VI in female respondents. However, male respondents showed only the association between short sleep duration and VI (OR = 1.45, 95% CI: 1.29–1.62). The association between long sleep duration and VI (OR = 1.11, 95% CI = 0.90–1.36) was absent among the male respondents.

DISCUSSION

This study examined the association between sleep duration and VI in a nationally representative sample of older adults in China. The use of large-scale population-based data in this study revealed several findings. First, self-reported VI was highly prevalent among middle-aged and elderly adults in China. Second, short (≤6 h/night) and long (>8 h/night) sleep durations were significantly associated with VI risks after adjusting for internal and external factors. Our findings suggest that both short and long sleep durations could be predictors of VI.

The prevalence of VI in China was higher than that reported in the US or Asia (32). The rapidly aging Chinese population may account for this higher rate of VI. Chen et al. (33) reported that cataracts were the leading cause of bilateral or monocular VI among adults 50 years and older in the Binhu District of Wuxi City, China, followed by high myopic macular degeneration, age-related macular degeneration, and eye loss/atrophy. Bourne et al. (34) reported that the leading causes worldwide were cataracts for blindness and uncorrected refractive error for moderate and severe VI. Moreover, more women than men were blind or showed moderate and severe VI due to cataracts and macular degeneration worldwide (34). Our results also revealed a higher prevalence of VI in women than in men, in agreement with previous studies. Therefore, more targeted efforts are required to prevent low vision and blindness in high-risk groups.

The mechanism that regulates sleep duration has not been fully explained. A short sleep duration may be attributed to difficulty in falling asleep, sleep fragmentation, and early awakening. Long sleep duration may occur due to poor circadian entrainment, compensation for fragmented sleep, and lower sleep efficiency (10, 35). Sleep deterioration and related VI may also result from several diseases (36). In turn, VI may further increase mood disturbances and even worsen sleep disorders. Further, respondents with VI tend to exhibit a shortened photoperiod and reduced circadian entrainment (8). The decline in or loss of light perception may lead to circadian misalignment, further contributing to abnormal sleep durations. Therefore, ophthalmologists must recognize the possibility of sleep disturbance in subjects with VI and participate in effective sleep management.

In addition to the above biological and clinical reasons, social factors should not be underestimated. Certain socioeconomic factors (including country of origin, acculturation, education, and annual income) have been found to be significantly associated with both short and long sleep duration (37, 38). These relationships persisted when controlling for overall health status. On the other hand, socioeconomic status is known to be an important determinant of VI (39). As such, socioeconomic status may play a role in the relationship between sleep duration and VI.

In particular, the results from the multilevel logistic regression models indicated a more significant potential for VI with short sleep duration than with long sleep duration. This suggests that persons who sleep for a short duration may require greater amounts of sleep and that worse sleep conditions pose a greater risk of VI. Additional studies examining the causal relationship between sleep durations and VI are needed.

To our knowledge, this is the first large-scale population-based study to explore the associations between self-reported sleep

TABLE 3 | Associations between sleep duration and risk of vision impairment in middle-aged and elderly Chinese (CHARLS 2011–2012).

	Sleep duration groups (h/night)		
	≤6 h OR (95%CI)	6–8 h OR (95%CI)	>8 h OR (95%CI)
All	*n* = 6,970	*n* = 5,784	*n* = 1,205
Model 1	1.50 (1.39–1.61)*	1.00 (Ref.)	1.23 (1.07–1.40)*
Model 2	1.47 (1.36–1.58)*	1.00 (Ref.)	1.18 (1.03–1.35)*
Model 3	1.45 (1.34–1.56)*	1.00 (Ref.)	1.18 (1.03–1.34)*
Age			
≥45 and ≤58 years	*n* = 3,320	*n* = 3315	*n* = 604
Model 1	1.50 (1.35–1.68)*	1.00 (Ref.)	1.15 (0.95–1.41)
Model 2	1.47 (1.32–1.64)*	1.00 (Ref.)	1.12 (0.91–1.36)
Model 3	1.45 (1.30–1.62)*	1.00 (Ref.)	1.11 (0.91–1.35)
>58 years	*n* = 3,655	*n* = 2,464	*n* = 601
Model 1	1.46 (1.31–1.63)*	1.00 (Ref.)	1.35 (1.12–1.62)*
Model 2	1.45 (1.30–1.62)*	1.00 (Ref.)	1.29 (1.07–1.55)*
Model 3	1.44 (1.29–1.60)*	1.00 (Ref.)	1.30 (1.08–1.57)*
Sex			
Male	*n* = 3,172	*n* = 2,849	*n* = 553
Model 1	1.50 (1.34–1.67)*	1.00 (Ref.)	1.15 (0.94–1.41)
Model 2	1.47 (1.31–1.65)*	1.00 (Ref.)	1.11 (0.90–1.36)
Model 3	1.45 (1.29–1.62)*	1.00 (Ref.)	1.11 (0.90–1.36)
Female	*n* = 3,798	*n* = 2,935	*n* = 652
Model 1	1.49 (1.35–1.65)*	1.00 (Ref.)	1.29 (1.08–1.54)*
Model 2	1.46 (1.32–1.62)*	1.00 (Ref.)	1.23 (1.03–1.48) *
Model 3	1.45 (1.30–1.60)*	1.00 (Ref.)	1.24 (1.03–1.48)*

Model 1 adjusted for age and sex. Model 2 adjusted for covariates in model 1 plus marital status, smoking status, drinking status, and education. Model 3 adjusted for covariates in model 2 plus hypertension, dyslipidemia, diabetes, and chronic kidney disease.
**Significant.*

duration and VI among Chinese persons. Self-reported sleep duration and the prevalence of VI are known to reflect ethnic differences (40, 41). Therefore, investigation of the association between VI and sleep duration is essential among older adults in China. This type of research would be more convincing after adjusting for sociodemographic characteristics, lifestyle factors, and health conditions, as all these factors can affect the relationship between self-reported sleep duration and VI.

In fact, the potential impact between sleep and vision is underestimated. A health care and rehabilitation system that covers vision and sleep must be established and popularized. The system should take into account the possibility of VI in subjects with abnormal sleep duration as well as abnormal sleep duration in subjects with VI and engage in effective management accordingly. As for subjects with abnormal sleep duration, their vision function should be taken care of and examined regularly. As for subjects with VI, their sleep-wake cycles should be given close attention. Sleep medication, physical therapy, or psychotherapy treating sleep difficulties may be helpful in reducing the incidence of VI. Vision impairment medication or surgery may contribute to setting up circadian rhythm and improving abnormal sleep duration (42, 43).

The present study is not without limitations, which can be summarized as follows:

1. Due to the cross-sectional nature of the study, causality could not be established. Prospective cohort studies may need to clarify the causality between sleep duration and VI.
2. Sleep duration and visual function were subjectively assessed through self-reported questionnaires. If an objective assessment of sleep quality had been obtained using polysomnography or actigraphy, and vision had been tested by visual acuity chart, the results would be more robust. However, self-reported questionnaires of sleep duration and visual function are widely accepted in a number of large-scale population-based studies, and self-reported sleep duration is sufficiently consistent with objective methods, such as actigraphy (44, 45).
3. Self-reported sleep duration could not allow for the differentiation between total sleep time and time in bed. However, previous studies have shown that objective measures of total sleep time and time in bed were highly correlated (7, 46).
4. The correlation between the severity of VI and the severity of sleep difficulties was not explained. There was a lack of data about the severity of VI and the severity of sleep difficulties in the CHARLS survey. Future studies may need to address this problem.
5. The study was not adjusted for mood, medications, or exposure to artificial light at night, which may affect sleep duration (47, 48). They were not taken into account in previous studies (37, 48). However, we found the relationship was maintained throughout all three models after adjusting for sociodemographic data, lifestyle factors, and health conditions. Future studies may need to take more factors into account.

CONCLUSIONS

In summary, based on large-scale population-based data in China, both short and long sleep durations showed an association with VI. However, the cause-and-effect relationship is unclear. The relationship of VI to sleep in the elderly requires more attention because of a lack of epidemiological studies in China. A more comprehensive and integrated healthcare and rehabilitation system that addresses vision and sleep is also needed.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

MS, QB, and MZ performed material preparation, data collection, and analysis. MS wrote the first draft of the manuscript and all authors commented on previous versions of the manuscript. All authors contributed to the study

conception and 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.2021.778117/full#supplementary-material

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The Effectiveness of Traditional Chinese Yijinjing Qigong Exercise for the Patients With Knee Osteoarthritis on the Pain, Dysfunction, and Mood Disorder: A Pilot Randomized Controlled Trial

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Background: Although traditional Chinese Yijinjing Qigong Exercise (YJJQE) is popularly used in China, to alleviate symptoms of people with knee osteoarthritis (KOA), no randomized controlled trials (RCTs) are available to evaluate the effects of YJJQE in patients with KOA. The purpose of this trial is to assess the clinical efficacy of YJJQE for patients with KOA.

Methods: A total of 50 participants clinically diagnosed with KOA are randomly (1:1) assigned to the YJJQE group ($n = 25$) and to the stretching training exercise (STE) group ($n = 25$), for a 40-min exercise session twice a week for 12 weeks. All outcome measures are collected at baseline and at 12-week ending intervention, which includes the primary outcomes of Western Ontario and McMaster Universities Osteoarthritis Index Scale (WOMAC), the secondary outcomes of visual analog scale (VAS), mental component summary (MCS), physical component summary (PCS), Beck depression inventory (BDI), perceived stress scale (PSS), Berg balance scale (BBS), and the Gait functional mobility data.

Results: The YJJQE group did not have any significant changes compared to the control group on the WOMAC score after the 12-week intervention ($P > 0.05$), though the YJJQE group demonstrated better performance in MCS, BDI, and PSS ($P = 0.002$, $P = 0.001$, and $P = 0.026$, respectively) than the control group. No serious adverse events occurred in either group, and only mild muscle soreness was reported during both exercise treatments.

Conclusion: Because no difference between both groups was shown, with regards to the primary outcome measurement (WOMAC), it can hardly explain that the YJJQE had an advantageous effect on patients experiencing the pain and dysfunction of

knee osteoarthritis. However, compared to the control group, YJJQE appeared to be associated with improvements in psychological well-being including reduced stress, anxiety, depression, and mood disturbance to manage KOA. Further trials with larger sample sizes and follow-up studies will be required.

Clinical Trial Registration: https://www.chictr.org.cn/edit.aspx?pid=60357&htm=4, ChiCTR2000037256.

Keywords: knee osteoarthritis, Yijinjing Qigong Exercise, stretching training exercises, efficacy, randomized controlled trial

INTRODUCTION

Knee osteoarthritis (KOA) accounts for ∼85% of the worldwide burden of osteoarthritis (1), a major age-related and public health problem that can cause pain, functional limitations, disability, and reduced quality of life. Approximately 27 million people in the United States suffer from osteoarthritis (2). With the increase in population, aging, and obesity, the prevalence of KOA also increases, as well as the burden of disease in healthcare services worldwide (3, 4). Currently, no effective approach is available to prevent the progression of the two major clinical problems, namely, disease pain and dysfunction. Oral antipyretic, analgesic, and non-steroidal anti-inflammatory drugs, as well as opioids, were associated with evident side effects, such as clinical gastrointestinal reactions, drug resistance, and addiction (5, 6). Joint cavity injection therapy is widely used, but the clinical efficacy is still controversial; excessive use of hormones may also lead to the risk of steroid arthropathy (7). Improving symptoms with prevention programmers is key to minimizing the social burden of KOA (8, 9). Exercise therapy, as an active treatment recommended by the American Rheumatology Guidelines with strong evidence (10), is increasingly used by clinical staff for the prevention and treatment of KOA. Recent trials have demonstrated that patients with KOA have experienced reduced pain and improved function after stretching training exercises (STE) (11). Yijinjing Qigong Exercise (YJJQE) is a multicomponent and traditional Chinese psychosomatic therapy that combines meditation with slow, gentle, stretching muscle movements, deep diaphragmatic breathing, and relaxation; it has been preliminarily proven to be beneficial for patients with KOA in some clinical research (12–14). However, no RCTs have been specifically conducted, using YJJQE, to evaluate its therapeutic benefits for those with KOA. To fill these gaps, we designed an RCT to determine the efficacy of YJJQE intervention to pain, functional mobility, and psychological well-being outcomes with KOA. Based on prior research, we hypothesized that YJJQE intervention has a better efficacy to improve functional mobility and to reduce pain symptomatology in patients with KOA.

MATERIALS AND METHODS

Trial Design

The study used a parallel-group RCT design to compare an YJJQE intervention with an STE control across a 12-week period, which was conducted in Yue Yang Hospital of Integrated Traditional Chinese and Western Medicine affiliated with Shanghai University of Traditional Chinese Medicine. The study results and procedures were reported according to the CONSORT checklist. A total of 50 patients, who qualified to the inclusion criteria, had been recruited and randomly assigned to YJJQE group and STE group with a 1:1 ratio. Both exercise interventions are performed twice a week for 12 consecutive weeks, and all outcome measurements are performed at baseline and within the timeline. This trial protocol has been approved by the Ethics Committee of Yue Yang Hospital of Integrated Traditional Chinese and Western Medicine, which is affiliated with Shanghai University of Traditional Chinese Medicine (project number: KYSKSB-2020-138) and is registered in the Chinese Clinical Trial Registry (ChiCTR2000037256).

Participants

Subjects were recruited mainly through online social platform advertising and hospital out-patient service from September 2020 to April 2021. We obtained an informed consent prior to baseline assessments for eligibility. Participants were required to satisfy the following criteria: (1) persons aged between 45 and 65, regardless of gender; (2) diagnostic criteria were in accordance with "Guidelines for the Diagnosis and Treatment of Osteoarthritis 2018 Edition." Subjects were required to have the following pain symptoms, such as flat-surfaced walking, walking up and down stairs, standing up, and lying down, in the past month; (3) Kellgren/Lawrence was graded 1–2; (4) Body mass index $\leq$36 kg/m^2; (5) all participants were examined based on pain and dysfunction by an orthopedic surgeon for inclusion; lastly (6) Visual analog scale (VAS) $\geq$2 points (0–10 points). The exclusion criteria were as follows: (1) YJJQE and stretching training experience in the last 3 months; (2) having the following serious diseases: severe coronary heart disease, heart failure, hypertension, cerebral infarction, cerebral hemorrhage, epilepsy, liver or kidney dysfunction, active bleeding, and cancer; (3) Recent one month history of segmental injection and surgery; (4) unable to independently complete the gait analysis test; (5) cognitive status evaluation score is below 24; lastly (6) unable to commit to exercise intervention and indicator collection as required by the protocol.

Randomization, Allocation Concealment, and Blinding

Statistical software was used to generate a list of random numbers, and the third-party personnel has placed the digital

TABLE 1 | Details of the operation of Yijinjing Qigong Exercise (YJJQE).

Sequence of actions	Action details
Action 1	The subject slowly squats and puts his palms together in front of his chest. While inhaling, he slightly flexes the knee joints, keeping the knees not exceeding the toes as a suitable squatting angle. Keep the eyes on the ground about 3 m in front of your body. Concentrate and maintain the above position for 10 s. Then exhale while slowly straightening the knee joint. During this process, the eyes are closed tightly, and the participant feels the position of the knee joint. The operations at this stage also lasts for 10 s.
Action 2	The subject adopts a posture of standing back and forth with both feet, with the toes of the front feet on the ground, and the center of gravity on the other foot that is back. Place one hand 30 cm above the side of the head, and place the other hand on the lumbosacral area, and then perform knee flexion and extension with inhalation and exhalation. The rhythm is the same as Action 1. Keep his eyes on the fingertips when flexing the knees, and close his eyes when extending the knees which can focus on feeling the position of the knee joint.
Action 3	The subject stand upright, raised his arms forward and inhaled, his heels slowly lifted off the ground, and the toes were held on the ground. While extending the knees, the subject looked at the ground about three meters in front and below, stabilized his center of gravity, maintained balance for 10 s; then, while flexing the upper arm, the heel slowly drops, and he also need to feel the position of the knee joint.
Action 4	Stand with the lower limbs separated by a distance of 1 m, and extend the upper limbs to the limit in the horizontal direction. Then make a lunge with both lower limbs in the left and right directions, with the center of gravity on the forefoot, while inhaling, staring at the floor 3 m ahead for 8–10 s. Then the hip joint of the front lower limb is externally rotated, the knee joint is extended, and the knee joint of the rear lower limb is flexed, the center of gravity is on the hind foot, and the exhale is also maintained for 10 s, and finally restored to the initial preparation stage posture.
Action 5	Put his hands in front of the chest, and then flex his knee joint with inhalation (the range of flexion angle is larger than any other movement), put hands on the outside of the knee joint, holding for 2 s, and keep the eyes on the ground 3 m ahead; Then exhale, straighten the knee joint, close the eyes, feeling the position of the knee joint.

numbers in opaque envelopes, marked it with time and signature, then unified it to the research coordinator. The research coordinator was responsible for directly recruiting potential subjects and randomly grouping them. Physical function assessors and data managers were unaware of the treatment assignments during enrollment and follow-up observations. All statistical analyses were performed with a maintained masking.

Interventions

Yijinjing Qigong Exercise (YJJQE) and STE ran concurrently to minimize seasonal influences on disease activity. We encouraged participants to maintain their regular daily activities and to not start any new exercise programs. Both groups received educational information about the daily precautions, the knowledge of the physiology and pathology of KOA, and the importance of physical activity and home practice. A 12-week intervention program, with a frequency of twice a week, was provided to patients with KOA. Each exercise session included a 5 min warm-up, a 30 min practice, and a 5 min cool-down period. The intervention protocol included three distinctive phases, with the first phase (Weeks 1–2) focusing on fundamental principles, movement techniques, and safety precautions. The second phase (Weeks 3–4) focused on learning and practicing forms with their associated movements. The third phase (Weeks 5–12) emphasized completion of the family exercise plan independently by instructors to review video and homework materials. The instructors were required to have more than 5 years of professional experience. Training intensity was assessed using the modified Borg Fatigue Rating Scale, with a score of $\geq$5 as qualified (15).

YJJQE Group

The exercise protocol consists of five Qigong operation processes compiled by the State Sports General Administration of China (16); the specific action characteristics of which are shown in **Table 1**. The overall training protocol followed an easy-to-difficult progression that focused on the center of the body mass, shift of garment, moderate knee flexion, extension and rotation movement, and coupled with breathing exercises, generally at the movement of knee flexion with inhalation. The entire YJJQE movements were closely integrated with rhythmic breathing and mindfulness meditation of scanning awareness of the knee movement (**Figure 1**).

STE Group

The prescription of STE consisting of quadriceps training and neuromuscular training is shown in **Table 2**. The five specific items of the program include lower limb flexion and extension while in supine position, lower limb flexion and extension while in prone position, sit and stand test training, alternating one-legged stair support tasks, and static squatting training against the wall, as recommended by the guideline (17) (**Figure 2**).

Outcome Measurements

All outcomes are collected at the baseline and at the end of the 12-week intervention period by the researchers.

Primary Outcome Measurement

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

It mainly includes three aspects, namely, pain, stiffness, and joint function to evaluate the structure and functional state of the knee joint. This approach is widely used in clinical evaluation of KOA symptoms with high reliability and validity (18).

Secondary Outcome Measurement

Secondary outcome measures include pain degree, quality of life, joint function, psychological evaluation, kinetic, and kinematic of human gait.

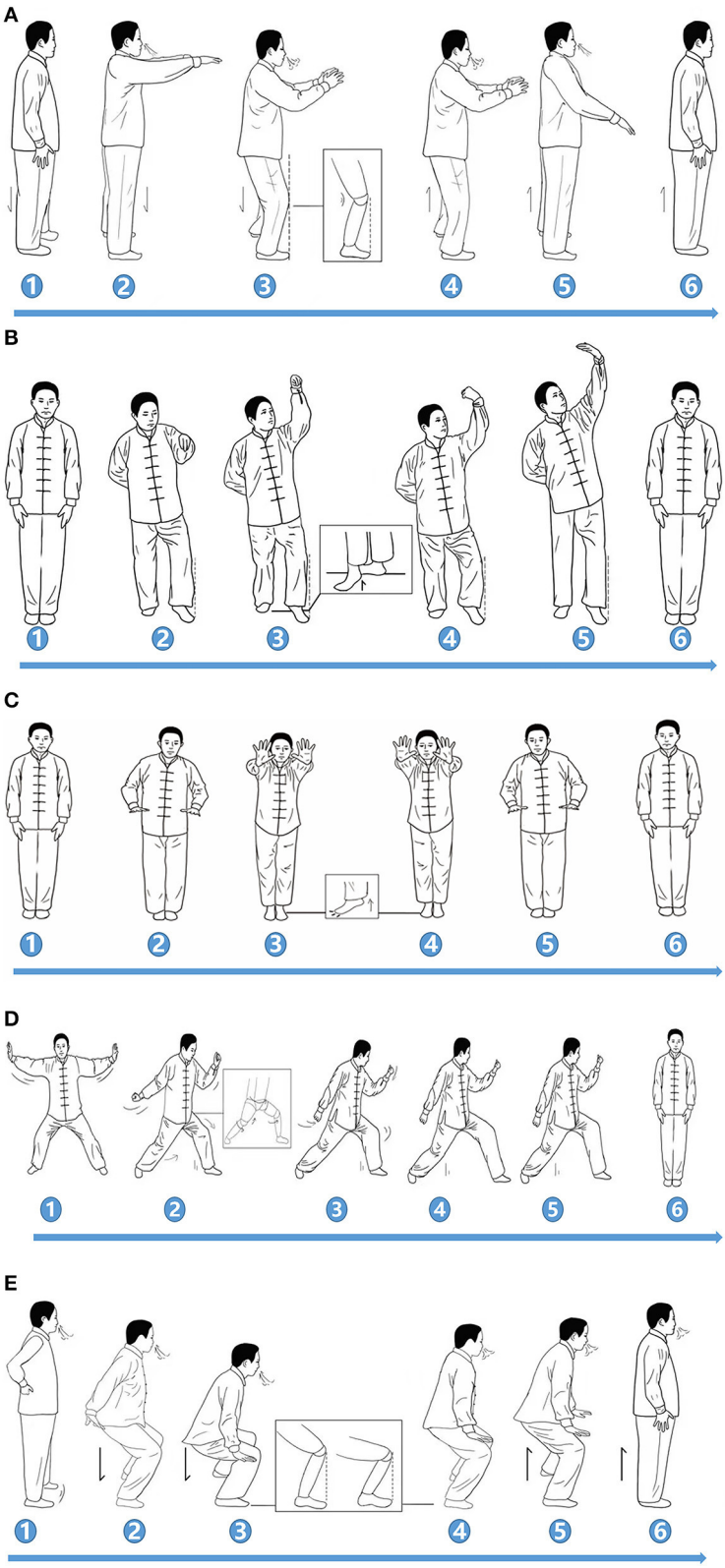


FIGURE 1 | Demonstration of YJJQE. The figure was a schematic diagram of five actions, mainly including knee flexion, timing of exhalation and inhalation, and the direction of eye observation. **(A)** Movement: Place both elbow joints flexed in front of the chest, Bilateral flexion (2,3), and extension (4,5) of the knee joint. Breathing

(Continued)

FIGURE 1 | rhythm: Inhalation (2,3), Exhalation (4,5). Meditation: Staring at the floor 3 m ahead (2,3), focus on the position of the knee joint (4,5). **(B)** Movement: Extend one side of the upper limb to 45° outside of the head, Standing on one leg with knee flexed (2,3), with extended (4,5). Breathing rhythm: Inhalation (2,3), Exhalation (4,5). Meditation: Staring at the raised palm (2,3), focus on the position of the knee joint (4,5). **(C)** Movement: Both heels off the ground, toes grasping, both arms extended forward (2,3). Both heels fall to the ground with both upper limbs flexed backwards (4,5). Breathing rhythm: Inhalation (2,3), Exhalation (4,5). Meditation: Staring at the floor 3 m ahead (2,3), focus on the position of the knee joint (4,5). **(D)** Movement: Lateral lunge, center of gravity forward foot (2,3), Lateral lunge, the center of gravity moves backward and the hip joint rotates outward (4,5). Breathing rhythm: Inhalation (2,3), Exhalation (4,5). Meditation: Staring at the floor 3 m ahead (2,3), focus on the position of the knee joint (4,5). **(E)** Movement: Press both hands down on both sides of the knee joint with knee flexion (maximum Angle) (2,3), with knee extension flexion (maximum Angle) (4,5). Breathing rhythm: Inhalation (2,3), Exhalation (4,5). Meditation: Staring at the floor 3 m ahead (2,3), focus on the position of the knee joint (4,5).

TABLE 2 | Details of the operation of stretching training exercise (STE).

Sequence of actions	Action details
Action 1	The subjects are seated on the ground with both upper limbs supporting the ground for balance, and both lower limbs are placed horizontally in front of the ground. Then, the knee joint of one lower limb slowly centripetal flexed to 90°, held for 1–2 s, and then returned to the initial position. Contralateral leg stretching is the same.
Action 2	Subjects are in prone position with both elbows supporting their entire body weight. Both lower limbs are extended backward to the extreme position. Then one lower limb is supported and the opposite lower limb is extended backward and upward.
Action 3	Subjects performed the sit-stand alternating task with the help of a chair.
Action 4	Subjects performed alternating one-legged stair support tasks
Action 5	Subject's back is pressed against the wall to maintain static squat task, knee flexion is about 120°

Visual Analog Scale

The visual analog scale (VAS) is a 10-point scale selected to quantitatively measure the level of osteoarthritis pain during the study, for which 0 indicates "no pain," while 10 represents "unbearable pain" (19).

Short-Form 36 Item Health Survey Questionnaire (SF-36)

The SF-36 scale provides a comprehensive assessment of the overall quality of life of patients with KOA, which can be divided into two categories: physical component summary (PCS) and mental component summary (MCS), in accordance with the item attributes. The PCS score is the average of the scores of the first four dimensions (physiological function, physical function, physical pain, and general health) added together, while MCS is the average of the scores of the last four dimensions (emotional function, social function, mental health, and vitality) (20).

Beck Depression Inventory

Beck Depression Inventory (BDI) consists of a 21-question and validated self-evaluation scale tool used to measure the severity of depressive symptoms (21).

Perceived Stress Scale

Perceived Stress Scale (PSS) is mainly composed of 14 questions, a validated self-evaluation tool used to measure the severity of stress; the higher score reflects the increasing severity of symptoms (22).

Berg Balance Scale

The balance of the patients is mainly measured by evaluating the performance in 14 functional tasks including the following: from sitting to standing test, standing without support, circle test, step test, and standing on one foot (23).

Gait Analysis

Gait analysis could be used to realize the kinematics and dynamics of the lower limbs of patients with KOA; it can reflect the pathomechanical mechanism of patients (24). The following are the test procedures: (1) The participants were required to walk on a 10-m walkway in the laboratory, with three one-way walking tasks for each test. (2) The 3D marker trajectories were recorded at 100 Hz using a Vicon 16-camera MX13+ motion system (Vicon, Oxford Metrics Ltd., Oxford, UK). (3) A total of 28 marking points were pasted for body surface marking according to the anatomical position specified by the pyCGM2-LowerLimbCGM23 model. (4) Two force platforms (1200 Hz, Advanced 130Mechanical Technology, Inc., Watertown, MA, USA) were used to collect 3D kinematic data using Vicon Nexus software (Vicon Motion Analysis, Inc., Oxford, UK).

Safety Evaluation

Adverse events were recorded by participants through a case report form, defined as any problem they believed to be caused by an exercise program that required seeking treatment and/or that lasted more than 3 days, while drug (pain medications for KOA) combinations were recorded.

Sample Size Calculation

The sample size was calculated using the WOMAC pain scale as the primary outcome measurement. Previous research (25) showed that the mean value and standard deviation of the control group were 9.37 and 5.23, respectively, whereas the mean value and standard deviation of the intervention group were 5.15 and 3.24, respectively. Supposed that $\alpha = 0.05$ and $\beta = 0.10$ and considering 20% rate of dropping out, the sample size was calculated according to the calculation formula. In the end, a total of 50 cases needed to be recruited, with 25 cases in each group.

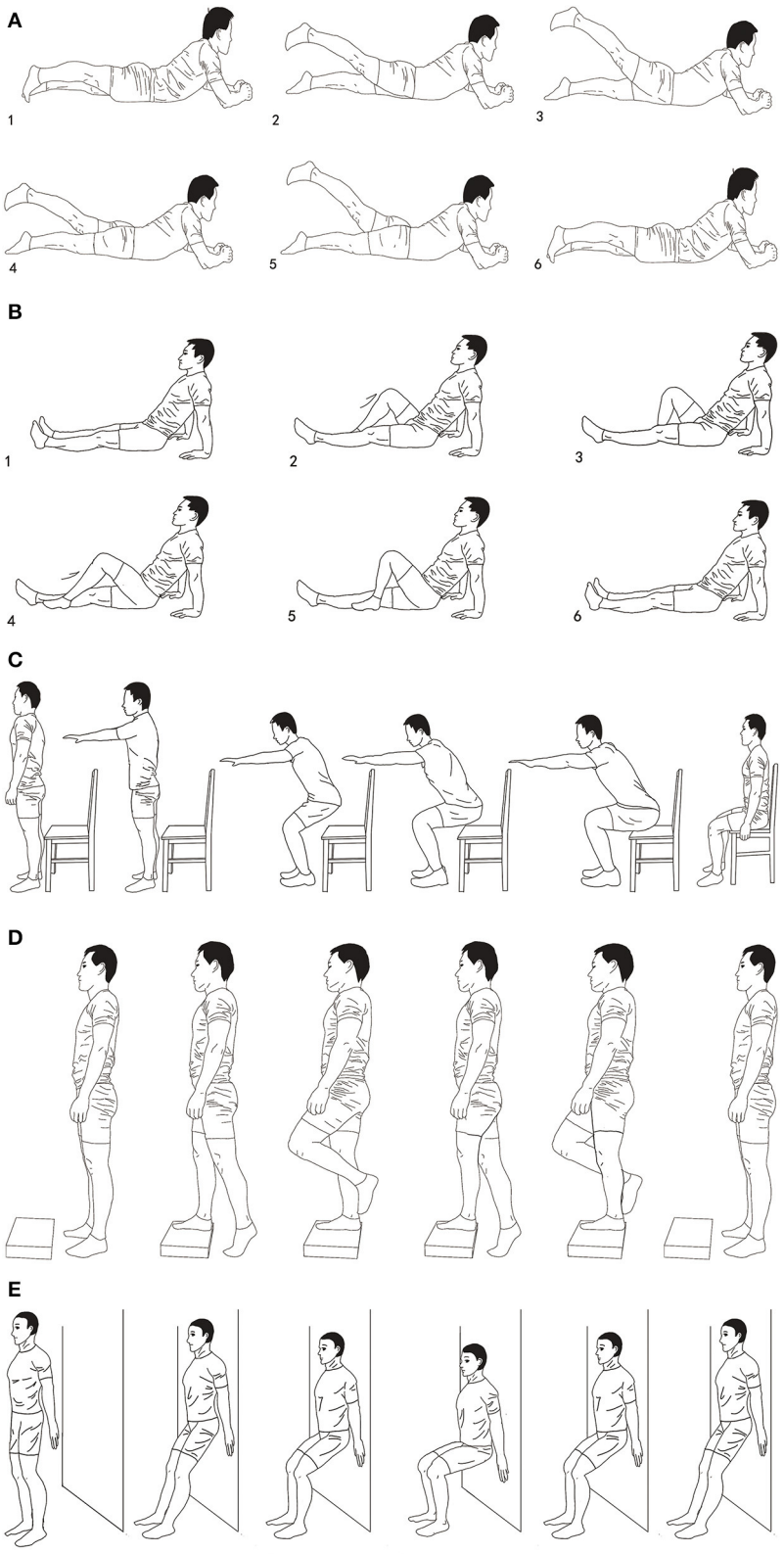


FIGURE 2 | Demonstration of stretching training exercise (STE). The figure mainly described the stretching exercise flow of knee joint flexion and extension in different postures. **(A)** Lower limb flexion and extension in supine position, **(B)** lower limb flexion and extension in prone position, **(C)** sit and stand test training, **(D)** alternating one-legged stair support tasks, **(E)** static squatting training against the wall.

TABLE 3 | Demographic and clinical characteristics of the YJJQE and STE groups*.

Characteristic	YJJQE group ($n = 25$)	STE group ($n = 25$)	*P*
Age, years	55.76 ± 8.37	53.40 ± 10.66	0.38
Height, cm	163 ± 6.84	166 ± 7.14	0.82
Body mass, kg	62.8 ± 10.49	64 ± 10.48	0.69
Body mass index, kg/m^2	23.5 ± 3.23	22.9 ± 2.98	0.51
Males/Females (n)	4/21	9/16	0.107
Exercise compliance (number of completions, n)	76.56 ± 4.79	75.28 ± 5.43	0.382
Manual labor/non-manual labor (n)			
Current pain medication use, n (%)[&]	17 (68%)	18 (72%)	0.556
Non-steroidal anti-inflammatory drugs	14 (56%)	17 (72%)	0.239
Topical anti-inflammatory drugs	14 (56%)	15 (64%)	0.733
Adverse events	6 (24%)	12 (48%)	0.04

**Indicated values are the mean ± SD and P < 0.05 was considered statistically significant difference. &: at any time; Adverse events were defined as any treatment-related problem that lasted for 3 days. YJJQE, Yijinjing Qigong Exercise; ST, Stretching Training Exercise.*

Statistical Analyses

SPSS25.0 statistical software was used for statistical analysis by the independent party who was blinded to the group allocation. The *P*-values <0.05 were considered significant. Shapiro–Wilk test was used to judge the normality of the data, and then the mean, standard deviation, maximum, minimum, median, credible interval, and frequency (composition ratio) were obtained. The primary result analysis would be an intention-to-treat analysis, where all participants were analyzed in the group and the missing data were imputed for three patients in the YJJQ group, and also for four patients in the STE group, using single mean or median interpolation. For continuous outcome measures, ANCOVA was used to adjust baseline outcome values to compare differences in mean change between groups (follow-up minus baseline). Results are presented as estimated differences with 95% confidence intervals (95% CIs). The likelihood of improvement in pain and function was compared between groups using log-binomial regression. Results are presented as relative risks with 95% CIs. Multivariate analysis was used to adjust for confounding factors.

RESULTS

Among the 125 participants, 75 (60%) did not satisfy the inclusion criteria or were unwilling to participate in the clinical trial. A total of 50 subjects with KOA were randomly assigned in a 1:1 ratio to the YJJQE group and to the STE group. The result showed no difference between the two groups in terms of demographic and characteristics of baseline data ($P > 0.05$, **Table 3**). The entire trail flow is shown in **Figure 3**, where 43 patients in the two groups completed the entire procedure while seven patients dropped out; three and four cases were disqualified in the YIIQE group and STE group, respectively, due to worsening symptoms. All participants attended at least 68 compliance diary sessions, and 88% of the participants attended all sessions; the data were comparable between groups, as shown in **Table 3**. Use of pain medications was similar across groups, without serious safety issues on either exercise regimen. However, generally, minor and transient problems were reported by some participants in the STE group [$n = 12$ (48%) participants] than in the YJJQE group [$n = 6$ (24%), $p = 0.04$] as increased muscle soreness [15 (60%) vs. 10 (40%)] in each group, respectively.

Between groups, albeit there were no differences between the YJJQE and STE groups for changes in the WOMAC pain score [mean difference 1.16 units (95% CI −0.46, 2.78)], WOMAC stiffness score [mean difference 0.2 units (95% CI −0.72, 1.12)], or WOMAC function score (0.32 units; −3.2, 3.84), no evidence of between-group differences for changes in any of the secondary outcomes was found, except the MCS score, BDI score, or PSS score, where the YJJQE group improved the unit values more significantly ($P = 0.002$, $P = 0.001$, and $P = 0.026$, **Table 4**). The application of the linear regression to adjust gender factors has shown consistent results (**Additional file1**). Also, no significant difference was found in the improvement of overall pain and dysfunction between the two groups. Improvement in pain was reported by 17 (68%) of 25 patients in the YJJQE group and 15 (60%) of 25 patients in the STE group (relative risk 1.41 [95% CI 0.44, 4.52], $p = 0.56$). Improvement in function was reported by 13 (52%) of 25 patients in the YJJQE group and 15 (60%) of 25 patients in the STE group (relative risk 0.72 [95% CI 0.23, 2.21], $P = 0.57$).

DISCUSSION

Chronic pain of KOA often coexists with symptoms of anxiety and depression; it is a neuroscience problem that needs to be solved worldwide (26). The present study has focused on the effects of YJJQE on the pain, quality of life, and function for patients with KOA. This research showed the evidence that YJJQE, a mind-body exercise therapy, may potentially provide benefits over those of STE for the evaluation of mood disorders. Evidence of systematic review for Qigong has shown to improve depression (27, 28), and this study provided corresponding evidence for YJJQE. This finding might benefit from the fact that psychosomatic therapy has the dual mechanism of exercise and meditation that can relieve KOA pain and mood disorders (29, 30). The underlying mechanism that physical exercise, combined with continuous cognitive challenge training, can maintain a new neuron pool experiences, more complex cognitive tasks, and even recruits new neurons to improve brain function (31). A functional magnetic resonance study has shown that the functional connectivity of dorsolateral prefrontal cortex with left hippocampus and amygdala was enhanced in Qigong group. Therefore, the psychosomatic therapy can regulate the default network, amygdala, and also reward circuitry of emotion-related brain regions, while focusing on movement posture (32). Furthermore, the results showed that YJJQE and STE led to similar improvements in the WOMAC pain and function

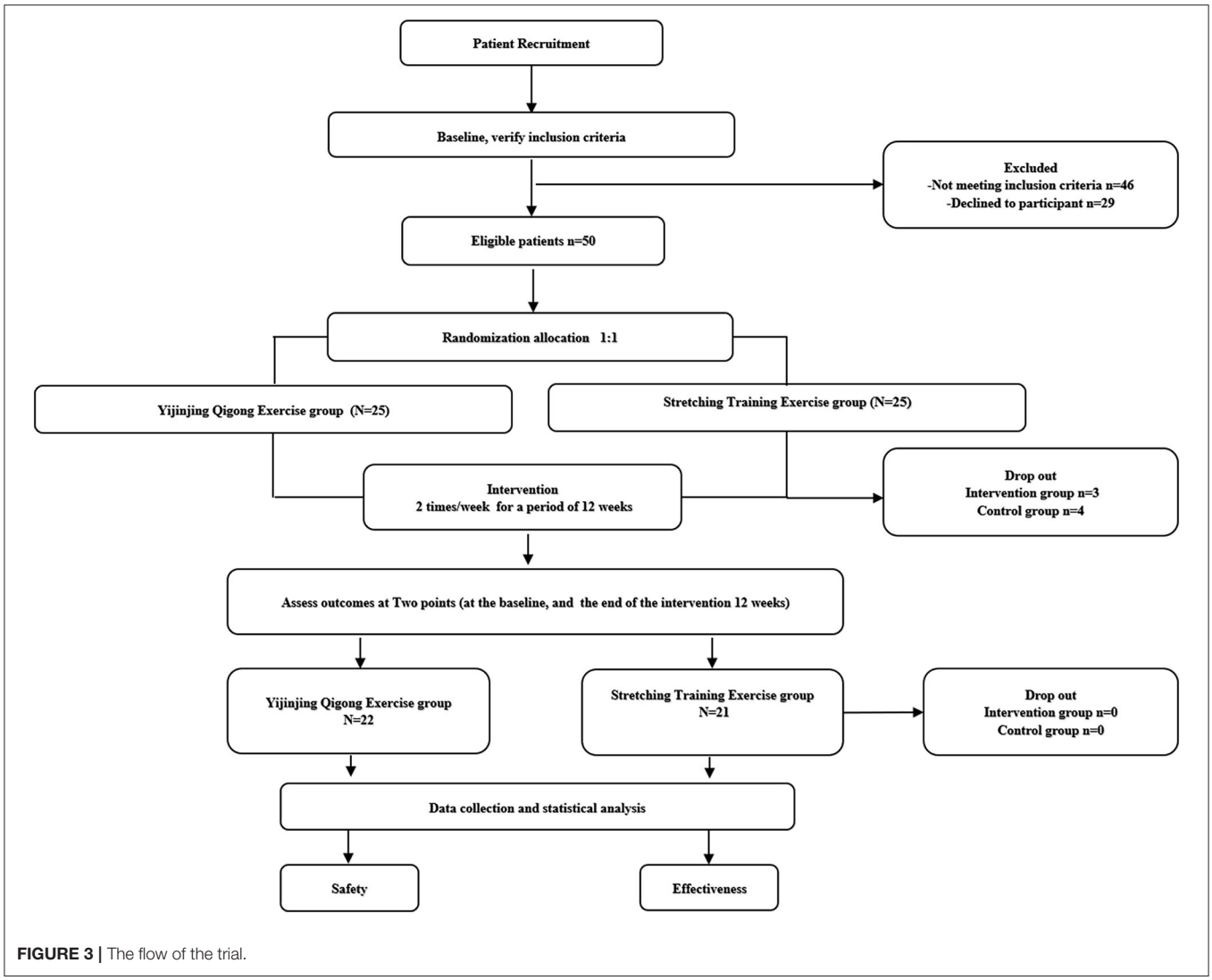


FIGURE 3 | The flow of the trial.

over 12 weeks. The five movements that adopted YJJQE can exercise the quadriceps muscle strength, improving the balance control ability and the proprioception, and is consistent with the previous results of traditional Qigong exercise (33). We have previously launched the clinical application of Taijiquan Qigong in elderly people with KOA, and the results showed that it can improve proprioception, knee motion, and pain symptom (25, 34, 35). The YJJQE movement operation is easier to learn and promote than the Taijiquan studies. In addition, a combination of quadriceps and neuromuscular stretching program was used as a control intervention, which was commonly prescribed for patients with KOA because it can reduce pain and improve function with a series of dynamic maneuvers of increased complexity (36, 37). Gait characteristics in KOA patients were pathologically abnormal in speed and in other spatiotemporal parameters (38). This study confirmed that YJJQE could improve the walking speed and restore the trend of normal gait, and also further kinematic and kinetic mechanisms continue to be published. Although no serious adverse reactions occurred, the STE group experienced more muscle soreness, where the dosage control in exercise prescription should be investigated in the follow-up study. Advantages of this study included a randomized controlled design and attention to key methodological features to compare the clinical efficacy of YJJQE and STE in patients with KOA. However, there are some limitations in this experiment. The physical therapists cannot be easily grouped blindly, but we asked the therapist to intervene with both groups, and the guidance was designed in advance to ensure the homogeneity of the therapist and intervention. We did not have a no-exercise control group and no significant difference in the primary outcome measurement, thus, between-group exercise effects should be interpreted with caution. The subjects were also followed up for 3 months, but the finding is not covered in this report. Although YJJQE can provide certain clinical evidence, it still cannot recommend specific exercise prescription dose.

TABLE 4 | Outcome measures in the YJJQE and STE groups*.

Outcome	Week 0		Week 12		Within-group difference, week 12 minus week 0, mean (95% CI)#		Between-group difference, YJJQE minus STE, mean (95% CI)#
	YJJQE (*N* = 25)	STE (*N* = 25)	YJJQE (*N* = 22)	STE (*N* = 21)	YJJQE (*N* = 22)	STE (*N* = 21)	
WOMAC pain score (range 0–50)	24.24 ± 3.07	23.68 ± 2.26	11.6 ± 1.44	12.2 ± 1.38	12.64 (11.32–13.96)	11.48 (10.38–12.57)	(1.16) (−0.46–2.78)
WOMAC stiffness score (range 0–20)	13.08 ± 1.22	13.72 ± 1.74	6.16 ± 1.49	7 ± 0.81	6.32 (5.66–6.98)	7.84 (6.95–8.73)	0.2 (−0.72–1.12)
WOMAC joint function score (range 0–170)	81.2 ± 6.27	79.84 ± 3.84	64.36 ± 5.13	63.32 ± 3.93	16.84 (14.53–19.16)	16.5 (14.81–18.22)	0.32 (−3.2–3.84)
VAS score for pain on walking	6.8 ± 0.71	7.08 ± 0.64	3.4 ± 0.91	2.96 ± 0.97	3.68 (3.25–4.10)	3.84 (3.34–4.34)	(−0.16) (−0.8–0.51)
MCS score	31.00 ± 6.38	32.75 ± 6.05	59.21 ± 9.04	47.08 ± 7.65	34.58 (30.22–38.95)	23.96 (20.15–27.78)	(−10.63) & [−17.07–(−4.19)]
PCS score	24.62 ± 6.40	23.12 ± 3.97	53.14 ± 6.64	54.61 ± 4.64	22.13 (18.78–25.49)	21.85 (19.13–24.57)	(−0.27) (−4.3–3.8)
BDI score	17.32 ± 2.15	18.48 ± 4.13	8.72 ± 1.42	13.4 ± 2.10	8.6 (7.6–9.5)	5.08 (3.4–6.8)	3.52& (1.59–5.44)
PSS score	44.64 ± 1.57	45.36 ± 1.52	40.48 ± 1.61	42.92 ± 2.1	4.16 (3.07–5.24)	2.44 (1.36–3.51)	1.72& (0.22–3.21)
BBS score	36.48 ± 2.04	35.84 ± 1.17	40.4 ± 3.20	39.2 ± 3.46	3.92 (2.52–5.31)	3.36 (2.1–4.59)	(−0.56) (−1.72–0.6)
Stride velocity (m/s)	0.71 ± 0.10	0.72 ± 0.11	1.21 ± 0.11	1.08 ± 0.09	0.49 (0.47–0.51)	0.5 (0.43–0.57)	0.003 (−0.06–0.07)
Stride length (m)	0.59 ± 0.04	0.57 ± 0.04	0.64 ± 0.03	0.64 ± 0.00	0.04 (0.02–0.07)	0.06 (0.04–0.08)	0.11 (0–0.02)
Stance phase time (s)	0.31 ± 0.05	0.31 ± 0.05	0.25 ± 0.09	0.26 ± 0.04	0.06 (0.02–0.1)	0.04 (0.01–0.08)	0.01 (−0.04–0.72)
Swing phase time (s)	0.36 ± 0.02	0.35 ± 0.06	0.38 ± 0.07	0.40 ± 0.06	0.01 (−0.05–0.01)	0.04 (−0.08–0)	0.02 (−0.02–0.06)

**Indicated values are the mean ± SD. 95% CI, 95% confidence interval; &: P < 0.05; #: Adjusted for baseline values. VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; MCS, Mental Component Summary; PCS, Physical Component Summary; BDI, Beck Depression Inventory; PSS, Perceived Stress Scale; BBS, Berg Balance Scale.*

CONCLUSION

After 12 weeks of regular exercise therapy with YJJQE, there were no significant difference between the two groups of the primary outcome measurement (WOMAC) score, in other words, the effect of relieving pain and of improving dysfunction was the same as STE. However, the secondary outcomes showed an advantage over STE on the improvement of mood disorders, such as anxiety, depression, and mental health score.

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Yue Yang Hospital of Integrated Traditional Chinese and Western Medicine affiliated with Shanghai University of Traditional Chinese Medicine. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SZ, GG, XL, FY, ZW, QZ, and MF drafted, reviewed, and revised the manuscript. QZ and MF managed the methodology of the study. 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/fmed.2021.792436/full#supplementary-material

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SYSTEMATIC REVIEW
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Association of Novel Androgen Receptor Axis-Targeted Therapies With Diarrhea in Patients With Prostate Cancer: A Bayesian Network Analysis

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Objective: To perform a systematic review and network meta-analysis to characterize the effect of novel androgen receptor axis-target (ARAT) agents on diarrhea and constipation.

Methods: We searched the Pubmed, Web of Science, and ClinicalTrials.gov up to September 2021 for phase 3 randomized controlled trials (RCTs) of patients receiving novel ARAT agents for prostate cancer (CaP). A Cochrane risk-of-bias tool was used to assess trial quality. The primary outcomes were risk ratio (*RR*) of any-grade diarrhea and constipation for patients receiving ARAT treatment. *RR*s of competing treatments were evaluated by pairwise and Bayesian network meta-analysis.

Results: In this study, 13 trials with 15,117 participants comparing 5 treatments (abiraterone, enzalutamide, apalutamide, darolutamide, and placebo) were identified. Use of novel ARAT agents was associated with a significant increased risk of any-grade diarrhea (*RR* = 1.30, 95% *CI* [1.16, 1.44]). As for subgroup analysis, abiraterone, enzalutamide, and apalutamide were all associated with significant increased risk of any-grade diarrhea (abiraterone: *RR* = 1.40, 95% *CI* [1.09, 1.81]; enzalutamide: *RR* = 1.17, 95% *CI* [1.02, 1.35]; apalutamide: RR = 1.35, 95% *CI* [1.03, 1.76]). Based on Bayesian modeling, abiraterone and enzalutamide showed the highest and lowest probability to rank first in terms of increasing risk of any-grade diarrhea. There were no significant differences of risk in any-grade constipation, grade 3 or greater diarrhea, and constipation between ARAT and control group.

Conclusion: The present study indicates that the use of novel ARAT agents is associated with a significantly higher risk of diarrhea. Across the four agents, abiraterone may relate to the highest risk of diarrhea among patients with metastatic hormone sensitive prostate cancer (mHSPC) and castration-resistant prostate cancer (CRPC).

Keywords: novel androgen receptor axis-targeted therapies, diarrhea, constipation, prostate cancer, network meta-analysis

INTRODUCTION

Prostate cancer (CaP) is the most common cancer in men, which accounts for 26% of diagnoses in the United States in 2021 (1). Androgen deprivation therapy (ADT) remains the mainstay of treatments in patients with advanced CaP (2). However, almost all patients invariably developed from hormone sensitive prostate cancer (HSPC) to castration-resistant prostate cancer (CRPC) (3). In recent years, several novel androgen receptor axis-targeted (ARAT) agents, such as abiraterone (Abi), enzalutamide (Enz), apalutamide (Apa), and darolutamide (Dar), were developed to further inhibit the AR signaling in patients with CRPC. Additionally, five large randomized controlled trials (RCTs) indicates that the addition of Abi, Enz, or Apa to ADT in men with metastatic HSPC (mHSPC) could significantly improve overall survival and progression-free survival compared with ADT alone (4–8).

Improved prognosis has created growing needs to address the unique health issues facing CaP survivors that result from CaP, its treatment, and related comorbid conditions. Previous studies have demonstrated that gastrointestinal (GI) complications, such as diarrhea and constipation, are one of persistent burdens for CaP survivors treated with ADT (9–11). Although the mechanisms associated with GI complications in CaP survivors are poorly clarified, available evidence indicate that a dysbiotic composition of GI microbiota may mediate GI complications in CaP survivors (12, 13). Furthermore, there is emerging evidence that circulating androgen levels and castration can affect the composition of GI microbiota (14–16). Recently, Sfanos et al. demonstrated that oral hormonal therapies, such as Abi and Enz, for CaP could alter the intestinal bacterial composition of fecal samples from rectal swabs (17). Furthermore, radiotherapy, chemotherapy, and immunotherapy have been demonstrated to induce dysbiosis that was associated with treatment toxicities, such as diarrhea (17, 18). It could be hypothesized that novel ARAT agents might further impact the function of GI and cause GI complications through altering composition of the GI microbiome. However, a paucity of research regarding this issue exists.

This study aimed to determine the effect of novel ARAT agents on GI complications utilizing the reconstructed clinical data derived from phase 3 RCTs to inform decision-making. As most of included trials only report part of GI complications, we focus on two of the most reported complications which are diarrhea and constipation. Additionally, diarrhea and constipation are both most concerned GI complications of cancer therapies.

METHODS

Search Strategy and Selection Criteria

We conducted a systematic review and network meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline and its extension for network meta-analysis (19, 20). We searched the Pubmed, Web of Science, and ClinicalTrials.gov up to September 2021. The following searching terms were used: ["Prostate Cancer"] AND ["Abiraterone" OR "Enzalutamide" OR "Apalutamide" OR "Darolutamide"]. We performed the study eligibility using the population, intervention, comparator, outcome, and study (PICOS) approach: (P) studies focused on patients with a diagnosis of CaP; (I) treated with Abi, Enz, Apa, or Dar; (C) in which placebo was performed as a comparator; (O) reporting one or both of the following outcomes: diarrhea and constipation; (S) in phase 3, placebo-controlled, double-blind, and randomized trials.

Study Selection and Data Extraction

Two investigators independently conducted title and abstract selection and full-text review. The PRISMA flowchart about the selection process are displayed in **Figure 1**. Two reviewers extracted data from all included studies, such as author (year), sample size, age, cancer status, follow-up time, duration of treatment, and interested outcomes. Any disagreements were resolved by a third reviewer.

Outcomes

The primary outcomes of the present meta-analysis were risk ratio (*RR*) for any-grade diarrhea and constipation of patients receiving any types of novel ARAT agents compared with control group. The secondary outcomes included: (a) combined incidence of any-grade and grade 3 or greater diarrhea or constipation in the total ARAT group, ARAT subgroups (Abi, Enz, Apa, and Dar), and control groups; (b) RR for grade 3 or greater diarrhea and constipation of patients receiving any types of novel ARAT agents. Any-grade adverse events are defined as events from grade 1 to higher grades.

Risk of Bias Assessment

Risk of bias (RoB) was independently determined by two investigators using the Cochrane Collaboration's tool (version 2.0) (21). To assess the RoB, 5 domains were considered: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. If the study is judged to be at low RoB for all domains for a specific result, the overall RoB would be low. If at least one domain was judged to be at high RoB or multiple domains were judged to have some concerns for a specific result, the overall RoB would be high. Any disagreements were resolved by a third investigator.

Statistical Analysis

Risk ratio with 95% *CI*s were estimated for diarrhea and constipation using pairwise and network meta-analysis. The analysis was performed in two steps: first, pairwise meta-analysis was performed to assess a particular outcome. The Mantel–Haenszel (M–H) random-effects model was applied to pooled RRs for any-grade and grade 3 or greater diarrhea or constipation, given the expected heterogeneity within part of the evaluated trials. Heterogeneity across studies was formally tested for using chi-square ($p < 0.05$) and the I^2 statistic. Subgroup analysis was based on the different types of ARAT agents that patients received in intervention groups. Publication bias was evaluated utilizing the funnel plots and the Peters test of funnel

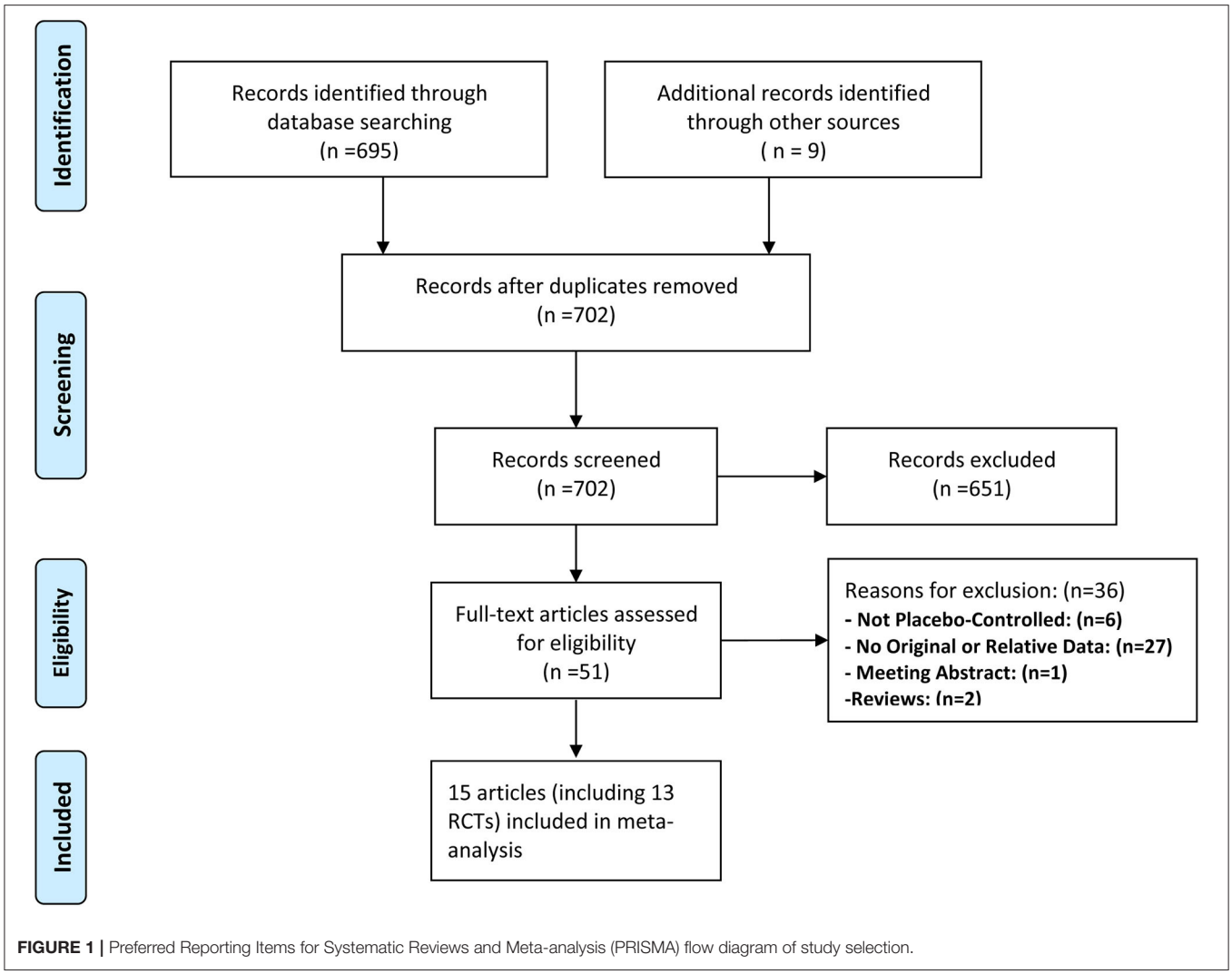


FIGURE 1 | Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram of study selection.

plot symmetry (22). Considering the different disease stages of our included studies, a subgroup analysis was performed for patients with mHSPC and mCRPC/nmCRPC. A $p < 0.05$ suggested significantly statistical risk of publication bias.

Second, Bayesian analyses were conducted for network meta-analysis with random-effects for any-grade diarrhea or constipation (23). To assess whether there was inconsistency between direct and indirect comparisons, we compared the random effects variances of consistency and inconsistency model for all the outcomes, which indicated similar random effects SD between the two models. Therefore, the results of consistency models were reported. Convergence is assessed using the Brooks-Gelman-Rubin method. This method compares within-chain and between-chain variance to calculate the potential scale reduction factor (PSRF). A PSRF close to 1 indicates that approximate convergence has been reached (24). There were 4 chains, initial values scaling was 2.5, tuning iterations were 20,000, simulation iterations were 50,000, and thinning interval was 10. For each iteration, the ranking of Abi, Enz, Apa, Dar, and placebo was determined using the RRs from that iteration. Surface under the cumulative ranking curve (SUCRA) was calculated from these rankings by summing the cumulative probabilities of all the ranks divided by the number of ranks minus 1 (25). This statistic has no known distribution and is a means of summarizing treatment rankings.

The significant level was $p < 0.05$ for statistical tests. All statistical analyses were performed and forest plots generated using the "gemtc," "rjags," "meta," and "metafor" packages from R 3.6.2 (R project) and Review Manager v5.2 software.

RESULTS

Study Selection and Network Geometry

A total of 702 unique records were screened for eligibility, of which 651 were excluded based on the evaluation of titles and abstracts. Full-text screening was assessed for 51 articles, eventually, 15 unique studies (such as 13 RCTs) fulfilled inclusion criteria (**Figure 1**).

In total, 13 trials comparing five treatments were assessed, including placebo, Abi, Enz, Apa, and Dar (**Table 1**). The well-connected network structure for both diarrhea and constipation are displayed in **Figures 2A,B**. The width of the lines represents the number of trials comparing each pair of treatments. The size of the circle represents the sample size in each arm. More details of numbers of trials and sample size of each treatment are presented in **Figure 2**.

Characteristics of Included Trials

Tables 1, **2** presented the characteristics of included studies. All 13 included trials were phase 3, double-blind, placebo-controlled, randomized studies published between 2011 and 2020, involving a total of 15,117 patients (6,484 in control group, 3,178 in Abi group, 3,173 in Enz group, 1,328 in Apa group, and 954 in Dar group). Median age of participants in ARAT and control group were both ranged from 67 to 74. Ten trials reported the related data of diarrhea, and all 13 trials displayed the data of constipation. There were 4, 3, 5, and 1 trials included patients diagnosed with mHSPC, nmCRPC, mCRPC, and CRPC, respectively. The median (range) duration of treatment was 16.6 (8.0–24.0) month in the ARAT group and 11.6 (3.0–18.3) month in the control group. For diarrhea, 6 trials were assessed with low overall RoB (60.0%) and 4 were judged as some concerns (40.0%). For constipation, the overall RoB was low in six trials (46.2%) and the remaining seven trials raised some concerns (53.8%) (**Table 2**). As for publication bias, statistical analysis of Peters test indicated no evidence of publication bias both in diarrhea and constipation (*p* were 0.82 and 0.63, respectively) (**Supplementary Figures 1**, **2**).

Safety Assessment

Incidence of Diarrhea and Constipation

In ARAT group, the reported any-grade diarrhea was 1,309 (17.8%) and that of grade 3 or greater diarrhea was 45 (0.5%). In the control group, the reported any-grade diarrhea was 756 (14.5%) and that of grade 3 or greater diarrhea was 24 (0.3%). The reported incidence of constipation in the ARAT group was 1,463 (16.9%) and that grade 3 or greater constipation was 28 (0.2%). The reported incidence of constipation in the control group was 991 (15.3%) and that grade 3 or greater constipation was 24 (0.2%) (**Table 3**). As for the reported incidence of any-grade diarrhea in groups of individual ARAT agents, Abi had the highest rate at 25.4% (95% *CI* [23.7–27.2%]), followed by Apa at 20.3% (95% *CI* [17.7%, 23.2%]), followed by Enz at 14.5% (95% *CI* [13.3%, 15.7%]), followed by Dar at 7.4% (95% *CI* [5.9%, 9.3%]) (**Supplementary Table 1**). Similarly, the highest rate of any-grade diarrhea in individual control groups was also Abi, followed by Apa, Enz, and Dar (**Supplementary Table 1**). As for the rate of any-grade constipation in groups of individual ARAT agents, Abi was associated with the highest rate at 22.3% (95% *CI* [20.8%, 23.7%]), followed by Enz at 17.5% (95% *CI* [16.2%, 18.9%]), Apa at 10.1% (95% *CI* [8.8%, 11.8%]), and Dar at 6.9% (95% *CI* [5.5%, 8.7%]) (**Supplementary Table 1**). The sequence of incidence of any-grade constipation in individual control groups was also similar with the sequence of ARAT groups (**Supplementary Table 1**).

TABLE 1 | Baseline characteristics of included studies.

References	Trial	Phase	Intervention	Patients, No.			Cancer status	Age, Median/Mean (Range/SD)		Duration of treatment, Median, mo	
				Total	Experimental	Control		Experimental	Control	Experimental	Control
Smith et al. (26)	SPARTAN	3	Apalutamide	1,201	803	398	nmCRPC	74 (48–94)	74 (52–97)	60.9%	29.9%
Fizazi et al. (27); Fizazi et al. (28)	ARAMIS	3	Darolutamide	1,508	954	554	nmCRPC	74 (48–95)	74 (50–92)	14.8	11.6
Sternberg et al. (29); Hussain et al. (30)	PROSPER	3	Enzalutamide	1,395	930	465	nmCRPC	74 (50–95)	73 (53–92)	18.4	11.1
Beer et al. (31)	PREVAIL	3	Enzalutamide	1,715	871	844	mCRPC	72 (43–93)	71 (42–93)	16.6	4.6
Chi et al. (8)	TITAN	3	Apalutamide	1,052	525	527	mHSPC	69 (45–94)	68 (43–90)	20.5	18.3
Armstrong et al. (7)	ARCHES	3	Enzalutamide	1,146	572	574	mHSPC	70 (46–92)	70 (42–92)	12.8	11.6
Fizazi et al. (5)	LATITUDE	3	Abiraterone	1,199	597	602	mHSPC	68 (38–89)	67 (33–92)	24	14
James et al. (4)	STAMPEDE	3	Abiraterone	1,908	948	960	mHSPC	67 (42–85)	67 (39–84)	23.7	NR
Ryan et al. (32)	COU-AA−302	3	Abiraterone	1,082	542	540	mCRPC	71 (44–95)	70 (44–90)	NR	NR
Scher et al. (33)	AFFIRM	3	Enzalutamide	1,199	800	399	CRPC	69 (41–92)	69 (49–89)	8.3	3.0
de Bono et al. (34)	COU-AA−301	3	Abiraterone	1,185	791	394	mCRPC	69 (42–95)	69 (39–90)	8	4
Ye et al. (35)	–	3	Abiraterone	313	157	156	mCRPC	69.7 (8.72)*	70.8 (8.64)*	3.8	3.4
Sun et al. (36)	–	3	Abiraterone	214	143	71	mCRPC	68.2 (8.30)*	67.7 (7.75)*	8.1	4.2

NO, Number; nmCRPC, nonmetastatic castration–resistant prostate cance; mCRPC, metastatic castration–resistant prostate cancer; mHSPC, metastatic hormone–sensitive prostate cancer; CRPC, castration–resistant prostate cancer; NR, Not Reported.
**Mean (SD).*

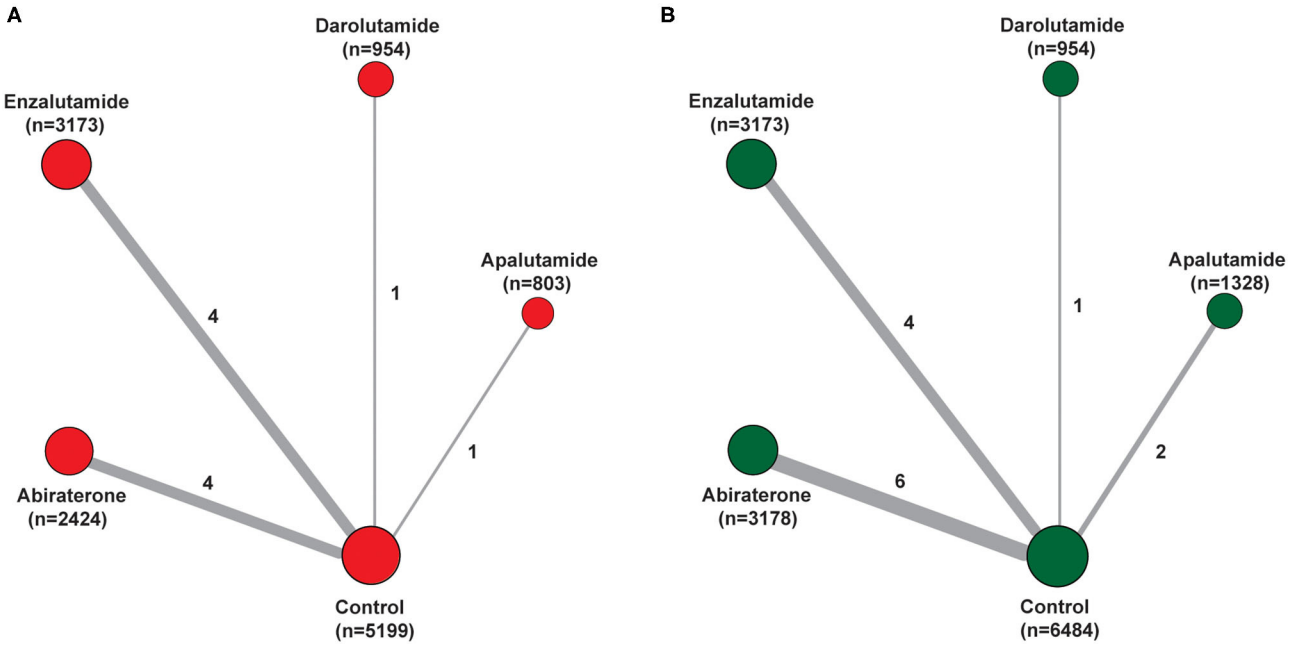


FIGURE 2 | Network of the comparisons for the Bayesian network meta-analysis. **(A)** Diarrhea; **(B)** constipation. The size of the nodes is proportional to the number of patients (in parentheses) randomized to receive the treatment. The width of the lines is proportional to the number of trials (beside the line) comparing the connected treatments.

Risk of Diarrhea

Pairwise meta-analysis indicated significantly increased risk of any-grade diarrhea for patients treated with novel ARAT agents compared with placebo (RR = 1.30, 95% CI [1.16, 1.44], I^2 = 32%) (**Table 3**). As for subgroup analysis, all the four novel ARAT agents had the potential to increase the risk of any-grade diarrhea, moreover, treated with Abi, Enz, and Apa could significantly increase the risk of any-grade diarrhea compared with placebo group (Abi vs. placebo: RR = 1.40, 95% CI [1.09, 1.81]; Enz vs. placebo: RR = 1.17, 95% CI [1.02, 1.35]; Apa vs. placebo: RR = 1.35, 95% CI [1.03, 1.76]; and Dar vs. placebo: RR = 1.33, 95% CI [0.88, 2.00]) (**Figure 3A**). As for the grade 3 or greater diarrhea, there was no significant difference between ARTA and placebo group (ARAT vs. placebo: RR = 1.24, 95% CI [0.73, 2.09], I^2 = 0%) (**Table 3**). Subgroup analysis indicated consistent results for risk of any-grade diarrhea between patients with mHSPC and mCRPC/nmCRPC (p = 0.321) (**Supplementary Table 2**).

As for network meta-analysis, Abi could significantly increase the risk of any-grade diarrhea compared with placebo (RR = 1.55, 95% CI [1.08, 2.13]) (**Table 4**). Although there were no significant differences, Enz, Apa, and Dar could also show the potential for increased risk of any-grade diarrhea (**Table 4**). Furthermore, risk of any-grade diarrhea among the four novel ARAT agents did not show significant difference (**Table 4**). Based on Bayesian modeling, Abi showed the highest probability to rank first, Apa and Dar displayed similar probability to rank first, and Enz showed lowest probability to rank first in terms of increasing risk of any-grade diarrhea (**Figure 4**). Last, we ranked the probability that each ARAT agents (Abi, Enz, Apa, and Dar) resulted in higher risk of diarrhea using the SUCRA. The SUCRA for Abi, Enz, Apa, Dar, and placebo were 76, 40, 64, 62, and 8% for risk of any-grade diarrhea, respectively.

Risk of Constipation

For the risk of constipation, the pairwise meta-analysis did not show significant difference both in any-grade and grade 3 or greater between ARAT and control group (**Table 3**). As for subgroup analysis, all the four agents could not significantly influence the risk of any-grade constipation compared with placebo (**Figure 3B**). Additionally, subgroup analysis suggested consistent results for risk of any-grade constipation between patients with mHSPC and mCRPC/nmCRPC (p = 0.992) (**Supplementary Table 2**).

Network meta-analysis showed consistent results with pairwise meta-analysis between ARAT and control group (**Table 4**). Similarly, risk of any-grade constipation among the four novel ARAT agents did not show significant difference (**Table 4**). Bayesian modeling showed that Enz had the highest probability to increase the risk of any-grade constipation (**Figure 4**). As for SUCRA, Abi, Enz, Apa, Dar, and placebo were 64, 77, 15, 56, and 38% for risk of any-grade constipation, respectively.

DISCUSSION

Across 13 RCTs, such as patients with CaP treated with novel ARAT agents, we found that the use of ARAT agents was associated with the risk of diarrhea. The use of ARAT agents

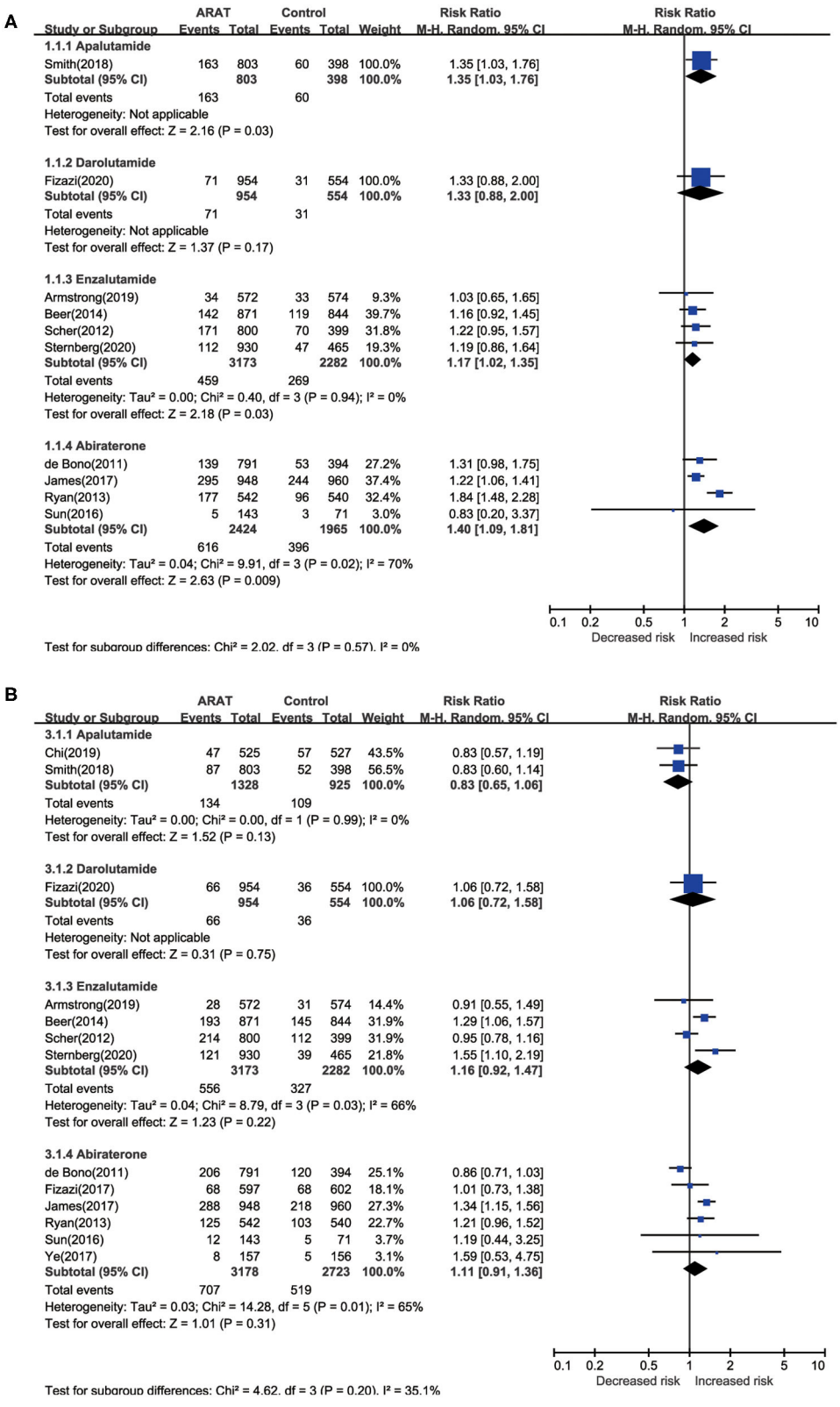


FIGURE 3 | Pairwise meta-analysis for risk of diarrhea and constipation among included ctudies. **(A)** Diarrhea; **(B)** constipation.

TABLE 2 | Risk of bias within trials.

Trial	R	D	Mi	Me	S	O
Diarrhea						
SPARTAN	Low	Low	Low	Low	Low	Low
ARAMIS	Low	Low	Low	Low	Low	Low
PROSPER	Low	Low	Low	Some concerns	Low	Some concerns
PREVAIL	Low	Low	Low	Low	Low	Low
ARCHES	Low	Low	Low	Low	Low	Low
STAMPEDE	Low	Low	Some concerns	Low	Low	Some concerns
COU-AA-302	Low	Low	Low	Some concerns	Low	Some concerns
AFFIRM	Low	Low	Low	Low	Low	Low
COU-AA-301	Low	Low	Low	Low	Low	Low
Sun et al. (36)	Low	Low	Low	Some concerns	Low	Some concerns
Constipation						
SPARTAN	Low	Low	Low	Low	Low	Low
ARAMIS	Low	Low	Low	Low	Low	Low
PROSPER	Low	Low	Low	Some concerns	Low	Some concerns
PREVAIL	Low	Low	Low	Low	Low	Low
TITAN	Low	Low	Low	Some concerns	Low	Some concerns
ARCHES	Low	Low	Low	Low	Low	Low
LATITUDE	Low	Low	Low	Some concerns	Low	Some concerns
STAMPEDE	Low	Low	Some concerns	Low	Low	Some concerns
COU-AA-302	Low	Low	Low	Some concerns	Low	Some concerns
AFFIRM	Low	Low	Low	Low	Low	Low
COU-AA-301	Low	Low	Low	Low	Low	Low
Ye et al. (35)	Low	Low	Low	Some concerns	Low	Some concerns
Sun et al. (36)	Low	Low	Low	Some concerns	Low	Some concerns

Risk of bias legend: R, Bias arising from the randomisation process; D, Bias due to deviations from intended interventions; Mi, Bias due to missing outcome data; Me, Bias in measurement of the outcome; S, Bias in selection of the reported result; O, Overall risk of bias.

TABLE 3 | Pooled analysis of ARAT use with diarrhea and constipation risk.

Adverse event	Experimental groups			Control groups			Pool estimate			
	Patients, No.	Adverse events, No.	Incidence (%)	Patients, No.	Adverse events, No.	Incidence (%)	Studies, No.	RR (95% CI)	*p* value	I^2
Diarrhea										
All grades	7,354	1,309	17.80	5,199	756	14.54	10	1.30 (1.16, 1.44)	<0.001	32%
Grade ≥3	7,354	45	0.61	5,199	23	0.44	10	1.24 (0.73, 2.09)	0.43	0%
Constipation										
All grades	8,633	1,463	16.94	6,484	991	15.28	13	1.08 (0.95, 1.22)	0.25	59%
Grade ≥3	8,458	28	0.33	6,328	24	0.38	12	0.84 (0.49, 1.46)	0.54	0%

No, Number; RR, Risk Ratio.

was associated with 1.30 times higher risk of diarrhea. As for individual ARAT agents, Abi, Enz, Apa, and Dar were associated with 1.40, 1.17, 1.35, and 1.33 times higher risk of diarrhea, respectively. There were no significant differences for risk of constipation between ARAT and control groups. Based on Bayesian modeling, Abi might be associated with highest risk of diarrhea, among the four ARAT agents.

The sequence of incidence for diarrhea and constipation among groups of individual ARAT agents might be caused by both the heterogeneity of participants and the effect of agents, which could be evidenced by similar sequence of incidence in individual control groups and different *RR* of each ARAT agents for risk of diarrhea. The present study highlighted several insights. First, we evidenced that novel ARAT agents could significantly increase the risk of diarrhea for patients with CaP based on data from phase 3, placebo-controlled, double-blind, and randomized trials. There were potential links between CaP and treatment

TABLE 4 | Network meta-analysis for RR of diarrhea (below diagonal) and constipation (above diagonal).

Abiraterone	1.15 (0.66, 1.99)	1.08 (0.51, 2.07)	0.96 (0.63, 1.52)	1.15 (0.87, 1.54)
1.08 (0.51, 2.15)	**Apalutamide**	0.93 (0.40, 2.15)	0.83 (0.47, 1.50)	1.00 (0.62, 1.60)
1.13 (0.53, 2.46)	1.06 (0.42, 2.72)	**Darolutamide**	0.90 (0.42, 1.95)	1.07 (0.54, 2.16)
1.30 (0.79, 2.06)	1.20 (0.60, 2.48)	1.13 (0.53, 2.42)	**Enzalutamide**	1.20 (0.86, 1.66)
1.55 (1.08, 2.13)	1.43 (0.77, 2.69)	1.36 (0.67, 2.67)	1.19 (0.85, 2.64)	**Control**

Bold values indicate statistically significant.

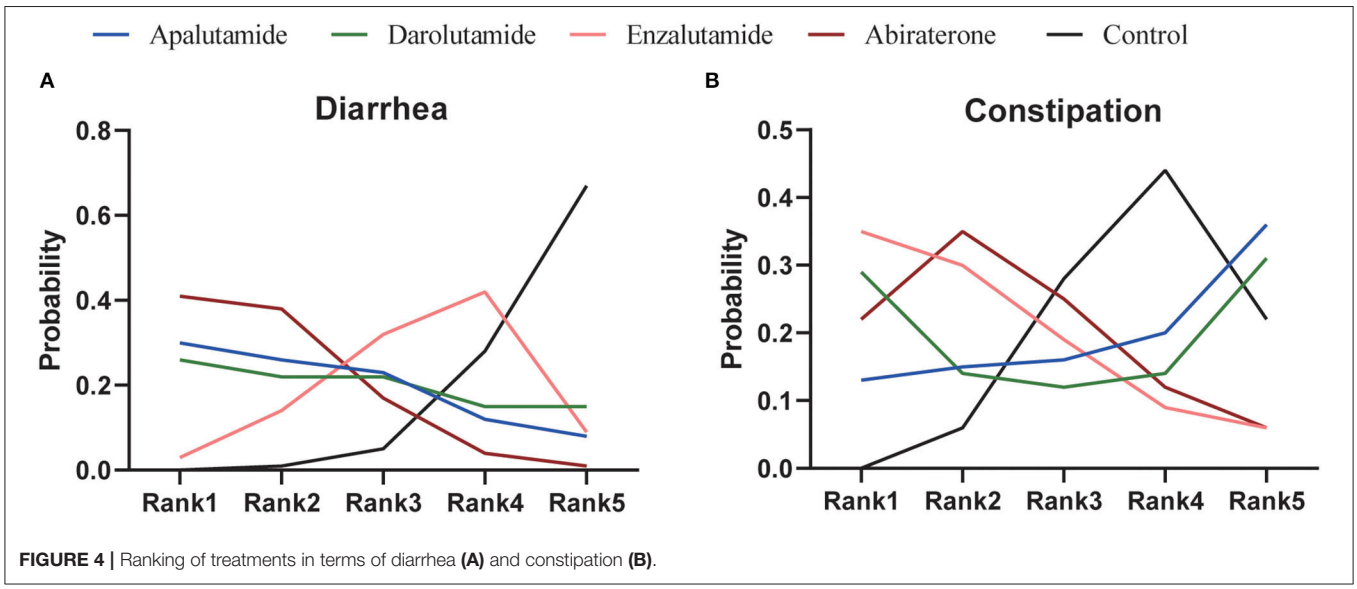


FIGURE 4 | Ranking of treatments in terms of diarrhea **(A)** and constipation **(B)**.

and increased inflammatory levels from GI dysbiosis (37). As mentioned, the components of GI microbiota could be affected by serum androgen levels and castration (14–16), and both Enz and Abi could alter the components of GI microbiota (17). Recently, Pernigoni et al. indicated that the GI microbiota could also provide an alternative source of androgen in patients and mice with CRPC (38). Therefore, our results indirectly evidenced the hypothesis that we mentioned previously.

Second, based on our results, we might highlight two potential interventions for diarrhea caused by novel ARAT gents, especially patients treated with Abi, which were probiotics and exercise. Many elderlies are less fit physiologically to withstand the effect of diarrhea on fluid balance and nutritional balance (39), therefore, it is necessary to intervene in the treatment-related diarrhea for the elderly. Previous studies have shown that probiotics supplements could modify the GI side effects induced by radiotherapy, chemotherapy, and immunotherapy, as the three treatments modality could induce GI dysbiosis and subsequently cause diarrhea, mucositis, and so on (40). Even though, probiotics supplements could enhance the action of chemotherapy drugs. Therefore, considering the high incidence and significant increased risk of diarrhea in patients receiving treatment of novel ARAT agents, it is necessary to explore the role of probiotics supplements in toxicity modification and treatment action of novel ARAT agents. Perhaps unsurprisingly, emerging evidence has suggested that exercise might exert a positive effect on the components of GI microbiota (41). The results of a meta-analysis included 14 RCTs supported a strong recommendation for supervised exercise therapy for improving disease-specific quality of life in patients receiving ADT (42). Excitedly, an ongoing single-blinded, two-armed, RCT was designed to explore the influence of a 3-month exercise program (3 days/week) for gut health in men receiving ADT (37).

Our study has some limitations. First, clinical consequences of diarrhea and constipation on therapy, and the use of potential interventions were not reported in our included studies. Therefore, the two potential interventions that we mentioned needs further investigations. Second, we could not conduct age-stratified or other subgroup analysis for risk of diarrhea or constipation, because the cut-off levels were different across trials and the included studies were not focused on reporting risk factors for diarrhea and constipation related to age or other valuables. Third, the duration of treatment was different across trials. The relatively short therapy duration for novel ARAT agents may bias against their long-term effectiveness estimation. Interestingly, meta-regression analysis regarding the duration of hormone therapy both for risk of diarrhea and constipation indicated that the duration of hormone therapy might not affect the stability of our present results ($p = 0.963$ and 0.062 for risk of diarrhea and constipation).

Fourth, there were no time-based data to calculate the diarrhea and constipation person-year incidence rates. Fifth, the present study only included 2 and 1 trials focused on Apa and Dar, therefore, it might need further update. Sixth, the present results are from network meta-analysis, therefore, prospective clinical trials regarding this issue are suggested in the future.

CONCLUSION

The present study indicates that the use of novel ARAT agents is associated with a significantly higher risk of diarrhea. Across the four agents, Abi may relate to the highest risk of diarrhea and Enz may relate to the lowest risk of diarrhea among patients with mHSPC and CRPC. Considering the high incidence and significantly increased risk of diarrhea in patients receiving novel ARAT agents, it is necessary to develop potential interventions regarding the novel ARAT agent-related diarrhea.

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

LY and SQ were responsible for the conception, design of the study, and obtained public funding. XX, HX, and SW did the analysis and interpreted the analysis. XL, XY, and KJ were responsible for the acquisition of data. XX, HX, SB, and HL wrote the first draft of the manuscript. KJ, SB, and LY interpreted the data and wrote the final version. All authors critically revised the article 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/fmed.2021.800823/full#supplementary-material

Supplementary Figure 1 | Funnel plot for the included studies of diarrhea.

Supplementary Figure 2 | Funnel plot for the included studies of constipation.

Supplementary Table 1 | Outcomes of reported diarrhea and constipation adverse events (AEs) in combined studies.

Supplementary Table 2 | Subgroup analysis of ARAT use with diarrhea and constipation risk.

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Metabolomics-Based Frailty Biomarkers in Older Chinese Adults

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Background/Objectives: Owing to accelerated population aging, health in older adults is becoming increasingly important. Frailty can reflect the health status and disease risks of older adults; however, appropriate biomarkers for early screening of frailty have not been identified. Here, we applied metabolomics to identify frailty biomarkers and potential pathogenic mechanisms of frailty.

Methods: Serum metabolic profiles from 25 frail and 49 non-frail (control) older adults were systematically investigated by liquid chromatography-mass spectrometry-based metabolomics.

Results: We identified 349 metabolites of 46 classes, with four increased and seven decreased metabolites in frail older adults. Pearson correlation analysis identified 11 and 21 metabolites that were positively and negatively correlated with grip strength, and 7 and 76 metabolites that were positively and negatively correlated with gait speed, respectively. Pathway analysis identified 10 metabolite sets and 13 pathways significantly associated with one or more frailty phenotype criteria.

Conclusion: These results revealed the metabolite characteristics of serum in frail older adults. Intermediates of carbohydrate metabolism (e.g., isocitrate, malate, fumarate, cis-aconitate, glucuronate, and pyruvate), saturated fatty acids (e.g., palmitic acid), unsaturated fatty acids (e.g., arachidonate and linoleic acid), and certain essential amino acids (e.g., tryptophan) may be candidate biomarkers for the early diagnosis of frailty. Mitochondrial function disorders, saturated fatty acid-mediated lipotoxicity, aberrant unsaturated fatty acid metabolism, and increased tryptophan degradation could be potential mechanisms of frailty.

Keywords: frailty, metabolomics, physical function, biomarker, older adults

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INTRODUCTION

Aging is an inevitable life process, characterized by a time-dependent decline in functional capacity and stress resistance associated with increased risks of morbidity and mortality (1). Preventing aging-related damage, disease, and disability in older adults has become a priority in the public health sector. However, the functional decline of an individual is only loosely consistent with the

advancement in chronological age (2). Frailty can better reflect the physiological status and disease risk of older adults than the chronological age (3). Therefore, the early screening of frailty is critical for personalized intervention in age-related diseases and the prevention of adverse outcomes. Given the lack of a unified definition for frailty, researchers commonly identify frailty using different assessment tools, such as the Fried frailty phenotype (4) and the frailty index (5). However, these assessment tools are not objective enough. Sensitive and specific biomarkers for frailty are urgently needed for more accurate identification in older adults (6).

Currently, studies on frailty biomarkers suggest that frailty involves crosstalk between multiple physiological pathways and various molecular changes (7). Instead of a single biomarker, a group of biomarkers may be more promising for the identification of frailty (8). However, no frailty biomarkers have been widely recognized, and the relationships between candidate biomarkers and frailty phenotypes are largely unknown. These issues represent major challenges in the field.

Metabolomics is a platform used to analyze the terminal metabolites of different samples from diverse organisms. This approach has promising applications in the elucidation of the metabolic spectrum among older adults and could facilitate the identification of the pathways underlying frailty (9). Recent metabolomics studies have demonstrated strong associations between certain metabolites and frailty. However, most of these studies were performed in European and American populations, and most of them only apply targeted metabolomics analyses for some metabolites, leading to a lack of clear consensus among studies (10–14).

Thus, we hypothesized that frailty may involve characteristic metabolites, which may contribute to the early identification and personalized intervention of frailty. Accordingly, in the current study, we used untargeted metabolomics platforms to analyze metabolites in the serum of frail and non-frail Chinese older adults to identify potential biomarkers of frailty. We expect that our findings may provide insights into the underlying biological pathways involved in frailty and identify effective targets for the treatment of age-related diseases.

MATERIALS AND METHODS

Participants

In total, 74 participants aged 60 years and older were recruited for this study. The mean age was 76.34 ± 8.31 years, and 64.9% of the participants were men. Individuals with cancer, rheumatic diseases, severe infections, severe liver (with Child-Pugh class B or C) or renal (with GFR < 60 mL/min/1.73 m^2) insufficiency, or receiving hormone or immunosuppressive therapy were excluded. All participants were divided into two groups: the frail group (case group, $n = 25$) and the non-frail group (control group, $n = 49$). Age and sex were matched between the two groups. All subjects gave written informed consent following the Declaration of Helsinki and the study was approved by the ethical review board of Xuanwu Hospital Capital Medical University with the approval number of [2020]043.

We collected data on general information (including age, sex, education, height, body weight, smoking, and drinking), blood pressure, medical history of chronic diseases, and some laboratory test results from each participant. The body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters.

Frailty Assessment

Frailty status was assessed according to the frailty phenotype (4) composed of five criteria: weakness, slowness, inactivity, fatigue, and shrink. The standing grip strength of both hands was measured twice, and the maximum value was adopted. Weakness was defined after adjusting for sex and BMI (15). Gait speed was measured with a 4-m-walk test at the usual speed. The cutoff point of slowness was adjusted for sex and height (15). Inactivity was defined as not walking 2.0 h per week. Fatigue was identified if participants said, "I felt everything I did was an effort" or "I could not get going" more than 3 days per week. Shrink was defined as the unintentional loss of at least 5% of weight from the previous year or BMI <18.5 kg/m^2. Participants with poor performance in three or more criteria were defined as frail, and those with two or fewer were defined as non-frail (4).

Serum Sample Collection

All blood samples were collected using serum separation tubes between 6:00 and 6:30 a.m. after overnight fasting, and the serum was extracted and stored in centrifuge tubes at −80°C.

Metabolomics Analysis

Reagents

Water was purified using an ultrapure water preparation system. Liquid chromatography-mass spectrometry (LC-MS) grade acetonitrile and methanol were purchased from Merck (Germany). High-performance LC-grade formic acid was obtained from Sigma (Germany). All internal standard references were purchased from Cambridge Isotope Laboratories (USA).

Metabolome Analysis

The extraction protocol and metabolomics are described as previously reported (16). Briefly, 50 μl serum was added to 200 μl ice-cold methanol, incubated for 30 min at 1,500 rpm and 4°C, and centrifuged for 10 min at 12,000 rpm and 4°C. The supernatant was removed into a clean 1.5-ml centrifuge tube and dried using a SpeedVac (Genevac miVac, Tegent Scientific Ltd., England), and the dried extracts were redissolved in 1% acetonitrile in water. The upper layer liquids were collected for LC-MS analysis. Quality control (QC) samples were prepared by mixing all serum samples in steps identical to those for the actual serum samples. In order to judge the stability of the instrument, one QC sample was tested after every 10 samples, and there was also one QC sample tested before the first and after the last sample, respectively. ACQUITY UPLC HSS T3 (1.8 μm, 2.1 × 100 mm) columns (Waters, Dublin, Ireland) were used in the current study. Ultra Performance Liquid Chromatography (UPLC) (Agilent 1290 Infinity II; Agilent Technologies, Germany) coupled with high-resolution mass spectrometry (5600 Triple TOF Plus, AB Sciex, Singapore) was

used to acquire the metabolome data. The temperatures of the column and auto-sampler were maintained at 40 and 4°C, respectively. The injection volume was 5 μL per run, and the flow rate was 0.35 mL/min. The MS parameters for detection were: ESI (-) source voltage −4.5 kV and +5.5 kV for ESI (+); vaporizer temperature, 500°C; drying gas (N2) pressure, 50 psi; nebulizer gas (N2) pressure, 50 psi; curtain gas (N2) pressure, 35 psi; the scan range was m/z 60–600. Information-dependent acquisition mode was used for MS/MS analyses of the metabolites. The collision energy was set at 35 ± 15 eV. Data acquisition and processing were performed using Analyst TF 1.7.1 (AB Sciex, Concord, ON, Canada). Each sample was tested once.

Metabolite identification was compared with standard references, HMDB (the Human Metabolome Database) and METLIN (the METLIN Metabolite and Chemical Entity Database). A total of 48 isotopically labeled internal standards were spiked into the samples for the semi-quantification of metabolites. Metabolite intensities were normalized according to the following rules and referred to as intensity (16).

Statistical Analysis

For basic information, continuous variables were presented as means and SD, and categorical variables were presented as numbers and percentages (%). The student's *t*-test was used to compare the continuous variables, and Pearson's χ^2 test was used to compare the categorical variables. Pairwise comparison was used to test the consistency of QC and the stability of the instrument. For metabolomics datasets, missing values were replaced with 0. Sparse partial least squares (sPLS) regression was used to observe the differentiation of samples within groups, and the association between differential metabolites and frailty phenotypes with R package mixOmics Version 6.16.3 (17). We used the *limma* package Version 3.48.3 of R (18) to identify differentially expressed metabolites between frail and non-frail groups, as well as participants with each frailty criterion and their counterparts without that criterion, respectively. We made Logistic regression on the different metabolites identified and receiver operating characteristic (ROC) analysis on the diagnostic models. Pearson correlation analysis was used to identify correlations between metabolites and physical functions (gait speed and grip strength). Differences were considered to be statistically significant for a two-tailed $P < 0.05$. All statistical analyses were performed in SPSS Statistics 26 (Armonk, NY: IBM Corp) and R 4.10.

Pathway Analysis

To identify the metabolic pathways significantly associated with the frailty phenotype, metabolite set enrichment analysis (19) and metabolic pathway analysis (20) were performed based on the Small Molecule Pathway Database (https://smpdb.ca) and the Kyoto Encyclopedia of Genes and Genomes (https://www.kegg.jp/), respectively. Metabolites with a $P < 0.05$ in two-tailed Mann-Whitney U tests were used for pathway analysis, and those with no matched HMDB ID were removed. A pathway with a fold change >2 and a raw $P < 0.05$ in metabolite set enrichment analysis or with a raw $P < 0.05$ in metabolic pathway analysis indicated that it contained more differentially expressed metabolites with respect to the frailty phenotype.

RESULTS

There were no significant differences in age, sex, BMI, smoking, drinking, blood pressure, chronic diseases, and laboratory tests between the frail and non-frail groups (**Table 1**). A pairwise comparison of QC showed good consistency and high data quality (**Supplementary Figure S1**). UPLC-quadrupole time-of-flight (QTOF) mass spectrometry-based untargeted metabolomics platform analysis identified 349 metabolites of 46 categories (**Figure 1A**). Sparse partial least squares (sPLS) regression shows that the subjects can be moderately well-separated based on frailty status, as well as by their individual indices, including weakness, slowness, inactivity, fatigue, and shrink (**Figure 1B**). As the correlation circle plot for the first two sPLS components shown in **Figure 1C**, frailty had a positive correlation with each frailty phenotype criteria and a negative correlation with gait speed and grip strength. Besides, **Figure 1C** showed associations between frailty phenotypes and metabolites. Metabolites including pyruvic acid, dihydroxybutanoic acid, 1-methylguanine, etc. showed a positive correlation with frailty, slowness, weakness, and fatigue, while glyceric acid, DL-2-aminooctanoic acid, etc., showed a positive correlation with grip strength. A group of lysophospholipids and acyl-carnitine were clustered along with the 2nd component which indicated a positive correlation with inactivity and a negative correlation with gait speed. The heat map showed the correlation between frailty phenotype and 24 metabolites from the first two components in sPLS regression in color (**Figure 1D**). Compared with non-frail participants, frail older adults showed significant suppression and enhancement of seven and four metabolites, respectively (**Figure 1E**). Moreover, we regrouped participants according to each frailty phenotype domain criteria. There were 19, 18, 46, 6, and 8 different metabolites observed in the weakness, slowness, inactivity, fatigue, and shrink groups, respectively, compared with those in the control groups. The details of the different metabolites are shown in **Supplementary Figure S2**. We successfully built Logistic regression models of frailty, slowness, weakness, inactivity, and shrink with their differential metabolites, respectively. Their diagnostic efficacy and ROC analysis were shown in **Supplementary Figure S3**. Pearson's correlation analysis showed that 11 and 21 metabolites were positively and negatively correlated with grip strength, respectively, whereas 7 and 76 metabolites were positively and negatively correlated with gait speed, respectively (**Figure 1F**, **Supplementary Tables S1**, **S2**).

Next, we generated metabolite sets for enrichment analysis and metabolic pathway analysis. **Table 2** shows metabolite sets with a fold change of >2 and a raw $P < 0.05$ from the enrichment analysis for each frailty phenotype. The two most significantly enriched metabolite sets were fatty acid metabolism (upregulation of l-carnitine, palmitic acid [PA], and l-palmitoylcarnitine) and mitochondrial beta-oxidation of long-chain saturated fatty acids (upregulation of l-carnitine and

TABLE 1 | Comparison of characteristics between non-frail and frail groups.

Variables		Non-frail ($n = 49$)	Frail ($n = 25$)	*P value*
General information	Age (years), mean (SD)	76.22 (8.26)	76.56 (8.58)	0.871
	Male, no (%)	31 (63.3)	17 (68.0)	0.687
	High school and above, no (%)	29 (70.7)	11 (47.8)	0.069
	Body mass index (kg/m^2), mean (SD)	24.88 (3.80)	25.40 (3.77)	0.580
	Smoking, no (%)	17 (34.7)	11 (44.0)	0.435
	Drinking, no (%)	13 (26.5)	10 (40.0)	0.236
Frailty assessment	Walking speed (m/s), mean (SD)	0.97 (0.25)	0.67 (0.30)	<0.001*
	Grip strength (kg), mean (SD)	28.18 (7.94)	21.71 (8.50)	0.004*
	Shrink, no (%)	3 (6.1)	6 (24.0)	0.026*
	Inactivity, no (%)	6 (12.2)	15 (60.0)	<0.001*
	Self-reported fatigue, no (%)	24 (49.0)	17 (68.0)	0.119
Blood pressure	Systolic blood pressure (mmHg), mean (SD)	139 (16.04)	141 (24.00)	0.751
	Diastolic blood pressure (mmHg), mean (SD)	74 (11.20)	75 (11.46)	0.757
Chronic diseases	Hypertension, no (%)	38 (77.6)	21 (84.0)	0.514
	Diabetes mellitus, no (%)	17 (34.7)	9 (36.0)	0.911
	Coronary heart disease, no (%)	19 (38.8)	13 (52.0)	0.277
	Pulmonary disease, no (%)	7 (14.3)	2 (8.0)	0.434
	Chronic kidney disease, no (%)	3 (6.1)	1 (4.0)	0.703
Laboratory tests	Cholesterol (mmol/L), mean (SD)	3.97 (0.82)	4.16 (1.07)	0.424
	Triglycerides (mmol/L), mean (SD)	1.38 (0.92)	1.66 (1.21)	0.277
	Low density lipoprotein (mmol/L), mean (SD)	2.32 (0.70)	2.56 (0.94)	0.235
	High density lipoprotein (mmol/L), mean (SD)	1.24 (0.35)	1.16 (0.31)	0.373
	Hemoglobin A1c (%), mean (SD)	6.26 (1.27)	6.65 (1.65)	0.265
	Fasting plasma glucose (mmol/L), mean (SD)	5.62 (1.86)	6.43 (3.02)	0.228

*$p < 0.05$.

stearoylcarnitine). **Table 3** presents 13 pathways that involved at least one metabolite associated with one or more frailty phenotype criteria. The top three significant pathways were ascorbate and aldarate metabolism, pentose and glucuronate interconversions, and lysine degradation. However, certain pathways associated with the frailty phenotype had low impacts, such as inositol phosphate metabolism, pentose phosphate pathway, vitamin B6 metabolism, fatty acid degradation, and unsaturated fatty acid biosynthesis.

DISCUSSION

In this exploratory metabolomics investigation, we showed that frail and non-frail individuals exhibited distinct metabolite signatures. Carbohydrate, lipid, and amino acid metabolism pathways were significantly associated with the frailty phenotype, suggesting that regulation of these pathways may affect frailty (**Figure 2**).

Carbohydrate metabolism is the main energy source for the body and can provide necessary intermediate metabolites for various important biochemical reactions *in vivo*. The citrate cycle is the ultimate aerobic metabolic pathway of carbohydrate, lipid, and amino acid in the mitochondrial matrix (21). Our results showed a negative correlation between gait speed and isocitrate, l-malic acid, fumarate, and cis-aconitate. Accumulation of these citrate cycle-related metabolites in the serum of frail older adults may result from impaired mitochondrial function and downregulation of the citrate cycle in frailty. Indeed, in the Framingham Offspring Study, researchers found that participants with higher concentrations of isocitrate tended to have lower odds of longevity (beyond the age of 80 years) (22). Additionally, aconitate, isocitrate, and malate were significantly associated with the incidence of all-cause mortality after adjusting for baseline data (22). A study on community-dwelling older black men from America also showed that isocitrate positively correlated with the Scale of Aging Vigor in Epidemiology (SAVE) scores for frailty (23). In addition, Ubaida-Mohien et al. (24) quantitatively characterized the proteins in the citrate cycle and observed that malate dehydrogenase, isocitrate dehydrogenase, fumarate hydratase, and succinate-CoA ligase were significantly lower in older individuals, which indicated decreased mitochondrial function and downregulation of citrate cycle during aging. In addition, we observed that certain carbohydrate metabolism-related pathways, such as glycolysis, gluconeogenesis, pyruvaldehyde degradation, inositol metabolism, ascorbate, and aldarate metabolism, pentose and glucuronate interconversions, and starch and sucrose metabolism, were associated with the frailty phenotype, particularly slowness. The accumulation of D-glucuronate, pyruvate and beta-D-glucuronoside in these pathways may result from impaired mitochondrial function in frailty. Garvey et al. (25) performed a semiquantitative global

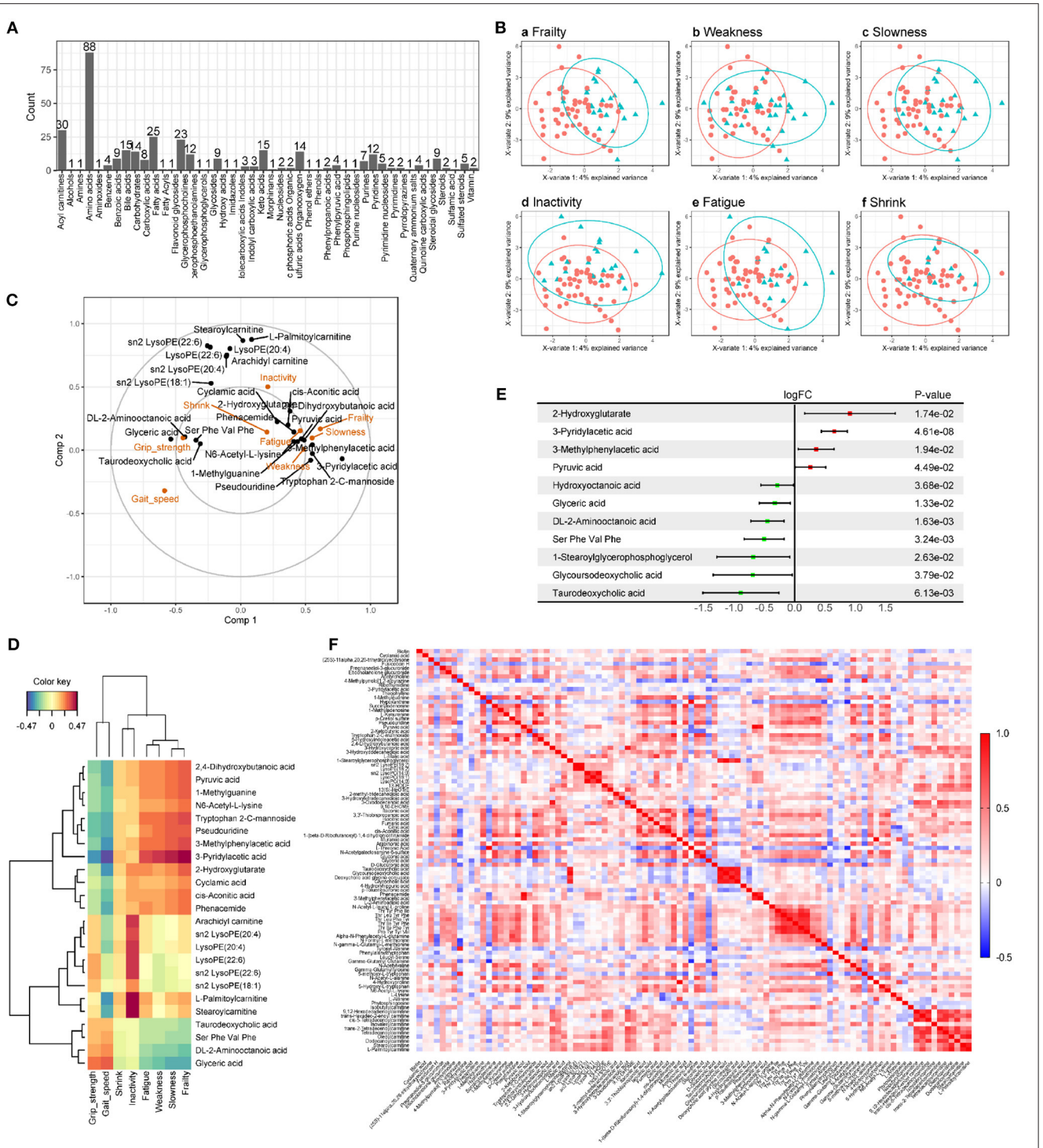


FIGURE 1 | Metabolomics analysis of serum from older adults. **(A)** Metabolome summary. There were 349 metabolites in 46 categories detected from serum samples of participants, among which Amino acids had the most identified species (88). **(B)** The sparse partial least squares (sPLS) regression score plots of the first two components within each pair of groups. The green triangle represents the case group (frailty, weakness, slowness, inactivity, fatigue, and shrink are shown in **Ba–f**), the red circle represents the control group, and the ellipses represent the 95% confidence regions for each group. As the score plots show, the metabolites detected have well-separated within groups. **(C)** Correlation circle plot for the first two sPLS components. The projection of each variable on the axis represents the correlation between the variable and the corresponding component. To simplify the plot, 16 and 8 metabolites were retained in Comp1 and Comp2, respectively. **(D)** Heat map of correlation between the clinical variables associated with frailty phenotype and 24 metabolites from the first two components in sPLS regression. Negative and positive correlations are shown in blue and red ranging from −0.47 to 0.47. **(E)** Forest plot of different metabolites for frailty identified by *limma* package of R with $P < 0.05$. Serum of frail older adults had higher levels of 4 metabolites and lower levels of 7. **(F)** Heat map of Pearson correlation analysis of 96 metabolites associated with gait speed or grip strength. Negative and positive correlations are shown in blue and red ranging from −0.5 to 1.0.

TABLE 2 | Enriched metabolite sets in frailty phenotype.

Frailty phenotype	Metabolite set	Match status	Fold change	Metabolites		Raw *p*
				Up-regulated	Down-regulated	
Frailty	Glycolysis	1/1	56.5	Pyruvic acid	–	0.0177
	Pyruvaldehyde degradation	1/1	56.5	Pyruvic acid	–	0.0177
	Glycine and serine metabolism	2/16	7.07	Pyruvic acid	Glyceric acid	0.0190
	Glycerolipid metabolism	1/2	28.25	–	Glyceric acid	0.0352
Slowness	Inositol metabolism	1/1	56.5	D-Glucuronic acid	–	0.0177
	Starch and sucrose metabolism	1/1	56.5	D-Glucuronic acid	–	0.0177
	Glycerolipid metabolism	1/2	28.25	–	Glyceric acid	0.0352
Inactivity	Fatty acid metabolism	3/3	10.27	L-Carnitine, Palmitic acid, L-Palmitoylcarnitine	–	0.0007
	Mitochondrial beta-oxidation of long chain saturated fatty acids	2/2	10.26	L-Carnitine, Stearoylcarnitine	–	0.0087
Fatigue	Vitamin B6 metabolism	1/1	37.74	–	4-Pyridoxic acid	0.0265
Shrink	Transfer of acetyl groups into mitochondria	2/5	7.555	Citric acid	Oxalacetic acid	0.0220

muscle metabolomics profiling of FBN F1 hybrid male rats and showed that glycolysis intermediates, such as pyruvate, accumulated in the gastrocnemius of aged rats, consistent with mitochondrial dysfunction. In a proteomics analysis of the muscles of a $Sod1^{-/-}$ mouse model of accelerated sarcopenia, enzymes participating in carbohydrate metabolism were downregulated in the case group (26), which may disrupt normal mitochondrial function and result in muscle mass loss. Taken together, these findings suggest that intermediate metabolites of carbohydrate metabolism, such as isocitrate, malate, fumarate, cis-aconitate, pyruvate, and glucuronate, may be potential biomarkers for frailty.

Fat tissue is crucial for energy storage, immune and endocrine processes, thermoregulation, mechanical protection, and tissue regeneration. Fat metabolism disorders with aging lead to fat tissue redistribution in different fat depots, even in non-adipose tissue (27). We observed fat metabolism upregulation in the inactivity group, including both saturated and unsaturated fatty acid metabolism.

In our study, PA levels were higher in the serum of older adults with low physical activity. PA, a common saturated fat, exhibits lipotoxicity, which can induce ectopic lipid deposition and cellular dysfunction (28). PA causes lipotoxicity in tissues, cells, and organs, such as the bone (29), hepatocytes (30), and testes (31), and may increase the risk of diabetes (32). Thus, PA may reflect abnormal fat distribution in frailty. Additionally, rapamycin blocks PA-dependent lipotoxicity in the bones by modulating apoptosis and autophagy through the mammalian target of rapamycin (mTOR) complex 1 pathway (33) as mTOR signaling regulates *de novo* lipid synthesis (21). Further exploration of these relevant pathways may facilitate elucidation of the mechanisms of lipotoxicity and improve our ability to treat or prevent frailty.

Furthermore, we observed higher levels of circulating unsaturated fatty acids, such as arachidonate (AA) and linoleic acid (LA), in frail older adults. AA and LA are common omega-6 polyunsaturated fatty acids (n-6 PUFAs). Our results indicated that higher levels of circulating n-6 PUFAs were characteristic of frailty. The effects of n-6 PUFAs on health have long been controversial. In the Framingham heart study, higher n-6 PUFA intake increased fasting triglyceride levels, remnant-like particle concentrations, and very-low-density lipoprotein sizes. Moreover, n-6 PUFAs decreased low-density lipoprotein size, which may increase the risk of cardiovascular disease (34). Because unsaturated fatty acids are closely related to the differentiation and inflammatory responses of T cells (35), B cells (36), and macrophages (37), the negative effects of n-6 PUFAs on the cardiovascular system may result from increased inflammation activated by it (38). However, other researchers have recently demonstrated the health-protective effects of n-6 PUFAs. For example, higher n-6 PUFA intake could reduce total cholesterol levels in the serum and benefit people at high risk of myocardial infarction (39), could modestly reduce risk of mortality from all causes (40) and have long-term preventive effects on type two diabetes in the population. Higher levels of circulating and tissue LA were associated with a lower risk of major cardiovascular events (41). Overall, although we observed higher levels of circulating unsaturated fatty acids (particularly n-6 PUFAs) in older adults with low physical activity, the clinical significance of these molecules in frail individuals is still unclear. Further research on the related mechanisms is required.

Tryptophan (Trp) is an essential amino acid linked to muscle metabolism (42) and the nervous system (43). We observed upregulation of Trp metabolites, such as 5-hydroxyindoleacetate and 2-oxoadipate, in the serum of weak older adults, although we detected no differences in Trp contents. Trp metabolism is associated with grip strength. Similar to our results, researchers observed that circulating Trp level reduced in frail old patients with breast cancer (44) and frail older black men living in community (23). Even in muscle biopsies,

TABLE 3 | Over-represented pathways associated with frailty phenotype with raw $P < 0.05$.

Frailty phenotype	KEGG ID	Pathway	Match status	Metabolites		Raw *p*	Impacts score
				Up-regulated	Down-regulated		
Frailty	hsa00260	Glycine, serine and threonine metabolism	2/11	Pyruvate (C00022)	D-Glycerate (C00258)	0.0101	0.0242
	hsa00630	Glyoxylate and dicarboxylate metabolism	2/12	Pyruvate (C00022)	D-Glycerate (C00258)	0.0121	0.0794
	hsa00561	Glycerolipid metabolism	1/1	–	D-Glycerate (C00258)	0.0190	0.0935
	hsa00010	Glycolysis / Gluconeogenesis	1/2	Pyruvate (C00022)	–	0.0379	0.1004
	hsa00030	Pentose phosphate pathway	1/2	–	D-Glycerate (C00258)	0.0379	0.0000
Weakness	hsa00310	Lysine degradation	2/4	N6,N6,N6-Trimethyl-L-lysine (C03793), 2-Oxoadipate (C00322)	–	0.0156	0.1409
	hsa00380	Tryptophan metabolism	2/6	5-Hydroxyindoleacetate (C05635), 2-Oxoadipate (C00322)	–	0.0371	0.0139
Slowness	hsa00040	Pentose and glucuronate interconversions	2/2	Beta-D-Glucuronoside (C03033), D-Glucuronate (C00191)	–	0.0011	0.2656
	hsa00053	Ascorbate and aldarate metabolism	1/1	D-Glucuronate (C00191)	–	0.0381	0.5000
	hsa00561	Glycerolipid metabolism	1/1	–	D-Glycerate (C00258)	0.0381	0.0935
	hsa00562	Inositol phosphate metabolism	1/1	D-Glucuronate (C00191)	–	0.0381	0.0000
Inactivity	hsa01040	Biosynthesis of unsaturated fatty acids	3/6	Hexadecanoic acid (C00249), (9Z)-Octadecenoic acid (C00712), Arachidonate (C00219)	–	0.0053	0.0000
	hsa00071	Fatty acid degradation	2/3	Hexadecanoic acid (C00249), L-Palmitoylcarnitine (C02990)	–	0.0148	0.0000
Fatigue	hsa00260	Glycine, serine and threonine metabolism	2/11	–	Betaine (C00719), D-Glycerate (C00258)	0.0285	0.0745
	hsa00561	Glycerolipid metabolism	1/1	–	D-Glycerate (C00258)	0.0286	0.0935
	hsa00750	Vitamin B6 metabolism	1/1	–	4-Pyridoxate (C00847)	0.0286	0.0000

Trp levels were found to be lower in frail older adults (12). The reduction in serum Trp with aging in rats was similar to that observed in humans (25). These studies reported reduction in Trp contents with aging or aggravated frailty, although the mechanisms of this phenomenon are unclear. Based on metabolomics profiling of mice and humans, Westbrook et al. revealed that the tryptophan degradation pathway was significantly activated in frail individuals with down-regulated Trp levels and up-regulated Trp metabolites like kynurenine, which had links with chronic inflammation (45). In our study, Trp metabolite contents increased in the weak group; these results may be explained by enhanced Trp degradation, consistent with the Trp concentration reduction in the aforementioned studies. However, the mechanisms are still not known, and it is unclear whether Trp synthesis is disrupted in frail individuals.

In this study, we explored the metabolic profiles of frailty in older Chinese adults. Our study identified candidate biomarkers for physical frailty, which are of practical value for both clinical diagnosis and basic research on frailty. However, this study has certain limitations. First, the sample size was limited; thus, we did not perform an additional sex control analysis. Second, since this was a single-center study, we did not evaluate people of different regions, races, lifestyles, dietary habits, cultures, and economic levels. Therefore, our results may not represent the entire Chinese population. Despite these limitations, we observed differences between the metabolite profiles in frail and non-frail groups, suggesting that it may be feasible to identify frailty biomarkers through metabolomics platforms. Further studies are needed to test our findings in larger cohorts and more populations, focus on dynamic changes in distinct metabolites and build a diagnostic model of frailty to confirm a set of sensitive and

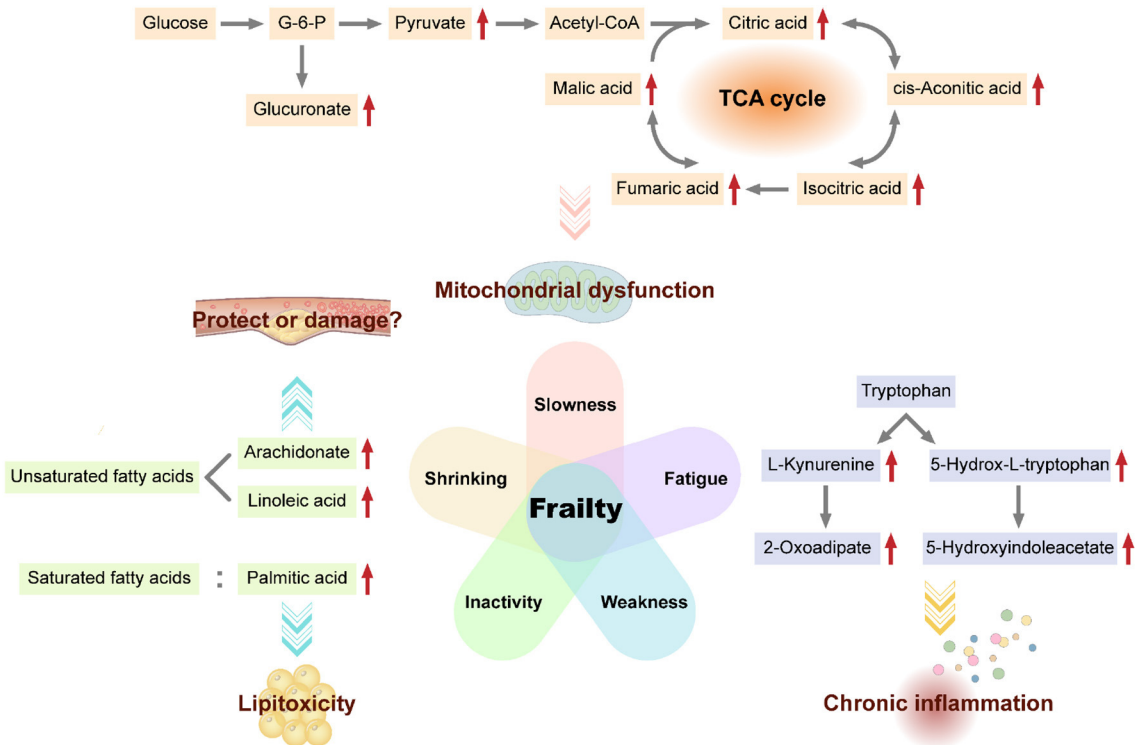


FIGURE 2 | Potential biomarkers and mechanisms of frailty. Some metabolites of carbohydrate metabolism (e.g., glucuronate, pyruvate, citric acid, cis-aconitate, isocitrate, fumarate, and malate), fatty acids (e.g., arachidonate, linoleic acid, and palmitic acid), and certain amino acids (e.g., tryptophan) are candidate biomarkers for frailty. Mitochondrial dysfunction, saturated fatty acid lipotoxicity, cardiovascular effects of unsaturated fatty acids, and chronic inflammation caused by increased tryptophan degradation may be possible mechanisms for frailty.

specific biomarkers for early diagnosis. In addition, technological advancements in metabolomics are expected to promote the study of frailty biomarkers.

CONCLUSION

Our findings emphasized the value of metabolomics in the search for frailty biomarkers and initially revealed the metabolomic signatures in the serum of frail older adults from China. Isocitrate, malate, fumarate, cis-aconitate, glucuronate, pyruvate, PA, AA, LA, and Trp could be potential candidate biomarkers for frailty. Disorders of mitochondrial function, lipotoxicity of saturated fatty acids, disturbances in unsaturated fatty acid metabolism, and increased Trp degradation were identified as potential mechanisms and therapeutic targets of frailty. Future studies are needed to replicate our results in different populations and provide more evidence on the underlying mechanisms of frailty.

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 Ethical Review Board of Xuanwu Hospital Capital Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LM: study concept and design. YL: leading of study. YP, PL, and YZ: acquisition of subjects and/or data. YP, BL, ZL, GS, and LM: analysis and interpretation of data, and preparation of the manuscript. All authors critically revised the manuscript for important intellectual content and 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.2021.830723/full#supplementary-material

Supplementary Figure S1 | Pairwise comparison of 13 quality control (QC) samples transformed by log10. Each point in the scatter plot represents a metabolite. All the points are distributed in a tight straight line, and the corresponding correlation coefficient is >0.99, indicating that the data is highly consistent in the two QC samples. On the diagonal is the data distribution diagram of a single sample.

Supplementary Figure S2 | Forest plot of different metabolites for each frailty phenotype criteria (weakness, slowness, inactivity, fatigue and shrink) identified by limma package of R with $P < 0.05$. The upregulated metabolites in case groups are shown in red dots and downregulated ones in green.

Supplementary Figure S3 | The receiver operating characteristic (ROC) curve of frailty and some frailty phenotype. The figures show the performance of Logistic regression models of differential metabolites in distinguishing frailty, slowness, weakness, inactivity, and shrink from corresponding control groups. The sensitivity, specificity, and area under the ROC curve (AUC) are shown in the images.

Supplementary Table S1 | Pearson correlation of metabolites associated with grip strength.

Supplementary Table S2 | Pearson correlation of metabolites associated with gait speed.

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Conflict of Interest: BL is employed by the LipidALL Technologies Company Limited.

The remaining 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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Specific Metabolites Involved in Antioxidation and Mitochondrial Function Are Correlated With Frailty in Elderly Men

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Background: As an age-related syndrome, frailty may play a central role in poor health among older adults. Sarcopenia overlaps with the physical domain of frailty, and most existing studies have analyzed the associated factors of frailty and sarcopenia as an isolated state. Perturbations in metabolism may play an important role in the presence of frailty or sarcopenia; however, the metabolites associated with frailty, especially overlapping with sarcopenia remain unclear. In this study, we aimed to explore whether amino acids, carnitines, acylcarnitines and lysophosphatidylcholines, as specific panels, are significantly correlated with frailty, especially overlapping with sarcopenia, to gain insight into potential biomarkers and possible biological mechanisms and to facilitate their management.

Methods: We applied a targeted high-performance liquid chromatography-tandem mass spectrometry approach in serum samples from 246 Chinese older men (age 79.2 ± 7.8 years) with frailty (n = 150), non-frailty (n = 96), frailty and sarcopenia (n = 52), non-frail and non-sarcopenic control (n = 85). Frailty was evaluated using Freid phenotype criteria, sarcopenia was defined by diagnostic algorithm of Asian Working Group on Sarcopenia, and the participants were diagnosed as frailty and sarcopenia when they met the evaluation criteria of both frailty and sarcopenia. A panel of 29 metabolomic profiles was assayed and included different classes of amino acids, carnitines, acylcarnitines, and lysophosphatidylcholines (LPCs). Multivariate logistic regression was used to screen the metabolic factors contributing to frailty status, and orthogonal partial least squares discriminant analysis was used to explore important factors and distinguish different groups.

Results: In older men demonstrating the frail phenotype, amino acid perturbations included lower tryptophan and higher glycine levels. With regard to lipid metabolism, the frailty phenotype was characterized by lower concentrations of isovalerylcarnitine (C5), LPC16:0 and LPC18:2, while higher levels of octanoyl-L-carnitine (C8), decanoyl-L-carnitine (C10), dodecanoyl-L-carnitine

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(C12) and tetradecanoyl-L-carnitine (C14). After adjusting for several clinical confounders, tryptophan, LPC18:2, LPC 16:0 and C5 were negatively correlated with frailty, and C8 and C12 were positively related to frailty. We preliminarily identified metabolic profiles (LPC16:0, LPC18:2, glycine and tryptophan) that may distinguish older men with frailty from those without frailty. Importantly, a set of serum amino acids and LPCs (LPC16:0, LPC18:2, and tryptophan) was characterized in the metabotype of older adults with an overlap of frailty and sarcopenia. The metabolites that were most discriminating of frailty status implied that the underlying mechanism might be involved in antioxidation and mitochondrial dysfunction.

Conclusions: These present metabolic analyses may provide valuable information on the potential biomarkers and possible biological mechanisms of frailty, and overlapping sarcopenia. The findings obtained may offer insight into their management in older adults.

Keywords: frailty, sarcopenia, metabolomics, multivariate analysis, biomarker

INTRODUCTION

As an age-related clinical syndrome, frailty is caused by a progressive discrepancy between the accumulation of damage and resilience of the body, and can explain some of the health heterogeneity among people with the same chronological age (1). Frailty-related adverse consequences in older adults such as falls, dependency, hospitalization, and death result in increased medical costs and demand for long-term care (2). With respect to rapidly aging populations in China, the overall weighted prevalence of frailty is 9.9%, and increases with age (3, 4). Moreover, sarcopenia overlaps with the physical domain of frailty and may represent the biological substratum of complex pathophysiology. In patients aged 70 years or older, the concurrent occurrence of frailty and sarcopenia syndromes (overlap) is 19% (5). Other studies have indicated that 58% of frail elderly individuals have sarcopenia, and men have higher prevalence of sarcopenia than women in China (6, 7), which may challenge their management.

The biological mechanisms underlying frailty have been extensively studied in recent years. Scientific progress in understanding frailty has been hampered by disagreement about its pathophysiology and operational diagnosis in research and clinical settings (8). Frailty encompasses several multisystem derangements, which means that there is no single diagnostic tool or biomarker available to identify the presence and extent of frailty. Advances in metabolism and other omics platforms have provided new information on the molecular mechanisms underlying frailty. Circulating metabolites have emerged as a possible tool for capturing this complexity and hold the potential to identify metabolic factors or biomarkers that contribute to frailty, offering opportunities to develop strategies for its identification and management (9, 10). However, there is a lack of stable and reliable frailty-related biomarkers for use in clinical practice (11, 12). Moreover, the various biomarkers for frailty thus far discovered in metabolomics have focused mostly on amino acids (13, 14), and relatively less is known about the association of frailty with lipid metabolism such as carnitine, acylcarnitines (AcyCNs) and lysophosphatidylcholines (LPCs), in part because of their structural diversity and the sheer number of discrete molecular species (15). Carnitines and AcyCNs may play some role in muscle weakness, cognitive diseases, and inflammatory conditions (16, 17), whereas, the circulating LPCs content has been used to predict a decline in gait speed or cognitive impairment (18–20). It is therefore important to carry out extensive measurements of these metabolic species to further our insights into the metabolic basis of frailty. However, the metabolites associated with sarcopenia have not been comprehensively profiled and examined. Most of existing studies have analyzed the associated factors of frailty and sarcopenia as isolated states, and only a few studies have merged the two conditions into one entity (i.e., overlapped frailty and sarcopenia; F&S) (21). Although some studies on frailty or sarcopenia with investigation of metabolism have been conducted in other countries, limited data are available about the association of metabolites with frailty and sarcopenia in older Chinese adults.

With the aim of expanding knowledge in this area, in the current study, we determined the serum metabolomic profile using targeted tandem mass spectrometry coupled with multivariate statistical analysis, to simultaneously analyze different classes of amino acids, LPCs, carnitines and AcyCNs in older Chinese men. We explored the metabolic factors of frailty, and then narrowed down the range to study the discriminating metabolites of frailty overlapped with sarcopenia. We aimed to explore whether amino acids, carnitine, AcyCNs and LPCs, as specific panels, are significantly correlated with frailty, especially F&S, to gain insight into possible biological mechanisms, as well as to facilitate the management of frailty.

MATERIALS AND METHODS

Participants

A total of 246 elderly men (62–100 years old) attending the Geriatric Medicine department of Beijing Hospital for physical examination from August 2016 to May 2018 were recruited using random numbers after the inclusion and exclusion. The

inclusion criteria were as follows: participants were older than age 60 years, had the ability to understand and complete the questionnaires, and did not have severe mental or cognitive disorders. People with malignant tumors, blood system diseases, chronic obstructive pulmonary disease, autoimmune diseases, infectious diseases, and individuals who were taking amino acid supplements were excluded. This study was approved by the Medical Ethics Committee of Beijing Hospital of the National Health Commission.

In order to assess the health status related to frailty or sarcopenia, we administered comprehensive geriatric assessment consisting of general clinical information and demographic data. Each participant self-reported their smoking and alcohol drinking status (past, present or never smoker/alcohol intake). Polypharmacy was defined as the use of more than five medications (22). Comorbidities were slightly modified from the Charlson Comorbidity Score (23), and the following comorbidities were retained: hypertension, coronary artery disease, arrhythmia, diabetes mellitus, peripheral vascular disease, cerebrovascular disease, stroke, chronic pulmonary disease, kidney disease, prostatic disease, gastric ulcer, liver disease and osteoporosis. The presence of depressive symptoms was defined using the Geriatric Depression Scale-5; cognitive function was evaluated with Mini–Mental State Examination and malnutrition risk was evaluated using the Mini-Nutritional Assessment Short-Form. Participants were assessed for dependence in six basic activities of daily living (ADL) and eight instrumental ADL tasks.

Frailty and Sarcopenia Assessment

In this study, frailty was defined according to the Fried phenotype criteria, which include exhaustion, weakness, slowness, physical inactivity and weight loss (24). Exhaustion was defined using the two statements of the Center for Epidemiologic Studies-Depression scale. The maximum handgrip strength of either hand was measured two times using a digital dynamometer (WCS-II, Beijing) for assessment of weakness. Slowness was evaluated using the average of two timed- walk tests over a 6 m course. Physical activity was evaluated using the Chinese version of the International Physical Activity Questionnaire (25). Weight loss was defined as having involuntary weight loss of >5% in the previous year or 3 kg within the past 3 months. Older adults were considered to be frail if they met three or more of these five criteria, prefrail if they met one or two criteria, and non-frailty if they met none of these criteria. A combined group of prefrail together with frail was analyzed as the "frailty" group (non-frailty was the reference group) because of the small sample size of the frail group, according to the previous study.

We defined sarcopenia using the diagnostic algorithm of the Asian Working Group on Sarcopenia (AWGS) according to the presence of both low muscle mass and low muscle function (slow walking speed or low grip strength) (26). Appendicular skeletal muscle mass (ASM) was determined using a bioelectrical impedance data acquisition system (Inbody 720; BiospaceCo, Ltd, Seoul, Korea). The skeletal muscle mass index (SMI) or relative ASM was calculated as ASM divided by height (m) squared (ASM/height^2, kg/m^2). Low muscle strength was defined as handgrip strength < 28 kg for men and low physical performance was defined as a 6-m walk speed < 1.0 m/s. The cutoff for height-adjusted muscle mass (i.e., SMI) *via* bioelectrical impedance data was <7.0 kg/m^2 in men. Participants were diagnosed with F&S when they met the evaluation criteria of both frailty and sarcopenia; non-frail and non-sarcopenic control did not meet the criteria for either sarcopenia or frailty (27).

Sample Preparation and Routine Chemical Parameters

Blood samples were collected in the morning using venipuncture of the median cubital vein after participants had completed an overnight fast. For serum separation, samples were left at room temperature for 20 min and subsequently centrifuged at 1,000 × *g* for 10 min at 4°C. Aliquots of serum were subsequently stored at –80°C until analysis. Blood samples were measured using an automatic biochemical analyzer and enzymatic colorimetric tests for laboratory routine parameters.

Measurements of Serum Metabolites

A panel of 29 Serum metabolites was measured using our previously reported targeted liquid chromatography-tandem mass spectrometry method for simultaneous quantification of three branched-chain amino acids (BCAAs; leucine, isoleucine, valine), three aromatic amino acids (AAAs; phenylalanine, tryptophan, and tyrosine), glutamate (Glu), glutamine (Gln), Gln/Glu ratio, alanine, glycine, four subclasses of LPC, carnitine, and 12 species of AcyCN, trimethylamine-N-oxide (TMAO) and betaine (28, 29). Briefly, 0.01 mL aliquots of the calibrators or serum samples were mixed with 0.01 mL of isotopically labeled internal standards, followed by the addition of 1 mL of isopropanol. After vortexing and centrifuging, 0.2 mL of the supernatant was transferred to another vial and reconstituted. LC–MS/MS analysis was performed using an AB Sciex 5500 QTRAP tandem mass spectrometer (Framingham, MA, USA) equipped with an Agilent 1260 Series high-performance liquid chromatography system (Santa Clara, CA, USA).

Statistical Analyses

Continuous variables are expressed as mean ± standard deviation or median (25th percentile, 75th percentile; P25, P75), and categorical data are expressed as percentage. The normal distribution of data was ascertained using the Kolmogorov–Smirnov test. Metabolites with a skewed distribution were log-transformed. Comparisons between two groups for normally distributed continuous variables were performed using the *t*-test. The non-parametric Wilcoxon test was applied to assess differences in non-normally distributed continuous data. Differences in categorical variables between groups were determined *via* χ^2 or Fisher's exact tests. A Benjamini–Hochberg correction was used to account for multiple comparisons. Significance levels in prior exploratory analyses (30, 31) guided the choice of statistical significance in this study, which was set at $p < 0.05$ with a false discovery rates (FDR) ≤ 0.30.

Spearman correlations were used to examine the relationship between metabolites. In multivariable logistic models of metabolites and frailty, clinical potential confounding covariates,

that were significantly associated with frailty in the above univariate analyses and previous studies (32–34) were adjusted in three models, as follows: Model 1: age, body mass index, and smoking status; Model 2: further controlled for malnutrition, cognitive decline, ADL, polypharmacy, and comorbidities; Model3: further controlled for red blood cell count and hemoglobin, alanine aminotransferase (ALT), and uric acid. Statistical analyses were performed using the SAS statistical package, version 9.3 (SAS institute Inc., Cary, NC, USA). All tests were two-sided, with statistical significance set at $p < 0.05$.

Orthogonal partial least squares discriminant analysis (OPLS-DA) in SIMCA-P v.14.1 was applied to distinguish those metabolites related to frailty and to enhance the separation between groups using rotating principal component analysis. Among the possible classifiers, OPLS-DA was selected because of its versatility and ability to deal with highly correlated predictors (35–37) and because it is more effective in focusing the correlated information onto the first predictive component instead of scattering it onto the subsequent components. The quality of the OPLS-DA model was validated using cross-validation: the goodness of fit (R2) and the goodness of prediction indicated by the cumulated Q2 value (Q2 cum). Permutation tests were used to assess whether the model was overfitted. The area under the receiver operating characteristic (ROC) curve can be used as an indicator of discriminatory power of the model. The important factors were identified using S-Plot and variable importance in projection (VIP) score. A VIP score > 1 indicated that the independent variable was an important factor in distinguishing frailty status. Metabolites with VIP > 1 were further subjected to univariate analysis to measure the significance of each metabolite.

RESULTS

Clinical Characteristics of the Study Participants

The participants included in the analysis comprised 246 men aged 62–100 years. According to the Fried phenotype criteria, the participants were stratified into 96 non-frailty (39.0%), 132 prefrail men (53.7%) and 18 frail men (7.3%). In this study, prefrail and frail men were combined into the frailty group (150, 61.0%). In terms of frailty criteria constituents, 57 men (51.8%) in the frail group and 15 men (15.96%) in the non-frailty group had lower grip strength. The frailty group had a slower walking speed, greater reductions in physical activity, and a higher proportion of participants with exhaustion than the non-frailty group. Similarly, the SMI was smaller in the frailty group than in the non-frailty group. Study participants included 65 (26.4%) older men with sarcopenia and 181 (73.6%) non-sarcopenic elderly men; moreover, 52 (21.1%) men had F&S, whereas, 85 (34.6%) men were non-frailty and non-sarcopenia (non-frail and non-sarcopenic control).

The main clinical and functional characteristics of the study population are presented in **Table 1**. The frailty group was older than non-frailty group. Compared with non-frailty participants, frailty participants had a lower body mass index (BMI), were less likely to smoke, and had lower diastolic blood pressure. No participants were classified as ADL-dependent in non-frailty group, whereas 21.6% of frailty men were ADL-dependent. Men in the frail group more frequently had cognitive decline, comorbidities and malnutrition in comparison with non-frailty men. However, polypharmacy and depression did not differ significantly between the two groups.

With respect to routine chemistry parameters, frailty participants had lower concentrations of red blood cells and hemoglobin. Serum uric acid and ALT levels in frailty participants were significantly lower than those in non-frailty participants. No other blood chemical parameters, such as albumin, fasting blood glucose, triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and aspartate aminotransferase were found to be significantly different between the two groups.

Differences in Serum Concentration of Metabolites Between With and Without Frailty

A description of metabolic species levels is provided in **Table 2**. The frailty phenotype showed specific amino acid alterations. The serum concentration of tryptophan was significantly lower in the frailty group; in contrast, the concentration of glycine was markedly higher relative to that in the non-frailty group. We detected no significant difference in other amino acids, such as BCAAs, Glu, Gln, and other AAAs. Among AcyCNs in the frailty group, the concentrations of octanoyl-L-carnitine (C8), decanoyl-L-carnitine (C10), dodecanoyl-L-carnitine (C12), and tetradecanoyl-L-carnitine (C14) were higher, whereas that of isovalerylcarnitine (C5) was lower compared with those observed in the non-frailty group; however, these did not remain significant after multiple adjustments. This change trend was not found in other AcyCN species. The perturbation of serum LPC occurring in frailty individuals was evident, especially for lower levels of 1-palmitoyl-2-hydroxy-sn-glycero-3-phosphocholine (LPC16:0) and 1-linoleoyl-2-hydroxy-sn-glycero-3-phosphocholine (LPC18:2) subclasses. Serum levels of trimethylamine-N-oxide and betaine showed no significant differences between the two groups.

Correlation Analyses Between the Significant Metabolites

Figure 1 shows the correlations among metabolites that were significantly relevant to frailty. Variations in these metabolites were not independent, and many showed significant intercorrelations with one another. Tryptophan showed positive associations with C5 and slight associations with LPC16:0 and LPC18:2. In turn, C5 was moderately associated with LPC16:0 and LPC18:2. Glycine presented significant positive associations with C8, C12, and C14 and inverse associations with LPC16:0, whereas, a significant positive correlation between LPC16:0 and LPC18:2 was found ($r = 0.70$).

TABLE 1 | Clinical characteristics of elderly individuals with frail and non-frail status.

Variables	Non-frailty ($n = 96$)	Frailty ($n = 150$)	$t/\chi^2/Z$	p-value
Age (years)[a]	78.01 ± 6.99	79.94 ± 8.21	−2.04	**0.042**
past/present smoking	25.0%	12.7%	6.173	**0.013**
Alcohol intake	20.62%	13.64%	2.123	0.145
BMI (kg/m^2)[b]	26 (23, 27)	25 (22, 27)	2.351	**0.019**
Diastolic BP (mmHg)[b]	75 (70, 80)	70 (65, 80)	3.044	**0.002**
Systolic BP (mmHg)[b]	130 (120, 140)	130 (120, 140)	0.082	0.934
Malnutrition	18.63%	33.95%	7.285	**0.007**
Comorbidities[a]	3.5 ± 1.4	4.2 ± 1.8	3.235	**0.001**
Polypharmacy	82.61%	85.33%	Fisher	0.747
ADL decline	0.00%	21.60%	25.405	**<0.001**
Cognitive decline	0.98%	7.41%	5.522	**0.019**
Depression	41.18%	50.62%	2.24	0.135
Slowness	22.77%	57.24%	29.329	**<0.001**
Weakness	15.96%	51.82%	28.542	**<0.001**
Lower SMI	21.43%	39.53%	8.43	**0.004**
Lower activity	4.95%	29.11%	22.749	**<0.001**
Exhaustion	0.01%	12.96%	14.365	**<0.001**
Blood general parameters				
Red blood cell (10^{12}/L)[b]	4.69 (4.49, 4.93)	4.55 (4.22, 4.94)	2.469	**0.014**
White blood cell (10^9/L)[a]	5.89 ± 1.21	6.03 ± 1.71	−0.26	0.795[c]
Platelets (10^9/L)[b]	187 (162, 215)	183 (159, 211)	0.862	0.389
Hemiglobin (g/L)[b]	144.3 (138.0, 151.0)	139.0 (131.0, 148)	3.289	**0.001**
Fasting glucose (mmol/L)[b]	5.8 (5.3, 6.5)	5.7 (5.3, 6.2)	0.516	0.606
HbALc (%)[b]	5.85 (5.50, 5.92)	5.8 (5.60, 6.37)	−1.772	0.076
Triglyceride (mmol/L)	1.3 (0.92, 1.75)	1.21 (0.83, 1.69)	1.103	0.270
Total cholesterol (mmol/L)[b]	4.22 (3.38, 5.00)	4.13 (3.33, 4.84)	0.738	0.461
LDL-C (mmol/L)[b]	2.45 (1.83, 3.08)	2.34 (1.81, 2.86)	0.983	0.325
HDL-C (mmol/L)[b]	1.19 (0.99, 1.35)	1.22 (1.03, 1.37)	−0.504	0.614
ALT (U/L)[b]	19 (16, 24)	17 (14, 22)	1.964	**0.049**
AST (U/L)[b]	27 (23, 30)	27 (24, 31)	−0.417	0.677
Albumin (g/L)[a]	42.53 ± 1.58	42.13 ± 1.82	1.748	0.080
Uric acid (μmo/L)[b]	369.6 (312, 443)	342 (298, 397)	1.983	**0.047**
Creatinine (μmo/L)[b]	77 (68, 88)	77 (68, 93)	−0.870	0.384
BUN (mmo/L)[a]	5.57 ± 1.21	6.05 ± 1.86	−1.92	0.056[c]

[a]*Mean ± standard deviation.*
[b]*Median and interquartile range (P25, P75).*
[c]*After log transformation.*
Bold values mean statistical significance ($p < 0.05$). ADL, activities of daily living; BMI, body mass index; HbALc, glycosylated hemoglobin; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; ALT, glutamate pyruvate transaminase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; SMI, skeletal muscle index.

Significant correlations were also observed between acylcarnitines, indicating that they change in ways that are interrelated. Very strong positive correlations between C8 and C10, and between C12 and C14 were observed, and moderate correlations were observed between C8 and C14 and between C10 and C14. The correlation coefficients of C8 with C10 and C12 were $r = 0.86$ and 0.73, respectively, whereas, those of C10 with C12, and of C12 with C14 were r = 0.78 and 0.81, respectively.

Metabolic Factors Associated With Frailty Status in Logistic Regression Analysis

Table 3 summarizes the results of logistic regression analyses. Multivariate adjustment was used to control for clinical factors, including age, BMI, current smoking, malnutrition, cognitive decline, ADL, polypharmacy, comorbidities, red blood cell count, hemoglobin, ALT and uric acid. After adjusting for these clinical factors, the levels of tryptophan, C8, C12, LPC16:0, LPC18:2, and C5 were found to be independent factors for frailty. When these metabolites were used as categorical variables, the odds ratio

TABLE 2 | Serum concentrations of metabolites in participants with and without frailty.

Variables	Non-frailty ($n = 96$)	Frailty ($n = 150$)	t/Z	p-value	FDR
Valine[a]	39.9 ± 5.9	39.0 ± 6.8	1.09	0.276	0.037
Ileucine[a]	12.7 ± 2.4	12.4 ± 2.4	0.93	0.354[c]	0.305
Leucine[a]	25.9 ± 3.9	25.3 ± 4.4	1.29	0.198[c]	0.194
Tyrosine[a]	16.2 ± 2.7	15.5 ± 3.3	1.96	0.051	0.245
Phenylalanine[a]	19.4 ± 3.3	19.6 ± 4.0	−0.07	0.942[c]	0.740
Tryptophan[a]	17.6 ± 2.5	16.6 ± 3.2	3.25	**0.001** [c]	**0.185**
Glutamine[a]	26.1 ± 7.3	26.3 ± 6.9	−0.30	0.761[c]	0.480
Glutamate[a]	22.2 ± 3.8	21.8 ± 4.9	1.25	0.212[c]	0.335
Glycine[b]	37.38 (32.49, 43.45)	40.07 (35.36, 48.19)	−2.393	**0.017**	**0.048**
Alanine[a]	50.3 ± 10.3	49.8 ± 10.9	0.46	0.649[c]	0.309
Gln/Glu	1.2 ± 0.4	1.3 ± 0.5	−0.61	0.545[c]	0.392
BCAA[a]	78.7 ± 11.8	76.8 ± 12.8	1.25	0.213	0.336
AAA[a]	53.0 ± 6.6	51.8 ± 9.1	1.20	0.230	0.254
Carnitine (μg/mg)[a]	10.6 ± 1.9	10.2 ± 2.2	1.74	0.084[c]	0.287
Acylcarnitines (μg/mg)					
C2[a]	2.2 ± 0.7	2.2 ± 0.7	0.30	0.766[c]	0.378
C3[a]	0.1 ± 0.0	0.1 ± 0.0	1.02	0.308[c]	0.715
C5[b]	0.028 (0.020, 0.034)	0.024 (0.018, 0.029)	3.322	**0.001**	0.441
C6[b]	0.021 (0.016, 0.025)	0.021 (0.017, 0.027)	−0.884	0.377	0.727
C8[b]	0.057 (0.042, 0.075)	0.066 (0.050, 0.082)	−2.513	**0.012**	0.808
C10[b]	0.088 (0.061, 0.115)	0.095 (0.075, 0.128)	−2.016	**0.044**	0.763
C10:1[b]	0.118 (0.10, 0.160)	0.132 (0.102, 0.181)	−1.695	0.090	0.745
C12[b]	0.027 (0.020, 0.035)	0.029 (0.024, 0.038)	−2.06	**0.040**[c]	0.833
C14[b]	0.01 (0.008, 0.013)	0.011 (0.009, 0.014)	−2.30	**0.022**[c]	0.785
C16[b]	0.054 (0.048, 0.061)	0.053 (0.046, 0.062)	0.13	0.896[c]	0.744
C18[a]	0.0245 (0.022, 0.028)	0.024 (0.02, 0.028)	1.35	0.177[c]	0.753
C18:1[b]	0.098 (0.084, 0.113)	0.0925 (0.082, 0.109)	1.528	0126	0.772
LPC16:0 (μg/ml)[b]	121.07 (95.71, 148.01)	105.21 (84.55, 129.62)	2.929	**0.003**	**0.205**
LPC18:0 (μg/ml)[b]	37.09 (31.30, 41.97)	36.55 (30.73, 42.48)	−0094	0.925	0.247
LPC18:1 (μg/ml)[a]	17.9 ± 3.7	17.3 ± 4.2	1.48	0.140	0.221
LPC18:2 (μg/ml)[b]	30.11 (22.54, 36.06)	24.14 (17.46, 33.40)	3.296	**0.001**	**0.022**
TMAO (μg/ml)[b]	0.40 (0.26, 0.56)	0.46 (0.28, 0.73)	−1.915	0.056	0.478
Betaine (μg/ml)[b]	7.65 (6.37, 8.66)	7.886 (6.41, 9.35)	−0.070	0.481	0.458

[a]*Mean ± standard deviation.*

[b]*Median and interquartile range (P25, P75).*

[c]*After log transformation.*

Bold values mean statistical significance ($p < 0.05$), and false discovery rates (FDR) ≤ 0.30. BCAA, branched-chain-aminoacids; AAA, aromatic-aminoacids; C2, acetylcarnitine; C3, propionyl-L-carnitine; C5, valeryl-L-carnitine; C6, AcyCNhexenoyl-L-carnitine; C8, octanoyl-L-carnitine; C10, decanoyl-L-carnitin; C10:1, decenoyl-L-carnitine; C12, dodecanoy-L-carnitine; C14, tetradecanoyl-L-car-nitine; C16, hexadec-anoyl-L-carnitine; C18, octadecanoyl-L-carnitine; C18:1, octadecenoyl-L-carnitine; LPC16:0, 1-palmitoyl-2-hydroxy-sn-glycero-3-phosphocholine; LPC18:0, 1-stearoyl-2-hydroxy-sn-glycero-3-phosphocholine; LPC18:1, 1-oleoyl-2-hydroxy-sn-glycero-3-phosphocholine; LPC18:2, 1-linoleoyl-2-hydroxy-sn-glycero-3-phosphocholine; TMAO, trimethylamine oxid.

(OR) (95% CI) of the second quartile was 0.278 (0.118–0.655) for tryptophan, that of the second quartile for C8 was 2.435 (1.066–5.564), that of the lower quartile for C12 was 4.059 (1.919–8.586), that of the third quartile for LPC16:0 was 0.322 (0.136–0.76), and that of the second quartile for LPC18:2 was 0.18 (0.072–0.447), compared with the lowest quartile. Additionally, when analyzed as continuous variables, C5, LPC16:0, and LPC18:2 were dependently associated with frailty in three adjustment models (all $p < 0.05$ **Supplementary Table 1**).

No significant relationship was found between levels of glycine, C10, C14, and frailty in Models 2 and 3, whereas, a significant association was observed in Model 1 (**Supplementary Table 2**). When the data were examined, taking into account malnutrition and chemical indices, the results for tryptophan, C8, and LPC16:0 were changed slightly and remained significantly associated with frailty; however, the effects of glycine, C10, and C14 on the presence of frailty were reduced or remained non-significant after further adjustment.

Orthogonal Partial Least Squares Discriminant Analysis of Frailty and Sarcopenia

To better understand the correlation between measured metabolic factors and frailty status, OPLS-DA was performed

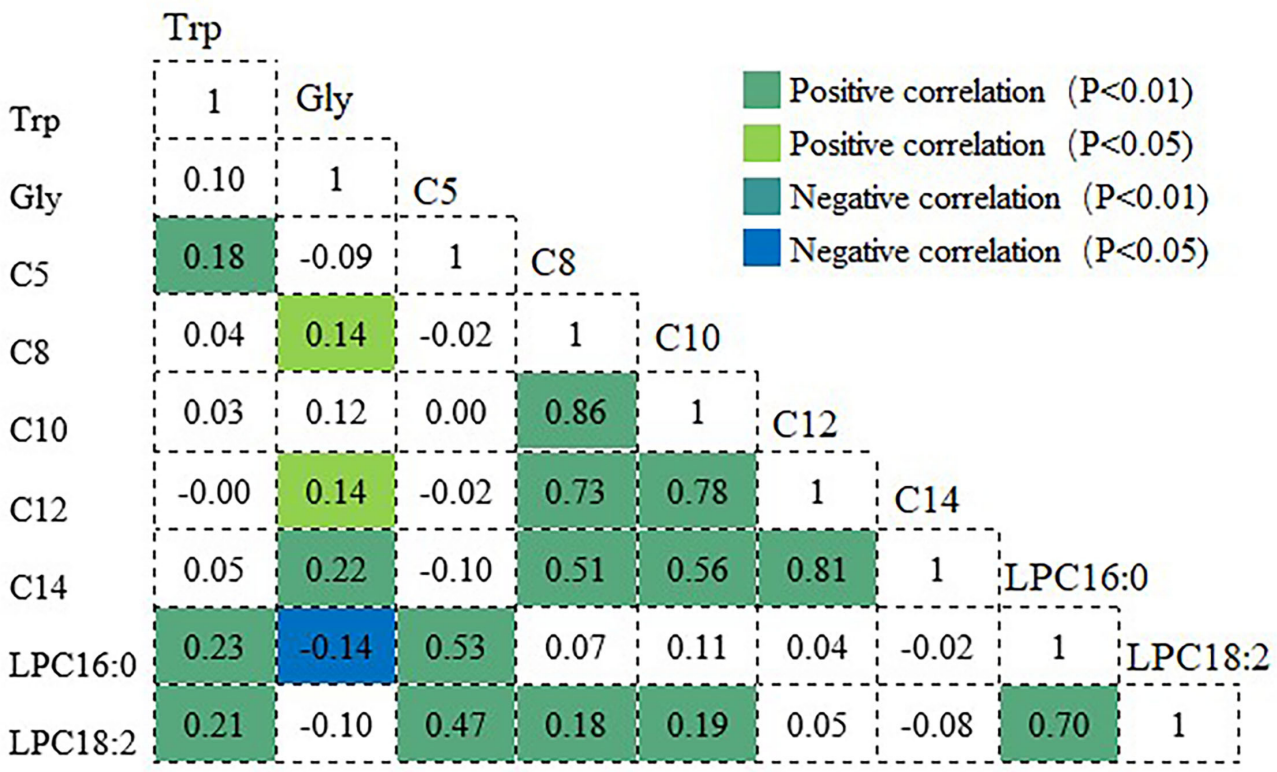


FIGURE 1 | Correlation coefficients among the metabolites significantly associated with frailty. Positive and negative correlations are shown in green and blue, respectively. Trp, tryptophan; Gly, glycine; C5, valeryl-L-carnitine; C8, octanoyl-L-carnitine; C10, decanoyl-L-carnitin; C12, dodecanoy-L-carnitine; C14, tetradecanoyl-L-car-nitine; LPC16:0, 1-palmitoyl-2-hydroxy-sn-glycero-3-phosphocholine; LPC18:2, 1-linoleoyl-2-hydroxy-sn-glycero-3-phosphocholine.

to identify the main components that could discriminate the two groups. Unfortunately, the OPLS-DA score plot yielded no clear separation and merely showed a trend distinguishing frailty elderly men from their non-frailty counterparts (**Figure 2A**). The parameters of goodness of fit and goodness of prediction in the OPLS-DA model showed that this model had a certain ability to explain but low ability to predict frailty (R2X = 0.517, R2Y = 0.231, Q2 = 0.025), suggesting that it was not optimal for discriminating the two groups with these metabolites. This exploratory result showed that the most important metabolites for frailty status were LPC16:0, LPC18:2, glycine, valine, and tryptophan (**Figures 2C,E**); however, univariate analysis showed no significant difference in valine level between the two groups (**Table 2**).

With regard to the OPLS-DA model of F&S vs. non-frail and non-sarcopenic control, the clustering trend was not sufficiently ideal; a separation trend was only found for the main principal components, and the predictive capacity was low, although this model had certain explainability (R2X = 0.615, R2Y = 0.172, Q2 = 0.032) (**Figure 2B**). This exploratory model showed that the best discriminant metabolites contributing to the model included a subset of LPC16:0, LPC18:2, valine, and tryptophan (**Figures 2D,F**). Among these discriminant metabolites, most showed reduced levels in F&S compared with non-frail and non-sarcopenic control; however, the glycine concentration was increased in F&S. These discriminant metabolites in F&S are presented in **Table 4**; the univariate analysis showed a significant difference in C5 concentration (VIP $<$ 1) between F&S vs. non-frail and non-sarcopenic control, however, no significant differences of valine (VIP $>$ 1) and glycine levels (VIP $<$ 1) were found between the two groups.

Permutation tests indicated that the above models were reliable and had a low risk of over-fitting. The area under the curve (AUC) of the above two models were all $>$0.7 with the discriminatory power to some accuracy (**Supplementary Figure 1**).

DISCUSSION

Frailty is associated with a higher risk of disability, hospitalization, and death in older people, playing a central role in poor health later in life. Related biomarkers of frailty can be used in diagnosis and treatment decisions concerning frailty (38, 39). As a reflection of the comprehensive interaction between the genome and environment at the individual level, metabolomics methods are increasingly becoming the preferred approach to uncover frailty- contributing biomarkers and

TABLE 3 | Logistic regression analysis for significant associations of serum metabolites with frailty.

Variables	Model1				Model 2				Model 3			
	β	*SE*	*OR* (95% *CI*)	*P*	*β*	*SE*	*OR* (95% *CI*)	*P*	*β*	*SE*	*OR* (95% *CI*)	*P*
Tryptophan -M3	−0.612	0.395	0.542 (0.250, 1.177)	0.122	−0.325	0.432	0.722 (0.310, 1.684)	0.451	−0.298	0.446	0.743 (0.310, 1.780)	0.505
-M2	−1.378	0.391	0.252 (0.117, 0.543)	**0.000**	−1.270	0.428	0.281 (0.121, 0.65)	**0.003**	−1.282	0.438	0.278 (0.118, 0.655)	**0.003**
-M1	−0.312	0.401	0.732 (0.334, 1.607)	0.437	−0.382	0.441	0.683 (0.288, 1.62)	0.387	−0.297	0.453	0.743 (0.306, 1.805)	0.512
C8-M3	0.909	0.394	2.481 (1.147, 5.367)	**0.021**	0.788	0.432	2.198 (0.942, 5.129)	0.069	0.789	0.454	2.202 (0.905, 5.359)	0.082
-M2	0.864	0.376	2.373 (1.135, 4.962)	**0.022**	0.809	0.411	2.245 (1.002, 5.027)	**0.049**	0.890	0.422	2.435 (1.066, 5.564)	**0.035**
-M1	0.507	0.366	1.661 (0.811, 3.402)	0.166	0.382	0.400	1.465 (0.669, 3.206)	0.340	0.248	0.413	1.282 (0.571, 2.879)	0.548
C12-M3	0.201	0.439	1.222 (0.517, 2.887)	0.647	0.322	0.486	1.38 (0.533, 3.577)	0.507	0.267	0.495	1.305 (0.495, 3.443)	0.590
-M2	0.430	0.445	1.538 (0.643, 3.679)	0.333	0.244	0.492	1.276 (0.486, 3.349)	0.621	0.301	0.523	1.351 (0.485, 3.762)	0.565
-M1	1.212	0.335	3.36 (1.741, 6.484)	**0.000**	1.249	0.369	3.488 (1.692, 7.191)	**0.001**	1.401	0.382	4.059 (1.919, 8.586)	**0.000**
LPC16:0-M3	−0.852	0.374	0.427 (0.205, 0.887)	**0.023**	−0.850	0.413	0.427 (0.190, 0.960)	**0.040**	−1.134	0.438	0.322 (0.136, 0.76)	**0.010**
-M2	−0.323	0.378	0.724 (0.345, 1.518)	0.393	−0.193	0.412	0.824 (0.368, 1.848)	0.639	−0.294	0.433	0.745 (0.319, 1.74)	0.496
-M1	0.084	0.392	1.087 (0.505, 2.344)	0.831	0.109	0.429	1.116 (0.481, 2.588)	0.799	0.014	0.443	1.014 (0.426, 2.418)	0.974
LPC18:2-M3	−0.715	0.389	0.489 (0.228, 1.048)	0.066	−0.749	0.427	0.473 (0.205, 1.092)	0.079	−1.171	0.460	0.31 (0.126, 0.763)	**0.011**
-M2	−1.225	0.386	0.294 (0.138, 0.625)	**0.002**	−1.362	0.434	0.256 (0.109, 0.600)	**0.002**	−1.718	0.466	0.18 (0.072, 0.447)	**0.000**
-M1	−0.080	0.401	0.923 (0.421, 2.025)	0.841	−0.078	0.439	0.925 (0.392, 2.184)	0.858	−0.336	0.462	0.714 (0.289, 1.765)	0.466

Model1: age, body mass index, smoking status; Model2: further controlled for malnutrition, cognitive decline, activities of daily living, polypharmacy, comorbidities; Model3: further controlled for red blood cell and hemoglobin, alanine aminotransferase and uric acid; Measured metabolites were used as categorical variables: lower quartile (M1), median (M2), upper quartile (M3) vs. lowest quartile. C5, valeryl-L-carnitine; C8, octanoyl-L-carnitine; C10, decanoyl-L-carnitin; C12, dodecanoy-L-carnitine; C14, tetradecanoyl-L-car-nitine; LPC16:0, 1-palmitoyl-2-hydroxy-sn-glycero-3-phosphocholine; LPC18:2, 1-linoleoyl-2-hydroxy-sn-glycero-3-phosphocholine. Bold values mean statistical significance ($p < 0.05$).

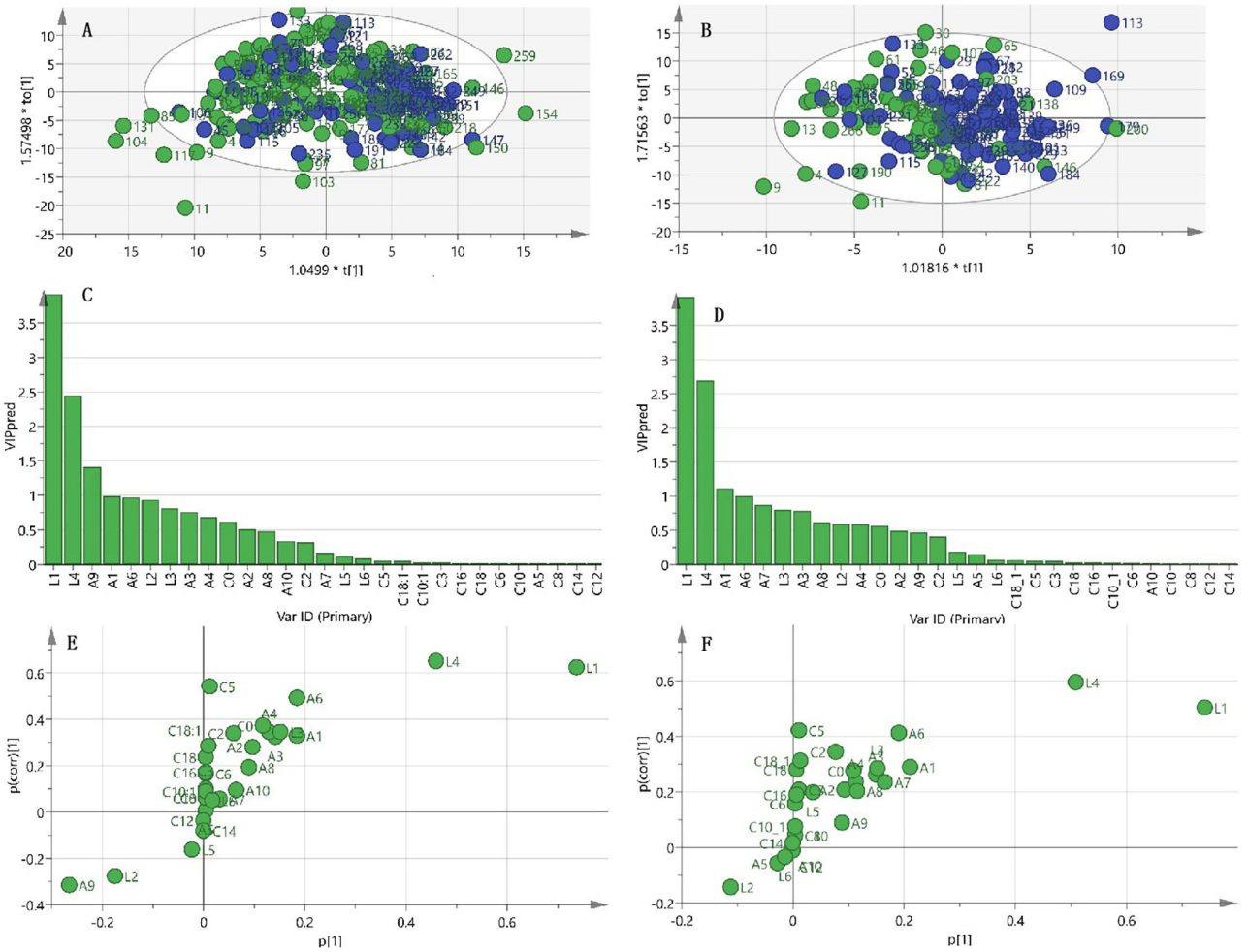


FIGURE 2 | OPLS-DA analysis for frailty status using metabolism data. **(A)** Scatter plot of OPLS-DA model analysis for frailty (green circle) vs. non-frailty groups (blue circle) by the main components. **(B)** Scatter plot of OPLS-DA model analysis for frailty and sarcopenia (F&S) (green circle) vs. non-frail and non-sarcopenic control (blue circle) by the main components. **(C)** Ordered list of metabolites with higher discrimination ability based on variable importance for the projection (VIP) score for separation of frailty and non-frailty groups. **(D)** Ordered list of metabolites with higher discrimination ability based on VIP for separation of frailty and sarcopenia (F&S) vs. non-frail and non-sarcopenic control. **(E)** S-plot of the OPLS-DA model of the frailty and non-frailty groups. **(F)** S-plot of the OPLS-DA model of frailty and sarcopenia vs. the non-frail and non-sarcopenic control. A9, glycine; A1, valine; A6, tryptophan; A3, leucine; A4, tyrosine; A2, Ileucine; A8, glutamate; A10, alanine; A7, glutamine; A5, phenylalanine; C0, carnitine; C2, acetylcarnitine; C3, propionyl-L-carnitine; C5, valeryl-L-carnitine; C6, AcyCNhexenoyl-L-carnitine; C8, octanoyl-L-carnitine; C10, decanoyl-L-carnitin; C10:1, decenoyl-L-carnitine; C12, dodecanoy-L-carnitine; C14, tetradecanoyl-L-car-nitine; C16, hexadec-C16anoyl-L-carnitine; C18, octadecanoyl-L-carnitine; C18:1, octadecenoyl-L-carnitine; L1, 1-palmitoyl-2-hydroxy-sn-glycero-3-phosphocholine (LPC16:0); L2, 1-stearoyl-2-hydroxy-sn-glycero-3-phosphocholine (LPC18:0); L3, 1-oleoyl-2-hydroxy-sn-glycero-3-phosphocholine (LPC18:1); L4, 1-linoleoyl-2-hydroxy-sn-glycero-3-phosphocholine (LPC18:2); L5, trimethylamine-N-oxide (TMAO); L6, betaine.

explore the mechanismof frailty (11–13). To our knowledge, the relationship of frailty with AcyCNs and LPCs, as well as amino acids, in older adults has not been well characterized. In the current study, we found that in older men demonstrating the frailty phenotype, amino acid perturbations involved in lower tryptophan and increased glycine levels. With regard to lipid metabolism, the frailty phenotype was characterized by decreased concentrations of C5, LPC16:0, and LPC18:2 and increased levels of C8, C10, C12, and C14. After adjusting for several clinical factors, logistic regression analysis showed that tryptophan, LPC 18:2, LPC16:0, and C5 were negatively associated with frailty whereas C8 and C12 were positively associated with frailty. As an OPLS-DA-based strategy, owing to its ability to handle multiple interdependent variables, we preliminarily identified specific profiles of circulating metabolites LPC16:0, LPC18:2, glycine, and tryptophan that discriminate older men with frailty from non-frailty individuals. Additionally, a combination of serum amino acids and LPCs, specifically LPC16:0, LPC18:2, and tryptophan, were preliminarily identified as characteristic metabotypes in older adults, with an overlap of frailty and sarcopenia in this study. The presence of metabolic differences between older men with and without frailty has the potential

TABLE 4 | Serum concentrations of discriminant analytes in frailty and sarcopenia (F&S).

Variables	Non-frailty and non-sarcopenia ($n = 85$)	Frailty and sarcopenia ($n = 52$)	VIP	t/Z	*P*-value	FDR
LPC16:0 (μg/ml)[a]	121.3 (93.21, 147.59)	104.28 (85.27, 129.33)	**3.918**	−2.601	**0.009**	**0.135**
LPC18:2 (μg/ml)[a]	30.46 (24.22, 36.06)	24.36 (17.73, 33.02)	**2.69**	−2.600	**0.009**	**0.091**
valine (μg/ml)	40.69 ± 6.48	39.48 ± 8.92	**1.114**	−1.435	0.151	0.439
Tryptophan (μg/ml)	17.61 ± 2.74	16.36 ± 3.37	**1.006**	−2.553	**0.011**	0.078
Glutamine (μg/ml)	26.13 ± 7.84	25.21 ± 5.24	0.874	−0.126	0.899	0.932
LPC18:1 (μg/ml)	18.20 ± 4.05	17.42 ± 3.93	0.800	−1.200	0.230	0.477
Leucine (μg/ml)	26.06 ± 4.07	25.31 ± 5.43	0.786	−1.124	0.261	0.504
Glutamate (μg/ml)	22.28 ± 3.85	21.10 ± 5.92	0.615	−1.812	0.070	0.338
LPC18:0 (μg/ml)[a]	36.45 (30.29, 39.26)	35.48 (30.24, 43.04)	0.595	0.326	0.744	0.864
Tyrosine (μg/ml)	16.23 ± 2.85	15.80 ± 3.83	0.593	−0.690	0.494	0.753
carnitine (μg/mg)	10.61 ± 2.21	10.05 ± 2.05	0.570	−1.308	0.191	0.461
Ileucine (μg/ml)	12.92 ± 2.52	12.57 ± 3.28	0.493	−1.220	0.222	0.496
glycine (μg/ml)[a]	37.81 (32.42, 48.12)	39.54 (35.36, 43.44)	0.470	0.809	0.418	0.713
C2 (μg/mg)	2.26 ± 0.78	2.12 ± 0.64	0.410	−0.736	0.462	0.744
TMAO (μg/ml) [a]	0.43 (0.27, 0.59)	0.43 (0.28, 0.7)	0.189	0.333	0.739	0.893
Phenylalanine (μg/ml)	19.25 ± 3.58	19.72 ± 4.15	0.151	0.481	0.630	0.831
C18:1 (μg/mg)[a]	0.10 (0.09, 0.12)	0.09 (0.08, 0.11)	0.066	−1.713	0.087	0.315
C5 (μg/mg)[a]	0.03 (0.02, 0.03)	0.02 (0.02, 0.03)	0.059	−2.995	**0.003**	**0.080**
C3 (μg/mg)	0.11 ± 0.03	0.10 ± 0.04	0.054	−0.581	0.561	0.814
C18 (μg/mg)[a]	0.03 (0.02, 0.03)	0.02 (0.02, 0.03)	0.029	−0.545	0.586	0.809

[a]*Median and interquartile range (P25, P75).*

Bold values mean VIP > 1 statistical significance ($p < 0.05$), and false discovery rates (FDR) ≤ 0.30. C2, acetylcarnitine; C3, propionyl-L-carnitine; C5, valeryl-L-carnitine; C18, octadecanoyl-L-carnitine; C18:1, octadecenoyl-L-carnitine; LPC16:0, 1-palmitoyl-2-hydroxy-sn-glycero-3-phosphocholine; LPC18:0, 1-stearoyl-2-hydroxy-sn-glycero-3-phosphocholine; LPC18:1, 1-oleoyl-2-hydroxy-sn-glycero-3-phosphocholine; LPC18:2, 1-linoleoyl-2-hydroxy-sn-glycero-3-phosphocholine; TMAO, trimethylamine oxide.

to be used as a biomarker for frailty, and overlapped sarcopnia. This may represent a relevant step toward the integration of specific metabolite measurements into the management of frailty and sarcopenia in research and clinical settings.

Specific patterns of circulating amino acids have been associated with frailty; among amino acid profiles, tryptophan breakdown products have been found in many studies. Tryptophan is an essential amino acid that exerts multiple roles in immune, nervous, and muscular system functions (40, 41). Alterations in tryptophan metabolism have been described in the context of low muscle quality, insulin resistance, and frailty in older adults (42). Marron et al. identified metabolites and biological pathways associated with frailty among 287 black men aged 70–81 years from the Health, Aging, and Body Composition (ABC) study. Using LC–MS/MS, they found that lower values of tryptophan, methionine, tyrosine, asparagine, C14:0 sphingomyelin, as well as 1-methylnicotinamide and higher values of glucoronate, N-carbamoyl-beta-alanine, isocitrate, creatinine, C4-OH carnitine, cystathionine, hydroxyphenylacetate, and putrescine were associated with frailty Scale of Aging Vigor in Epidemiology scores in partial Pearson correlation analysis (30). Additional study have demonstrated the occurrence of lower levels of tryptophan, serine, histidine, glycerol, and sphingosine phospholipids and higher levels of hydroxyproline, 3-methylhydropyridine, cystine, and β-aminoisobutyric acid metabolites in variance analysis and linear regression analysis among patients with breast cancer who have frailty (43). Consistent with recent findings, Kameda et al. (44) applied untargeted, comprehensive LC-MS metabolomic analysis to human blood from 19 frail and non-frail elderly patients who were clinically evaluated using the Edmonton Frail Scale. Those authors found that among the 15 frailty markers, tryptophan, proline, isoleucine, leucine, and methionine were reduced. In a population of Spanish older adults recruited from several associations of retired older people, nursing homes, and daycare centers, significant decreases in tryptophan, nitrite, and tyrosine concentrations were noted in frail individuals compared with non-frail persons (45). In the "BIOmarkers associated with Sarcopenia and Physical frailty (PF&S) in ElderRly pErsons" (BIOSPHERE) study, 11 elderly adults aged 70 years and older with PF&S and 10 non-frail and non-sarcopenic controls were included. The results of that study showed that a decline in tryptophan was one of the best predictors for discriminating older people with and without PF&S (46). Our data support those previous studies. It can be deduced that tryptophan, as a radical scavenger, its diminished level could be an important vulnerability for antioxidative defense and might be involved in the pathogenesis of frailty, and overlapped sarcopenia. Notwithstanding, our finding on lower level in tryptophan is not consistent with previous investigation that have reported higher tryptophan concentrations in patients with frailty and type 2 diabetes, according to the European Metabofrail study, which applied a partial least squares-discriminant analysis (PLS-DA)-based

analytical strategy to characterize the metabotype (47). Thus, it is essential that further research be performed to confirm the specific role of tryptophan in frailty.

Glycine is a major amino acid and the simplest non-essential amino acid. Recent metabolomics studies have found a relationship between serum levels of glycine and cardiometabolic disease (28, 29). Glycine is involved in anti-inflammatory processes, immune function, and antioxidation reactions (48). In the present study, we observed that the glycine level was higher, after adjusting for clinical factors in logistic regression of Models 2 and 3, and its relationship with frailty did not remain significant, whereas, showed no significant difference in F&S. Valine is a BCAA that has a stimulatory effect on glutamine synthesis and is a major source of nitrogen (49). Although it was found to be involved in distinguishing between the two groups, no significant differences were observed between groups in the serum levels of BCAAs (valine, leucine, and isoleucine) and Glu in the present study. In particular, lower plasma concentrations of the BCAAs leucine and isoleucine have been found in sarcopenic older Norwegian community dwelling adults (50). Additionally, frail older Japanese people showed lower levels of essential amino acids (histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, valine) and tryptophan than their non-frail counterparts (40). Older individuals with frailty and sarcopenia showed higher levels of circulating asparagine, aspartic acid, citrulline, ethanolamine, glutamic acid, sarcosine, and taurine and lower levels of alpha-amino butyric acid and methionine in PLS-DA (46). Notwithstanding, our finding regarding BCAAs is not consistent with previous investigations reporting changes in BCAA concentrations in relation to frailty and sarcopenia. These discrepancies may be owing to differences in clinical characteristics, operational definitions of frailty and experimental designs among studies. Additionally, heterogeneity in dietary and lifestyle habits among participants in the different studies may also contribute to the contrasting results.

LPCs are a major class of glycerophospholipids in human blood. The most abundant LPC in human plasma is LPC 16:0, followed by LPC 18:2, LPC 18:0/18:1, LPC 20:4, and other minor LPC species. LPC has been relevant to muscle mass and mitochondrial oxidative capacity in skeletal muscle (20, 51). Previous studies have demonstrated the occurrence of lower levels of glycerol and sphingosine phospholipids in frail patients with breast cancer (43). In the current study, both frailty individuals and overlapped sarcopenia showed perturbation in the metabolism of LPC16:0 and LPC18:2 in which serum concentrations were lower than those observed in non-frailty individuals. Decreased blood LPC18:2 has previously been shown to be an independent predictor of decline in gait speed, in addition to glucose tolerance, insulin resistance, type 2 diabetes, coronary artery disease, and memory impairment in older adults (19). The homeostasis of phospholipids is achieved by balancing biosynthesis, degradation, recycling, and other processes that add or remove sphingolipids from tissues. The depletion of circulatory phospholipids observed in frailty elderly men could reflect an enhanced demand for lipids to reconstitute cellular membrane turnover. The biological mechanisms by which LPCs play important roles in antioxidation, inflammation and insulin resistance may be important contributors to frailty and sarcopenia (52).

As short-chain AcyCNs, propionyl (C3), methylmalonyl (C4-DC), and isovalerylcarnitine (C5), as well as medium-/long-chain AcyCNs (C6–C20) are produced during fatty acid oxidation (53). The main function of AcyCNs is the transport of long-chain fatty acids to the inner mitochondrial membrane to permit β-oxidation. Other functions of AcyCNs include buffering the mitochondrial acyl-CoA/CoA ratio, oxidation of BCAAs and a protective effect on the endogenous antioxidant defense system (54). Carnitine was found to be correlated with frailty, grip strength, gait speed, or muscle mass (55), but not sarcopenia. In a cross-sectional study of frailty phenotype compiled from older outpatients, the researchers evaluated the carnitine levels in patients with frailty and observed that high levels of carnitine may have a favorable effect on functional status and may be used to treat frailty in older people, however, no specific species of carnitine was detected (56). In this study, we found a lower level of C5 in frailty and overlapped sarcopenia, whereas, higher levels of C8, C10, C12, and C14 in the frailty group; after adjusting for several confounders, C8 and C12 and C5 were independently associated with frailty. In a previous study, C5 was also positively related to SMI (55). Blood level of C5 has been associated with muscle metabolites in frailty. Moreover, C5, Glu, and Gln have been found to be markers of frailty in skeletal muscle (57). Thus, a reduction in C5 level is expected to cause reduced availability of long-chain fatty acids in the mitochondria and an energetic deficit, especially in the most energy-demanding tissues, like skeletal muscle, playing a role in modulating cellular energy production (58). Previous studies have also found higher plasma concentrations of medium- and long-chain AcyCNs, which are correlated with lower levels of physical performance (59) and a greater risk of lower Short Physical Performance Battery score (including balance, gait speed, and 5-repetition sit-to-stand) (17). Similar to the above results, frail participants showed perturbation of acylcarnitine, as shown by the higher levels in medium/long-chain AcyCNs (C8, C10, C12, and C14) in our study. Moreover, Rattray et al. (10) identified 12 significant metabolites, including six carnitines, comprising tetradecanoyl carnitine C14:1, trans-hexadec-2-enoyl-carnitine, linoleyl-carnitine C18:2, vaccenyl-carnitine, stearoyl-carnitine, and hexacosanoyl-carnitine, that could differentiatefrail and non-frail phenotypes, providing evidence that the dysregulation of carnitine shuttle pathways plays a key role in the risk of frailty. The increased level of AcyCNs can indicate mitochondrial dysfunction and a potential increase in the production of reactive oxygen species.

In our study, the significant relationship observed between these frailty-related metabolites indicate that they change in interrelated ways. These metabolites are at the crossroads of multiple biological processes, notebly, mitochondrial function and redox homeostasis besides inflammation and insulin resistance, all of which may contribute to frailty or sarcopenia as per the above discussion. As an intermediate product of fatty acid oxidation, significantly positive correlations were observed among the AcyCNs C8, C10, C12, and C14. The accumulation of these medium-/long-chain AcyCNs may point

toward the inability of mitochondria to properly metabolize fatty acids (54, 60). The decline in tryptophan concentration may be related to malnutrition in this study, and a lower C5 concentration showed a positive relationship with tryptophan, possibly because both of these are metabolites are associated with BCAA metabolism (61). C5 was also moderately associated with LPC16:0 and LPC18:2, and the reduction in C5 and LPCs levels may be owing to impaired mitochondrial oxidative capacity (62). The accumulation of non-oxidized fatty acids promotes their conjugation with glycine and carnitine and alternate ways of oxidation (63). The underlying mechanism of the correlations among other metabolites are still unclear, and future research is needed in metabolic pathway analysis.

In the present study, in either univariate or multivariate analysis, the three shared metabolites of frailty and F&S included LPC16:0, LPC18:2 and tryptophan. Two reasons may help to explain the relationship between characteristic metabotypes of frailty and that of F&S. First, at definition level, frailty encompasses several domains (i.e., physical and cognitive), and sarcopenia overlaps with the physical domain of frailty. Gait speed and grip strength are both used to define frailty and sarcopenia, and the above mentioned metabolites are related to these two muscle traits (19). Additionally, specific patterns of circulating tryptophan and LPCs have been associated with muscle mass which is essential in sarcopenia (42, 51); hence, the above metabolites might be more pronounced in metabotype changes with F&S status. Conversely, the existing research findings showed that glycine and some subclasses of AcyCNs are related to frailty (10, 42); however, no studies have reported that these are related to sarcopenia, only related to one or more sarcopenic components (55). Second, from a pathophysiologic point of view, the study of metabolic responses in specific biochemical pathways are of great interest considering the close association between the characteristic metabotypes of frailty and that of F&S. F&S may be considered a prototypical geriatric/geroscience condition, spanning muscle-specific processes to systemic changes (9, 64), even though frailty and sarcopenia are different concepts. We believe that this correlation of metabotypes of frailty with that of F&S emphasizes the interrelation of the above pathophysiological mechanisms.

Body composition, neuroendocrine dysregulation, and immune dysfunction may represent the underlying biologic dynamics that influence the development of frailty in both men and women (65, 66). According to these physiological differences, sex differences in metabolites would be expected, however, the existing evidence is sparse on whether the relationship between metabolic markers and risk of frailty/sarcopenia is the same in men and women. Among previous studies, one study reported that the best multivariate predictive models of of evolution toward pre-frailty include dimethyloxazole, glutamine, and isovalerylcarnitine in men, and dihydroxyphenyl acetic acid, threonine, and mannose in women (58). There are several metabolic studies concerning elderly men. To identify metabolic perturbations that may affect functional decline, non-targeted metabolomics was used in 313 black men in the Health ABC Study, the potential role of amino acid derivatives and products and kidney function early in the development of mobility disability was highlighted (18). Marron et al. identified metabolites associated with frailty among 287 black men, they found that lower values of tryptophan, methionine, tyrosine, asparagine, C14:0 sphingomyelin, etc. were associated with the frailty (30). Murphy et al. (55) performed metabolomics analysis of plasma from 319 black men; the metabolites most strongly correlated with ASM included AcyCN C5 and BCAAs. Of importance, the causes of impaired muscle mass and strength with aging were examined in 119 older men; the results demonstrated a fundamental role of altered mitochondrial metabolism in the pathological losses in sarcopenia among older people (67). In contrast, most previous studies in women have addressed sarcopenic components. A study among community-dwelling older Japanese women found that those with sarcopenia showed lower plasma leucine, BCAA, and essential amino acid concentrations than normal and pre-sarcopenic older women (68) and compounds involved in nitrogen metabolism could be affected in sarcopenia, with an inherent risk in women (51). Importantly, previous metabolic studies have replicated associations between metabolites and phenotypes (55) across populations comprising both men and women, with diverse race/ethnicities and demographics, suggesting some biological variations may have a minimal impact on metabolite relationships. Our study did not include analysis of frail women because of the small sample of female patients who met the inclusion criteria. Gender factor should be considered using reasonable grouping or matching to minimize bias in the future study.

There are some limitations in the present study. First, the study population was relatively small; also, a large number of experimental variables were included in the analyses, which may limit the statistical power. Second, the participants in our study were mostly older men with prefrail status; thus, the findings cannot necessarily be generalized to populations owing to social and cultural differences. Third, other factors may affect circulating metabolites levels, such as lifestyle and dietary habits. Thorough investigations regarding the effect of lifestyle variables, dietary intake, and medication on potential biomarkers should be conducted in further studies to understand all important confounders. Last, this study is a cross-sectional study sought to assess the relationship of metabolites with frailty, and a causal relationship and potential diagnostic biomarkers of metabolic changes in frailty should be investigated in future follow-up studies.

CONCLUSION

Our metabolic profiling analysis can provide valuable information regarding the potential biomarkers and possible biological mechanisms in older men. In addition to identifying LPC16:0, LPC18:2, tryptophan, C5, C8 and C12, which appear to be independently correlated with frailty status, we preliminarily demonstrate that the characteristic metabotypes of frailty and that of F&S shared a set of tryptophan, LPC16:0 and LPC18:2, and glycine may specifically discriminate individuals with frailty from non-frailty. The metabolites that were most discriminating

of frailty status may imply an underlying mechanism involved in antioxidation and mitochondrial function. These findings offer important references for the management of frailty and sarcopenia. Subsequent studies are needed to confirm our findings and to further determine whether these metabolites can indeed be used as potential biomarkers for frailty.

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Beijing Hospital of the National Health Commission. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LM: designed the study, analyzed the data, and drafted the paper. R-yY: performed the study, detection of metabolites, and contributed to the writing of the manuscript preparation. HS: contributed to the design of the work, and helped in execution of research. D-gW: sample collection and preparation, detection of blood chemical parameters. JShi, W-bW, JShe, Y-mD, and G-qF: performed the study and collected the data. P-lY and JD: helped in execution of research. HX: initiated the study, supervised the writing of the manuscript. 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.2022.816045/full#supplementary-material

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How Healthcare Utilization Due to Dizziness and Vertigo Differs Between Older and Younger Adults

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Background: Vertigo and dizziness are common in older adults. We describe self-reported healthcare utilization because of dizziness and vertigo in older adults attending a tertiary care specialized vertigo center.

Methods: Data from 765 patients (45% were ≥60 years old) with chronic dizziness and vertigo who attended a daycare multimodal treatment program were recorded. Data included sociodemographic parameters, dizziness-related characteristics, the Body Sensations Questionnaire (BSQ), the Agoraphobic Cognitions Questionnaire (ACQ), and the Hospital Anxiety and Depression Scale (HADS). Also, healthcare utilization, including (1) physician and clinical services, (2) hospitalizations in the year before consulting the vertigo center, (3) prescription of drugs and other professional services were included. Descriptive statistics, exploratory data analysis, and regression models were used.

Results: Intensity of dizziness was similar in both age groups, however, distress due to dizziness was more severe in younger persons. Dizziness symptoms lasted longer in older adults than in younger persons. Older adults had a somatic diagnosis (74.6 vs. 35.0%) more frequently and reported more falls (37.2 vs. 28.5%) than younger individuals. Anxiety about bodily sensations was higher in younger patients (mean BSQ1 = 9.33 ± 5.6) than in older patients (mean BSQ1 = 6.72 ± 5.4). Older persons had fewer depressive symptoms (mean HADS depression = 5.8 ± 3.6 vs. 6.5 ± 4.1) and less anxiety (mean HADS anxiety = 5.7 ± 3.7 vs. 7.8 ± 4.1) than younger individuals. Younger people were more frequently hospitalized (24.4%) than older adults (16.3%) in the year before consulting the vertigo center. Also, younger patients and patients with non-somatic etiologies had considerably more consultations with healthcare providers than older patients. Older adults received less medication (50.3%), less physiotherapy (41%), and less psychological therapy (11.6%) for vertigo than younger people (59.7, 52.2, 20.4%, respectively).

Conclusion: Age-associated differences in healthcare utilization were defined in selected patients attending a specialized vertigo center. Since dizziness is frequently a heterogeneous disorder requiring interdisciplinary care, its diagnostic and therapeutic work-up must be improved for older patients with dizziness.

Keywords: dizziness, vertigo, healthcare utilization, older age, hospitalization

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INTRODUCTION

Vertigo and dizziness have a high lifetime prevalence of about every fifth adult suffering from dizziness or vertigo (1). Data on the lifetime prevalence of dizziness and vertigo show an increasing prevalence of 30% to 50% in older people (2–5). In older patients, multifactorial, degenerative, and chronic causes of vertigo/dizziness prevail (6, 7). Older adults with dizziness often suffer from multisensory deficits, such as central vertigo bilateral vestibulopathy, and benign paroxysmal positional vertigo (8, 9). Especially in older individuals, vertigo and dizziness contribute to physical inactivity (10), social isolation, depression (11), dizziness-associated disabilities (12), and a higher risk of falls (13, 14). Therefore, dizziness and vertigo *per-se* and commonly associated psychiatric comorbidities, such as anxiety or depression, can cause increased healthcare utilization (15), incurring a high economic burden (16, 17). It is, therefore, necessary to identify factors that influence a person's use of healthcare services.

In general, healthcare services can be used to diagnose or treat disorders, improve or maintain function, or obtain information about health status. Healthcare utilization depends on the need for care, the will to obtain care, and access to care (18–20). Among other, healthcare utilization includes the prescription of drugs and hospital, physician, clinical, and nursing care services (21).

We describe self-reported healthcare utilization because of dizziness in older adults before attending a specialized vertigo center. We aimed to (1) describe differences for consulting healthcare providers, hospitalizations, and therapy in younger and older adults, (2) explore if these differences are associated with age or can be attributed to other factors.

METHODS

Participants

Overall, 765 patients with chronic dizziness and vertigo attended a daycare multimodal treatment program (22) between June 2013 and September 2017 in the Center for Vertigo and Dizziness of Jena University Hospital. The Center for Vertigo and Dizziness is a tertiary care outpatient project consisting of neurology, ear, nose, and throat (ENT), and physiotherapy departments. The center provides interdisciplinary diagnoses of patients with chronic vertigo and dizziness and day care multimodal therapy (23). Requirements for participation in this outpatient treatment program were: Chronic dizziness and vertigo (i.e., symptoms have persisted for at least 3months or attacks have recurred at least 5 days per month), physical independence (i.e., walking independently) and no cognitive limitations that may affect the activities of daily living.

The study was approved by the local ethics committee (Ethics Committee of the Friedrich-Schiller-University Jena, Number 5426-02/18), and written informed consent for study participation was obtained from all patients.

Assessments

We assessed the following self-reported sociodemographic and vertigo- and dizziness-related data on the first day of the treatment: age (metric; years), gender (binominal; male/female), a rough description of symptoms (binominal; the presence or absence of attacks, permanent dizziness/vertigo, or falls in the last 12 months), and the duration of symptoms (multinomial, $\leq$2 months, 2–6 months, 6–12 months, 1–2 years, 3–5 years, >5 years). In the last 3 months, the intensity of vertigo/dizziness and the distress due to vertigo/dizziness were quantified using a visual analog scale from 0 (no distress) to 10 (maximal distress). As defined at our center, advanced neurologists and vertigo specialists medically diagnosed and psychologically evaluated every patient.

The Body Sensations Questionnaire (BSQ) and the Agoraphobic Cognitions Questionnaire (ACQ) were also administered via self-report. The BSQ consists of 17 items measuring anxiety about bodily sensations on a 5-point Likert scale and comprises two questionnaires: the BSQ1 assesses the amount of fear and the BSQ2 measures how often the sensations are experienced when the patient feels anxious or tense (24). The ACQ is a 14-item questionnaire that measures maladaptive thoughts about the potential for catastrophic consequences of anxiety or panic. Cronbach's alphas of both questionnaires were high in our sample (BSQ1: $\alpha = 0.85$; BSQ2 $\alpha = 0.94$; ACQ: $\alpha = 0.81$). Earlier studies used the ACQ and BSQ to evaluate patients with dizziness/vertigo (25, 26). The Hospital Anxiety and Depression Scale (HADS) was used to estimate anxiety and depression (27) and evaluate general psychological distress in patients with dizziness (28).

The different types of healthcare utilization were assessed according to the Centers for Medicare & Medicaid Services (CMS) categories via self-report (29): (1) physician and clinical services, (2) hospitalizations in the year before consulting the vertigo center, (3) prescription of drugs, and other professional services (physiotherapy). The utilization of "physician and clinical services" included consultations with a physiotherapist/chiropractor, alternative practitioner, general practitioner, ENT specialist, orthopedist, neurologist, psychiatrist, psychologist, or emergency department physician.

Statistics

All data were analyzed with the Statistical Package for the Social Sciences software (version 25.0; IBM Corporation, USA) and R (R Foundation for Statistical Computing, Vienna, Austria) version 3.6.2 or JASP 0.16. Values are the mean and standard deviation (SD) or numbers and percentages. Normal distribution was determined using the Shapiro–Wilk test. Missing data were treated according to the pairwise deletion process.

First, the cohort was analyzed using descriptive statistics. Differences between younger (<60 years old) and older persons ($\geq$60 years old) were determined by the *t*-test, *U*-test, and Chi-square test.

Elastic net regularization and binominal logistic regressions (backward selection) were used to determine the association between healthcare utilization and clinical variables (after excluding multicollinearity and autocorrelation) (30). Elastic

TABLE 1 | Baseline characteristics of patients.

		< 60 years ($n = 414$) Mean ± SD	≥ 60 years ($n = 351$) Mean ± SD	All Mean ± SD	Significance
Age	Years	46.3 ± 9.6	71.2 ± 6.9	57.7 ± 15.0	$P < 0.001$, r = −1.0
Intensity of dizziness/vertigo	VAS 0–10	6.03 ±1.8	5.93 ± 1.8	5.1 ± 1.8	$P > 0.05$
Distress due to dizziness/vertigo	VAS 0–10	6.7 ± 2.0	6.3 ± 1.9	6.5 ± 2.0	$P = 0.005$, r = 0.11
		***N* (%)**	***N* (%)**	***N* (%)**	
Gender	Female	244 (58.9)	225 (64.1)	469 (61.3)	$P > 0.05$
	Male	170 (41.1)	126 (35.9)	296 (38.7)	
Medical diagnosis	BPPV	6 (1.5)a	17 (4.8)b	23 (3.0)	$P < 0.001$, r = 0.31
	BV	14 (3.4)a	21 (6.0)a	35 (4.6)	
	CV	12 (2.9)a	32 (9.1)b	44 (5.8)	
	MD	30 (7.3)a	25 (7.1)a	55 (7.2)	
	MultD	10 (2.4)a	110 (31.3)b	120 (46.8)	
	PPPD	269 (65.0)a	89 (25.4)b	358 (46.8)	
	VM	21 (5.1)a	9 (2.6)a	30 (3.9)	
	VN	43 (10.4)a	31 (8.8)a	74 (9.7)	
	VP	5 (1.2)a	5 (1.4)a	10 (1.3)	
	VS	4 (1.0)a	12 (3.4)b	16 (2.1)	
Diagnosis category	Somatic	145 (35.0)a	262 (74.6)b	407 (53.2)	$P < 0.001$, r = 0.38
	Non-somatic, psychogenic	233 (56.3)a	68 (19.4)b	301 (39.4)	
	Non-somatic, unspecific	36 (8.7)a	21 (19.4)a	57 (7.5)	
Permanent dizziness/vertigo	Yes	219 (56.6)	188 (56.8)	407 (56.7)	$P > 0.05$
	No	168 (43.4)	143 (43.2)	311 (43.3)	
Attacs	Yes	249 (67.5)	159 (52.3)	408 (60.6)	$P < 0.001$, r = −0.15
	No	120 (32.5)	145 (47.7)	265 (39.4)	
Falls	Yes	108 (28.5)	119 (37.2)	227 (32.5)	$P = 0.017$, r = 0.085
	No	271 (71.5)	201 (62.8)	472 (67.5)	
Disease duration	≤2 months	16 (4.0)a	5 (1.5)b	21 (2.9)	$P < 0.001$, r = −0.18
	2–6 months	53 (13.4)a	23 (7.0)b	76 (10.5)	
	0.5–1 years	93 (23.4)a	58 (17.6)a	151 (20.8)	
	1–2 years	95 (23.9)a	83 (25.2)a	178 (24.5)	
	3–5 years	66 (16.6)a	80 (24.2)b	146 (20.1)	
	>5 years	74 (18.6)a	81 (24.6)a	155 (21.3)	

Significance refers to comparison between younger and older patients. Values in the same row and sub-table where the subscript is not identical differ strongly at $p < 0.05$ in the two-tailed test for equality for column proportions. The r indicates effect size by the Rank-Biserial correlation. SD, standard deviation; VAS, visual analog scale; BPPV, benign paroxysmal positional vertigo; BV, bilateral vestibulopathy; CV, central vertigo; MD, Meniere's disease; MultD, multisensory deficit; VM, vestibular migraine; VN, vestibular neuritis; VP, vestibular paroxysmia; VS, vestibular schwannoma.

net regularization generated parsimonious models, which are easier to interpret. Variable selection was performed by shrinking the parameters toward zero and attenuating overfitting, a well-known problem when applying regression models with a large number of predictors. Tenfold cross-validation was performed to choose the best model with the lowest mean cross-validation error. Variables remain in the model within the elastic net algorithm if the prediction error averaged over the tenfold cross-validation samples is reduced. In contrast to ordinary least squares regression or least absolute shrinkage and selection operator regularization, the elastic net algorithm performs well in highly correlated variables. It includes all variables with similar regression coefficients or excludes all variables from the best model. Regression coefficients of the model with 95% confidence intervals (CIs) were reported. Elastic net regularization was performed using the package *glmnet* version 4.1-3 in R version 3.6.2.

A principal component analysis with varimax rotation was performed to reduce the variation among healthcare providers among different factors.

All statistical tests were applied two-sided at a significance level of 0.05.

RESULTS

Description of the Two Age Groups

Sociodemographic parameters and vertigo characteristics of the entire cohort and the two age groups are given in **Table 1**. Symptoms lasted longer in older adults than in younger persons **Table 1**). Compared with the younger group, older adults had

TABLE 2 | Body Sensations Questionnaire (BSQ), Agoraphobic Cognitions Questionnaire (ACQ), and Hospital Anxiety and Depression Scale (HADS) in both age groups.

	<60 years (n = 414)				≥60 years (n = 351)			
	Mean	**SD**	**95% CI lower**	**95% CI upper**	**Mean**	**SD**	**95% CI lower**	**95% CI upper**
BSQ1	9.33_a	5.60	8.77	9.89	6.72_b	5.36	6.13	7.31
BSQ2	34.63_a	74.38	27.12	42.14	33.20_a	103.46	20.82	45.57
HADS anxiety	7.78_a	4.09	7.38	8.18	5.71_b	3.68	5.31	6.10
HADS depression	6.54_a	4.05	6.14	6.94	5.75_b	3.64	5.35	6.14
ACQ	20.61_a	6.30	19.92	21.29	17.92_b	4.44	17.28	18.57
ACQ physical crisis	1.60_a	0.78	1.52	1.68	1.60_a	0.81	1.50	1.70
ACQ loss of control	1.57_a	0.82	1.48	1.65	1.56_a	0.87	1.46	1.67

Values in the same row and subtable where the subscript is not identical differ strongly at $p < 0.05$ in the two-tailed test for equality for column means. SD, standard deviation; CI, confidence interval; BSQ, Body Sensations Questionnaire; ACQ, Agoraphobic Cognitions Questionnaire; HADS, Hospital Anxiety and Depression Scale.

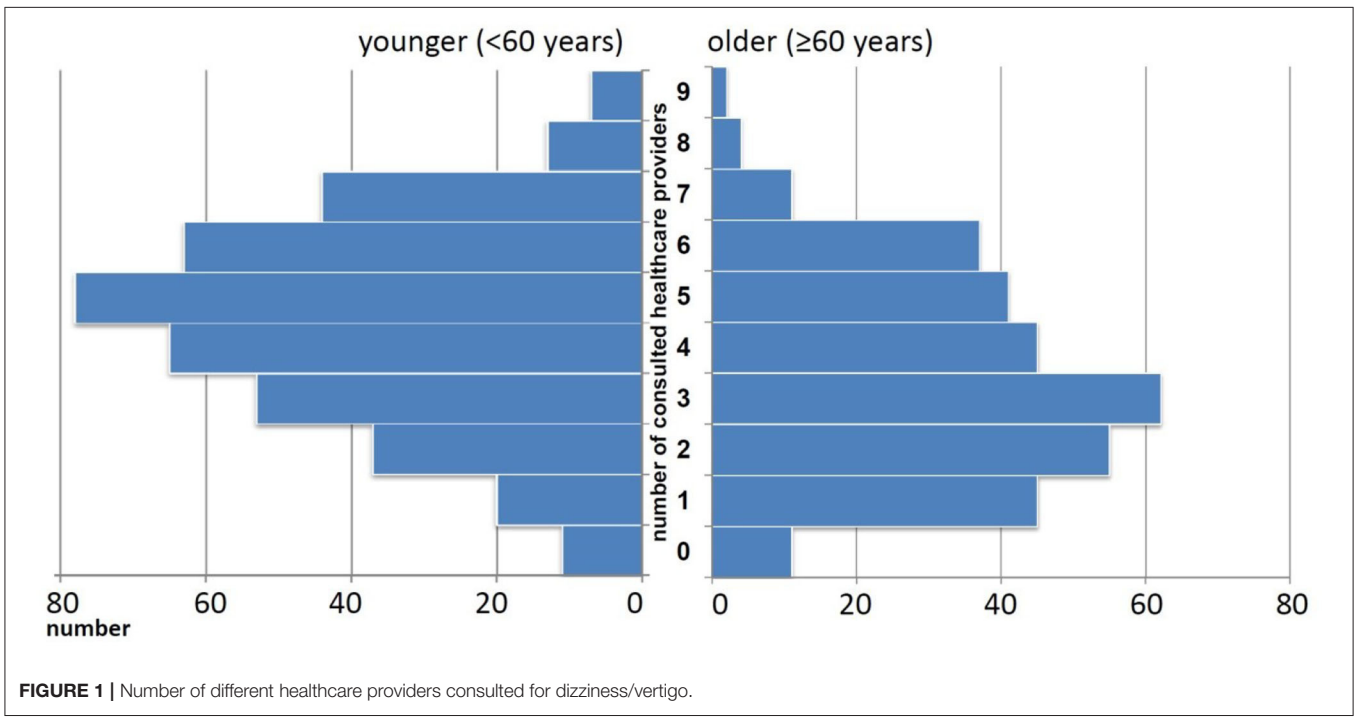


FIGURE 1 | Number of different healthcare providers consulted for dizziness/vertigo.

a somatic reason for dizziness/vertigo more frequently. Older persons reported more falls related to dizziness/vertigo, however the effect size was small for this difference (**Table 1**). The amount of anxiety about bodily sensations (BSQ1) was higher in younger than in older adults (**Table 2**). However, both age groups did not differ in the BSQ2, which measures how often the sensations are experienced when the patient feels anxious or tense. Regarding emotional symptoms, older persons had fewer depressive symptoms and less anxiety according to the HADS and less vertigo-related maladaptive thoughts according to the adapted ACQ than younger individuals (**Table 2**). The two subscales computed from the adapted ACQ (physical crisis and loss of control) did not differ between both age groups (**Table 2**).

Healthcare Providers

In the previous year, most people saw more than one healthcare provider for dizziness/vertigo. On average, they consulted four ± two healthcare providers. The numbers of different healthcare providers consulted for dizziness/vertigo are displayed as histogram in **Figure 1**. In general, older adults indicated that they sought fewer healthcare providers for dizziness/vertigo (mean 3.4 ± 1.9, 95% CI 3.2, 3.6) than younger people (mean 4.5 ± 2.0, 95% CI 4.3, 4.7). This finding concerned both somatic (e.g., ENT specialist, orthopedist) and psychologically oriented healthcare providers (**Figure 2**). The different healthcare providers could be reduced to two factors: psychological and psychiatric loaded on one factor, and somatic-oriented healthcare providers loaded on a second factor (**Table 3**). Of the 681 people who consulted at least one healthcare provider, 396 (58.1%) consulted somatic-oriented and 285 (41.9%) psychologically oriented healthcare providers.

People who consulted more healthcare providers were characterized by younger age, the presence of psychiatric reasons for dizziness/vertigo, a higher HADS-A, and a higher BSQ1

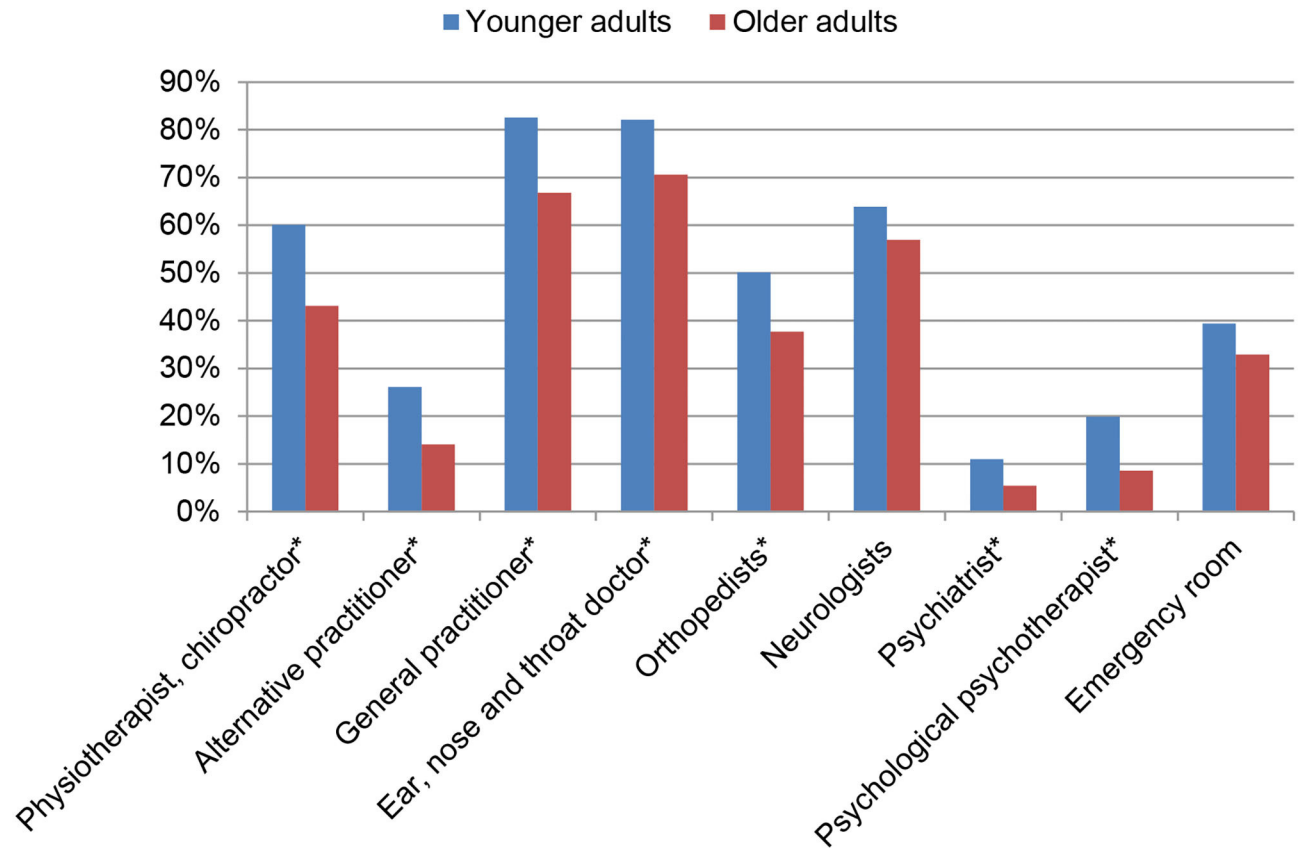


FIGURE 2 | Utilization of medical assistance for dizziness in younger and older adults. * indicates significant group difference at $P < 0.001$.

TABLE 3 | Principal component analysis (PCA) of healthcare providers.

Rotated component matrix	Factor 1	Factor 2
Ear, nose and throat specialist	0.679	
General practitioner	0.640	
Orthopedist	0.619	
Physiotherapist/chiropractor	0.561	
Emergency unit		
Alternative practitioner		
Neurologist		
Psychiatrist		0.789
Psychologist		0.738
Eigenwert	2.391	1.147
% of variance	26.567	12.745
Cronbachs alpha	0.60	0.44

Extraction method: Principal component analysis. Rotation method: Varimax with Kaiser normalization. Kaiser-Meyer-Olkin (KMO) = 0.76. Bartlett significance < 0.001.

TABLE 4 | Linear regression: predictors of consulted healthcare providers.

Variable	Estimate	2.5% CI	97.5% CI	*P*
(Intercept)	4.23	3.17	5.30	<0.001
Age	−0.02	−0.03	−0.00	0.01
Diagnosis category	0.34	−0.09	0.78	0.12
HADS anxiety	0.09	0.04	0.15	<0.001
BSQ1	0.02	−0.01	0.06	0.18

Dependent variable: number of consulted healthcare providers. Independent variables: age, sex, diagnosis category [somatic vs. non-somatic (psychogenic and unspecific)], Hospital Anxiety and Depression Scale -Anxiety, Hospital Anxiety and Depression Scale -Depression, Agoraphobic Cognitions Questionnaire, Body Sensations Questionnaire-1, duration of vertigo (< or > 6 months). $\chi^2(4) = 162.88$, $p = 0.00$, *Pseudo-*R^2 *(Cragg-Uhler)* $= 0.12$, *AIC* $= 1444.10$, *BIC* $= 1467.28$.

(**Table 4**). In the logistic regression, the likelihood of consulting somatic-oriented healthcare providers was higher for a lower ACQ and shorter disease duration of vertigo. However, the explained variance in this model was low (**Table 5**).

Hospitalizations

Overall, 285 (37.8%) individuals were hospitalized due to dizziness/vertigo in the year before their appointment at our Center for Vertigo and Dizziness. Younger people were more frequently hospitalized ($n = 171$, 24.4%) than older adults ($n = 114$, 16.3%) ($P = 0.024$). In the logistic regression, hospitalizations due to dizziness/vertigo were associated with younger age, a higher BSQ1, a higher HADS-D, and a lower

TABLE 5 | Binominal logistic regression: dependent variable consultation of somatic- (= 1) or psychologically (= 0) oriented healthcare provider (backward selection).

		Coefficient	Standard error	*P*	Exp(B)	Nagelkerkes R^2	Hosmer-Leme show test
Step 1	Age	−0.011	0.007	0.119	0.989	0.028	0.109
	Sex	−0.118	0.203	0.560	0.888		
	Disease duration	−0.598	0.309	0.053	0.550		
	BSQ1	−0.010	0.019	0.608	0.990		
	HADS Anxiety	0.008	0.036	0.821	1.008		
	HADS Depression	−0.030	0.032	0.354	0.970		
	ACQ	−0.027	0.021	0.187	0.973		
	constant	3.041	0.852	0.000	20.927		
Step 2	Age	−0.012	0.007	0.103	0.989	0.027	0.186
	Sex	−0.123	0.202	0.544	0.885		
	Disease duration	−0.596	0.309	0.054	0.551		
	BSQ1	−0.009	0.019	0.634	0.991		
	HADS Depression	−0.026	0.028	0.348	0.974		
	ACQ	−0.026	0.020	0.189	0.975		
	Constant	3.059	0.849	0.000	21.299		
Step 3	Age	−0.011	0.007	0.107	0.989	0.027	0.208
	Sex	−0.116	0.202	0.566	0.891		
	Disease duration	−0.597	0.309	0.053	0.551		
	HADS Depression	−0.028	0.028	0.309	0.972		
	ACQ	−0.029	0.019	0.121	0.972		
	Constant	3.033	0.846	0.000	20.766		
Step 4	Age	−0.011	0.007	0.106	0.989	0.026	0.596
	Disease duration	−0.596	0.309	0.054	0.551		
	HADS Depression	−0.028	0.028	0.314	0.972		
	ACQ	−0.028	0.018	0.130	0.972		
	Constant	2.852	0.783	0.000	17.321		
Step 5	Age	−0.011	0.007	0.117	0.989	0.024	0.891
	Disease duration	−0.579	0.308	0.060	0.560		
	ACQ	−0.036	0.017	0.037	0.965		
	Constant	2.773	0.780	0.000	16.010		
Step 6	Disease duration	−0.639	0.305	0.036	0.528	0.018	0.544
	ACQ	−0.029	0.016	0.077	0.972		
	Constant	2.159	0.666	0.001	8.662		

BSQ, Body Sensations Questionnaire; ACQ, Agoraphobic Cognitions Questionnaire; HADS, Hospital Anxiety and Depression Scale.

HADS-A (**Table 6**). Results in the logistic regression did not change when additionally diagnosis category (somatic vs. non-somatic) was entered as independent variable.

Therapy

Older adults received less medication, less physiotherapy, and less psychological therapy for vertigo than younger people (**Table 7**).

DISCUSSION

Dizziness and vertigo are common complaints associated with a substantial healthcare burden (16, 17, 31, 32). Here, we analyzed three domains of healthcare utilization of patients attending a specialized vertigo center. For all studied healthcare utilization domains, we found age-dependent effects.

Approximately every second patient attending our vertigo center was at least 60 years old. In line with earlier studies, older patients had vertigo diagnoses with mainly degenerative or multifactorial etiologies, i.e., multisensory deficits or central vertigo (7, 23, 33). Taking the effect sizes of group comparison into account, one can summarize that the main difference between older and younger patients was found for the diagnosis category [somatic vs. non-somatic (psychogenic and unspecific)]. Somatic and multifactorial etiologies of dizziness were more common in older patients than younger patients who more frequently had non-somatic etiologies. This agrees with the observation that chronic conditions are often associated with balance dysfunction and dizziness in older patients (6). Older patients perceived slightly less distress due to dizziness than younger patients; however, the effect size was low to moderate. Older patients had less frequently attack-like dizziness. Anxiety about bodily sensations (BSQ1) was higher in younger patients than in older patients. Compared with younger patients, older patients reported fewer depressive and anxiety symptoms

TABLE 6 | Logistic regression: predictors of hospitalization (dependent variable, backward selection).

		Coefficent	Standard error	*P*	Exp(B)	Nagelkerkes R^2	Hosmer-Lemeshow test
Step 1	Age	−0.014	0.007	0.051	0.986	0.073	0.708
	Sex	−0.283	0.204	0.165	0.753		
	Disease duration	−0.437	0.275	0.112	0.646		
	BSQ1	0.061	0.020	0.003	1.063		
	HADS Anxiety	−0.093	0.036	0.010	0.911		
	HADS Depression	0.070	0.033	0.033	1.072		
	ACQ	−0.002	0.021	0.921	0.998		
	Constant	1.332	0.786	0.090	3.788		
Step 2	Age	−0.014	0.007	0.051	0.986	0.073	0.616
	Sex	−0.283	0.204	0.165	0.754		
	Disease duration	−0.439	0.274	0.110	0.645		
	BSQ1	0.060	0.019	0.002	1.062		
	HADS Anxiety	−0.094	0.034	0.006	0.910		
	HADS Depression	0.069	0.032	0.033	1.072		
	Constant	1.304	0.735	0.076	3.685		
Step 3	Age	−0.014	0.007	0.054	0.986	0.067	0.977
	Disease duration	−0.444	0.274	0.105	0.642		
	BSQ1	0.061	0.019	0.002	1.063		
	HADS Anxiety	−0.089	0.034	0.009	0.915		
	HADS Depression	0.067	0.032	0.038	1.069		
	Constant	0.871	0.662	0.188	2.388		
Step 4	Age	−0.015	0.007	0.030	0.985	0.060	0.732
	BSQ1	0.061	0.019	0.002	1.062		
	HADS Anxiety	−0.092	0.034	0.007	0.912		
	HADS Depression	0.070	0.032	0.030	1.073		
	Constant	0.139	0.482	0.773	1.149		

BSQ, Body Sensations Questionnaire; ACQ, Agoraphobic Cognitions Questionnaire; HADS, Hospital Anxiety and Depression Scale. Disease duration (1 = <6 months, 2 = >6 months).

TABLE 7 | Therapy for vertigo/dizziness in both age groups.

		<60 years		≥60 years		*P*
Treatment		*N*	%	*N*	%	
Medication	No	162	40.3	171	49.7	0.010
	Yes	240	59.7	173	50.3	
Physiotherapy	No	192	47.8	203	59.0	0.002
	Yes	210	52.2	141	41.0	
Psychological therapy	No	320	79.6	304	88.4	
	Yes	82	20.4	40	11.6	0.001

according to the HADS and less vertigo-related maladaptive thoughts according to the ACQ. Other studies showed an age-dependent decrease of the HADS in adults with vestibular neuritis (34). In a study of outpatients with otolaryngologic complaints, the age group between 30 and 50 years old had the highest scores for depression and was followed by anxiety in patients younger than 30 years old (35).

Vertigo and dizziness substantially contribute to population-attributable disability, especially during advanced age (36). In addition, major risk factors for falls can lead to fatal and nonfatal injuries, disability, and death (37, 38), escalating healthcare costs (39). Recurrent falls are often indicator events for admitting previously independent older people to long-term care institutions (14). Of note, 37% of our patients at least 60 years old reported falls due to dizziness and/or vertigo. This rate was higher than in the younger age group. Although, the effect size for different fall rate was low, this is aligned with existing data in community-dwelling individuals (40).

Although, when compared with younger individuals, older patients have somatic reasons for dizziness more frequently, experience more falls, and have similar distress due to dizziness, we observed remarkable differences in healthcare utilization between younger and older individuals.

First, the number of consultations with healthcare providers was considerably higher in younger patients than in older patients. Also, in the regression model, consultations with healthcare providers were associated with younger age patients after correcting for cofactors. General practitioners referred 48% of their patients with dizziness to at least one specialist. In 18% of cases, the specialist's diagnosis differed from the general practitioner's (41). In agreement with a large cohort of US-American patients who were ≥65 years old with balance disorders, most patients consulted multiple providers (42).

Second, hospitalizations due to dizziness and vertigo were associated with younger age after correcting for cofactors. We did not assess the reason for hospitalization (planned diagnostic stay vs. emergency). Therefore, one cannot conclude from a higher hospitalization rate on more serious pathology in younger adults. In our cohort, the hospitalization rate in the year before consultation at our outpatient clinic was relatively high. This is remarkable because our hospitalization rate is based on self-reports that are prone to recall bias and not on ICD 10-diagnosis based information. A study in Germany of 21 primary care practices demonstrated that 2% of patients with dizziness initially seen by a general practitioner were referred to a hospital because of severe symptoms or psychosocial reasons (41). The rate of inpatient treatment in ENT departments for acute dizziness in Thuringia (one of the 16 German federal states) was 54.71 per 100,000. Also, the incidence increased with age, with the highest incidence for patients 71–80 years old (43). In contrast, specialized centers for vertigo and dizziness generally treat dominantly chronic or refractory cases. They may, therefore, treat a higher number of patients with non-somatic syndromes, longer disease duration, and more frequent previous hospitalizations (23, 44).

Third, older patients in our study received less medication for dizziness/vertigo, less physiotherapy, and less psychological therapy for vertigo than younger patients. This agrees with a retrospective cohort study in patients referred to a tertiary care balance clinic in Germany, where older patients received fewer diagnostic and therapeutic measures and less medication than younger patients (45). Receiving less medication may not be a drawback *per-se*, as it was shown that, in many cases, potentially inappropriate drugs were prescribed in patients aged 70 and older (45). In addition, polypharmacy may be harmful in older patients with a detrimental effect on balance function (46). Many agents might contribute to the causes of dizziness than cure it in older adults (45, 47). In addition, anxiety and depression may play a minor role in older patients with dizziness/vertigo compared with younger patients (22). Therefore, healthcare providers may assume that psychological therapy may have less beneficial effects in older than in younger patients. However, with this assumption in mind, physiotherapy and occupational therapy should be primary therapeutic measures for dizziness/vertigo in the older population, which is not the case.

Due to the design of the study, we cannot explore the reasons for these differences in healthcare utilization in our study. We propose several suggestions. Diagnostic subgroups differ significantly regarding several diagnostic measures, therapies, and medications (45). One reason for these differences in healthcare utilization may be based on a different distribution of diagnoses, causing dizziness and vertigo between the age groups (7). Dizziness combined with anxiety is associated with increased subjective impairment and healthcare utilization (45). Anxiety, in contrast, was more pronounced in the younger age group. In addition, younger patients may consult healthcare services earlier, e.g., their capability to work.

Moreover, older patients may tolerate symptoms of dizziness and vertigo longer because patients, and possibly some medical doctors, may also believe that dizziness and balance disturbances may be age-associated phenomena (i.e., ageism). However, this is not true. Vertigo/dizziness is mainly not a consequence of normal aging of the vestibular and sensory systems (45). It is not adequate regarding the increasing burden of chronic and degenerative diseases and the increase in multifactorial origins of dizziness/vertigo in the older population. Especially regarding the increased risk of falls, and thereby, the increased danger of immobility and disability, the challenging target is a careful and comprehensive work-up of dizziness and vertigo in the older population.

As dizziness is often a heterogeneous disorder requiring interdisciplinary care, diagnostic accuracy must be improved with appropriate diagnostic testing to facilitate effective care plans for older patients with dizziness (45).

Our study has several limitations. Our sample of 765 patients with chronic dizziness/vertigo was physically and mentally independent. They consulted our specialized and multidisciplinary tertiary care outpatient clinic for dizziness and vertigo. Therefore, the results cannot be generalized to people with severe mobility impairments or cognitive deficits. Moreover, there is a selection bias regarding their underlying diagnoses. For example, only a few people had BPPV in our cohort, a common cause of dizziness among older adults (8). This is because today, general practitioners know how to diagnose, treat, and manage BPPV themselves. Patients are referred to our tertiary care center only if symptoms become chronic. As mentioned previously, due to the cross-sectional study design, we cannot make causal statements about the reasons for healthcare utilization differences. This must be addressed by qualitative and longitudinal studies.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the corresponding authors upon reasonable request for scientific purpose only.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Friedrich-Schiller-University Jena, Jena, Germany. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TP: design of the study and writing of the paper. HA and SF: collection of data. TP and HA: analysis. HA: revision of the paper. All authors contributed to the article and approved the submitted version.

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Correlation Analysis of Plasma Myeloperoxidase Level With Global Registry of Acute Coronary Events Score and Prognosis in Patients With Acute Non-ST-Segment Elevation Myocardial Infarction

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Background: Myeloperoxidase (MPO) and global registry of acute coronary events (GRACE) risk scores were independently used to predict adverse outcomes in patients with acute coronary syndrome (ACS). However, the relationship between MPO level and GRACE score, and whether the combination of MPO and GRACE can better predict major adverse cardiovascular events (MACEs) in patients with acute non-ST-segment elevation myocardial infarction (NSTEMI), have not been previously investigated.

Methods: A prospective cohort of 271 consecutive patients with NSTEMI were enrolled in this study. Plasma MPO levels were measured by ELISA. Baseline demographic and clinical information was collected, and GRACE scores were calculated at admission. The correlation between MPO and MACEs was evaluated with the GRACE score during a 1-year follow-up.

Results: The results showed that plasma MPO level was correlated with inflammatory indices (including high-sensitivity C-reactive protein (hs-CRP), leukocyte count, neutrophil count, and fibrinogen), N-terminal pro-B type natriuretic peptide (NT-proBNP), and hypersensitive troponin T (hsTNT) levels (All p-values < 0.05), and there was a statistically significant correlation between plasma MPO level and GRACE score ($r = 0.22$, $p < 0.001$). The Kaplan-Meier curves showed that patients with higher MPO levels had lower event-free survival (Log-rank $P < 0.001$). The multivariate Cox model showed MPO was an independent risk factor for 1-year MACEs in patients with NSTEMI (HR: 3.85, 95% CI: 1.4–10.6, $p = 0.009$). Subgroup analysis showed that MPO was a strong prognostic biomarker, and its prognostic value was more significant in

patients with age >65 years and N-terminal pro-B type natriuretic peptide (NT-proBNP) level >1,000 pg/ml. For high-risk patients with GRACE scores, a higher level of MPO has a higher prognostic value.

Conclusion: Elevated plasma MPO levels are associated with high inflammatory status and GRACE scores in patients with NSTEMI. For high-risk patients with GRACE scores, higher MPO levels were more predictive of future MACEs.

Keywords: myeloperoxidase, NSTEMI, prognosis, MACE, GRACE score

INTRODUCTION

In recent years, the incidence of non-ST segment elevation myocardial infarction (NSTEMI) is on the rise, gradually exceeding that of ST-segment elevation myocardial infarction (STEMI) (1–3). Patients with NSTEMI have more comorbidities and a higher prevalence of multiple coronary artery diseases (CADs), and the long-term prognosis of the patients is poor (4). Some patients still have major adverse cardiovascular events (MACEs) after discharge (5). Therefore, how to assess and predict the occurrence of MACEs as early as possible has become a key topic of clinical research, which is of great clinical significance for early intervention measures to improve the prognosis.

Most acute coronary syndromes (ACS) have two mechanisms: plaque fibrous cap rupture and intimal surface erosion. Inflammation plays an important role in the occurrence and development of ACS. It can mediate the weakening of the fibrous cap of atherosclerotic plaque and make plaque rupture more easily, thus inducing ACS (6). Many studies have shown that inflammatory biomarkers can predict the future risk and adverse clinical outcome of NSTEMI. Among all the inflammatory biomarkers, myeloperoxidase (MPO) is secreted by inflammatory cells and catalyzes various oxidative reactions, which is one of the markers of inflammation and oxidative stress. It participates in almost all stages of atherosclerosis, from endothelial dysfunction, oxidative modification of LDL and HDL to plaque instability and vulnerability, increasing the sensitivity of NSTEMI diagnosis (7–9). Early clinical studies have also shown that MPO levels strongly predict the increased risk of subsequent cardiovascular events in patients with NSTEMI, expanding prognostic information from traditional biochemical markers such as cardiac troponin and brain natriuretic peptide (10, 11). However, the value of MPO for risk stratification in patients with NSTEMI has not been widely studied.

The Global Registry of Acute Coronary Events (GRACE) scoring system is a predictive tool for risk stratification of patients with NSTEMI. However, biomarkers with pathophysiological mechanisms are not included. Therefore, this study intends to investigate the relationship between plasma MPO level and GRACE score, and whether the combination of the two can better predict the occurrence of MACEs in patients with NSTEMI, to provide further reference data for judging the disease and choosing treatment options.

METHODS

Study Population

We recruited 271 patients diagnosed with NSTEMI from January 2016 to December 2017 in Tianjin Chest Hospital. The inclusion criteria were: all participants who underwent clinical evaluation, including a history of chest pain, physical examination, a series of serum cardiac biomarker tests, 12-lead electrocardiogram, and coronary angiography. Participants who met the European Society of Cardiology/American College of Cardiology NSTEMI diagnostic criteria: troponin and/or CK-MB exceeded the reference value by 99% at the baseline, and at least one of them was associated with: (1) ST-segment depression or T-wave inversion; (2) with chest pain symptoms lasting more than 30 min (12, 13) were also included. The exclusion criteria were severe infectious or immune diseases, other malignancies, severe liver or kidney dysfunction, serious heart disease other than coronary heart disease, cognitive or communication disorders, and patients who refused to participate in the study at any stage.

All patients and their families agreed to participate in the study and signed informed consent forms after being informed of the procedures and risks involved. The study was carried out in accordance with the Declaration of Helsinki. This study had been approved by the ethical committee of Tianjin Chest Hospital. This study was registered at ClinicalTrials.gov (identifier NCT03600259).

Sample Collection and Laboratory Testing

Patients fasted overnight on the day of admission (≥8 h), and blood samples were taken in the morning. For the patients whose GRACE score was rated as high-risk group (>140) and who needed emergency intervention, the sampling time was before the intervention. The blood sample was stored at 4°C, centrifuged for 10 min at 3,000 rpm for 2 h after collection, and then stored at -80°C until measurement. Plasma MPO levels were determined by ELISA using a commercial kit (R&D Systems, Minneapolis, MN, United States).

Data Collection

Demographic data, characteristics of admission, complications, treatment modalities, medications, and laboratory tests were recorded. Eight variables were used to calculate GRACE scores for all patients at admission, including age, systolic blood pressure, heart rate, serum creatinine, Killip grade, cardiac arrest

at admission, elevated cardiac injury biomarker, and ST-segment offset. The total score of the GRACE scale was 372. A score >140 is considered high risk; 109–140 is medium risk; <108 is classified as low risk.

Study Endpoints

A total of 271 NSTEMI patients were followed up for 1 year. Patients were followed up by case review, telephone follow-up, or outpatient follow-up by a trained nurse or physician until the last day of the follow-up period, or the occurrence of MACEs. The study endpoints were MACEs, which included all-cause death, non-fatal recurrent myocardial infarction (MI), target lesion revascularization (TLR) and hospital admission for heart failure (HF). Non-fatal MI was defined by typical angina of ≥ 20 min duration, ECG changes, and a rise in troponin or creatine kinase level above the 99 percentile of the upper reference limit. TLR refers to revascularization [percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)] due to ischemic symptoms or objective journal evidence and target stenosis >50%.

Statistical Methods

Plasma MPO levels were classified into three levels: low, medium, and high using an X-tile procedure (Yale University, New Haven, CT, United States). The X-tile plots can provide a single, global assessment of every possible way of dividing a cohort into low-, medium-and high-level marker expressions. Moreover, this project gives rise to a rigorously statistical estimation by dividing a single cohort into training and validation subsets for the best *P*-value evaluation when separate training and validation cohorts are not available. The X-tile analysis considers variables and patient survival when selecting cut-off points to ensure homogeneity within and heterogeneity between groups as much as possible (14).

Continuous data are expressed as mean ± standard deviation or median (quartile range). Categorical variables are expressed as counts (percentages). The *T*-test, one-way ANOVA, and the Kruskal-Wallis H test were used to evaluate the differences in continuous variables between groups. The chi-square test was used for categorical variable comparison, and Fisher's exact probability method was used when the theoretical frequency of counting data was less than 5. Multiple comparisons were performed using the Bonferroni method. Patients were divided into different groups based on plasma MPO levels. The Kaplan-Meier curve used a logarithmic rank test to estimate the event-free survival rate between groups. The univariate and multivariate Cox proportional risk models were used to determine the major impact of MPO levels on the above adverse outcomes. Exploratory subgroup analysis was performed based on expertise. SPSS 26.0 software was used for data processing, and $P < 0.05$ was considered as a statistically significant difference.

RESULTS

Myeloperoxidase Cut-Off Point Selection

The optimal cut-off points for plasma MPO determined by the X-tile are: low level (6.89–49.17 ng/ml), medium level (49.17–85.47 ng/ml), and high level (85.47–241.45 ng/ml) (**Table 1** and **Supplementary Figure 1**).

Myeloperoxidase and Baseline Characteristics

Baseline characteristics of 271 NSTEMI patients were stratified based on plasma MPO levels (**Table 2**). There were 188 men (69.37%) and 83 women (30.63%). The older the age, the higher the MPO level ($p = 0.012$). There was a negative correlation between MPO level and LVEF ($p = 0.01$). The most common history was hyperlipidemia in 208 cases (77.9%), followed by hypertension in 176 cases (64.94%), current/former smoking in 155 cases (57.20%), diabetes in 91 cases (33.58%), stroke in 55 cases (20.30%), and family history in 28 cases (10.33%). Among 271 patients, 48 (22.02%) had a single-vessel disease and 166 (76.15%) had a multi-vessel disease. A total of 90 patients (33.21%) chose medication treatment, 162 patients (59.78%) underwent PTCA/PCI, and 19 patients (7.01%) underwent CABG. According to patients' clinical characteristics and doctors' judgment, 268 patients (98.89%) received DAPT, 227 (83.76%) received beta-blockers, 164 (60.52%) received ACEI/ARB, 270 (99.63%) received anticoagulant, and 227 (83.76%) received statin. There were no significant differences in IABP application, breathing machine, heart rate, systolic pressure, diastolic pressure, history, Killip classification, revascularization strategy, type of CAD, and medication during the follow-up in groups with high, medium, and low MPOs (All values of $p > 0.05$).

Myeloperoxidase and Other Biomarkers

Spearman rank correlation analysis showed that in patients with NSTEMI, plasma MPO level was correlated with high-sensitivity C-reactive protein (hs-CRP) ($r = 0.162$, $p = 0.008$), leukocyte count (R = 0.215, $p < 0.001$), neutrophil count ($r = 0.221$, $p < 0.001$), fibrinogen ($r = 0.3$, $p < 0.001$), NT-proBNP ($r = 0.215$), $p < 0.001$), and hypersensitive troponin T (hsTNT) ($r = 0.16$, $p = 0.009$) (**Figure 1**). However, plasma MPO level was not correlated with serum lipid, D-Dimer, and creatinine levels, and serum lipid included TG, TC, HDL-C, LDL-C, ApoA, ApoB, and Lp(a) (all values of $P > 0.05$) (**Table 2**).

Follow-Up and Results

A total of 271 patients with NSTEMI were followed up for 1 year, of which 11 were lost to follow-up. A total of 36 (13.28%) patients with NSTEMI had MACE events, all-cause death in eight cases (2.95%), non-fatal recurrent MI in eight cases (2.95%), target lesion revascularization in 14 cases (5.17%), and hospital admission for heart failure in 11 cases (4.06%). The incidence of MACEs increased significantly with low, medium, and high MPO levels (6.98 vs. 13.95 vs. 26.79%, $P = 0.001$). In addition, all-cause

TABLE 1 | Cut-off point of MPO by X-tile method.

Group	Range (ng/mL)	Patient	Percent (%)	Event
Low	6.89–49.17	129	47.6	9
Medium	49.17–85.47	86	31.73	12
High	85.47–241.45	56	20.66	15
Total	6.89–241.45	271	100	36

TABLE 2 | Baseline characteristics of the NSTEMI patients in different MPO level.

Characteristics	Overall (*N* = 271)	Low (*N* = 129)	Medium (*N* = 86)	High (*N* = 56)	*p*-value
Age, years	65 (57, 73)	62 (54.75, 71.25)	65 (59.5, 74)	67 (62.5, 76.25)	0.012
Male, n (%)	188 (69.37)	99 (76.74)	61 (70.93)	28 (50.00)	0.001
IABP, n (%)	15 (5.54)	8 (6.20)	5 (5.81)	2 (3.57)	0.884
Breathing machine, n (%)	36 (13.3)	19 (14.7)	9 (10.50)	8 (14.3)	0.671
Heart rate	74 (63, 84)	72 (62, 84.25)	72 (63.5, 83.25)	78 (65, 84.25)	0.309
Systolic pressure, mmHg	133.07 ± 21.55	134.56 ± 23.11	132.43 ± 20.54	130.61 ± 19.31	0.493
Diastolic pressure, mmHg	75 (69, 85)	75 (67.75, 86.25)	76 (70, 85)	75 (67, 82)	0.597
LVEF, n (%)	54 (47, 57)	55 (48.5, 58.75)	55 (50, 57)	48 (36, 52.5)	0.010
Past history					
Current/former smoking, n (%)	155 (57.20)	81 (62.79)	47 (54.65)	27 (48.21)	0.153
Hypertension, n (%)	176 (64.94)	78 (60.47)	58 (67.44)	40 (71.43)	0.304
Diabetes, n (%)	91 (33.58)	45 (34.88)	28 (32.56)	18 (32.14)	0.902
Previous stroke, n (%)	55 (20.30)	21 (16.28)	20 (23.26)	14 (25.00)	0.281
Previous MI, n (%)	37 (13.65)	19 (14.73)	10 (11.63)	8 (14.29)	0.825
Hyperlipidemia, n (%)	208 (77.90)	103 (80.47)	67 (79.76)	38 (69.09)	0.214
Family history of CAD, n (%)	28 (10.33)	16 (12.40)	8 (9.30)	4 (7.14)	0.529
Biochemical characteristics					
TG, mmol/L	1.61 (1.2, 2.25)	1.63 (1.23, 2.32)	1.59 (1.13, 2.23)	1.61 (1.23, 2.13)	0.519
TC, mmol/L	4.58 (3.76, 5.19)	4.49 (3.74, 5.12)	4.61 (3.92, 5.23)	4.61 (3.56, 5.2)	0.882
HDL-C, mmol/L	0.97 (0.85, 1.16)	0.96 (0.82, 1.14)	0.98 (0.85, 1.15)	0.99 (0.85, 1.19)	0.694
LDL-C, mmol/L	3.03 (2.3, 3.58)	3.09 (2.35, 3.68)	2.88 (2.38, 3.59)	2.84 (2.17, 3.25)	0.545
ApoA, g/L	1.13 (1.03, 1.27)	1.13 (1.02, 1.29)	1.12 (1.03, 1.24)	1.14 (0.98, 1.28)	0.893
ApoB, g/L	1.08 (0.87, 1.31)	1.06 (0.85, 1.31)	1.11 (0.95, 1.3)	1.11 (0.87, 1.33)	0.702
Lp(a), nmol/L	62.6 (22.18, 129.23)	67.5 (17.05, 136.2)	57.4 (26.75, 128.75)	65.35 (25.78, 113.1)	0.906
D-Dimer, μg/mL	0.43 (0.28, 0.72)	0.42 (0.29, 0.6)	0.39 (0.27, 1.02)	0.5 (0.32, 1.03)	0.15
Cr, μmol/L	77 (65.75, 95.25)	77 (65.75, 95.25)	77 (67.75, 95.25)	79 (69, 94.75)	0.621
hsTNT, ng/mL	0.54 (0.24, 1.39)	0.49 (0.21, 1.06)	0.52 (0.23, 1.16)	0.91 (0.4, 2.1)	0.013
hs-CRP, mg/L	5.27 (2.53, 14.74)	4.29 (1.83, 10.67)	5.26 (2.76, 19.83)	10.27 (4.02, 55)	0.001
leukocyte count,/10^9	8.25 (6.7, 9.91)	7.71 (6.69, 9.58)	8.36 (6.51, 9.48)	9.58 (3.63, 32.99)	<0.001
Neutrophil count,/10^9	5.93 (4.59, 7.65)	5.55 (4.5, 7.01)	5.83 (4.5, 7.44)	7.44 (5.66, 9.36)	<0.001
NT-proBNP, pg/ml	864.15 (324.13, 2356.75)	719.85 (219.18, 1688.25)	821.95 (368.68, 2462.25)	2116 (575.28, 4537.75)	0.001
Fibrinogen, g/L	3.59 (3.02, 4.32)	3.4 (2.8, 3.93)	3.62 (3.05, 4.3)	4.46 (3.56, 5)	<0.001
Killip class					
Killip I, n (%)	222 (81.92)	109 (84.50)	73 (84.88)	40 (71.43)	
Killip II-IV, n (%)	49 (18.08)	20 (15.50)	13 (15.12)	16 (28.57)	
GRACE score, n (%)					
<109	85 (31.37)	52 (40.31)	25 (29.07)	8 (14.29)	
109–140	103 (38.01)	47 (36.43)	36 (41.86)	20 (35.71)	
>140	83 (30.63)	30 (23.26)	25 (29.07)	28 (50.00)	
Revascularization strategy, n (%)					0.307
MT	90 (33.21)	38 (29.46)	27 (31.40)	25 (27.78)	
PTCA/PCI	162 (59.78)	83 (64.34)	52 (60.47)	27 (48.21)	
CABG	19 (7.01)	8 (6.20)	7 (8.14)	4 (7.14)	
Type of coronary artery disease, n (%)					0.647
No lesions	4 (1.83)	2 (1.82)	1 (1.43)	1 (2.63)	
Single-vessel lesion	48 (22.02)	23 (20.91)	19 (27.14)	6 (15.79)	
Multi-vessel lesion	166 (76.15)	85 (77.27)	50 (71.43)	32 (81.58)	
Medication during follow-up, n (%)					
DAPT	268 (98.89)	129 (100.00)	84 (97.67)	55 (98.21)	0.203
Beta-blocker	227 (83.76)	109 (84.50)	69 (80.23)	49 (87.50)	0.496
ACEI/ARB	164 (60.52)	78 (60.47)	54 (62.79)	32 (57.14)	0.802
Anticoagulant	270 (99.63)	129 (100.00)	85 (98.84)	56 (100.00)	0.524
Statin	265 (97.79)	126 (97.67)	86 (100.00)	53 (94.64)	0.072

(Continued)

TABLE 2 | Continued

Characteristics	Overall (*N* = 271)	Low (*N* = 129)	Medium (*N* = 86)	High (*N* = 56)	*p*-value
Outcome, n (%)					
Composite MACEs	36 (13.28)	9 (6.98)	12 (13.95)	15 (26.79)	0.001
All-cause death	8 (2.95)	0	3 (3.49)	5 (8.93)	0.003
Non-fatal recurrent MI	8 (2.95)	3 (2.33)	4 (4.65)	1 (1.79)	0.637
Target lesion revascularization	14 (5.17)	4 (3.10)	3 (3.49)	7 (12.50)	0.03
Hospital admission for HF	11 (4.06)	2 (1.55)	5 (5.81)	4 (7.14)	0.096

IABP, Intra-aortic balloon pump; LVEF, left ventricular ejection fraction; MI, Myocardial infarction; CAD, coronary artery disease; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoA, apolipoprotein A; ApoB, apolipoprotein B; Lp-a, Lipoprotein a; Cr, creatinine; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro-B type natriuretic peptide; hsTNT, hypersensitive troponin T; GRACE, Global Registry of Acute Coronary Events; MT, medical therapy; PCI, percutaneous coronary Intervention; CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; Composite MACEs, consisted of all-cause death, non-fatal recurrent MI, target lesion revascularization, hospital admission for heart failure.

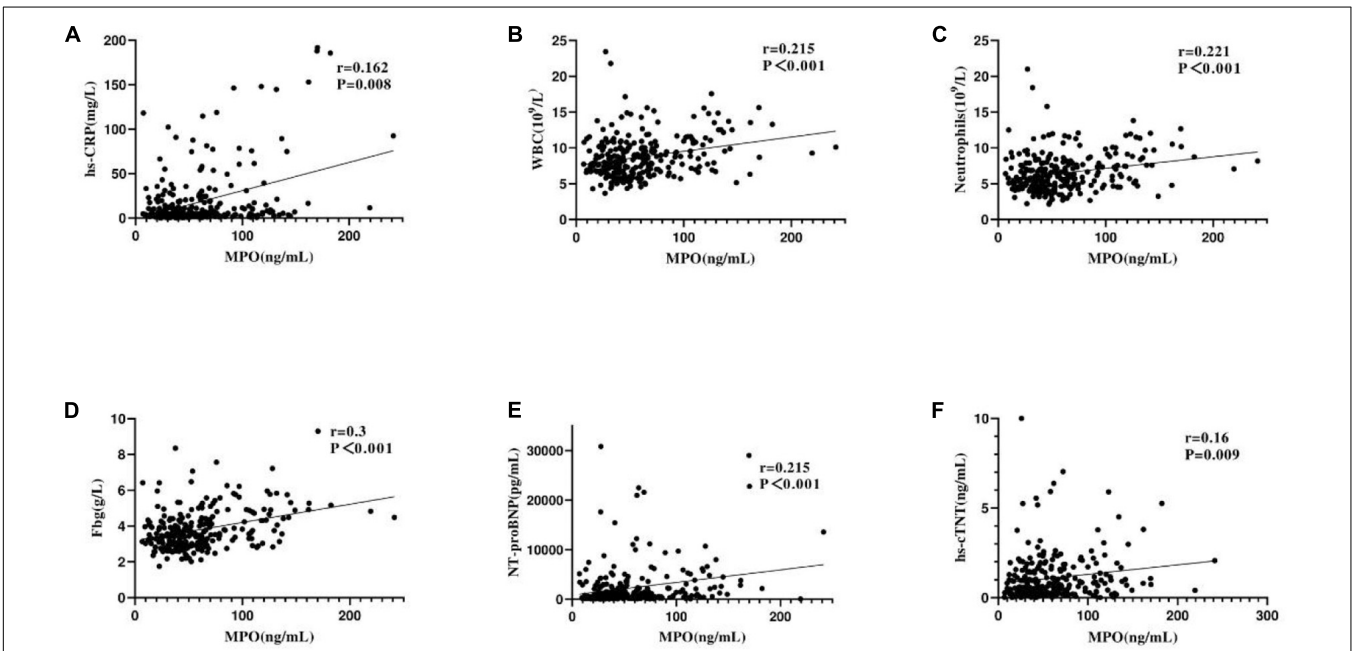


FIGURE 1 | Correlation between plasma MPO levels and other biomarkers. Panels **(A–F)** represent the correlation between plasma MPO levels and high-sensitivity C-reactive protein (hs-CRP), white blood cell (WBC) count, neutrophils, fibrinogen(Fbg), NT-proBNP, and hypersensitive troponin T (hs-cTNT).

death showed a similarly significant upward trend (0 vs. 3.49 vs. 8.93%, $P = 0.003$). The incidence of target lesion revascularization was higher in the high MPO group than in the low or medium MPO groups (12.5 vs. 3.49 vs. 3.10%, $P = 0.03$). The incidence of no-fatal recurrent MI and hospital admission for HF was not statistically significant with MPO levels (**Table 2**).

Prognostic Value of Myeloperoxidase

We found that MPO levels were higher in patients with MACEs than in patients without MACEs ($P = 0.003$) (**Figure 2C**). The Kaplan-Meier curves stratified by MPO levels showed a cumulative event-free survival rate during the 1-year follow-up. MPO levels were significantly associated with 1-year MACE events, and patients with higher MPO levels had a lower event-free survival rate (Log-rank $P < 0.001$) (**Figure 2D**).

The univariate Cox regression analysis showed that a high level of MPO was associated with the occurrence of composite MACEs (medium level vs. low level, HR: 2.08, 95%CI: 0.87–4.93, $P = 0.098$; high level vs. low level, HR: 4.53, 95%CI: 1.98–10.35, $P < 0.001$). The multivariate Cox regression analysis showed that after adjusting for traditional cardiovascular risk factors [including age, sex, current/former smoking, hypertension, hyperlipidemia, diabetes, previous stroke, and previous MI and family history of coronary heart disease (CHD)], there was statistical significance between the high level of MPO and composite MACEs (Model 1: medium level vs. low level, HR: 2.2, 95%CI: 0.87–5.59, $p = 0.096$; high level vs. low level, HR: 4.13, 95%CI: 1.66–10.29, $P = 0.002$). When inflammatory markers were added to Model 1, the results were similar (Model 2: medium level vs. low level, HR: 2.02, 95%CI: 0.78–5.19, $p = 0.146$; high level vs. low level, HR: 3.25, 95%CI: 1.15–9.17, $P = 0.026$). Finally, we added GRACE scores to Model 2, which still maintained the correlation between high MPO levels and composite MACEs (Model 3: medium level vs. low level, HR: 1.92, 95%CI: 0.74–4.95,

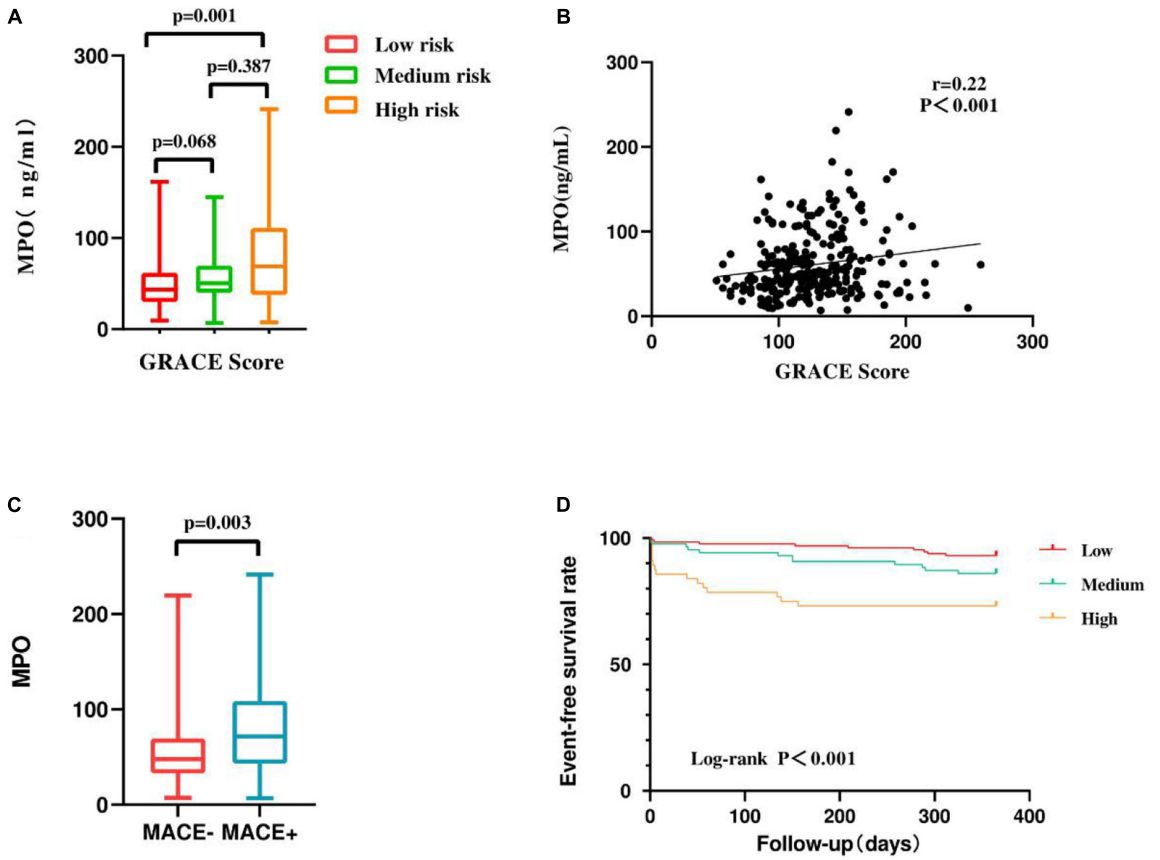


FIGURE 2 | (A) Comparison of plasma MPO levels among groups based on GRACE score. **(B)** Correlation between GRACE score and plasma MPO levels. **(C)** Comparison of plasma MPO levels among groups based on MACEs. **(D)** Kaplan-Meier survival curve of 1-year MACEs in 271 NSTEMI patients. Model 1: adjustment for traditional cardiovascular risk factors (age, sex, current/former smoking, hypertension, hyperlipidemia, diabetes, previous stroke, and previous MI and family history of CHD). Model 2: Model 1 + Inflammation Marker (hs-CRP; leukocyte count; neutrophil count; fibrinogen). Model 3: Model 2 + GRACE score.

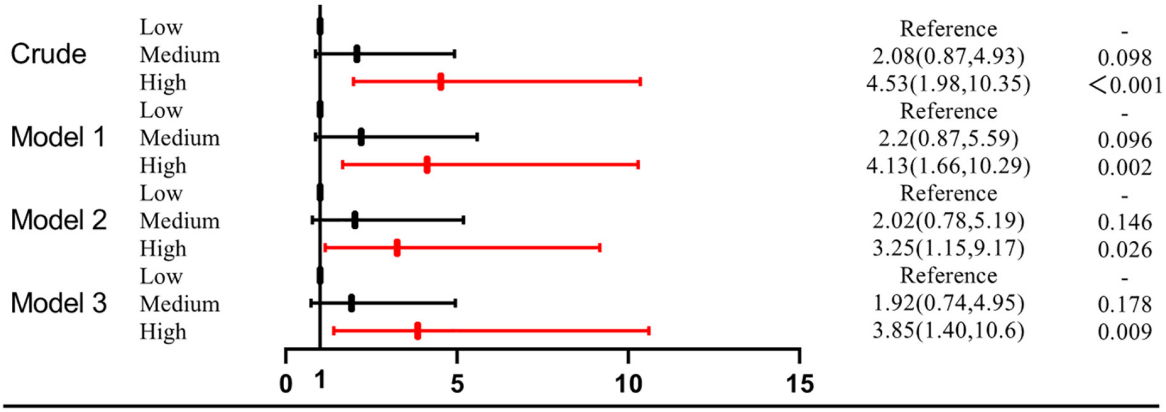


FIGURE 3 | Hazard ratio for MACEs associated with plasma MPO levels in different models.

p = 0.178; high level vs. low level, HR: 3.85, 95%CI: 1.4–10.6, P = 0.009) (**Supplementary Table 1** and **Figure 3**). In addition, the multifactor Cox model was used for subgroup analysis of composite MACEs at different MPO levels. We found that high levels of MPO were a strong prognostic biomarker for patients over 65 (medium level vs. low level, adjusted HR: 2.53, 95%CI: 0.79–8.09, p = 0.118; high level vs. low level, adjusted HR: 5.7, 95%CI: 1.54–21.05, P = 0.009). In patients

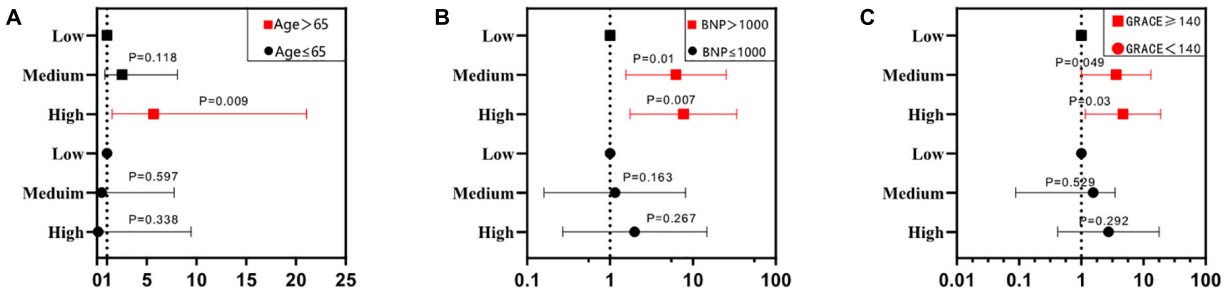


FIGURE 4 | Subgroup analysis of different patients. Panels **(A–C)** represent the subgroups across different ages, NT-pro BNP levels, and GRACE scores. The red line denotes a statistically significant subgroup.

with NT-proBNP > 1,000 pg/ml, moderate to high levels of MPO were a strong prognostic biomarker (medium level vs. low level, adjusted HR: 6.26, 95%CI: 1.56–25.12, $p = 0.01$; high level vs. low level, adjusted HR: 7.69, 95%CI: 1.75–33.71, $P = 0.007$) (**Supplementary Table 2** and **Figure 4**).

The global registry of acute coronary events scores at admission were divided into three grades: low risk < 109 (31.37%), medium risk 109–140 (38.01%), and high risk > 140 (30.63%) (**Table 1**). MPO levels were positively correlated with GRACE scores ($r = 0.22$, $p < 0.001$) (**Figure 2B**), and GRACE scores were higher in patients with high MPO levels than in patients with low and medium MPO levels ($p = 0.001$) (**Figure 2A**). Considering the correlation between MPO and GRACE scores, we investigated the predictive effect of MPO levels on MACEs in NSTEMI patients with different GRACE risk stratification. When GRACE scores were <140 and ≥140, the number of MACE events in the two groups was 12 and 24, respectively. The prognostic value of mid-to-high MPO level (medium level vs. low level, adjusted HR: 3.65, 95%CI: 1–13.25, $p = 0.049$; high level vs. low level, adjusted HR: 4.688, 95%CI: 1.161–18.928, $P = 0.03$) in GRACE score ≥140 was significantly higher than that in GRACE score <140 (medium level vs. low level, adjusted HR: 0.553, 95%CI: 0.088–3.498, $p = 0.529$; high level vs. low level, adjusted HR: 2.735, 95%CI: 0.42–17.8, $P = 0.292$) (**Figure 4C** and **Supplementary Table 1**).

DISCUSSION

The purpose of this prospective single-center cohort study was to investigate the association of plasma MPO level with GRACE score and prognosis in patients with NSTEMI. The main findings were: first, elevated plasma MPO levels were associated with inflammatory responses, and with increased MPO levels, hs-CRP, leukocyte count, neutrophil count, and fibrinogen levels also increased. Plasma MPO level was also positively correlated with NT-proBNP and hsTNT. Second, with the increase of MPO level, the 1-year incidence of MACEs in patients with NSTEMI was on the rise. Plasma MPO level can be used as an important indicator to predict the occurrence of MACEs in patients with NSTEMI. A subgroup analysis showed that MPO was a powerful prognostic biomarker, and its prognostic value was more significant in patients >65 years and NT-proBNP level >1,000 pg/ml. Finally, plasma MPO levels were positively correlated with GRACE scores, which may contribute to effective risk stratification in patients with NSTEMI. In particular, higher levels of MPO have greater prognostic value in patients classified as high-risk based on GRACE scores.

Myeloperoxidase is a key element of the innate immune system and is released primarily by neutrophils to defend against invading pathogens. During neutrophil activation, the fusion of lysosomes and phagosomes results in the release of MPO, which catalyzes the reaction of hydrogen peroxide (H_2O_2) with chloride ion (Cl-) to produce hypochlorous acid (HOCl), helping to destroy microorganisms in the phagocytic lysosomes (15). In "normal" inflammatory conditions (e.g., during infection), active molecules formed in the catalytic cycle are used to eliminate harmful substances, whereas MPO is harmful in chronic clinical or subclinical inflammatory conditions (16). MPO is not only involved in the inflammatory and oxidative stress process of NSTEMI. With the wide application of optical coherence tomography (OCT), more and more studies have confirmed that plaque erosion (PE) is mainly platelet and fibrinogen-based white thrombus, which is an important pathogenesis of NSTEMI (17). The autopsy results showed that a higher level of MPO was detected in the criminal plaque erosion site, and the whole body MPO concentration was also higher in the patients with criminal plaque erosion, indicating that MPO may be related to thrombosis and PE. Further *in vitro* studies have confirmed that MPO can locally produce HOCl, which is an effective oxidant that can induce endothelial cell apoptosis and tissue factor expression, leading to a prethrombotic state, thus promoting the occurrence and development of NSTEMI (18). The elevated level of MPO can provide supplementary information for the diagnosis of plaque types of NSTEMI criminals and achieve more accurate risk stratification and personalized treatment strategies.

In CHD, circulating inflammatory cells (e.g., neutrophils) are a poor prognostic indicator, contributing to the progression of cardiac failure and recurrent coronary events. Thus, identifying markers of inflammation and inflammatory cell activity could help stratify risk in patients with ACS and guide future treatment (19). Early epidemiological studies have assessed the association and clinical usefulness of inflammatory markers such as C-reactive protein, cytokines, white blood cell count, and

fibrinogen with CHD, and these inflammatory mediators have been associated with adverse outcomes in patients (20, 21). Kaya et al. showed that elevated plasma MPO level was an independent predictor of MACEs in STEMI patients, and that plasma MPO level was strongly correlated with CRP (r = 0.45, P = 0.004), but no relationship between MPO and leukocyte count was found. The authors explain that this may be because the study population was small (22). Our study proved that there was a positive correlation between MPO and hs-CRP, leukocyte count, neutrophils, and fibrinogen, reflecting the aggravation of inflammatory state during myocardial infarction. But unlike CRP, MPO is less involved in general systemic inflammation, making it a more specific coronary marker than CRP (23). In addition, MPO activity increases with age (24). In the subgroup analysis of this study, the prognostic value of MPO was more obvious in patients older than 65 years.

Myeloperoxidase can be used as a diagnostic marker for acute CAD. Plasma MPO levels can predict new chest pain early and independently in patients with AMI, even in patients with negative troponin levels, but additional diagnostic information provided by MPO is limited to patients with very early symptoms because MPO secretion occurs early in acute CAD (25). The role of MPO as a biomarker of heart failure has been supported by clinicopathological and epidemiological studies (7). Kaya et al.'s study showed that elevated MPO level was not only an independent predictor of MACEs but also plasma MPO level was positively correlated with NT-proBNP level and negatively correlated with left ventricular systolic function (22). Our study reached a conclusion similar to that of Kaya et al. that baseline MPO levels can predict prognostic information in patients with NSTEMI. In addition, the GUIDing Evidence-Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) trial showed that patients with NT-pro BNP declines of ≤1,000 pg/ml during the application of guideline-directed medical therapy (GDMT) have better outcomes. Conversely, the prognosis is worse (26). To this end, we performed a subgroup analysis with 1,000 pg/ml as the cut-off point for NT-pro BNP, and the results showed that for patients with NT-pro BNP >1,000 pg/ml, MPO had a stronger predictive effect on MACEs.

The results of a meta-analysis showed that a high level of MPO significantly predicted the mortality of patients with acute coronary syndrome (OR: 2.03; 95%CI: 1.4–2.94; P < 0001), supporting the potential role of MPO as part of a multi-marker risk stratification model to guide future individualized treatment of high-risk populations (19). There is evidence that elevated plasma MPO levels are associated not only with the incidence of CAD but also with the severity of the disease. A case-control study of 874 patients with angiographically confirmed CAD showed elevated MPO levels in patients with CAD and progressively increased MPO levels as CAD stabilization, non-ST-segment elevation acute coronary syndrome, and AMI progressed (27). At the same time, MPO was correlated with the degree of coronary artery stenosis. Heslop et al.'s study showed that plasma MPO levels were higher in patients with severe CAD (defined as stenosis with any lesion confirmed by coronary angiography > 50%) (28). In our study, MPO independently predicted 1-year MACEs in patients with NSTEMI, especially all-cause death and target lesion revascularization. We also found that MPO was positively correlated with GRACE score, especially for patients classified as high risk according to GRACE score, higher level of MPO had greater prognostic value. It suggests that in the future, the plasma MPO level can be used as a part of risk stratification to guide the individualized treatment of high-risk population to reduce the poor prognosis of patients.

Recent studies have pointed to several MPO inhibitors for the prevention and treatment of atherosclerotic cardiovascular disease, such as PF-1355, AZM198, azo radical, and thiocyanate (29). Targeting MPO has the potential to become one of the most promising therapies for coronary heart disease and other atherosclerotic cardiovascular diseases, such as PF-06282999 (8), which has effective and selective MPO inhibition properties, and has been advanced into clinical trials in human pharmacokinetics, safety, tolerance, and MPO inhibition studies (30). However, there are still some challenges to consider in the application of MPO inhibitors. For example, it is not clear whether systemic inhibition of MPO is necessary or whether MPO inhibitors are effective in protecting the heart in patients with an elevated inflammatory environment (29).

This study has some limitations. First, the number of patients was relatively small, which may be one of the reasons why we failed to draw a correlation between MPO and lipids. Second, we failed to dynamically monitor the changes in MPO levels to further understand the individual variability of plasma MPO. Reassessment of plasma MPO levels during follow-up may make our study more useful for prognostic purposes. Finally, given that this was a single-center study with all cases from China, our observations may not be applicable to other clinical settings.

In conclusion, elevated plasma MPO levels are associated with high inflammatory status in patients with NSTEMI. Elevated plasma MPO level is an independent risk factor for prognosis in patients with NSTEMI. The level of MPO is related to GRACE score. A higher level of MPO can independently predict MACEs, especially in patients with a higher GRACE score. It can increase the value of the routine GRACE score of patients with NSTEMI, improve the classification of different risk groups of NSTEMI, and help doctors to give more active treatment. It is recommended that this study be expanded to include large populations of all types of acute coronary syndromes, patients are followed for longer periods of time, markers are dynamically analyzed, and more experimental studies of MPO-targeting inhibitors are needed for early clinical application.

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

NZ and J-XW made substantial contributions to the conception, performed the experimental studies, and analyzed

the data. JG and YL contributed to the study design. NZ, J-XW, X-YW, YC, and Z-HZ collected the data. NZ, J-XW, JG, and YL prepared the manuscript. All authors read and approved the final version of the manuscript 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.2022.828174/full#supplementary-material

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Prognostic Gene Expression Signature for Age-Related Hearing Loss

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Background: Our study aimed to determine the pathological mechanism of presbycusis at the molecular level, and determine potential biomarkers for the same.

Methods: Differentially expressed genes (DEGs) for presbycusis were obtained by analyzing the microarray data sets (GSE6045 and GSE49543) downloaded from the Gene Expression Omnibus (GEO). Gene ontology (GO), Kyoto Encyclopedia of Genes and Genome (KEGG) pathway, and protein-protein interaction (PPI) network analyses, and Gene Set Enrichment Analysis (GSEA) were performed to analyze the biological functions, molecular pathways, autophagy-related molecular markers, and the immune microenvironment of the DEGs in presbycusis. Then the prognostic roles of the hub genes were analyzed and verified *in vivo*.

Results: In the old mild hearing loss group (27.7 ± 3.4 months old), 27 down-regulated and 99 up-regulated genes were significantly differentially expressed compared with those in the young control group (3.5 ± 0.4 months old). In the old severe hearing loss group (30.6 ± 1.9 months old), 131 down-regulated and 89 up-regulated genes were significantly differentially expressed compared with those in the young control group. The results of the GO, GSEA, KEGG pathway, and immune infiltration analyses showed that the enrichment terms were mainly focused on immune response in mild presbycusis, and immune response and cell death in severe presbycusis. In the PPI network, autophagy-related genes *ATG5, ATG7* showed the highest node scores in mild presbycusis; whereas *MTOR, BECN1* showed the highest scores in severe presbycusis. In the GSE49543 data set, four genes (*Ywhag, Mapre2, Fgf1, Acss2*) were used to construct the prognostic model, and those four genes were significantly up-regulated in the rat model of presbycusis.

Conclusion: Our study is the first to report the difference in autophagy factors and immune microenvironment among different degrees of hearing loss in presbycusis. Furthermore, we provide the prognostic gene expression signature for age-related hearing loss, intending to develop preventative therapies.

Keywords: presbycusis, differentially expressed genes, immune infiltration, autophagy, diagnostic value

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INTRODUCTION

Age-related hearing loss, the most common sensory disease, is also known as presbycusis. Over one quarter of the people over 60 years of age are affected by hearing loss disabilities (1). Presbycusis is multifactorial, and involves both genetic and environmental factors (2). The disease is characterized by bilateral, symmetrical high-frequency sensorineural hearing loss that can range from mild to severe (3). Presbycusis not only reduces the ability of hearing sensitivity and speech understanding, but untreated hearing loss can also contribute to social isolation, depression, and cognitive decline (4, 5).

The pathology of human presbycusis is characterized by the loss of hair cells, degeneration of the spiral ganglion neurons, and cell death in the stria vascularis. Besides the peripheral portion, the central auditory pathways also change (4, 6). In this study, we have predominantly focused on the peripheral auditory system. The degeneration of the cochlear cells does not affect people uniformly; in fact, the degeneration process appears to be not uniform even within an individual (7). This is not only due to individual causal factors, but also due to the interaction of the different mechanistic pathways. Several genome-wide association studies have found that the role of a hereditary factor has been overestimated (3), and there may be different underlying mechanisms leading to the development of different degrees of presbycusis.

Further, there is a lack of effective and specific prognostic molecular markers for presbycusis, and this disease cannot be prevented or treated with drugs. With the rapid development of molecular biology, it is now possible to clarify the biochemical processes and molecular biology of presbycusis and develop drugs to either decline or improve presbycusis. Presbycusis is caused by an imbalance between pro-aging and anti-aging mechanisms. Inflammation, oxidative stress, apoptosis, accumulation of DNA damage, and autophagy can lead to aging (7). Many studies have used microarray technology to understand the molecular mechanisms in presbycusis. Screening for methylation map changes in peripheral blood samples of women with presbycusis as compared to controls, *P2RX2* (purinergic receptor P2 × 2), *KCNQ5* (potassium voltage-gated channel subfamily Q member 5), *ERBB3* (erb-b2 receptor tyrosine kinase 3), and *SOCS3* (suppressor of cytokine signaling 3) have been associated with the progression of age-related hearing loss (8). In CBA/CaJ mice, *Hspb1* [heat shock protein family B (small) member 1] shows differential expression between mild and severe presbycusis (9). However, no study has reported the difference in autophagy factors and immune microenvironment among different degrees of hearing loss in presbycusis, and previous studies mostly used single-chip analysis which can lead the false positive rate higher. Accordingly, further comprehensive analyses based on cross-validation are needed to identify more robust and reliable biomarkers for the progression and prognosis of presbycusis.

We downloaded microarray data sets (GSE6045 and GSE49543) from the Gene Expression Omnibus (GEO) database, and determined significant differentially expressed genes (DEGs) between old hearing loss groups and young normal control group. Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway, and protein-protein interaction (PPI) network analyses along with Gene set enrichment analysis (GSEA) were performed to provide more information about the molecular mechanisms of the DEGs. We also analyzed the difference in immune microenvironment between the old hearing loss groups and young normal control group in 22 types of immune cells. Moreover, prognostic molecular markers were validated for presbycusis. Thus, our study may provide evidence of molecular mechanisms underlying the pathology of presbycusis.

MATERIALS AND METHODS

Data Source and Preprocessing

Microarray data sets were downloaded from the GEO database.[1] Two gene expression datasets [GSE6045 (10), and GSE49543 (11)] based on the same GPL339 platform (Affymetrix Mouse Expression 430A Array) and annotated using the "GEOquery" R package (12) were acquired. The species selected was Mus musculus. GSE49543 was designated as the training set and GSE6045 as the testing set. Additionally, the GSE49543 data set was categorized into four groups: young control (young adults with good hearing), middle control (middle aged with good hearing), old mild hearing loss (old mice with mild hearing loss), and old severe hearing loss (old mice with severe hearing loss) groups. The GSE6045 dataset was classified into two groups: mild and severe hearing loss groups. The details and characteristics of mice in the two datasets are showed in **Table 1**.

Identification of the Differentially Expressed Genes

The "limma" R package (13) was applied to the microarray data to filter DEGs. In GSE49543, we compared the DEGs in the young control vs. the old mild hearing loss and old severe hearing loss groups. P-value < 0.05 and absolute value of logFC $>$ mean {abs(logFC) + 2 × SD [abs(logFC)]}, where logFC is the log fold change value and SD is the standard deviation, were set as the cut-off criteria for determining the significant DEGs.

Functional and Pathway Enrichment Analyses

Gene ontology analysis was performed to identify enrichment terms associated with the DEGs. The GO terms included molecular function (MF) and cellular component (CC). The mouse organism annotation package "org.Mm.eg.db" was used to retrieve the relevant annotations. GSEA (14) was conducted to demonstrate significant differences and identify the signaling pathways in the young control group and each old hearing loss group. GO analysis (P-value was set to <0.99), KEGG pathway analysis (P-value was set to <0.01), and GSEA (P-value was set to <0.25) were conducted in R (version 4.0.5) using the "clusterProfiler" package (15). The gene set permutations were performed 10,000 times.

[1] http://www.ncbi.nlm.nih.gov/geo

TABLE 1 | Details and characteristics of mice in the two datasets (GSE49543 and GSE6045).

	Platform	Microarray	Group	Sample size	Age (months)
GSE49543	GPL339	Affymetrix mouse expression 430A array	Young control	8 (excluding GSM1201567)	3.5 ± 0.4
			Middle control	17	12.3 ± 1.5
			Old mild hearing loss	9	27.7 ± 3.4
			Old severe hearing loss	6	30.6 ± 1.9
GSE6045	GPL339	Affymetrix mouse expression 430A array	Mild hearing loss	3	2
			Severe hearing loss	3	8

Protein-Protein Interaction Network Construction

A PPI network can help us clarify the pathogenesis and progression of diseases. The identified DEGs were mapped to the STRING database (version 10)[2] to analyze the PPI of autophagy-related DEGs. The interactions with reliability scores more than 0.4 were selected for analysis. Cytoscape software (16) was applied to construct the PPI network and the plugin "cytoHubba" (17) was utilized to explore the PPI network. The top 20 percent of the hub genes were selected by "cytoHubba" based on the maximum correlation criterion algorithm. High ranked genes were represented by a redder color.

Immune Infiltration Analysis

The marker genes for immune cell types were referred from a previous study (18). Infiltration levels of immune cells were analyzed using the single-sample GSEA method. Spearman's correlation analysis was performed to show the association between different degrees of hearing loss and the infiltration of the immune cell types.

Survival Analysis

We analyzed the DEGs between the old mice with hearing loss (n = 15) and middle-aged mice with good hearing (n = 17). The relationship between the clinicopathologic characteristics and gene expression were assessed using hazard ratio (HR). Univariate Cox regression analysis was performed to obtain the prognostic genes and multivariate Cox analysis was applied to construct a prognostic model. The Kaplan-Meier curves were used to study the effects of the prognostic model in the training set. As the previous study did not describe the survival time clearly (11), we set the survival time as 8 months for the middle-aged mice group with good hearing and 24 months for the old mice group with hearing loss.

Animal Model and Treatment

Male Sprague Dawley rats (8 weeks old) were purchased from the Model Animal Research Center of Guangxi Medical University (Nanning, China). The rats were randomly divided into two groups: the control group and the presbycusis group (n = 4). All animals had no history of noise exposure and other drug use. ABR and DPOAE were performed before the experiment to determine their hearing normally. The rats in the presbycusis group were given 5% D-galactose (250 mg/kg) daily by intraperitoneal injection for 10 weeks; The control group was given a similar volume of saline daily by intraperitoneal injection for 10 weeks.

One day after the last administration, ABR and DPOAE were performed to ensure successful modeling. After recordings, animals were transcardially perfused and obtained cochlear tissue. The animal study was approved by the Institutional Ethics Committee for Animal Research of Guangxi Medical University. All procedures conformed to the Guide for the Care and Use of Laboratory Animals.

Reverse Transcription-Polymerase Chain Reaction

Total cochlear mRNA was extracted using TRIzol reagent and reverse transcribed into cDNA. RT-qPCR was performed by StepOneP^{TM} Real-Time PCR System (Thermo Fisher, Waltham, MA, United States) using the SYBERGreen kit of Takara company. The total volume of the reaction system is 20 μl [10 μl SYBERGreen (2×), 7 μl DEPCwater, 1 μl cDNA, 0.8 μl forward primer, 0.8 μl reverse primer, 0.4 μl Rox reference dye (50×)]. The reaction conditions were pre-incubated at 95°C for 30 s and one cycle, followed by denaturation at 95 °C for 10 s; and elongation at 60 °C for 30 sec, repeated for 45 cycles. Each sample was run in triplicate and averaged. The relative gene expression was calculated by the $2^{-\Delta\ \Delta}$ Ct method.

The primer sequence is as follows: *Fgf1* forward primer: 5′-AGCAGCAGGAATGCATTGAGG-3′, reverse primer: 5′-AACTGTCGATGGTGCGTTCAAG-3′. *Ywhag* forward primer: 5′- CAGCTGCTCCGAGACAACCTA-3′, reverse primer: 5′-AGGAACCATCCACGCTCA-3′. *Mapre2* forward primer: 5′- TGCCAAGACGCGTTAGCAG-3′, reverse primer: 5′-CAAGCAGCCAGGTGGTGAAG-3′. *Acss2* forward primer: 5′- GAACCACACACGTTTCGAGACC-3′, reverse primer: 5′- TCATCAATCCTGCCAGTGATCC-3′. β-*actin* forward primer: 5′- GCGCAAGTACTCTGTGTGGA-3′, reverse primer: 5′-GAAAGGGTGTAAAAC GCAGC-3′.

RESULTS

Identification of the Differentially Expressed Genes in Presbycusis

In GSE49543, each sample was standardized to the average gene expression (**Figure 1A**), the expression values for those genes were similar after normalized. GSM1201567 was excluded as it was not clustered with the other samples belonging to the control group in the heat maps. In the old-aged mild hearing

[2]http://string-db.org

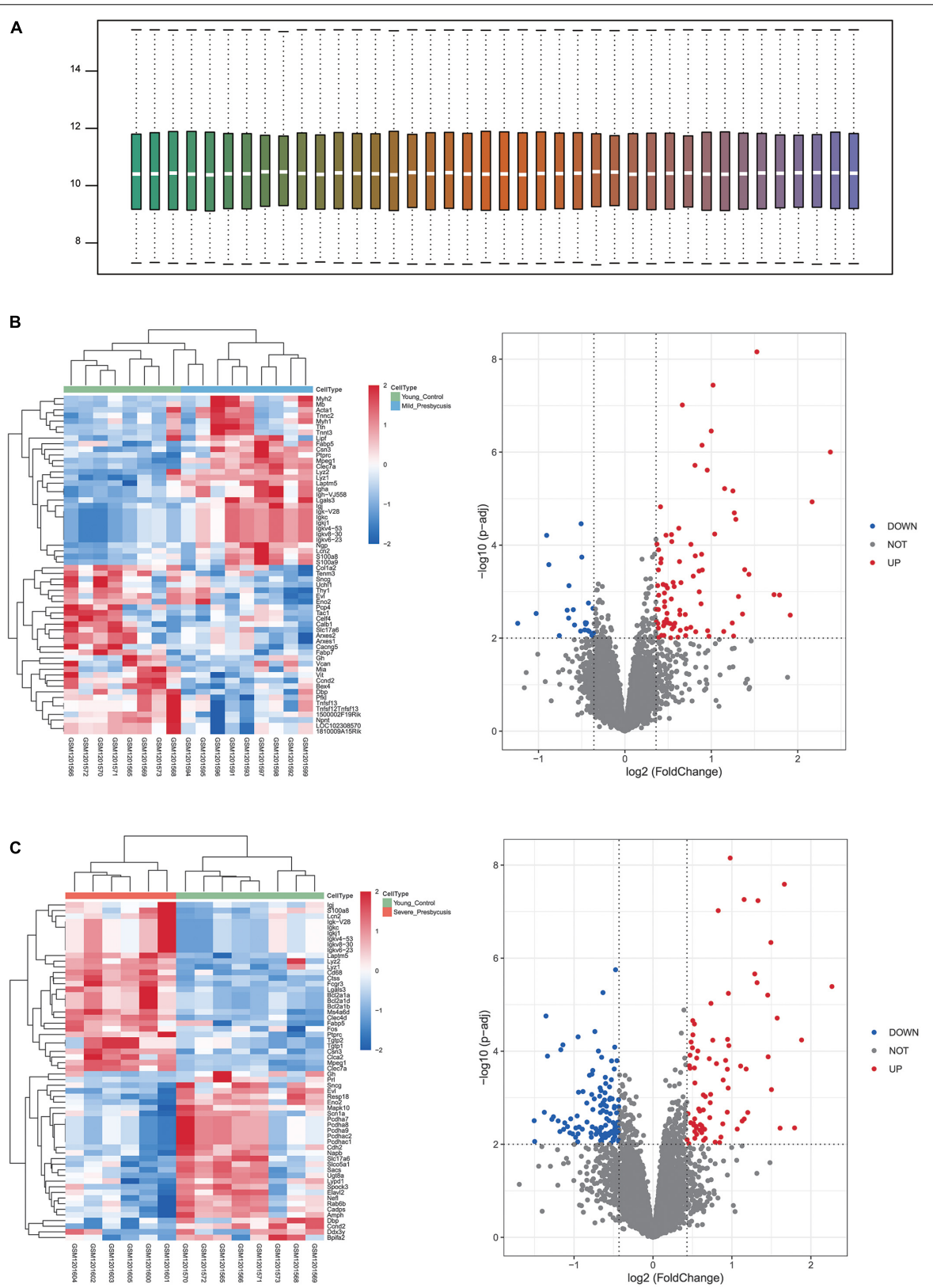


FIGURE 1 | Identification of the differentially expressed genes (DEGs) in presbycusis in GSE49543. **(A)** Differentially expressed mRNAs data sets were standardized. **(B)** The heat map and volcano plot of the top 30 up-regulated (red dots) and top 30 down-regulated (blue dots) DEGs in mild presbycusis. **(C)** The heat map and volcano plot of the top 30 up-regulated (red dots) and top 30 down-regulated (blue dots) DEGs in severe presbycusis.

TABLE 2 | Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis of differentially expressed genes (DEGs) in the most significant module.

Category	Mild presbycus				Severe presbycus			
	ID	Description	Count	*p*-adjust	ID	Description	Count	*p*-adjust
GOTERM_MF	GO:0034987	Immunoglobulin receptor binding	7	4.58E−08	GO:0051400	BH domain binding	4	2.16E−02
GOTERM_MF	GO:0003823	Antigen binding	9	2.78E−07	GO:0034987	Immunoglobulin receptor binding	4	4.78E−02
GOTERM_MF	GO:0042605	Peptide antigen binding	5	1.68E−04	GO:0030547	Receptor inhibitor activity	4	4.78E−02
GOTERM_MF	GO:0030548	Acetylcholine receptor regulator activity	4	1.68E−04	GO:0005509	Calcium ion binding	18	4.78E−02
GOTERM_MF	GO:0099602	Neurotransmitter receptor regulator activity	4	1.68E−04	GO:0048407	Platelet-derived growth factor binding	3	5.79E−02
GOTERM_MF	GO:0033130	Acetylcholine receptor binding	4	2.64E−04	GO:0030548	Acetylcholine receptor regulator activity	3	5.79E−02
GOTERM_CC	GO:0009897	External side of plasma membrane	19	1.27E−07	GO:0009897	External side of plasma membrane	17	6.39E−02
GOTERM_CC	GO:0042611	MHC protein complex	5	1.11E−04	GO:0042611	MHC protein complex	4	7.30E−02
GOTERM_CC	GO:0042571	Immunoglobulin complex, circulating	4	3.48E−04	GO:0043209	Myelin sheath	10	2.05E−01
GOTERM_CC	GO:0019814	Immunoglobulin complex	4	7.77E−04	GO:0005581	Collagen trimer	5	2.69E−01
GOTERM_CC	GO:0031985	Golgi cisterna	5	3.39E−03	GO:0005925	Focal adhesion	7	3.06E−01
GOTERM_CC	GO:0042612	MHC class I protein complex	3	3.39E−03	GO:0045335	Phagocytic vesicle	6	3.06E−01
KEGG_PATHWAY	mmu05150	*Staphylococcus aureus* infection	9	1.70E−06	mmu05150	*Staphylococcus aureus* infection	9	8.89E−07
KEGG_PATHWAY	mmu05416	Viral myocarditis	8	3.79E−06	mmu05323	Rheumatoid arthritis	7	1.54E−04
KEGG_PATHWAY	mmu04145	Phagosome	10	1.29E−05	mmu05416	Viral myocarditis	6	4.76E−04
KEGG_PATHWAY	mmu04612	Antigen processing and presentation	7	2.59E−05	mmu04145	Phagosome	8	5.21E−04
KEGG_PATHWAY	mmu05332	Graft-vs.-host disease	6	2.59E−05	mmu05322	Systemic lupus erythematosus	5	8.94E−04
KEGG_PATHWAY	mmu04514	Cell adhesion molecules	9	2.59E−05	mmu04514	Cell adhesion molecules	7	9.73E−04

MF, molecular function; CC, cellular component; GO, gene ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.

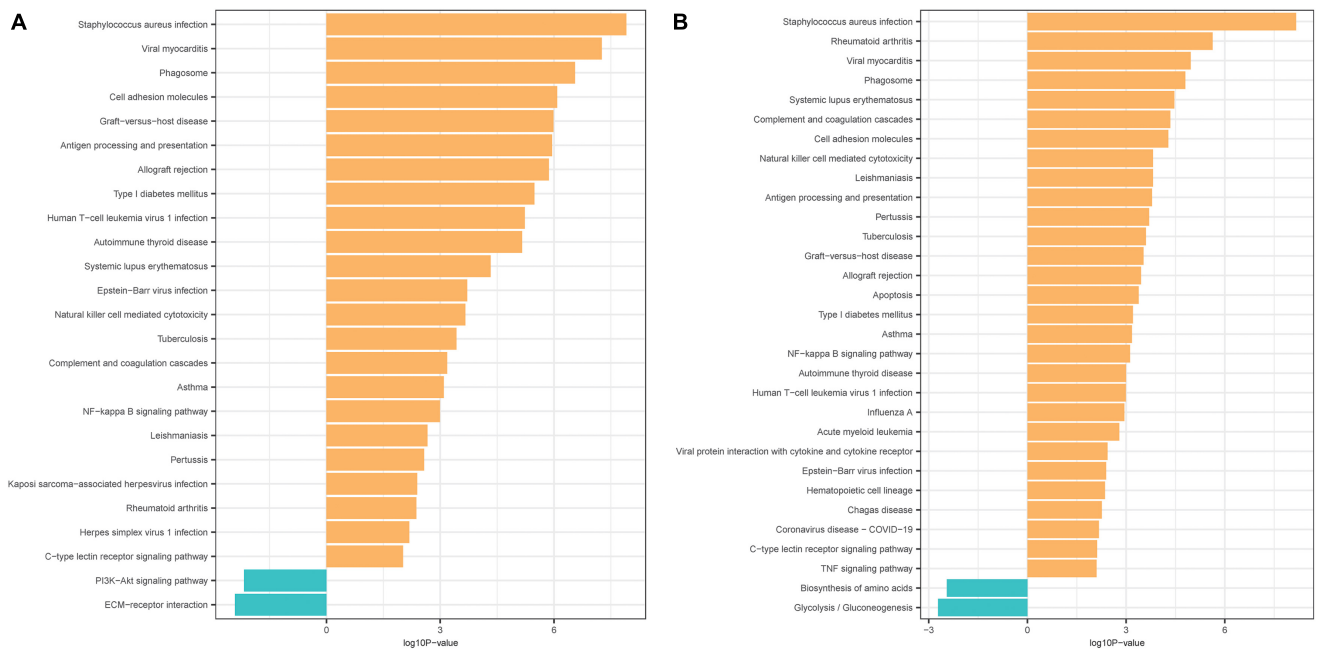


FIGURE 2 | Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses of the DEGs. **(A)** KEGG pathway analysis of the DEGs in mild presbycusis. **(B)** KEGG pathway analysis of the DEGs in severe presbycusis. Each row represents one pathway, and column represents log10P-value.

loss group, a total of 126 DEGs were identified, which comprised 99 up-regulated (logFC > 0.36 and *P*-adj. <0.01) and 27 down-regulated genes (logFC < −0.36 and *P*-adj. <0.01). The heat map and volcano plot of the top 30 up-regulated and top 30 down-regulated genes are shown in **Figure 1B** (There were not enough down-regulated genes in the old-aged mild hearing loss group, so the heatmap shows all of them). In the old aged severe hearing loss group, a total of 220 DEGs were identified, which comprised 89 up-regulated (logFC > 0.43 and *P*-adj. <0.01) and 131 down-regulated genes (logFC < −0.43 and *P*-adj. <0.01). The heat map and volcano plot of the top 30 up-regulated and top 30 down-regulated genes are shown in **Figure 1C**. In the heatmap, each row represents one gene, and each column represents one sample. The color difference among samples is a result of gene expression differences. In the volcano plot, gray dots represent no significantly different expression genes, red dots represent significantly up-regulated genes, and green dots represent downregulated.

Gene Ontology and Kyoto Encyclopedia of Genes and Genomes Pathway Analyses of the Differentially Expressed Genes

In the mild hearing loss group, GO analysis showed that the DEGs were considerable enriched in the terms "immunoglobulin receptor binding," "antigen binding," "peptide antigen binding," "acetylcholine receptor regulator activity," "neurotransmitter receptor regulator activity," and "acetylcholine receptor binding" in the MF category (**Table 2**), and in the terms "external side of plasma membrane," "MHC protein complex," "immunoglobulin complex," "circulating," "immunoglobulin complex," "Golgi cisterna," and "MHC class I protein complex" in the CC category (**Table 2**). KEGG pathway analysis indicated that the DEGs were mainly enriched in "*Staphylococcus aureus* infection," "viral myocarditis," "phagosome," "antigen processing and presentation," "graft-vs.-host disease," and "cell adhesion molecules" (**Figure 2A** and **Table 2**). Meanwhile, in the severe hearing loss group, GO analysis showed that the DEGs were remarkably enriched in the terms "BH domain binding," "Immunoglobulin receptor binding," "receptor inhibitor activity," "calcium ion binding," "platelet-derived growth factor binding," "acetylcholine receptor regulator activity" in the MF category (**Table 2**), and in the terms "external side of plasma membrane," "MHC protein complex," "myelin sheath," "collagen trimer," "focal adhesion," and "phagocytic vesicle" in the CC category (**Table 2**). KEGG pathway analysis expressed that the DEGs were mainly enriched in the terms "*Staphylococcus aureus* infection," "rheumatoid arthritis," "viral myocarditis," "phagosome," "systemic lupus erythematosus," and "cell adhesion molecules" (**Figure 2B** and **Table 2**).

Gene Set Enrichment Analysis of the Hearing Loss-Related Genes

We performed GSEA using the C2 (curated gene sets) collection. We identified biological pathways that were significantly altered in presbycusis groups compared with those in the young control

TABLE 3 | Gene set enrichment analysis (GSEA) indicating statistically significant enrichment.

Mild presbycusis				Severe presbycusis			
Description	**ES**	**NES**	***p*-adjust**	**Description**	**ES**	**NES**	***p*-adjust**
REACTOME_TRANSLATION	−0.62573	−2.44408	9.66E−17	KIM_ALL_DISORDERS_CALB1_CORR_UP	−0.59203	−2.44131	2.54E−25
REACTOME_MITOCHONDRIAL_TRANSLATION	−0.70011	−2.4343	3.37E−10	MCCLUNG_DELTA_FOSB_TARGETS_2WK	−0.77549	−2.31971	6.27E−07
STARK_PREFRONTAL_CORTEX_22Q11_DELETION_DN	−0.54477	−2.27383	6.21E−18	MCCLUNG_CREB1_TARGETS_UP	−0.65934	−2.29165	1.97E−07
YAO_TEMPORAL_RESPONSE_TO_PROGESTERONE_CLUSTER_17	−0.59278	−2.25034	1.23E−09	REACTOME_TRANSLATION	−0.59012	−2.29102	2.06E−11
KIM_ALL_DISORDERS_DURATION_CORR_DN	−0.59344	−2.17968	2.11E−07	MIKKELSEN_MEF_HCP_WITH_H3_UNMETHYLATED	−0.60184	−2.24356	5.07E−08
ICHIBA_GRAFT_VERSUS_HOST_DISEASE_35D_UP	0.741098	2.605496	2.80E−11	ICHIBA_GRAFT_VERSUS_HOST_DISEASE_35D_UP	0.737705	2.860085	6.20E−16
MCLACHLAN_DENTAL_CARIES_UP	0.693985	2.581421	3.24E−15	FLECHNER_BIOPSY_KIDNEY_TRANSPLANT_REJECTED_VS_OK_UP	0.737343	2.698483	6.98E−11
RICKMAN_HEAD_AND_NECK_CANCER_F	0.867346	2.532418	1.69E−08	WIELAND_UP_BY_HBV_INFECTION	0.744022	2.672265	3.57E−10
FLECHNER_BIOPSY_KIDNEY_TRANSPLANT_REJECTED_VS_OK_UP	0.739949	2.452244	4.33E−07	MCLACHLAN_DENTAL_CARIES_UP	0.636446	2.647871	4.20E−15
NAKAYAMA_SOFT_TISSUE_TUMORS_PCA1_UP	0.78259	2.435661	7.67E−07	BLANCO_MELO_COVID19_SARS_CoV_2_POS_PATIENT_LUNG_TISSUE_UP	0.695495	2.64333	1.19E−11

ES, enrichment score; NES: normalized enrichment score; E:10^.

group. The results of the gene expression profiles in GSE49543 are shown in **Table 3**. In the mild hearing loss group, the activated pathways were ichiba graft vs. host disease 35 d up, mclachlan dental caries up, rickman head and neck cancer f, flechner biopsy kidney transplant rejected vs. ok up, and nakayama soft tissue tumors pca1 up (**Figure 3A**); the suppressed pathways were: reactome translation, reactome mitochondrial translation, stark prefrontal cortex 22q11 deletion dn, yao temporal response to progesterone cluster 17, and kim all disorders duration corr dn (**Figure 3B**). In the severe hearing loss group, the activated enriched pathways were: ichiba graft vs. host disease 35 d up, flechner biopsy kidney transplant rejected vs. ok up, wieland up by hbv infection, mclachlan dental caries up, and blanco melo COVID-19 SARS-CoV-2 pos patient lung tissue up (**Figure 4A**); whereas, the suppressed pathways were: kim all disorders calb1 corr up, mcclung delta fosb targets 2 weeks, mcclung creb1 targets up, reactome translation, and mikkelsen mef hcp with h3 unmenthylated (**Figure 4B**). Together those shows that ichiba graft vs. host disease 35 d up pathway is a major pathogenic pathway of presbycusis, while reactome translation plays a protective role for inner ear. The abovementioned results indicated that the activated signaling pathways were mainly enriched in infection and immunity, whereas, the suppressed pathways were mainly enriched in the gene expression processes associated with presbycusis.

Protein-Protein Interaction Network Construction and Evaluation

The interactions of the autophagy-related DEGs were analyzed using the STRING database, which comprised 72 DEGs in the

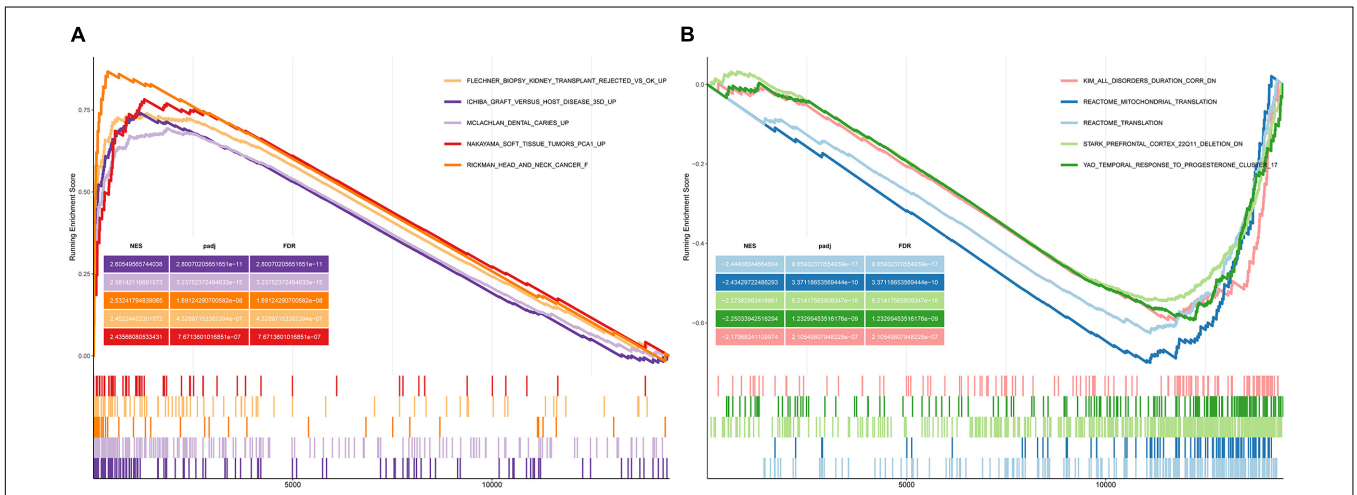


FIGURE 3 | Gene Set Enrichment Analysis (GSEA) plots showing the most enriched gene sets in C2 collection in mild presbycusis. **(A)** The top five most significant up-regulated enriched gene sets and **(B)** the top five most significant down-regulated enriched gene sets in GSE49543.

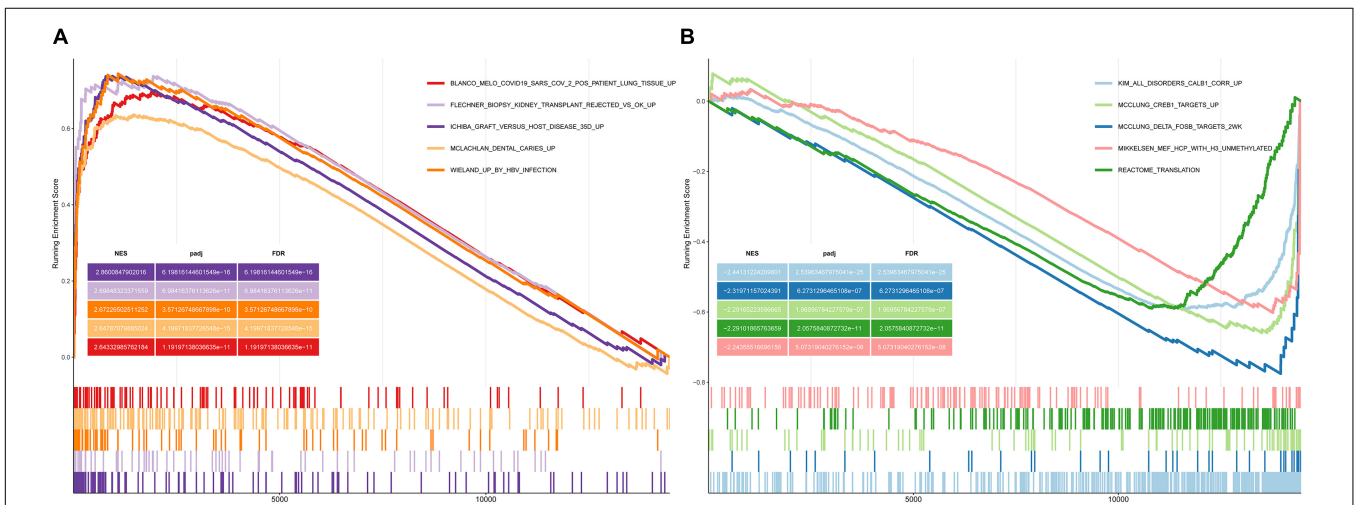


FIGURE 4 | Gene Set Enrichment Analysis plots showing the most enriched gene sets in C2 collection in severe presbycusis. **(A)** The top five most significant up-regulated enriched gene sets and **(B)** the top five most significant down-regulated enriched gene sets in GSE49543.

mild hearing loss group and 88 DEGs in the severe hearing loss group. The top 20 percent of the autophagy-related hub genes were identified using the cytoHubba plugin (**Figure 5**). The darker the color, the higher node score is in the PPI network. Among these genes, ATG5, ATG7 showed the highest node scores in the mild hearing loss group, whereas MTOR, BECN1 showed the highest node scores in the severe hearing loss group. These results suggested that these genes may play an important role in the development or progression of presbycusis and different degree of hearing loss may induce autophagy by different mechanisms.

The Relationship Between Hearing Loss Degree and Immune Infiltration

We investigated the differences in the immune cell infiltration between the presbycusis cochlea tissues and control cochlea tissues. The differential expression of the immune cells between

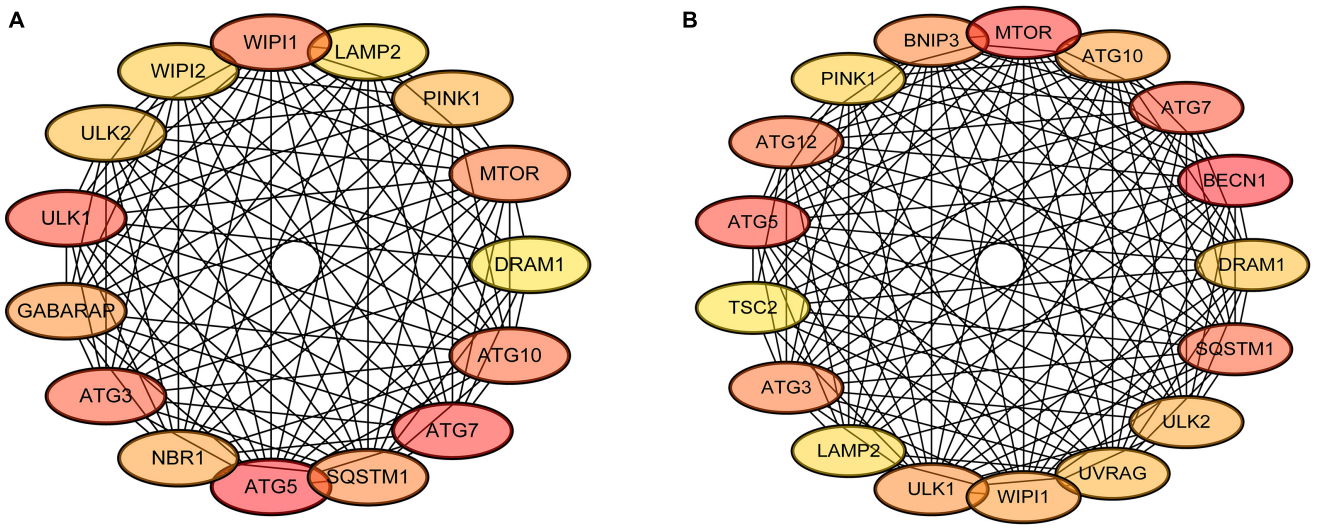


FIGURE 5 | Protein-protein interaction (PPI) network construction and major autophagy-related genes. The cytoHubba plugin was used to analyze the top 20 percent of the hub genes with maximum correlation criterion in mild **(A)** and severe **(B)** presbycusis.

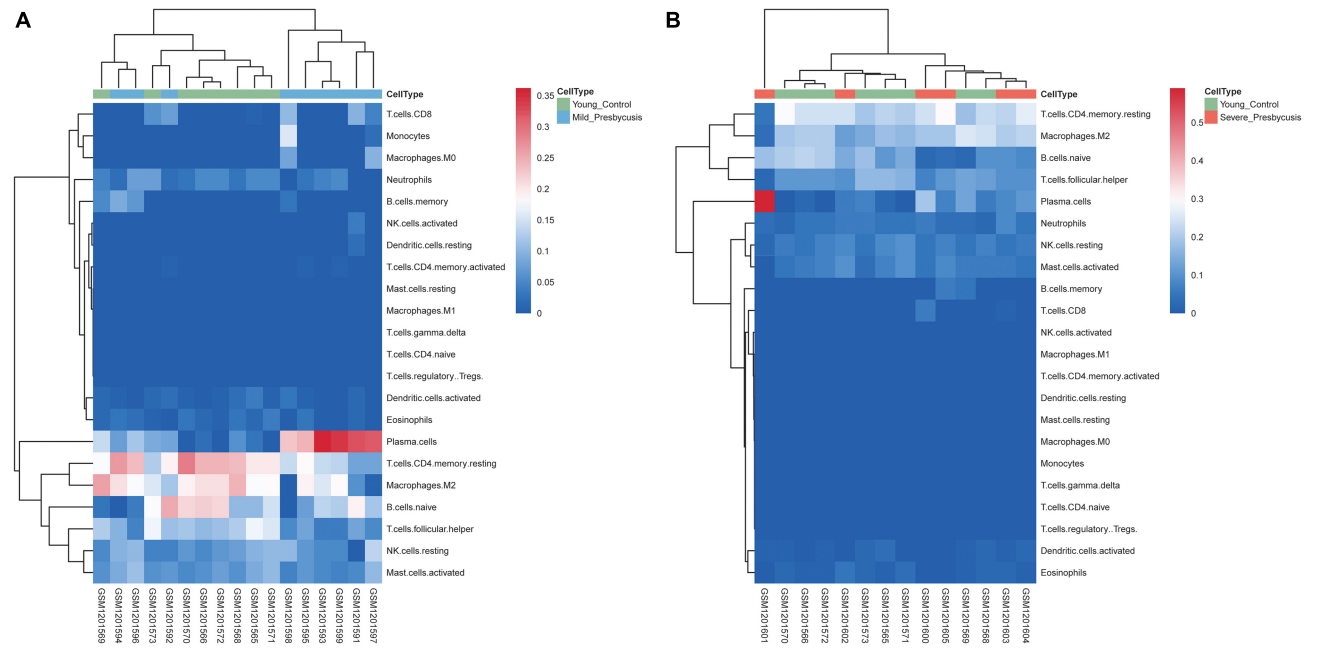


FIGURE 6 | Landscape of immune infiltration in presbycusis. **(A)** The heat maps of different types of immune cells expression between mild presbycusis and young control group. **(B)** The heat maps of different types of immune cells expression between severe presbycusis and young control group.

each presbycusis group and control group is shown in **Figure 6**. Each row represents one type of 22 immune cell, and each column represents one sample. Five immune cell subsets were differentially expressed: B cells naïve, plasma cells, CD4 memory resting T cells, follicular helper T cells, and M2 macrophages. The B naïve immune cells in the mild hearing loss group ($P = 0.038$) showed lower differential expression than that in the severe group ($P = 0.016$); the M2 macrophages in the mild group showed greater differential expression ($P = 0.019$) than that in the severe group ($P = 0.26$); the plasma cells ($P < 0.001$) in the mild group showed higher differential expression than that in the severe group ($P = 0.14$); the CD4 memory resting T cells in the mild group showed higher differential expression ($p = 0.026$) than that in the severe group ($P = 0.99$); and finally, the follicular helper T cells in the mild group showed higher differential expression ($p < 0.001$) than that in the severe group ($P = 0.0074$) (**Figure 7**).

Prognostic Value of the Hearing Loss-Related Genes in Presbycusis

Univariate Cox regression analysis was performed to identify the prognostic differentially expressed hearing loss related genes in GSE49543. Four genes were significantly correlated with the overall survival (OS) in presbycusis (**Figure 8A**). Considering the effect of the prognostic value, we further constructed a Cox regression hazard model: Risk score = $-2.8 \times$ (Ywhag + Mapre2 + Fgf1 + Acss2), where c-index is 0.745 (0.720–0.771). The risk scores for each gene were calculated using their expression levels and regression coefficients

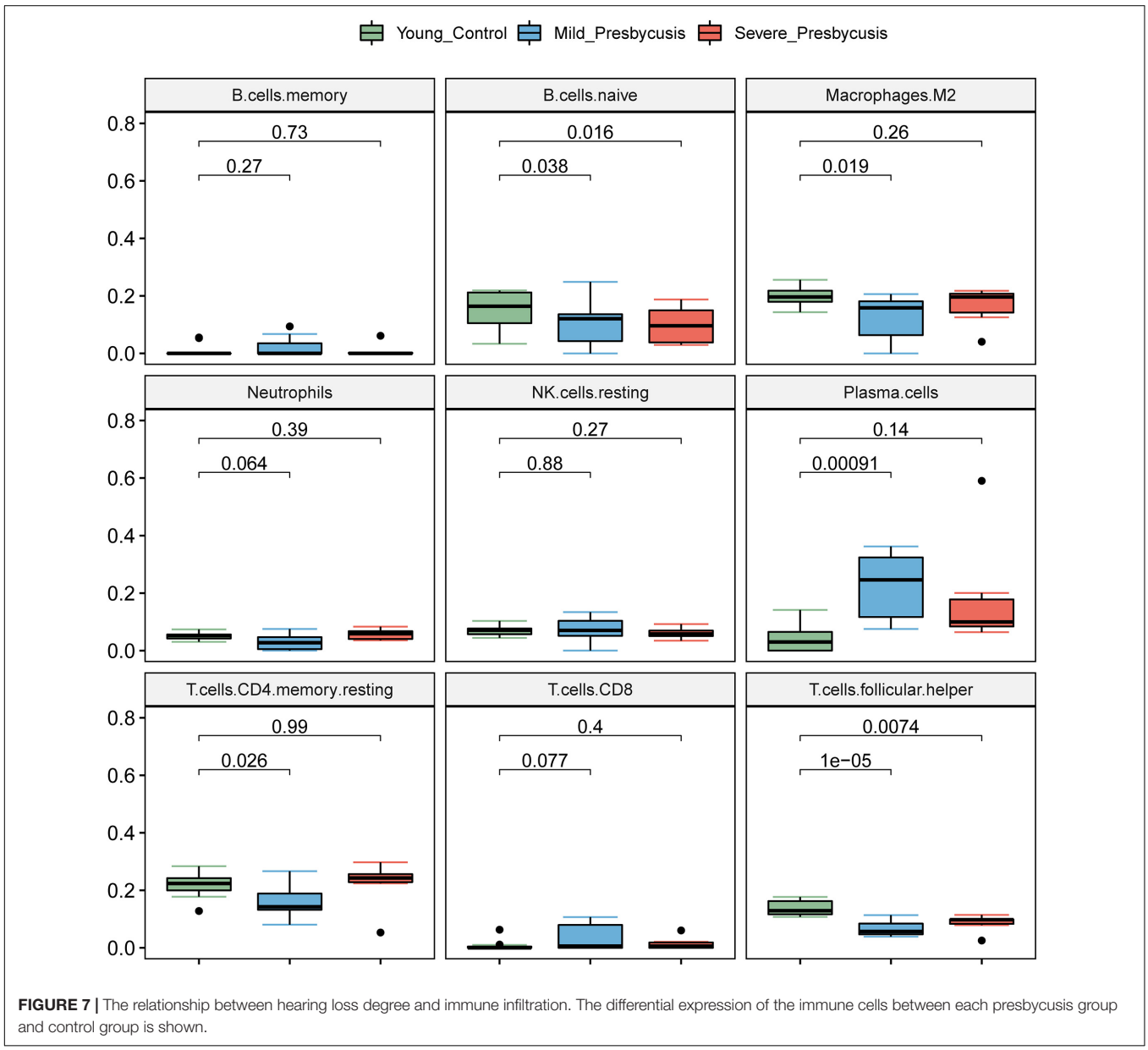


FIGURE 7 | The relationship between hearing loss degree and immune infiltration. The differential expression of the immune cells between each presbycusis group and control group is shown.

(**Figure 8B**). Higher risk scores indicated greater hearing loss risk for old people. The expression level of four signature genes (n = 15) from GSE49543 is shown in **Figure 8C**. A survival curve was drawn to validate the accuracy and repeatability of the four prognostic genes in GSE6045 (**Figure 8D**). We then used a time-dependent receiver operating characteristic (ROC) curve to confirm the predictive accuracy of the model, and the area under curve was 100% as the sample size was small (**Figure 8E**).

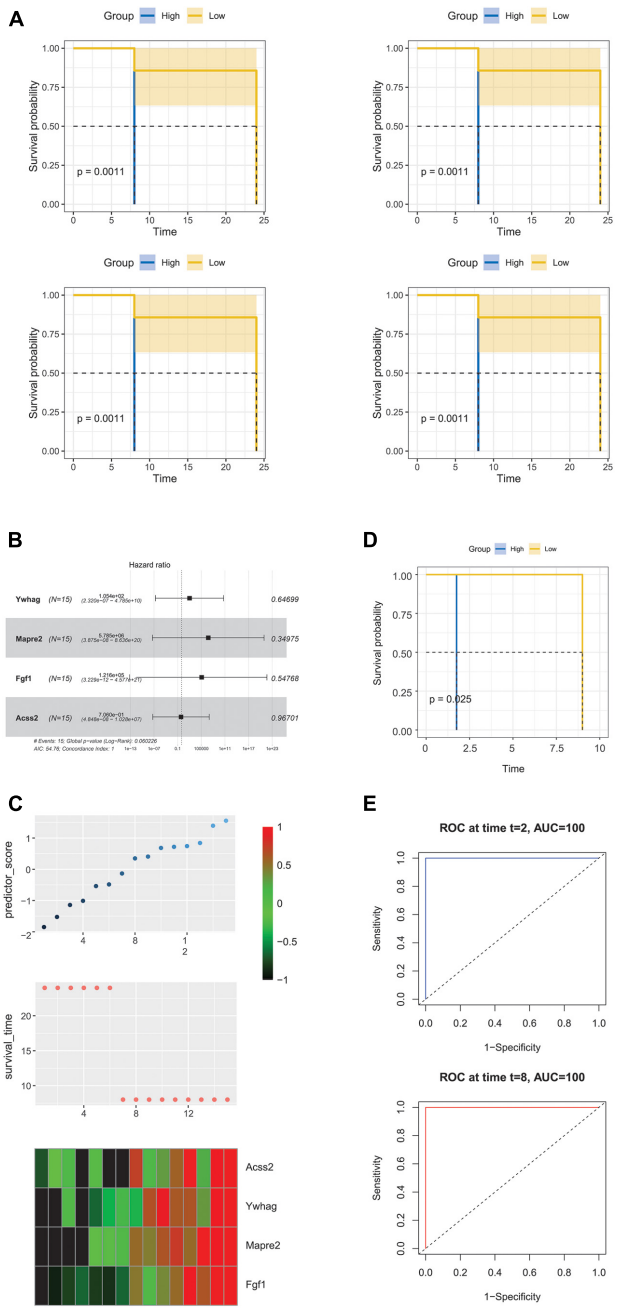


FIGURE 8 | Prognostic value of the hearing loss-related genes in presbycusis. **(A)** KM curve of overall survival (OS) prognosis of four genes in GES49543. **(B)** Forest map of OS multivariate analysis of four genes in presbycusis. **(C)** Top: the risk score of prediction model in validation set; Middle: corresponding survival status of each sample; Bottom: the mRNA expression of four signature genes in each sample. **(D)** KM curve of overall survival (OS) prognosis in GES6045. **(E)** ROC curve and AUC of prognostic model in GSE6045.

The Expression Level of the Prognostic Genes *in vivo*

Ten weeks post-intraperitoneal injection with D-galactose, rats are aging manifestations in hair, nerve reflex and hearing compared with contral rats. D-galactose-induced subacute aging model is most frequently used as an animal model for presbycusis. All of the four genes (*Ywhag, Mapre2, Fgf1*, and *Acss2*) were significantly up-regulated compared to the control group (**Figure 9**).

DISCUSSION

Presbycusis is a multifactorial disorder that is associated with genetic and environmental factors (3). While aging is inevitable, not everybody will suffer from presbycusis (7). Elucidating the mechanisms underlying the pathogenesis and progression of age-related hearing loss would aid in its prevention and therapy. With the technological advances of microarray and bioinformatic analyses, we can now identify the underlying molecular mechanisms of disease development and progression. In mammals, inner ear hair cells cannot easily regenerate after damage, and presbycusis animal models have been generated to study the pathogenesis and molecular basis.

Physiologically, autophagy maintains the internal environment of the body by degrading the cytoplasmic materials in lysosomes. When autophagy is dysregulated, it may cause adverse effects on the body (19, 20). Autophagy is enhanced in aging-related diseases (19–21), and increased autophagic stress occurs during premature age-related hearing loss in mice (22). In C57BL/6 mice, miR-34a/SIRT1 signaling activation can reduce age-related cochlear hair cell loss *via* regulated autophagy (23–25). Nevertheless, there are a few studies that have focused on autophagy in presbycusis. Thus, it is worth exploring whether there are differences between autophagy markers or their expression levels that are associated with different degrees of hearing loss in presbycusis.

Cancer, inflammation and aging are interconnected. Immune microenvironment determines the invasion capacity of the tumor cells, proliferation, and metastasis. Macrophages and T cells are the key components of the microenvironment, and immune checkpoint inhibitors have shown clinical benefits across a wide variety of tumor types (26, 27). Unlimited expression and production of inflammatory mediators are the key features of aging (28). As previously reported, aging has an impact on the Langerhans cells, dendritic cells, and natural killer cells. However, the role of the immune microenvironment in the pathogenesis of presbycusis remains unknown.

In this study, we performed an integrative analysis using two publicly available mouse mRNA microarray datasets (GSE6045 and GSE49543). On comparing the samples from the young

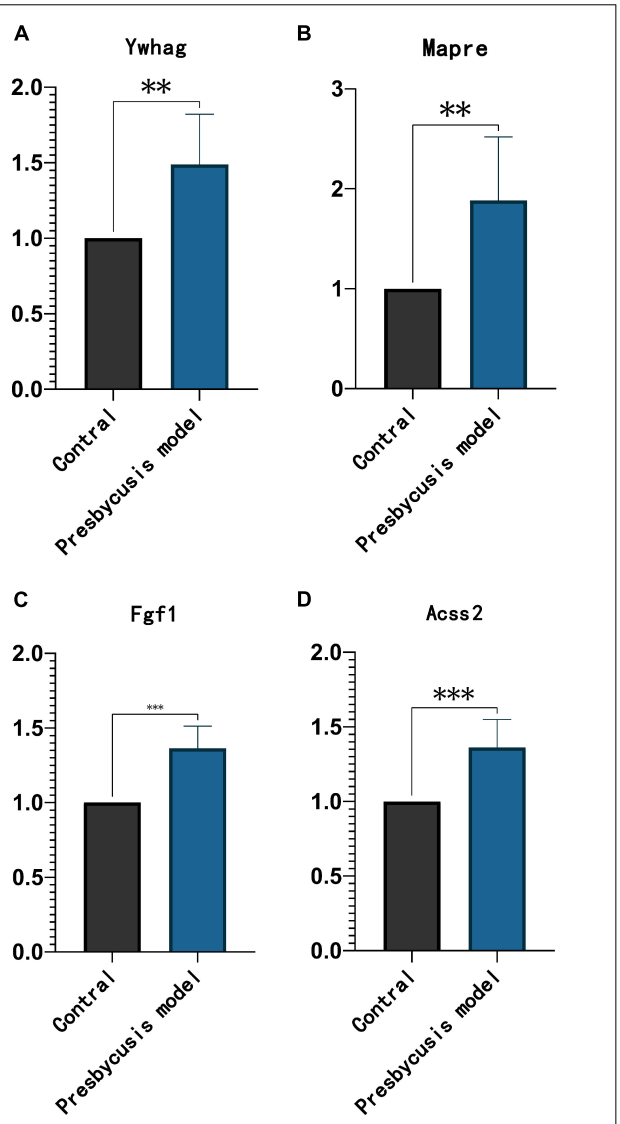


FIGURE 9 | The expression trend of prognostic factors in the inner ear of D-galactose induced rats. The expression of Ywhag **(A)**, Mapre2 **(B)**, Fgf1 **(C)**, and Acss2 **(D)**. $^{**}p < 0.01$ and $^{***}p < 0.001$ compared with control.

control group, we observed that samples with different degrees of hearing loss (ranging from mild to severe) did not have the same DEGs. Three autophagy-related genes (Dram1, Fkbp1b, and Fos) were differentially expressed in the mild hearing loss group, whereas five autophagy-related genes (Dram1, Fkbp1b, Fos, Capn2, and Eef2) were differentially expressed in the severe hearing loss group. The difference in the expression of the biochemical markers indicated that the autophagy process was involved in both groups, although, with different degrees. Based on the PPI network analysis and hub gene identification, we found that the mild and severe hearing loss groups had different autophagy-related hub genes, suggesting that different degrees of hearing loss may occur in different autophagy pathways. It is likely activating autophagy activity is the main mechanism in mild presbycusis and stimulus-induced autophagy plays important roles in severe presbycusis. The difference between the two pathogenesis is worthy of further discussion.

Gene ontology analyses revealed that the main GO terms were enriched in immune response in the mild hearing loss group, and with immune response and cell death in the severe hearing loss group. KEGG enrichment analysis of the DEGs revealed that the most enriched pathways in our analysis were associated with immune response, inflammation, and cell death. This result is consistent with that in previous studies reporting that inflammation and autophagy were the key mechanisms associated with aging cochlea (22, 23, 29). By combining GSEA results, we found many DEGs that were important in infection and immunity. Results revealed that there were different signaling pathways and biological processes in the mild and severe hearing loss groups.

The inner ear is not an immune-privileged organ, which is why we attempted to reveal the differences in immune cell infiltration in presbycusis. A high expression of T follicular helper cells and B cells has been strongly associated with good prognosis in patients with human colorectal cancer (18). Our results also showed that the expression of T follicular helper cells and B cells was reduced in the presbycusis groups. M2 macrophages expression was reduced in the mild hearing loss group but remained unchanged in the severe hearing loss group. However, previous studies have reported macrophage invasion in the cochlear of presbycusis mice models (22). M1 macrophages are proinflammatory, whereas M2 macrophages are anti-inflammatory (30). So far, there is no research about the changes in macrophage subsets observed in presbycusis. Thus, the role of different types of immune cells in the pathogenesis of presbycusis still needs to be clarified.

Hearing loss occurs with aging in presbycusis, and we found four genes that were significantly associated with aging. Ywhag is a member of the 14-3-3 family, which mediats signal transduction by binding to phosphoserine-containing proteins. A study has reported the upregulation of Ywhag in age-related hearing loss (31). Hypoxia can activate p53 through the inactivation of MDMX by the ATR-Chk1-MDMX-14-3-3γ pathway (32). Mapre2, a microtubule-associated protein RP/EB family member 2, impacts the microtubule formation in the developing organ of Corti. Normal fluid spaces in cochlea are necessary for proper hearing (33). Fgf1 is involved in a variety of biological processes, and belongs to the fibroblast growth factor (FGF) family. It is involved in several cell activities, such as embryonic development, morphogenesis, cell growth, tissue repair, tumor growth, and invasion. FGFs possibly regulate the activity of signaling axonal growth or intrinsic neurons in the cochlear nucleus of adult mice following acoustic overstimulation (34). Acss2 is a cytosolic enzyme, which can catalyze the activation of acetate for its use in lipid synthesis and energy generation. Acss2 produces acetyl-CoA from acetate in an ATP-dependent reaction, and ATP levels are declined in D-galactose-induced aging mouse (35). However, there is no literature suggesting the relationship between Acss2 and presbycusis. Those four genes vertified increased in presbycusis *in vivo* experiment. Our study indicates that this may be a new prognostic factor of presbycusis. Further

analyses were necessary to analyze through which pathway are those genes involved in regulation of presbycusis.

There are two main limitations of the present study. First, in order to clarify the mechanism of presbycusis, more clinical information needs to be considered, such as gender, age of onset, whether there are deafness susceptibility genes, etc. The prognostic factors of presbycusis, such as the degree of hearing loss and sex were not considered, and such a lack of consideration may have led to some biological information being overlooked. Second, the datasets based on the same sequencing company and sequencing platform is limit, thus the sample size in our study was not large enough. Further, *in vivo* and *in vitro* experiments are necessary to verify the association of these genes and pathways with presbycusis. Therefore, we aim to further increase the sample size and more clinical information to explore the pathogenesis of presbycusis. A series of molecular experiments may provide strong evidence for the possible phenotype and pathway regulation of these predicted genes recently.

To the best of our knowledge, this is the first study to report the difference in autophagy factors and immune microenvironment in different degrees of hearing loss in presbycusis. We used two microarray datasets to increase the reliability of our analysis. All data were downloaded from reliable GEO datasets. Furthermore, GO and KEGG analyses and GSEA were further carried out to analyze the main biological functions that were modulated by the DEGs. These data suggest that multiple biomarkers and pathways of presbycusis, in addition to different degrees of hearing loss may be caused by different molecular mechanisms in presbycusis. Thus, these results provide potential targets that can be employed to reduce or improve presbycusis progression.

CONCLUSION

In this study, we combined two datasets to explore the molecular mechanisms associated with different degrees of hearing loss in presbycusis. Our results revealed DEGs, molecular pathways, immune cell infiltration and prognostic molecular markers affecting hearing impairment in presbycusis. This study provided a molecular basis of mildly and severely impaired auditory functions, with the aim of developing preventative therapies. However, more molecular experiments, both *in vivo* and *in vitro* are needed to validate the findings of the current study.

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 below: https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE49543 and https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE6045.

ETHICS STATEMENT

The animal study was reviewed and approved by the Institutional Ethics Committee for Animal Research of Guangxi Medical University.

AUTHOR CONTRIBUTIONS

SY conceived and designed the study. NL and ZH performed data analysis. CQ contributed analysis tools. LP wrote the manuscript. All authors read and approved the final manuscript.

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The Impact of Alcohol Consumption on Cognitive Impairment in Patients With Diabetes, Hypertension, or Chronic Kidney Disease

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To investigate the impact of alcohol use on the risk of cognitive impairment in older adults with chronic illness, we used the Digit Symbol Substitution Test (DSST) to evaluate cognitive function in older adults (≥ 60 years) in the National Health and Nutrition Examination Survey. Participants were categorized as light drinkers, moderate and heavy drinkers. Logistic regression analyses were used to explore associations between cognitive impairment and alcohol drinking in patients with or without diabetes, hypertension, and chronic kidney disease (CKD). Multivariate analysis showed that alcohol heavy drinkers was significantly associated with a higher risk of cognitive impairment in patients with **hypertension** (aOR 6.089, 95% CI 1.318–28.13) and CKD (aOR 6.324, 95% CI 1.158–34.52) compared with light drinkers. The dose-response analyses revealed that moderate to heavy alcohol use was associated with a higher risk of cognitive decline in patients with diabetes and CKD, heavy drinking increased the risk of cognitive impairment in patients with hypertension. The impacts of alcohol drinking on cognitive impairment are significantly different in patients with different comorbidities.

Keywords: cognitive impairment, alcohol drinking, diabetes, hypertension, chronic kidney disease

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INTRODUCTION

Cognition refers to skills, such as learning, comprehension, memory, expression, language, communication, and execution (1). Cognitive impairment is a deficit of key brain functions, such as concentration, learning, memory, and decision-making. It ranges from mild to severe, and severe impairment may affect daily life and independence (2). The rate of cognitive impairment and dementia increases with age (3); generally, about 4–19% of 65-year-old persons have cognitive impairment (depending on the definition) (2). In addition to aging, genes, lifestyle, environmental risk factors, and chronic illnesses may affect cognitive function (2, 3). Cognitive impairment and dementia are significant causes of morbidity and mortality worldwide, imposing a heavy economic burden on patients, families, and caregivers. Identification of modifiable risk factors for cognitive impairment may help attenuate the global burden of dementia.

Abbreviations: DSST, digit symbol substitution test; MET, metabolic equivalent; CKD, chronic kidney disease; DM, diabetes mellitus; NMDA, N-methyl-D-aspartate.

Alcohol drinking can influence mood and cognition. Several studies have shown that chronic heavy alcohol drinking may lead to thiamine deficiency, ataxia, confusion, and oculomotor changes (Wernicke-Korsakoff syndrome) (4). Most, but not all, studies have shown that heavy alcohol drinking may increase the risk of cognitive impairment, but light to moderate amounts of alcohol consumption may attenuate the risk of cognitive impairment. Large amounts of alcohol may be metabolized to acetaldehyde, resulting in brain injury or nutritional deficiency and influencing neurocircuits. Light to moderate alcohol use may increase blood high-density lipoprotein (HDL), decrease oxidant stress, thrombosis, coagulation, and cardiovascular diseases (5).

The number of people with diabetes, hypertension, and chronic kidney disease (CKD) has increased recently, perhaps due to lifestyle, dietary changes and increased life expectancy worldwide. Approximately 22.8, 59.6, and 34.1% of 65 years and older persons have diabetes, hypertension, and CKD (6, 7). Hyperglycemia and insulin resistance increase the risk of cognitive impairment in patients with diabetes (2). The risk of new-onset cognitive impairment (up to 60%) is higher in persons with diabetes than those without diabetes (8). Hypertension, mediated by chronic mechanical stress, can significantly increase the risk of stroke and cerebral white matter lesions, leading to cognitive impairment (9). Studies have shown CKD (with accompanying risks of cardiovascular diseases and uremic metabolites) as a risk factor for cognitive dysfunction (10). Diabetes, hypertension, and CKD potentially contribute to a substantial proportion of cognitive impairment worldwide.

Many older people also have chronic diseases (11). People with more illnesses are more likely to develop cognitive impairment due to a lack of resilience and repair of cognitive function (2). These chronic diseases may compound the global burden of cognitive impairment. The relationship between alcohol drinking and cognitive change may be mediated or moderated by the presence of chronic illness. However, studies on the impact of alcohol use on cognitive function in patients with chronic diseases are scarce (12); and there is a close association among diabetes, hypertension, CKD and cognitive impairment. Therefore, we designed this study to investigate the effect of alcohol drinking on cognitive impairment in older people with diabetes, hypertension, or CKD.

MATERIALS AND METHODS

Data Source

This study used the dataset from the National Health and Nutrition Examination Survey (NHANES). Since the early 1960s, the NHANES program has been conducted as a series of surveys focusing on different health topics (13). The sample population for the NHANES survey is the non-institutionalized United States population. Further information on background, design, and operation is available on the NHANES website.[1]

[1]https://www.cdc.gov/nchs/nhanes/about_nhanes.htm

Ethics Statement

The NHANES data was de-identified and encrypted, and all participants in NHANES provided written informed consent consistent with the approval by the National Center for Health Statistics Institutional Review Board. Review and approval by the Institutional Review Board and the informed consent signed by participants were waived in the NHANES data analysis. In addition, the present study was approved under the authority of the Institutional Review Board of Chung Shan Medical University Hospital (CSMUH No: CS1-22004).

Study Subjects

Participants aged ≥ 60 years received the cognitive functioning assessment using Digit Symbol Substitution Test (DSST) (14) and completed the questionnaire of alcohol consumption in the NHANES cycles of 1999–2002 and 2011–2014. We excluded participants with incomplete DSST assessments or without alcohol drinking information. Patients diagnosed with brain tumors were also excluded. **Supplementary Figure 1** depicts the selection process.

Study Variables

Cognitive Impairment

Cognitive impairment was defined as a DSST score below the lowest quartile. The DSST requests the participant to code a series of symbols in 120 s with accuracy. This exercise demands sustained attention, response speed, visual-spatial skills, associative learning, and memory, providing a sensitive measure of cognitive function (14).

Alcohol Consumption

According to the Substance Abuse and Mental Health Services Administration (SAMHSA) criteria, and the limitation of NHANES questionnaire design, alcohol drinkers were classified into three groups: (1) Light drinkers (less or equal 1 drink/day); (2) Moderate drinkers (2–4 drinks/day in males, 2–3 drinks/day in females); (3) Heavy drinkers (≥ 5 drinks/day in males, ≥ 4 drinks/day in females) (15). We obtained information on alcohol consumption from the alcohol use questionnaire to estimate the average alcohol intake per day, and stratified the drinking dose based on the question:" In the past 12 months, on those days that you drank alcoholic beverages, on the average, how many drinks did you have?" One equivalent of alcoholic drink [12 fluid ounces of regular beer (5% alcohol), 5 fluid ounces of wine (12% alcohol), or 1.5 fluid ounces of 80 proof distilled spirits (40% alcohol)] contain about 14 g of alcohol.

Demographic

We obtained information on age, sex, marital status, race/ethnicity, education levels, and poverty income ratio (a ratio of family income to poverty threshold) from the NHANES database. Racial identity was grouped as non-Hispanic White, non-Hispanic Black, other Hispanic, Mexican American, and others (including multi-racial). Marital status was classified as married/living with a partner, widowed/divorced/separated, and never married. Educational status was collated as under 12th grade, high school graduate, and college or above. Poverty

income ratio (a ratio of family income to poverty threshold) was categorized as ≤ 1.30, 1.31–3.50, > 3.50 (richest).

Lifestyle

Smoking status was categorized as: (1) non-smokers: who have never smoked 100 cigarettes during their lifetime, and (2) smokers: who have smoked at least 100 cigarettes during their lifetime. We obtained information on physical activity from the questionnaire section, which covers an extensive array of questions related to leisure-time activities, daily activities, and sedentary activities at home. Metabolic equivalent (MET) scores of activities were calculated for each subject. Physical activities were divided into two groups: active (MET ≥ 500 per week) and inactive [MET < 500 per week (16)]. Body mass index (BMI): BMI (weight/height^2) was calculated during physical examinations at the NHANES mobile examination center (MEC). According to the World Health Organization (WHO) criteria, BMI was classified into four groups: underweight (< 18.5 Kg/m^2), normal (18.5∼24.9 Kg/m^2), overweight (25∼29.9 Kg/m^2), and obese (≥ 30.0 Kg/m^2). Difficulties in attending social events were self-reported data on functional limitations defined by the question "By yourself and without using any special equipment, how much difficulty do you have participating in social activities [visiting friends, attending clubs or meetings or parties]?" The responses were categorized into no difficulty and difficulty (including some difficulty, much difficulty, and unable to do).

Comorbidities

Comorbidities, including diabetes, hypertension, and stroke, were self-reported by patients using NHANES interviewer-administered questionnaires and defined by the question "Have you ever been told by a doctor or other health professional that you had . . .?" Chronic Kidney Disease (CKD) was defined by urine albumin and creatinine ratio (ACR) ≥ 30 mg/g.

Statistical Analysis

Analysis was aimed to explore the relationship between alcohol consumption and factors associated with cognitive impairment in different comorbidities in patients with diabetes, hypertension, or CKD.

Data on basic characteristics were expressed as unweighted counts (weighted%) for categorical variables and mean ± standard error for continuous variables. The Chi-square test was used to determine the differences in categorical variables, and differences in continuous variables were examined using the Complex Samples General Linear Model (CSGLM). Univariate and multivariate logistic regression analyses were performed to investigate associations between cognitive impairment and alcohol drinking. We selected variables with a significant p-value < 0.05 by univariate analysis and evaluated them using a multivariate logistic regression model. Interaction analysis was performed between alcohol drinking and related factors. Furthermore, to better delineate the dose-response relationship between alcohol use and cognitive impairment, the study subjects were divided into 1, 2, 3–4, 5–6, 7–8, 9–10, and 10 + drinks. Odds ratios (OR) and 95% confidence intervals (CI) were stated with different models.

All analyses included full sample MEC exam weight (WTMEC4YR for 1999–2002, WTMEC2YR for 2011–2014), stratum, and primary sampling units (PSU) per recommendations from the National Center for Health Statistics (NCHS) to perform complex sampling design analysis for address oversampling, non-response, non-coverage, and provide nationally representative estimates. Currently, NCHS recommends the use of Taylor Series Linearization methods for variance estimation in all NHANES surveys. In the present study, statistical analyses were performed using the statistical software package SPSS complex sample module version 22.0 (IBM Corp., Armonk, NY), which can be used to estimate sampling errors by the Taylor series (linearization) method. All statistical assessments were two-sided and evaluated at the 0.05 level of significance.

RESULTS

Study Population Characteristics

A total of 3,006 participants were eligible for the present study. Using the NHANES sample weight, the analytic sample size in the present study represented 27,162,844 non-institutionalized participants from the United States. Basic characteristics of the study subjects stratified by diabetes, hypertension, or CKD are shown in **Supplementary Tables 1–3**. A higher percentage of cognitive impairment, more light drinker, lower mean DSST scores (48.71 ± 0.777 vs. 54.73 ± 0.565, p < 0.001) was present in patients with diabetes than those without diabetes (**Supplementary Table 1**). Similar patterns also appeared in hypertension and CKD groups (**Supplementary Tables 2, 3**).

Factors Associated With Cognitive Impairment

In the diabetes group (**Supplementary Table 4**), after adjusting significant factors in univariate regression, the results of multivariate logistic regression indicated that moderate or heavy drinker vs. light drinker were positively associated with the risk of cognitive impairment, but not reach the significance [adjusted odds ratio (aOR) = 1.233 and 3.237, respectively]. Moreover, the following factors were significantly positively associated with cognitive impairment: age (70 + y vs. 60–69 y), race (other Hispanic, Mexican American, and non-Hispanic Black vs. non-Hispanic White), education (under 12th grade vs. college or above), attend social events difficulty and CKD.

In the hypertension group, the results of multivariate logistic regression indicated that heavy vs. light drinkers were significantly positively associated with the risk of cognitive impairment (aOR = 6.089, 95% CI = 1.318–28.13). Age, male, race, education (under 12th grade, high school graduate vs. college or above), marital status, income ratio (≤ 1.30 vs. ≥ 3.5), physical activity (inactive vs. active), social attendance (difficulty vs. no difficulty), and CKD were significantly positively associated with cognitive impairment (**Supplementary Table 5**). The interaction term for alcohol consumption and physical activity

in the multivariate model was also significant. In patients without hypertension, moderate or heavy alcohol consumption vs. light drinker were negatively associated with the risk of cognitive impairment, but not reach the significance (aOR = 0.491, and 0.383, respectively).

In the CKD group, heavy vs. light drinkers were significantly positively associated with the risk of cognitive impairment (aOR = 6.324, 95% CI = 1.158–34.52). Age, race (Black vs. White), education, and difficulty attending social events showed a significant positive association with cognitive impairment (**Supplementary Table 6**).

Dose-Response Relationship Between Alcohol Consumption and Cognitive Impairment

Supplementary Table 7 describes the characteristics of study subjects stratified by alcoholic drinks in diabetes, hypertension, and CKD groups. The diabetes group showed two peaks of DSST scores. DSST scores increased with alcohol dose up to 1 drink, and then gradually decreased. The second peak occurred in 9–10 drinks. The hypertension group showed a similar pattern between alcohol intake and cognitive impairment. DSST scores increased with increased alcohol dose, up to 2 drinks and then gradually decreased. The score of DSST of CKD group indicate sliding all the way down, but the number of people with alcohol intake $\geq$ 7 drinks was small, and the value was unstable.

Table 1 compiles the results of multivariate logistic regression from 4 models depicted in the diabetes group. Compared to light drinker (1 drink), 2 drinks had a lower risk of cognitive impairment (crude OR = 0.920), but 3–4, 5–6, 7–8 drinks had a higher risk of cognitive impairment (OR = 1.844, 8.966, and 4.377, respectively). We observed a bell-shaped curve between alcohol intake and cognitive impairment (**Figure 1A**) that remained consistent even after adjusting for demographic variables (Model 2), comorbidity variables (Model 3), and all significant variables (**Table 1**) (Model 4). In patients without diabetes, we noted a smoother wave between alcohol intake and cognitive impairment (**Figure 1B**). Compared to light drinker (1 drink), 2 drinks had lower odds of cognitive impairment (adjusted OR = 0.648, 95% CI = 0.432–0.970).

The hypertension group showed a lower flat bell shape association between alcohol intake and cognitive impairment (**Figure 2A**). Compared to light drinker (1 drink), 5–6 drinks had a significantly higher odds of cognitive impairment (OR = 3.714, 95% CI = 1.610–8.565). This association was consistent after adjusting for other confounders (OR = 5.288, 3.921, and 3.934, respectively) (**Table 2**). The odds ratio for cognitive impairment by different alcohol consumption categories was flat in those without hypertension (**Figure 2B**).

In the CKD group, it showed a slight J-shaped association between alcohol intake and cognitive impairment (**Figure 3**). The risk of cognitive impairment increased with alcohol consumption (adjusted OR = 0.618, 1.354, 4.988, and 3.266, respectively) (**Supplementary Table 8**). In the without CKD group, after adjusting for other influencing factors, there was no significant difference in the risk of cognitive impairment by different alcohol consumption amount.

DISCUSSION

This study demonstrated the effect of alcohol drinking on cognitive impairment is different in older people comorbid with diabetes, hypertension or CKD. In patients with diabetes and CKD, moderate to heavy amounts of alcohol drinking was associated with a higher risk of cognitive

TABLE 1 | Odd ratio for cognitive impairment by different alcohol consumption categories-stratified by diabetes.

Alcohol consumption	With diabetes				Without diabetes			
	Model 1	Model 2	Model 3	Model 4[a]	Model 1	Model 2	Model 3	Model 4[b]
	OR (95%CI)	aOR (95%CI)	aOR (95%CI)	aOR (95%CI)	OR (95%CI)	aOR (95%CI)	aOR (95%CI)	aOR (95%CI)
1 drink	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
2 drinks	0.920 (0.517–1.639)	0.766 (0.382–1.537)	1.093 (0.609–1.961)	1.045 (0.561–1.947)	0.837 (0.613–1.144)	0.802 (0.566–1.136)	0.875 (0.629–1.219)	0.648 (0.432–0.970)
3–4 drinks	1.844 (0.936–3.632)	1.515 (0.697–3.292)	2.069 (1.057–4.050)	1.684 (0.815–3.479)	1.467 (1.041–2.066)	1.196 (0.715–1.998)	1.445 (1.001–2.087)	1.000 (0.562–1.779)
5–6 drinks	8.966 (2.749–29.23)	11.36 (1.770–72.95)	7.500 (2.466–22.81)	3.909 (0.461–33.12)	2.527 (1.317–4.851)	1.711 (0.672–4.354)	2.674 (1.368–5.228)	1.981 (0.521–7.543)
7–8 drinks	4.377 (0.690–27.75)	1.490 (0.243–9.123)	5.810 (1.079–31.29)	3.656 (0.779–17.16)	4.337 (1.313–14.31)	0.583 (0.157–2.157)	4.638 (1.419–15.15)	1.580 (0.318–7.852)
9–10 drinks	0.043 (0.003–0.550)	0.102 (0.008–1.310)	0.055 (0.004–0.732)	0.134 (0.011–1.698)	1.008 (0.133–7.665)	0.362 (0.060–2.179)	1.068 (0.124–9.218)	0.536 (0.055–5.260)
10 + drinks	2.966 (0.560–15.71)	2.678 (0.197–36.48)	3.690 (0.749–18.18)	1.178 (0.294–4.715)	2.923 (0.602–14.19)	0.579 (0.068–4.921)	3.645 (0.658–20.19)	0.763 (0.077–7.609)

Model 1: crude OR (95%CI). Model 2: adjusted for demographic variables. Model 3: adjusted for comorbidity variables. Model 4[a]: adjusted for all significant variables in ***Supplementary Table 4*** *(age, race, education, social attendance, CKD). Model 4[b]: adjusted for all significant variables in* ***Supplementary Table 4*** *(age, gender, race, education, income, physical activities, social attendance, hypertension, CKD).*

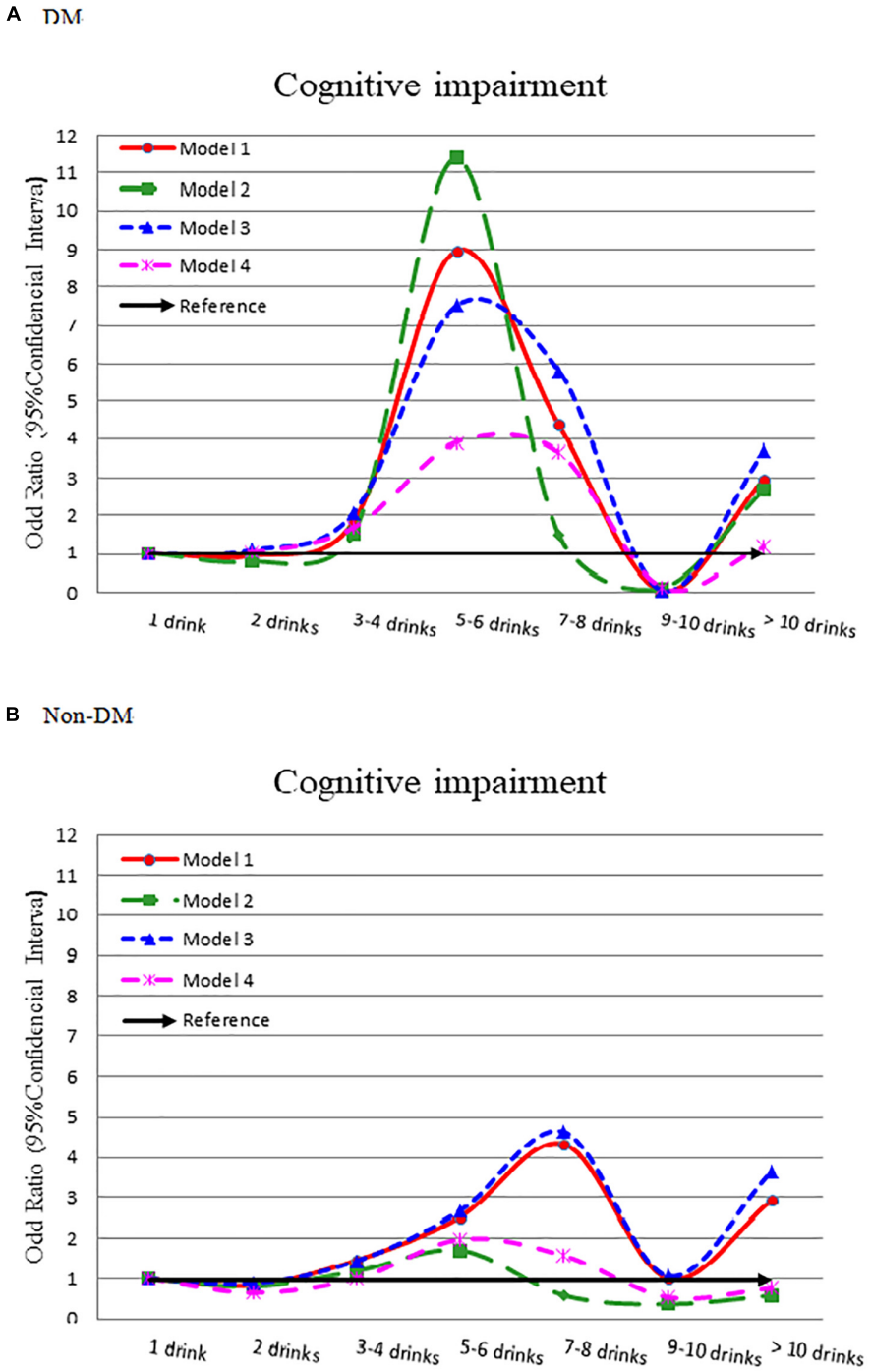


FIGURE 1 | Odds ratio for cognitive impairment by different alcohol consumption categories-stratified by diabetes. **(A)** With diabetes and **(B)** without diabetes. Model 1: crude OR (95%CI). Model 2: adjusted for demographic variables. Model 3: adjusted for comorbidity variables. Model 4: adjusted for the significant variables in **Supplementary Table 4**.

decline; in patients with hypertension, heavy drinking was associated with increased risk of cognitive impairment. While in patients without diabetes, hypertension or CKD, alcohol drinking seemed to have a neutral effect on cognitive function.

Diabetes is a long-known risk factor for cognitive impairment and dementia (2, 8). Chronic hyperglycemia can produce advanced glycation end-products, increase oxidative stress and chronic low-grade inflammation, cause brain microangiopathy and injury (17). Reports also suggest that insulin resistance

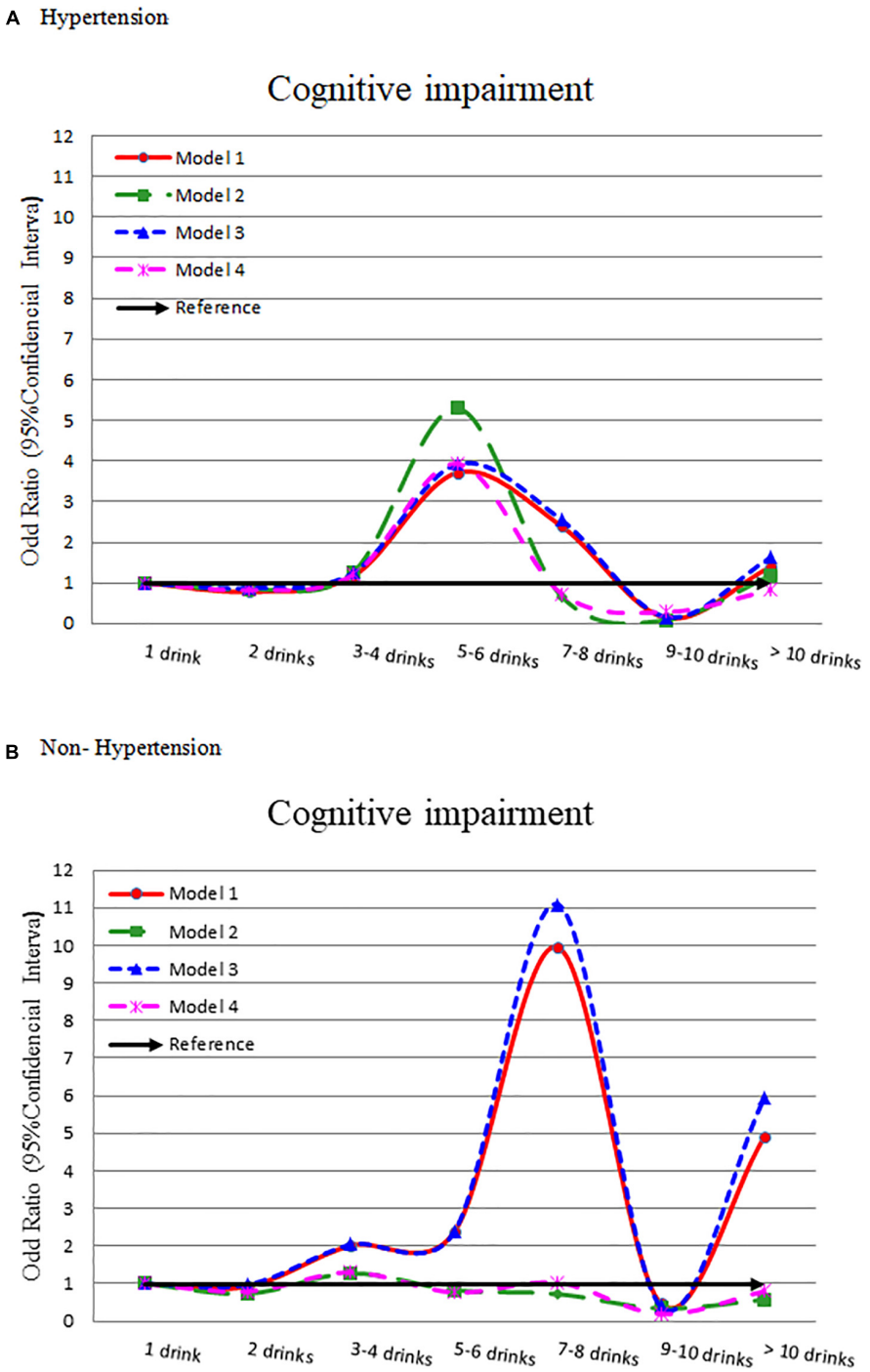


FIGURE 2 | Odds ratio for cognitive impairment by different alcohol consumption categories-stratified by hypertension. **(A)** With hypertension and **(B)** without hypertension. Model 1: crude OR (95%CI). Model 2: adjusted for demographic variables. Model 3: adjusted for comorbidity variables. Model 4: adjusted for the significant variables in **Supplementary Table 5**.

reduces regional cerebral glucose metabolism and utilization (18). Our study showed that in persons with diabetes, moderate to heavy alcohol drinking was associated with a higher risk of cognitive impairment compared with light drinkers. A Zutphen study disclosed that alcohol consumption was associated with a lower risk of cognitive decline, but older adults who drank ≧3 drinks were associated with higher risk of cognitive impairment than those who drank 1–2 drinks per day in patients with diabetes or cardiovascular diseases (12). Moderate to heavy alcohol drinking may aggravate brain injury caused by diabetes.

TABLE 2 | Odd ratio for cognitive impairment by different alcohol consumption categories–stratified by hypertension.

Alcohol consumption	With hypertension				Without hypertension			
	Model 1	Model 2	Model 3	Model 4[a]	Model 1	Model 2	Model 3	Model 4[b]
	OR (95%CI)	aOR (95%CI)	aOR (95%CI)	aOR (95%CI)	OR (95%CI)	aOR (95%CI)	aOR (95%CI)	aOR (95%CI)
1 Drink	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
2 Drinks	0.782 (0.541–1.131)	0.846 (0.544–1.314)	0.871 (0.588–1.290)	0.823 (0.525–1.291)	0.926 (0.596–1.438)	0.736 (0.459–1.182)	0.974 (0.607–1.562)	0.791 (0.460–1.359)
3–4 Drinks	1.172 (0.798–1.722)	1.267 (0.707–2.269)	1.251 (0.839–1.864)	1.203 (0.630–2.295)	2.017 (1.235–3.295)	1.275 (0.555–2.929)	2.045 (1.210–3.455)	1.303 (0.581–2.921)
5–6 Drinks	3.714 (1.610–8.565)	5.288 (1.705–16.39)	3.921 (1.822–8.438)	3.934 (1.065–14.53)	2.376 (1.198–4.714)	0.828 (0.402–1.705)	2.382 (1.222–4.643)	0.766 (0.371–1.579)
7–8 Drinks	2.385 (0.554–10.27)	0.658 (0.110–3.927)	2.538 (0.652–9.875)	0.731 (0.122–4.398)	9.955 (1.883–52.61)	0.725 (0.120–4.392)	11.09 (2.332–52.80)	1.026 (0.179–5.879)
9–10 Drinks	0.141 (0.056–0.352)	0.082 (0.005–1.248)	0.161 (0.052–0.495)	0.284 (0.018–4.442)	0.468 (0.044–4.987)	0.339 (0.056–2.055)	0.387 (0.031–4.796)	0.189 (0.016–2.207)
10 + drinks	1.398 (0.223–8.782)	1.181 (0.193–7.219)	1.622 (0.311–8.452)	0.820 (0.107–6.306)	4.906 (1.353–17.79)	0.571 (0.040–8.065)	5.937 (1.567–22.48)	0.796 (0.057–11.14)

Model 1: crude OR (95%CI). Model 2: adjusted for demographic variables. Model 3: adjusted for comorbidity variables. Model 4[a]: adjusted for all significant variables in ***Supplementary Table 5*** *(age, gender, race, education, marriage, income, social attendance, CKD). Model 4[b]: adjusted for all significant variables in* ***Supplementary Table 5*** *(age, gender, race, education, income, social attendance, CKD).*

However, further research is needed to confirm this finding. Therefore, old people with diabetes may be warned not to drink much alcohol.

Hypertension is the main attributor to global dementia (2). Many studies have shown that midlife high blood pressure is a risk factor for late-life cognitive impairment and dementia. Longstanding hypertension may result in atherosclerosis, arterial stiffness, and hypoperfusion of the brain, which can compromise cerebral oxygen supply, leading to neuronal injury (19). Our study showed that moderate to heavy alcohol drinking was associated with a higher risk of cognitive impairment than light drinking. Studies show that heavy alcohol drinking elevates acetaldehyde, which is neurotoxic (20). Alcohol can modify calcium channels in the brain and impair several neurocircuits. Ethanol can block N-methyl-D-aspartate (NMDA) receptors and increase glutamate release with neurotoxic effects (4, 21). Heavy alcohol drinking increased blood pressure and the incidence of hypertension (22, 23), which could have resulted in brain damage in our patients with hypertension. Our results suggested that the protective magnitude of light alcohol drinking on cognitive function could not prevent brain damage caused by hypertension and increased the risk of cognitive impairment. Older adults with hypertension should have small amounts of alcohol with exercise, intellectual stimulation, and leisure time to attenuate the risk of cognitive decline (2).

Recently, several studies have found that chronic kidney disease may increase the risk of cognitive impairment (10, 24). Patients with CKD have disproportionate levels of cerebrovascular disease, high prevalence of diabetes, hypertension, dyslipidemia, and uremic metabolites that can lead to cognitive impairment or dementia. Our study revealed that moderate to heavy alcohol drinking in patients with CKD was associated with increased risk of cognitive impairment. Old people with CKD should only drink small amounts of alcohol and moderate themselves to healthier living in dietary, physical, and mental perspectives.

This study had some limitations. First, diabetes and hypertension were reported by participants instead of objective measures. Misclassification bias could exist. Participants with chronic kidney disease usually have no symptoms and medication, they may not know their renal disease. The NHANES survey gets the information of chronic kidney disease through laboratory tests and not by reports of participants. We used different methods to obtain data of the three chronic diseases, which may influence outcomes of this research. Second, alcohol consumption status was asked twice in each cycle of NHANES, the recall bias may exist, but evidence has revealed that self-report of alcohol use may be a reliable and valid approach to measure alcohol consumption (25). Third, because the NHANES is a cross-sectional dataset, we could not investigate the impact of different durations and patterns of alcohol use in these patients. Fourth, we adopted the DSST to assess cognitive dysfunction. Although DSST is a sensitive method for cognitive decline (1), it does not provide all the different faces of cognitive function. However, a change in one cognitive domain may presage a change in other cognition domains. Fifth, NHANES participants resided in communities, not institutions; those who could not take the DSST test were excluded. Therefore, this study may have included relatively healthy people and is not representative of the entire population. Finally, this cross-sectional study had unknown and unobserved biases. Prospective studies abiding by stringent and rigorous methodologies are warranted to verify our results.

Our study demonstrated that the impacts of alcohol drinking on cognitive impairment are significantly different in patients with various comorbidities. Since older people are often

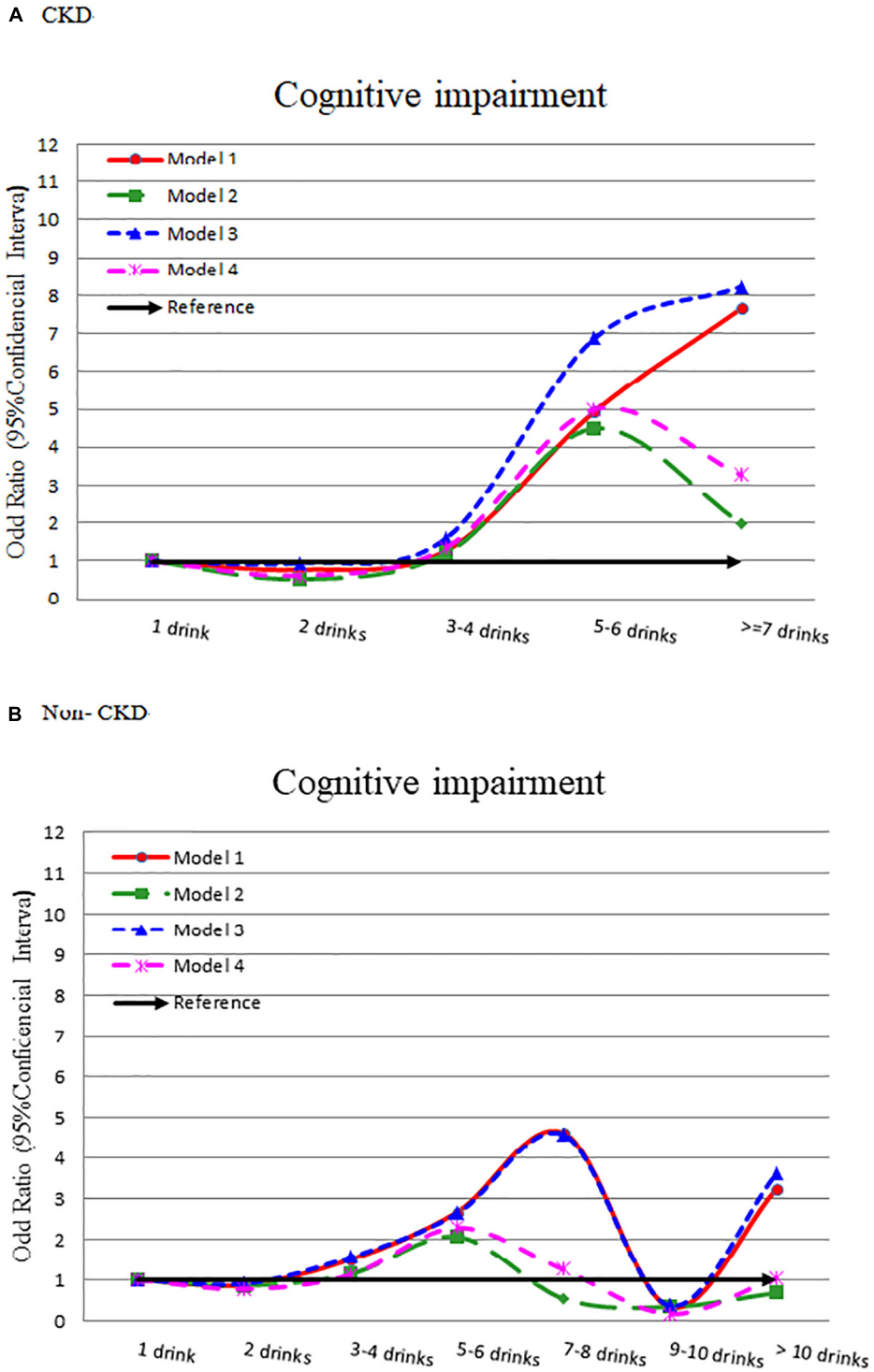


FIGURE 3 | Odds ratio for cognitive impairment by different alcohol consumption categories-stratified by CKD. **(A)** With CKD and **(B)** without CKD. Model 1: crude OR (95%CI). Model 2: adjusted for demographic variables. Model 3: adjusted for comorbidity variables. Model 4: adjusted for all significant variables in **Supplementary Table 6**.

accompanied by one or more chronic diseases, the results of this study can provide an empirical evidence for clinicians or health professionals to make alcohol drinking recommendations. Older adults with chronic illnesses should have adequate amounts of alcohol drinking to mitigate the future risks of cognitive decline.

DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in the article/**Supplementary Material**, 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. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

F-SY and JC-CW: conceptualization. S-IW and S-YL: methodology. S-IW and Y-HC: software. S-IW and JC-CW: validation and project administration. S-IW: formal analysis and visualization. F-SY and S-YL: investigation. S-IW and F-SY: data curation. F-SY, S-YL, and S-IW: writing—original draft preparation. JC-CW and Y-HC: writing—review and editing. JC-CW: supervision and resources. All authors have read and agreed to the published version of the 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.2022.861145/full#supplementary-material

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