Research Topics

Aging and frailty: from causes to prevention

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Aging and frailty: from causes to prevention

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Editorial: Aging and frailty: from causes to prevention

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Editorial on the Research Topic
Aging and frailty: from causes to prevention

Introduction

Recent improvement in sanitary, nutritional, and socioeconomic conditions has led to an increase in life expectancy. As a result, by 2050, people aged more than 60 years are expected to double, and people aged more than 80 years are expected to triple (https://www.who.int/news-room/fact-sheets/detail/ageing-and-health). Unfortunately, increased lifespan, is not always paralleled by an adequate healthspan, because of interference of social, behavioral, physiological, cellular, molecular, and less known factors (Balcombe and Sinclair, 2001). This complexity makes difficult the definition of aging, and challenging management of this period of life.

Aging is accompanied by decline of the individual resulting in a complex condition called frailty, characterized by loss of physical and psychological abilities, and by an amplified vulnerability to stress factors (Morley et al., 2013; Hoogendijk et al., 2019). To limit the impact of frailty on wellbeing and on society, to improve both preventive actions and management, a deep understanding of this condition is needed.

Considering frailty as a geriatric syndrome, we need to understand its etiology, define diagnostic parameters, and apply therapeutic and prevention approaches. This Research Topic was aimed at collecting new knowledge on different aspects of frailty. It comprises 13 research articles that provide new information in different aspects of aging and frailty, such as comprehension of molecular determinants and socioeconomic influence, frailty definition and biomarkers, impact on health outcomes, and prevention strategies.

Biological basis of frailty

Frailty is the result of a multisystem derangement that involves metabolic unbalance, systemic inflammation, musculoskeletal malfunctioning and altered responses to stress (Picca et al., 2022). Among the multiple biological variables involved in aging and muscle weakness (Picca et al., 2022; Li et al., 2024; Sato et al., 2024), the genetic background captures much interest (Baghdadi et al., 2022; Sirago et al., 2022). Interestingly, Krasniqi et al. report on the impact of genetic variants of vitamin D receptor on muscular fitness in middle aged and older adults. This evidence confirms the importance of biological mechanisms and calls for further analysis of genetic predisposition to develop individual strategies.

Socioeconomic influence on frailty

Recent data evidence that biological variables are not the only determinants of frailty, on the contrary, they highlight the role of variables related to the socioeconomic status of individuals, stimulating the interest to analyze the correlation among frailty and socioeconomic conditions. Accordingly, in the present topic several articles investigate this important theme. The Chinese Longitudinal Healthy Longevity Survey (CLHLS 2008–2018) reveals that higher levels of frailty and lower levels of social participation exhibit significant bidirectional relationships with age, education level, marital status, and drinking habits (Bi et al.). Analogously, Rahman et al., suggest that health outcomes following traumatic brain injury in Bangladesh depend on socioeconomic settings, since lower status individuals have limited access to treatments. Moreover, as highlighted by Czyżewski et al., geriatric patients, lacking their independence, need special care, that can be provided depending on their location. Their data propose that the number of accesses to emergency from rural areas-based patients prevail to those from the urban areas, maybe due to limited access to a primary care physician.

Frailty definition and biomarkers

Frailty is a dynamic condition that can appear with physiological, psychological signs or both, making difficult the evaluation of risk factors and formulation of a diagnosis (Morley et al., 2013). The multifactorial nature, and the diverse clinical manifestations limit the establishment of a unequivocal frailty score (Rockwood et al., 2007). According to above reported observations, the evaluation of frailty risk should include both biomarkers and socioeconomic parameters. From the physiological point of view, frailty is characterized by a low-grade chronic inflammation. Therefore, inflammatory markers seem good candidates to help to define and diagnose frailty. In this context, Zhang et al., based on data from the United States National Health and Nutrition Examination Survey (NHANES, 2007–2018), suggest that Systemic Immune-Inflammation Index (SII) and Systemic Inflammatory Response Index (SIRI) could be used as markers of frailty. From the analysis of 16,705 middle-aged and older participants to NHANES 1999–2018, Tang et al. found six complete blood count-derived inflammatory markers (neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio, SII, SIRI, and pan-immune inflammation value), which are associated with higher risk of frailty and mortality. Since frailty is also accompanied by a sensible reduction of skeletal muscle strength and endurance, Fujikawa et al. suggest bimanual coordinated movements analyses to assess levels of frailty. From a study on 358 community-dwelling older adults, they found that frail adults exhibit less movement during bimanual coordination tasks compared with non-frail adults. Interestingly, Lin et al., who aimed at assessing the risk of frailty in older adults affected by atrial fibrillation, suggest a comprehensive predictive model based on multiple risk factors, such as age, gender, history of coronary heart disease, number of chronic conditions, sleep quality, and mental health condition. In agreement with the multifactorial nature of frailty, a comprehensive method could be helpful in obtaining a broader picture of frail individuals and fundamental to frailty management.

Therapeutic, prevention and care approaches

In clinical situations, frail individuals could require different care and may have different outcomes to health challenges, therefore assessment of frailty may provide important decision-making information. In this context, the article from Adamuz et al. reports that COVID-19 patients older than 75 years presented more care complexity individual factors (CCIFs), especially those related to comorbidity, cognitive and social impairment, than younger subjects. On the other side, Ma et al. suggest that frailty is a good parameter to predict postoperative disability after cardiac surgery. Lastly, from their investigation on impact of age and frailty on key clinical outcomes from liver transplants, Valenti et al., found that frailty, rather than age, is a predictor of mortality. Considered the social impact of frailty in several aspects of daily life, there is a growing interest on both healthcare system and community interventions that could reduce the effects of frailty. A study from Ni et al., emphasize the consequence of different activities on frailty of older adults in China. Actually, from the China Health and Retirement Longitudinal Study (CHARLS 2020), it emerges that physical, social, economic, information and sleep activity have positive effects on frailty. Interestingly, a case study reporting a community-based early frailty intervention program delivered by trained laypersons in Singapore, indicates that in an initial phase older adults can be supported by non-healthcare professionals that control physical activity and nutrition of participants (Jayaprakash et al.). Nevertheless, although programs managed by trained laypersons could be an initial step towards awareness of frailty and an initial action towards its combat, these programs need supports and resources, and involvement of healthcare systems (Cesari et al., 2016).

Frailty is a complex multifactorial condition that can accompany aging with multiple pathophysiological manifestations, making each frail individual rather unique. Articles included in this topic provide new knowledge on frailty, confirm the role of biological variables and highlight the weight of socioeconomic factors, that should be considered in the evaluation of risks, diagnosis and therapeutical approaches. Hopefully, new knowledge will increase awareness of frailty, and involvement of society and healthcare systems to promote prevention and care strategies (Cesari et al., 2016).

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Geriatric patient in the practice of emergency medical teams – observation in 2020–2022

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Purpose: Analysis of interventions of medical rescue teams for geriatric patients in a three-year period, taking into account the causes, circumstances, medical management, pharmacology.

Materials and methods: The study included a 3-year retrospective analysis of the trips of medical rescue teams in the northern part of the Lubelskie Voivodeship in the period from January 1, 2020 to December 31, 2022. The data comes from medical documentation. Interventions caused by a health risk in a patient in the 90+ age group were qualified as events. 897 EMT interventions were qualified (2020–327, 2021–269, 2022–301) constituting 4.29% of all interventions carried out in the operational area. In addition, a quantitative analysis of a comparative group of patients aged 80–89 was performed.

Results: It was shown that the time of rescue activities was the longest for injuries and the shortest for mental disorders (60 ± 31 vs. 43 ± 21 min). It was shown that specialist EMT teams (S) were statistically significantly more often called for cardiology disorders (63%). It was shown that pharmacological agents were used statistically significantly more often in respiratory disorders (83%) compared to neurology disorders (47%, $p < 0.001$). It was also shown that patients whose call was caused by neurology disorders were statistically more often transported to the emergency department ($N = 76$, 76%, $p < 0.001$).

Conclusion: The causes of calls regarding disorders of the circulatory and respiratory systems most often require the implementation of pharmacology during EMT interventions, mainly short-term and symptomatic drugs. Interventions to rural areas dominate in the presented analysis in each year of the analysis and in each group of reasons for calls, which may be associated with more difficult access to a primary care physician. Most EMT interventions concern exacerbation of chronic diseases. Transport to the hospital was necessary mainly due to neurological and traumatic calls.

KEYWORDS
emergency medical team, geriatrics, 90+, health risks, medical interventions

Introduction

State Medical Rescue (SMR) system plays an important role in ensuring the safety of Polish residents. The system consists of emergency medical teams (EMT) and hospital emergency departments (ED). The field teams are divided into ground teams (ambulance) and air teams (helicopters) at the Helicopter Emergency Medical Service (HEMS) bases (1, 2).

SMR are responsible for interventions to people in a state of sudden health threat. The person calling medical teams is most often the family of the injured person or a bystander of the incident. Every day, emergency medical services respond to thousands of events that require medical assistance to injured people: emergencies, exacerbation of chronic diseases, injuries, mental disorders (3, 4).

According to data from the Central Statistical Office (CSO) in 2022, 1,592 EMT's intervened more than 3 million times. SMR based on paramedics, who are the most numerous in the system. Teams with a doctor constitute approximately 20%, but in recent years there has been a downward trend in the number of these teams (5, 6).

According to Eurostat data, in the European Union (EU) countries, there has been a slow increase in the number of older people since 2002, and life expectancy has been systematically increasing, and since 2020 there has been a slight decline in life expectancy (0.3) after taking into account the effects of the COVID-19 pandemic. Life expectancy in the EU in recent years has been as follows:

- 2017 – 80.9 years (almost 7.8 years more for women),
- 2019 – 81.3 years,
- 2020 – 80.4 years,
- 2021 – 80.1 years (approximately 5.7 more for women) (7).

In Poland, women live on average longer than men, with the average life expectancy being almost 8 years longer (74.1 men, 81.8 women) (8, 9).

The diseases most often diagnosed in the elderly include cardiovascular diseases, such as arterial hypertension (HT), ischemic heart diseases, respiratory diseases, bone weakness (osteoporosis), diabetes, vision and hearing disorders, as well as dementia and related cognitive disorders (10).

The aging process of Europe's population is predicted by demography specialists. The reason for this state of affairs is the low birth rate and the development of medicine, access to new technologies, imaging diagnostics, modern generations of drugs, and specialized therapies (11).

According to the World Health Organization (WHO), old age is divided into young-old age – 60-75 years old, old age – 75-90 years old and longevity – 90+ years old (12).

Neurodegenerative diseases are incurable, however, early diagnosis and initiation of treatment is important, slowing down the development of dementia diseases and mitigating their course. Drawing the attention of the society to the disorders of the elderly may mobilize many families to diagnose their relatives by directing them to early symptoms, which may translate into effective therapy that delays the development of some disorders in accordance with the principle: "prevention is cheaper and better than cure" (13).

Low-energy bone injuries in the course of osteoporotic changes ensuing from prosaic everyday functioning causes (falling as a result of tripping or dizziness) lead to serious health consequences. Bone injury in the elderly person is difficult to heal, and surgical osteosynthesis is often impossible due to comorbidities. Osteoporosis is more common in post-menopausal women. It is a metabolic bone disease characterized by low bone mass and impaired bone microarchitecture. This results in greater bone fragility and susceptibility to fractures (9, 14).

Purpose

Analysis of interventions of medical rescue teams for geriatric patients (old age) over a three-year period, taking into account the causes, circumstances, medical treatment, and pharmacology. The indirect aim is to observe quantitative data (number of patients) during medical interventions for the oldest part of the region's population.

Materials and methods

Research design

The research included a 3-year retrospective analysis of dispatches by EMTs from the northern part of the Lubelskie Province (eastern border of the European Union). The analysis covers the period from 01.01.2020 to 31.12.2022. The data was obtained from the official documentation of the dispatch units of the SMR system:

- dispatch order card (DOC) – this part is prepared by the medical dispatcher (MD) at the Rescue Notification Center (RNC),
- Medical Rescue Operations Card (MROC) – completed by the head (leader) of the EMT, i.e.:
- doctor – specialist team (S),
- a paramedic or nurse of the system - basic team (B) (3).
- In the operational area covered by the observation there are four round the clock teams, 2 type B and 2 type S teams. In addition, in the operational area there is a hospital ED in the county hospital, where the field teams transfer the transported patients for further hospital treatment, observation and diagnostics.

Research setting

Interventions that met the inclusion criteria were analyzed, taking into account the date and time of the intervention, the length of the intervention expressed in minutes, the location of the event (urban and rural areas), the type of EMT, the age and gender of the patient, rescue procedures, the use of pharmacological agents, medical diagnosis (as per ICD – 10). An analysis of the causes of calls was made, which were grouped according to the following classification: mental disorders, cardiology disorders, neurology disorders, injury, respiratory disorders, metabolism/nutrition, infection, other (pain/allergy/cancer).

Ethical considerations

The consent of the Director of the unit carrying out dispatch orders in the examined operational area for access to medical records was obtained in June 2022. All personal data (of patients, medical staff, and cooperating services) remained anonymous and were not used for analysis purposes. The analysis was carried out in accordance with the Declaration of Helsinki. Accordingly, the local bioethics committee was not asked for opinion and consent to carry out the research.

Statistical analysis

Results concerning quantitative variables were presented as average values ± standard deviation. In the comparative characteristics of characteristic of EMT interventions according to year of intervention and reasons of the call, a one-way analysis of variance (ANOVA). Simple linear regression analysis (Pearson) was applied to detect and describe the strength and direction of correlations of time of intervention to age of patients. Qualitative variables (age, sex) were presented as quantity (n) and percentage values of the whole group (%), while proportions in groups were assessed with a Chi-squared test. Statistica 13 software (StatSoft Inc., Tulsa, OK) was used in the statistical analysis. $p < 0.05$ was adopted as the significance level.

Inclusion criteria

1. EMT calls to a patient aged 90+.
2. dates of commencement of EMT interventions between 1.01.2020 at 0.00 a.m. and 31.12.2022 at 11.59 p.m.
3. the intervention for patients aged 80–89 was included as a comparison group (quantitative correlation – epidemiological data).

Justification for selecting the inclusion group in the study.

It was decided to select patients aged 90+ because, according to statistics, this age is above the average life expectancy for the inhabitants of Poland.

Moreover, according to the Polish insurance system, the estimated life expectancy is calculated for the purposes of granting and the hypothetical amount of capital pensions and annuities. The tool for these estimates are Pension Tables calculated according to the following scheme:

YM – current age (Y – years, M – months) + X(m) – estimated age of survival expressed in months.

The maximum age included in the Tables is 90 years for both sexes and estimates of further life expectancy are calculated from this age in Table 1 (15).

Exclusion criteria

1. absence of the patient at the place of call – incorrect address details.
2. false calls to the emergency phone number,
3. absence of the patient at the place of call, while waiting for the EMT, the family transported the patient to the hospital or general practitioner on their own.

Results

Using the inclusion and exclusion criteria, 897 EMT dispatches were selected from the analysis, accounting for 4.29% of all interventions (Table 2). It is worth emphasizing that interventions were analyzed, not patients. In the analysis, there is a difference between the number of interventions and the patient population, which results from repeated calls to the same patients (a maximum of 11 interventions to the same patient in the period covered by the analysis), the results are presented in Table 3.

In total, 168 re-interventions to 93 patients were performed in the 3-year analysis. Apart from the data in Table 3 describing 14 patients, up to 28 patients were intervened upon 3 times, and up to 51 patients twice. Repeated interventions accounted for 18.72% of all calls in this age group (90+), and they concerned women $n = 142$ (84.52%), and men $n = 26$ (15.48%).

Analysis of Simple linear regression analysis (Pearson) between time of intervention and age of patients showed no statistical significance ($R = -0{,}049$; $p = 0.140$).

Most interventions for the 90+ age group occurred in rural areas (76%). The results indicate the vast majority of interventions addressed to women (75.80%). Deaths concerned 5% ($N = 46$) of the study group of patients. Over the years of the analysis (2020 vs. 2021 vs. 2022), the following did not change: the location of the intervention ($p = 125$); intervention time ($p = 765$); call frequency by gender ($p = 0.680$); share of “S” teams ($p = 0.151$); frequency of pharmacotherapy use ($p = 0.470$) and number of deaths ($p = 0.389$). There was only a statistically significant difference in the frequency of patient transport to the ED ($p = 0.034$) and the age of the patients ($p = 0.017$; Table 4).

An analysis of the characteristics of the intervention and the reasons for the calls was made. Statistically significant differences were found in the duration of rescue action [min] depending on the reason for the call ($p < 0.001$; Figure 1). It was shown that the time of rescue actions was the longest for injuries and the shortest for mental disorders (60 ± 31 vs. 43 ± 21 min). It was shown that specialist EMT teams (S) were statistically significantly more often called to cardiology disorders ($N = 117$, 63%). It was shown that pharmacological agents were used statistically significantly more often in respiratory disorders ($N = 119$, 83%) compared to neurology disorders ($N = 47$, 47%, $p < 0.001$). It was also shown that patients whose call was caused by neurology disorders were statistically more often transported to the ED ($N = 76$, 76%, $p < 0.001$). In the comparative analysis of the year (2020 vs. 2021 vs. 2022) according to the causes of calls, it was shown that the share of cardiology disorders decreased in the analyzed years (41% vs. 32% vs. 27%, $p = 0.003$). There was no statistically significant effect of the affected person’s age ($p = 0.319$) and the location of the incident ($p = 194$; urban vs. rural) on the indicated reasons for the frequency of calls (data in Table 5).

Medical diagnoses described in EMT intervention charts were analyzed according to the International Statistical Classification of

TABLE 1 Life expectancy tables for age 90 in Poland.

	Age 90: months											
	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII
Life expectancy (months)	49,3	49,1	48,8	48,5	48,2	48,0	47,7	47,4	47,2	46,9	46,6	46,4

Source: World Health Organization, (15).

TABLE 2 General characteristic of all interventions.

Year	Overall events	N included in the analysis	%
2020	7,054	327	4,63
2021	7,069	269	3,80
2022	6,769	301	4,44
Total	20,892	897	4,29

TABLE 3 Patients included in the analysis for whom MRT intervened more than once (data for $n > 3$).

Interventions	Gender/age *	Interventions	Gender/age *
10	W102	4	M92
7	W92	3	W92
5	W100	3	W91
5	W91	3	W94
4	W93	3	W91
4	W92	3	M96
4	M90	3	W94

W, woman; M, man. *Age of the patient at the time of the last intervention included in the analysis.

TABLE 4 Univariate comparison of characteristic of EMTs interventions according to year of intervention.

	2020	2021	2022	All	*p*
N	327	269	301	897	
Age, y	93 ± 3	93 ± 3	93 ± 2	93 ± 2	0.017
Time, min	52 ± 26	52 ± 23	53 ± 24	52 ± 24	0.765
Sex, male, n(%)	74 (23)	69 (26)	74 (25)	217 (24)	0.680
S EMT, n (%)	175 (54)	152 (57)	146 (49)	473 (53)	0.151
City, n(%)	66 (20)	65 (24)	85 (28)	216 (24)	0.125
Pharmacology, n(%)	209 (64)	167 (62)	202 (67)	578 (65)	0.470
Death, n(%)	12 (4)	20 (7)	14 (5)	46 (5)	0.389
Transfer to ED, n(%)	190 (58)	140 (52)	189 (63)	519 (58)	0.034

ED, emergency department; S EMT, specialist Emergency Medical Team.

Diseases and Related Health Problems (ICD-10) guidelines (9). Figure 2 presents the most frequently used ICD-10 medical diagnoses in the analysis. 1,248 ICD-10 diagnoses were used for 897 interventions. In 351 interventions, 2 diagnoses were entered, mainly in patients with trauma (essential diagnosis and ICD-10 code describing the circumstances or mechanism of the injury).

The analyzed age group (90+) was compared with the age group of 80–89 years – the total number of interventions broken down by patients' gender was included in Table 6.

The purpose of the comparison was to show the scale of the number of interventions for patients in the age groups 89–89 vs. 90+. In each analyzed year, the population aged 80–89 was significantly more numerous than the main analyzed population (90+), additionally, it was found that in the comparison group, similarly to the study group, interventions for women had prevailed. In total, in the analyzed period, there were 3,128 interventions for patients aged 80–89 (2,107 for women, 1,021 for men) – Table 5. In total, for the age groups 80–89 and 90+ EMTs intervened a total of 4,025 times, which is 19.26% of all completed interventions in the three-year period.

Pharmacological treatment was used in 597 interventions (patients were administered from 1 to 4 preparations, including medical oxygen). The most common were drip infusions of 250 and 500 mL – 169 interventions, dexamethasone 121 times, metamizole 161 times, medical oxygen 89 times, ketoprofen 44 times, metoclopramide 37 times. According to Figure 3, pharmacotherapy was mainly used for ICD-10 diagnoses from group R (the largest group), group I (hypertension, heart failure, irregular heartbeat, stroke), and group S (this group includes injuries, mainly S72 – fracture of the femoral neck).

Discussion

Polish population is aging, as is most of the developed countries of the EU, of which Poland forms the eastern border. Trends in life expectancy rates in Europe show a shift in the limits of life expectancy, with an indication of longer life for women (16, 17). The results of our analysis are in line with these trends. In the oldest part of the population to which EMTs intervened in the three-year analysis, i.e., 80–89 years and 90+, there were definitely more female patients.

Geriatric patients are often unable to function independently, being cared for by their families or professional nursing homes. In our own analysis, there were cases of intervention of a medical team to a nursing home (senior home), the location of the event was not the main purpose of the analysis. A 24-h nursing home cannot replace a hospital. Accordingly, a significant part of the interventions required transporting patients to hospital treatment, e.g., exacerbation of a chronic disease, COVID-19 infection, bone injury with fracture in the course of osteoporosis in the low-energy mechanism (e.g., tripping and falling from own height, falling out of bed, out of a chair). Our own observations confirm the results of Głuszko et al. (9), who described the health problems of the elderly associated with bone decalcification and a high risk of fractures. In our own study, the diagnosis S72 (femoral neck fracture) predominated among the injuries.

Interesting data are presented by Linder et al. (18) on a geriatric patient in the Hospital ED. The results indicate that the geriatric patient accounts for 12–24% of all hospitalized patients, and the trends indicate that this group will increase in the future. The data obtained in our own observation indicate that 58% of patients need to be transported to the ED. Interventions of medical teams often cannot end at the call point, they require the patient to be transported to the hospital for further diagnosis, consultation and observation.

The period of our analysis is partly connected with the period of the COVID-19 pandemic. Interventions for patients with suspected COVID-19 ($n = 47$) accounted for 5.2% of the total. These were U07 diagnoses. Medical teams are equipped with rapid tests (nasopharyngeal swabs) that give results in a short time. However, full confirmation is provided by the polymerase chain reaction (PCR) laboratory test, which is available at the hospital. Noteworthy are the diagnoses R06 ($n = 58$) and R50 ($n = 52$), which could potentially be the beginning of COVID-19 infection, but a quick test at the pre-hospital stage did not confirm the infection (19–22).

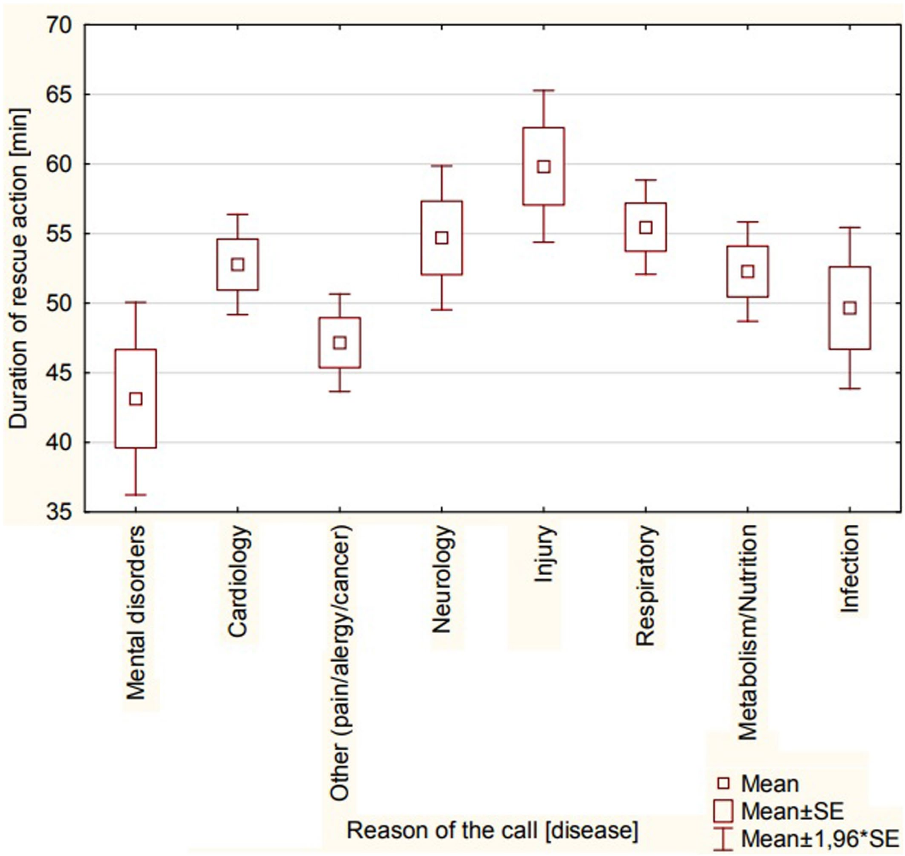

FIGURE 1
Duration of rescue action [min] according to reason of the call [disease].

TABLE 5 Univariate comparison of characteristic of MRTs interventions according to reasons of the call.

Parameters	Mental	Cardiology	Neurology	Injury	Respiratory	Metabol./ Nutr.	Infection	Other	*p*
N	35	187	100	124	144	128	26	112	
Age, y	94 ± 4	93 ± 3	93 ± 3	93 ± 2	93 ± 2	93 ± 2	93 ± 3	93 ± 3	0,319
Duration, min	43 ± 21	53 ± 25	55 ± 26	60 ± 31	55 ± 21	52 ± 21	50 ± 15	47 ± 19	<0,001
Sex, male, n(%)	9 (26)	34 (18)	17 (17)	36 (29)	40 (28)	26 (20)	10 (39)	34 (30)	0,031
S EMTs, n(%)	18 (51)	117 (63)	58 (58)	48 (39)	79 (55)	64 (50)	15 (58)	48 (42)	0,002
Localization, city, n(%)	13 (37)	51 (27)	26 (36)	30 (24)	24 (17)	29 (23)	7 (27)	23 (21)	0,194
Pharmacology, n(%)	16 (46)	137 (73)	47 (47)	74 (60)	119 (83)	95 (74)	22 (85)	68 (61)	<0,001
Transfer to ED, n(%)	11 (31)	109 (58)	76 (76)	89 (72)	88 (61)	80 (63)	13 (50)	53 (47)	<0,001
Year, n(%)									0,003
	2020	13 (37)	76 (41)	39 (39)	45 (36)	39 (27)	57 (45)	8 (31)	38 (34)
	2021	14 (40)	61 (32)	23 (23)	31 (25)	59 (41)	33 (26)	9 (35)	23 (21)
	2022	8 (23)	50 (27)	38 (38)	48 (39)	46 (32)	38 (30)	9 (35)	51 (46)

ED, emergency department; S EMT, specialist Emergency Medical Team.

The total number of SMR dispatches in the observed operational area did not change significantly during the COVID-19 period and the years preceding it. Data with the total number of interventions since 2015 come from published observations of the functioning of EMTs and interventions to other groups of patients. In 2015, there were 5,782 interventions, 2016–7,830, 2017–7,890, 2018–7,580, 2019–7,624, 2020–7,054, 2021–7,069 and 2022–6,769 (Mean 7,199,7, SD 700,2) (23, 24).

Most interventions in our observation occurred in rural areas ($n = 681$), which may be related to more difficult access to a general

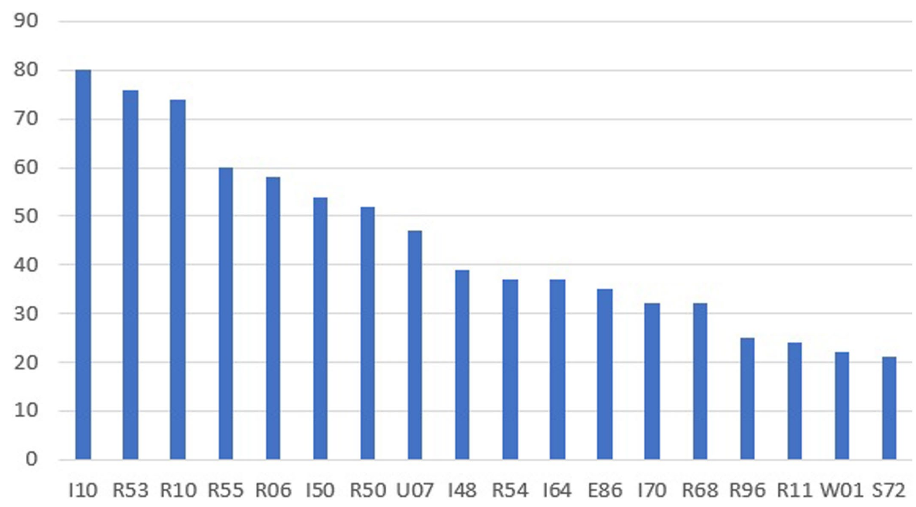

FIGURE 2
ICD-10 diagnoses for n > 20. I10-hypertension, R53-bad mod and fatigue, R10-stomachache, R55-fainting and collapse, R06-breathing disorders, I50-heart failure, U07-multisystem inflammatory syndrome associated with COVID-19, I48-atrium fibrillation, R54-old age, E86-excessive fluid loss, I70-atherosclerosis, R68-other general symptoms and signs, R96-other sudden death from an unknown cause, R11-nausea and vomiting, W01-falling on the same level due to tripping, slipping, S72-fracture of the femur.

TABLE 6 Comparative group – interventions for patients aged 80–90 years.

2020		2021		2022	
W	M	W	M	W	M
678	355	718	332	711	334

M, interventions to men; W, interventions to women.

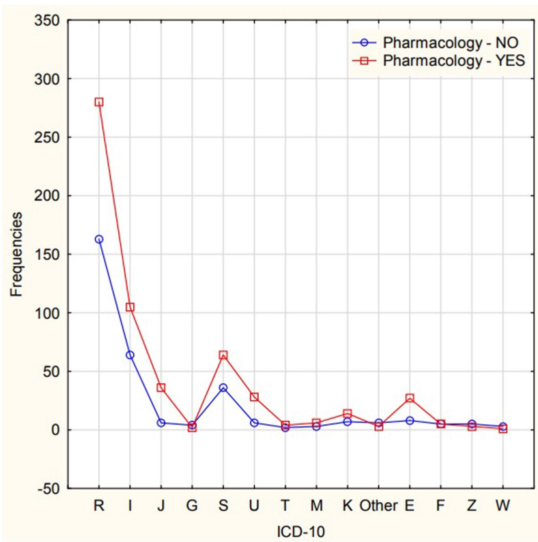

FIGURE 3
Interactions of frequency between the use of pharmacotherapy and ICD-10 groups.

practitioner (medical centers are more often located in cities). In addition, in rural areas, elderly people often live alone, and their families (professionally active) choose to live in the city for employment reasons. In the authors' opinion, another factor of frequent EMT interventions in rural areas may be insufficient care provided by the family. Hard work in agriculture and lack of time for proper care, lack of funds to finance a nursing home, inability to transport seniors for check-ups at the general practitioner's office, result in exacerbation of chronic diseases and the need to call a EMT.

Pharmacotherapy in interventions up to the age group of 90+ consists mainly of symptomatic drugs. Błeszyńska-Marunowska et al. draws attention to the difficulties of pharmacotherapy of seniors due to changes in metabolism, multi-morbidity and great interest in over-the-counter drugs, leading to polypharmacy of seniors, which consequently requires the implementation of combined medical and pharmaceutical care for geriatric patients. Our own observations did not include the analysis of self-pharmacotherapy by patients, only drugs administered by EMTs, mainly symptomatic ones, oxygen and drip infusions (25).

In the case of pharmacotherapy used by EMTs, it is important to limit the regulations (Minister of Health) regarding the number of pharmacological agents that EMTs have at their disposal, and the differences in the use of pharmacology between S teams (greater number of pharmacological agents due to the greater scope of physicians' authority) and B teams (without a physician) (26–28).

Nadolny et al. analyzed MRT interventions in Poland during the COVID-19 pandemic, he found that the overall number of interventions had decreased compared to the previous period. The authors classified all EMT interventions categorized by the reason for the call, including: death, syncope, mental disorder, traffic accident, trauma, stroke, sudden cardiac arrest, shortness of breath, pregnancy, chest pain, circulatory disorders. Our research also classified grouped interventions matched to the age group of patients (29).

Celiński et al. also analyzed geriatric patients in the EMT practice in eastern Poland. The results from 2019 to 2020 confirm our observations. Two thirds of the patients were transferred to the ED, mainly due to cardiovascular diseases, injuries arising from external causes and respiratory diseases (30).

Death in this age group is not very common. Diagnoses R96 and R98 ($n = 19$ – items not included in Figure 1 results for $n > 20$) occurred in a total of 46 interventions. Some of the patients in very serious condition were transported by medical teams to the ED. The consent to obtain the data did not cover the hospital documentation. Therefore, the authors do not know how many patients died in the subsequent hours of hospital stay. Based on our own data on repeated interventions ($n = 168$) and data from the CSO, it can be assumed that pre-hospital rescue, equipment, experience of medical teams, procedures, and pharmacotherapy have a positive impact on the life expectancy of the population (31).

Interestingly, one intervention in the "rural area" group ended with the transfer of the patient to the HEMS team, due to the patient's serious condition and the long distance to the hospital. This intervention shows that pre-hospital rescue in Poland is at a high level, has efficient coordination of various types of medical teams (ground and air), using all possible forces and means to save lives, regardless of the patient's age.

Limitations

The interventions included in the analysis in accordance with the assumed purpose of the paper account for a clear percentage of all EMT interventions, constituting a challenge for units providing pre-hospital rescue. The figures for interventions for groups 80–89 and 90 show that the aging population often needs pre-hospital assistance. The obtained consent for access to data covered only the documentation of the EMT dispatch teams, no access was granted to the documentation of further hospital treatment.

Conclusion

The causes of calls for disorders of the circulatory and respiratory systems most often require the implementation of pharmacology during EMT interventions, mainly short-term and symptomatic drugs. Interventions to rural areas dominate in the presented analysis in each year and in each group of reasons for calls, which may be associated with more difficult access to a primary care physician. Transport to the hospital was necessary mainly for neurological and traumatic calls, and the intervention time was the longest in the group of trauma patients, which is related to bone injuries and the need to transport to a facility further than the local hospital. The tendency of repeated interventions to the same patients may confirm the unstable health of this age group, the lack of proper care, the effectiveness of previous EMT interventions. Deaths in this age group are not significantly common during EMT interventions, which may be related to patients' stay in hospital wards and care facilities in the last period of life.

Data availability statement

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

Author contributions

ŁC: Writing – review & editing, Conceptualization, Data curation, Formal analysis, Software, Supervision. ŁD: Data curation, Supervision, Writing – review & editing, Investigation, Methodology, Visualization, Writing – original draft, Resources. JW: Formal analysis, Resources, Supervision, Validation, Visualization, Writing – review & editing.

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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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Association of two novel systemic inflammatory biomarkers and frailty based on NHANES 2007–2018

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Background: Frailty is a significant concern in the field of public health. However, currently, there is a lack of widely recognized and reliable biological markers for frailty. This study aims to investigate the association between systemic inflammatory biomarkers and frailty in the older adult population in the United States.

Methods: This study employed data from the National Health and Nutrition Examination Survey (NHANES) spanning 2007 to 2018 and conducted a rigorous cross-sectional analysis. We constructed weighted logistic regression models to explore the correlation between the Systemic Immune-Inflammation Index (SII), Systemic Inflammatory Response Index (SIRI), and frailty in the population aged 40 to 80 years. Using restricted cubic spline (RCS), we successfully visualized the relationship between SII, SIRI, and frailty. Finally, we presented stratified analyses and interaction tests of covariates in a forest plot.

Results: This study involved 11,234 participants, 45.95% male and 54.05% female, with an average age of 64.75 ± 0.13 years. After adjusting for relevant covariates, the weighted logistic regression model indicated an odds ratio (OR) and 95% confidence interval(CI) for the correlation between frailty and the natural logarithm (ln) transformed lnSII and lnSIRI as 1.38 (1.24–1.54) and 1.69 (1.53–1.88), respectively. Subsequently, we assessed different levels of lnSII and lnSIRI, finding consistent results. In the lnSII group model, the likelihood of frailty significantly increased in the fourth quartile (OR = 1.82, 95% CI: 1.55–2.12) compared to the second quartile. In the lnSIRI group model, the likelihood of frailty significantly increased in the third quartile (OR = 1.30, 95% CI: 1.10–1.53) and fourth quartile (OR = 2.29, 95% CI: 1.95–2.70) compared to the second quartile. The interaction results indicate that age and income-to-poverty ratio influence the association between lnSIRI and frailty. RCS demonstrated a nonlinear relationship between lnSII, lnSIRI, and frailty.

Conclusion: The results of this cross-sectional study indicate a positive correlation between systemic inflammatory biomarkers (SII, SIRI) and frailty.

KEYWORDS

frailty, SIRI, SII, systemic inflammatory biomarkers, NHANES

1 Introduction

Frailty, as a multifactorial syndrome, manifests a trend of increasing physiological system impairments with age and may significantly reduce survival rates at any age (1). A key characteristic of frailty is the gradual weakening of physiological systems and an exceptional sensitivity to various stresses and pressures in daily life (2). Frailty may trigger and exacerbate other health issues; therefore, prevention and slowing the progression of frailty are crucial. Frailty is determined by multiple indicators, including the Edmonton Frail Scale (3), the Geriatric Nutritional Risk Index (4), the Frailty Index (FI) (5), and the Fried phenotype, among others. Among these, FI performs well in distinguishing frailty states (6). An increased burden of inflammation also characterizes frailty (7). Systemic Immune-Inflammation Index (SII) (8) and Systemic Inflammatory Response Index (SIRI) (9) are novel markers linked with inflammatory conditions.

Blood inflammation markers are cost-effective and easily accessible biomarkers. Serving as indicators of both local immune response and systemic inflammation, SII is a robust and stable metric, integrating three types of inflammatory cells (lymphocytes, neutrophils, and platelets) (10–12). Numerous studies have indicated that the SII can predict the prognosis of patients with various cancers, acute ischemic stroke, heart failure, and acute kidney injury (13). SIRI, composed of lymphocytes, monocytes, and neutrophils, represents a more comprehensive indicator of chronic inflammation (14). Previous research suggests that SIRI is a potential marker for early diagnosis and prognosis monitoring in conditions such as stroke, inflammatory diseases, and cancer (15). Additionally, previous research has found an association between C-reactive protein and interleukin-6 with frailty (16).

Some studies have indicated an association between systemic inflammatory biomarkers and the risk of frailty (17). However, current research has limitations, including small sample sizes and a single definition of frailty. The universality and reliability of this association require validation and further confirmation through larger-scale studies. In this study, we conducted a rigorous analysis using a large sample from the National Health and Nutrition Examination Survey (NHANES) data spanning 2007 to 2018 to explore the correlation between SIRI, SII, and frailty. This research aims to gain deeper insights into the impact of systemic inflammatory biomarkers on frailty, ultimately providing more effective healthcare recommendations for individuals.

2 Methods

2.1 Study population

These data are available from the NHANES database (18). This database comprises a series of nationally representative surveys designed to assess U.S. citizens' health and nutritional status (19). The database has received approval from the National Center for Health Statistics Ethics Review Board, and the participants have obtained written consent (20). We conducted data analysis on the most recent six NHANES survey cycles (2007–2018), encompassing 15,155 participants, followed by a series of exclusions.

1. Exclusion of participants with less than 80% of FI features (< 40 items) (n = 244);
2. Exclusion of participants with age < 40 years (n = 1,396);
3. Exclusion of individuals with insufficient baseline information (gender, race, education, marital status, income poverty ratio) (n = 1,402);
4. Exclusion of individuals with missing covariates (alcohol consumption, smoking) (n = 500);
5. Exclusion of individuals with missing values for SII and SIRI (n = 379).

Ultimately, it includes 11,234 participants, as depicted in Figure 1.

2.2 Frailty

Following the approach proposed by Hakeem et al., we utilized the FI to assess the degree of frailty. This index comprises 49 variables spanning multiple systems, covering aspects such as cognition, dependency, depressive symptoms, comorbidities, general health status, hospital utilization, physical performance, body measurements, and laboratory test values (21–23). The eligibility survey required a completion rate of at least 80% (approximately 40 items) for the 49 frailty items. We assigned scores ranging from 0 to 1 based on the severity of defects (see Supplementary Table S1)[1]. The FI is the sum of defect scores obtained by participants divided by the potential total defect score. With a critical threshold for the FI set at 0.21, values greater than or equal to 0.21 are defined as frail, while values less than 0.21 are non-frail (24).

2.3 Systemic inflammatory biomarkers

An automated hematology analyzer will evaluate lymphocyte, neutrophil, platelet, and monocyte counts expressed as $\times 10^3$ cells/μL (25). We calculated two systemic inflammatory markers based on peripheral blood cell counts: SII and SIRI. The calculation formula for SII is platelet count × neutrophil/lymphocyte count (26). The calculation formula for SIRI is neutrophil count × monocyte count/lymphocyte count (27).

2.4 Covariates

Correlation logic and previously published literature guided the selection of covariates. We collected statistical data on basic participant information, including age, gender, race, education level, marital status, income poverty ratio, and statistics on alcohol and smoking habits. Specifically, age into two groups: <40 years and ≥ 40 years; gender into two groups: male and female; race into five groups:

Abbreviations: NHANES, National Health and Nutrition Examination Survey; SII, Systemic Immune-Inflammation Index; SIRI, Systemic Inflammatory Response Index; RCS, restricted cubic spline; OR, odds ratio; CI, confidence interval; ln, natural logarithm; FI, Frailty Index.

1 https://www.cdc.gov/nchs/nhanes/index.htm

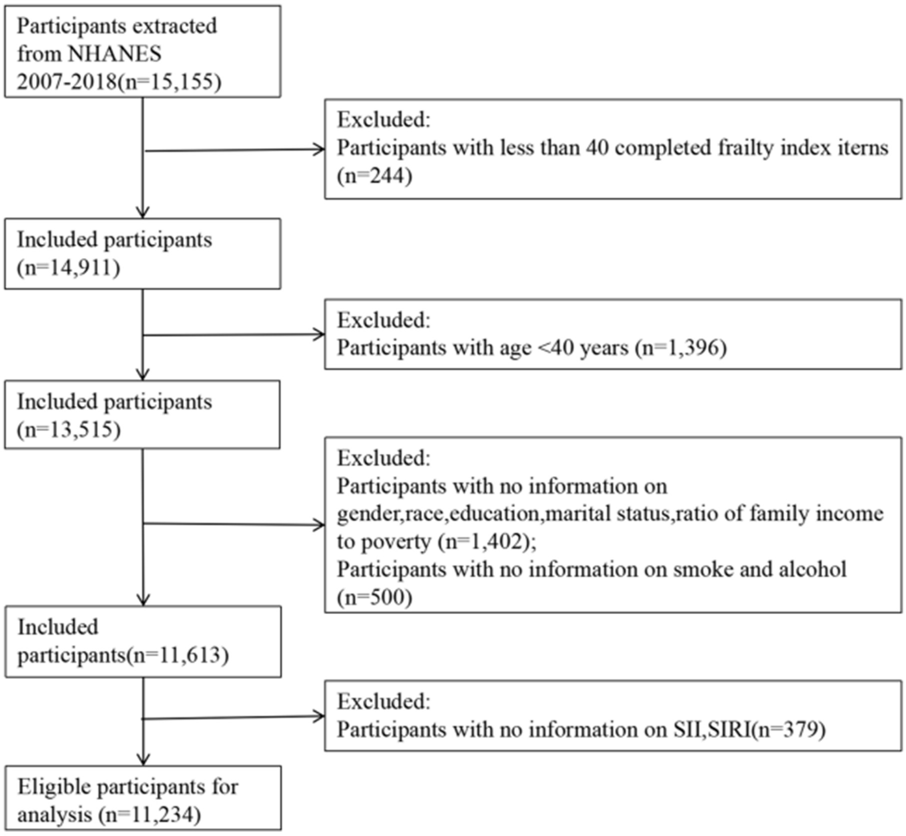

FIGURE 1
Flow chart of sample selection.

Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other races, including multiple races; education level into three groups: less than high school, high school or general education diploma, and more than high school (28); marital status into three groups: married/living with a partner, never married, and separated/divorced/widowed (29); The income poverty ratio is categorized into three groups: low (≤1.3), moderate (1.3–3.5), and high (>3.5). It is calculated by dividing the family's (or individual's) income by the poverty threshold specific to the survey year. A lower income poverty ratio indicates lower income for the family (or individual). Based on the response to the question, "Have you smoked at least 100 cigarettes in your entire life?" participants were categorized as smokers or non-smokers. Based on responses to questions about drinking at least 12 alcoholic beverages in the past year and ever drinking any alcoholic beverage, participants were drinkers or non-drinkers (30).

2.5 Statistical analysis

In this study, statistical analyses followed the recommendations of the Centers for Disease Control and Prevention guidelines. We were considering the complexity and multi-stage sampling design of NHANES data collection and sampling weights in the statistical analysis. We compared the baseline characteristics between frail and non-frail individuals, as well as the baseline characteristics of different quartiles of the natural logarithm (ln) transformed SII (lnSII) and SIRI (lnSIRI). For normally distributed quantitative data, we used the t-test, and for qualitative data, we employed the χ^2 test. Descriptive statistics presented continuous variables using mean ± standard deviation and categorical variables using percentages with 95% confidence intervals. Subsequently, weighted logistic regression models estimate the relationships between lnSII, lnSIRI, and frailty in three different models. Model 1 was a basic unadjusted model; Model 2 adjusted for age, gender, race, income poverty ratio, education level, and marital status; Model 3 included all variables in Model 2, plus smoking and drinking status. Furthermore, restricted cubic splines (RCS) were employed to detect potential non-linear relationships between lnSII, lnSIRI, and frailty. We performed Subgroup and interaction analyses for age, gender, education, marital status, income and poverty ratio, smoking, and drinking. All analyses use R software (V.4.3.2), Stata software (version 17), and SPSS software (version 27). Statistically significant: A significance level of $p < 0.05$ was considered.

3 Results

3.1 The baseline features of the participants

11,234 participants were included, with males comprising 45.95% and females 54.05%. Clinical characteristics of participants, stratified by frailty status, are presented in Table 1. The proportions of lnSII four quartiles among frail patients were 21.24, 21.80, 23.7, and 33.26%, respectively, while lnSIRI four quartiles were 20.08, 21.25, 25.01, and

TABLE 1 Baseline characteristics of weighted sample by frailty and non-frailty groups.

	Total	Non-frailty	frailty	*p*-value
Sample size	1,1,234	6,690	4,544	
Age, Mean	64.75 ± 0.13	65.02 ± 0.16	64.29 ± 0.22	<0.001
lnSII, Mean	6.18 ± 0.01	6.14 ± 0.01	6.23 ± 0.01	<0.001
lnSIRI, Mean	0.17 ± 0.01	0.12 ± 0.01	0.25 ± 0.01	<0.001
Gender				<0.001
Men	45.95(44.63–47.27)	49.78(48.05–51.51)	39.27(37.32–41.26)	
Women	54.05(52.73–55.37)	50.22(48.49–51.95)	60.73(58.74–62.68)	
Race				<0.001
Mexican American	4.41(4.13–4.71)	3.96(3.63–4.31)	5.19(4.69–5.74)	
Hispanic	3.86(3.59–4.14)	3.47(3.17–3.80)	4.53(4.03–5.09)	
Non-Hispanic White	76.87(76.02–77.69)	79.60(78.61–80.56)	72.10(70.58–73.58)	
Non-Hispanic Black	9.15(8.72–9.60)	7.51(7.04–8.01)	12.00(11.18–12.87)	
Other race	5.72(5.22–6.27)	5.46(4.90–6.09)	6.17(5.24–7.26)	
Marital				<0.001
Married/living with a partner	62.53(61.29–63.76)	66.92(65.34–68.47)	54.88(52.89–56.85)	
Never married	6.33(5.74–6.98)	5.66(4.95–6.47)	7.50(6.51–8.62)	
Separated/divorced/widowed	31.14(29.99–32.31)	27.41(25.98–28.90)	37.62(35.76–39.52)	
Education				<0.001
< High school	17.66(16.86–18.49)	13.64(12.74–14.60)	24.67(23.19–26.21)	
High school	25.38(24.25–26.55)	23.54(22.11–25.03)	28.59(26.77–30.49)	
> High school	56.96(55.67–58.23)	62.82(61.20–64.42)	46.73(44.71–48.77)	
Income poverty ratio				<0.001
< 1.3	22.10(21.20–23.03)	15.20(14.26–16.19)	34.14(32.39–35.93)	
(1.3–3.5)	38.41(37.15–39.68)	36.36(34.76–37.99)	41.97(39.99–43.97)	
≥3.5	39.49(38.13–40.86)	48.44(46.70–50.19)	23.89(21.98–25.91)	
Smoke				<0.001
Yes	52.84(51.52–54.16)	48.72(46.99–50.44)	60.03(58.05–61.99)	
No	47.16(45.84–48.48)	51.28(49.56–53.01)	39.97(38.01–41.95)	
Alcohol use				<0.001
Yes	75.92(74.86–76.94)	77.19(75.83–78.49)	73.69(72.02–75.30)	
No	24.08(23.06–25.14)	22.81(21.51–24.17)	26.31(24.70–27.98)	

33.67%, respectively. Frailty showed statistical significance ($p < 0.05$) concerning age, gender, race, education level, marital status, income poverty ratio, alcohol consumption, smoking status, lnSIRI, and lnSII. Compared to non-frail individuals, frail patients are often female, have lower educational levels, lower income poverty ratio, are less likely to be married or living with a partner, and are more likely to smoke. Additionally, they tend to have higher levels of lnSII and lnSIRI. The mean age of frail patients is 64.29 ± 0.22 years.

Among the 11,234 participants, 63.54% were non-frail, and 36.46% as frail. Stratifying by different levels of lnSIRI, significant differences in frailty, age, gender, race, education, marital status, income and poverty ratio, alcohol consumption, and smoking status were observed ($p < 0.05$). The proportions of the four categories of frailty were 34.96, 29.48, 34.43, and 46.69%, as illustrated in Table 2.

Stratifying by different levels of lnSII, significant differences in frailty, race, education, marital status, income and poverty ratio, and smoking status were observed ($p < 0.05$). The proportions of the four frailty categories were 35.91, 31.12, 33.05, and 45.35%, as illustrated in Table 3.

3.2 The relationship between lnSII, lnSIRI and frailty

Three weighted logistic regression models were employed to investigate the association between lnSII, lnSIRI, and frailty. The odds ratios (OR) and 95% confidence intervals (CI) for the ratio of frailty's correlation with lnSII and lnSIRI are presented in Table 4. Model 1, unadjusted; Model 2, adjusted for age, gender, race, education, marital status, income-to-poverty ratio; Model 3, additional adjustment for smoking and drinking status based on Model 2. There is a consistently significant positive correlation between lnSII, lnSIRI, and frailty in all

TABLE 2 Baseline characteristics of the study population stratified by quartiles of lnSIRI value.

	lnSIRI total	Q1(≥ − 0.29)	Q2(−0.29 to 0.11)	Q3(0.11–0.52)	Q4(≥0.52)	*p*-value
Sample size	11,234	2,808	2,808	2,808	2,810	
Year	64.75 ± 0.13	62.73 ± 0.25	63.94 ± 0.26	65.15 ± 0.26	66.77 ± 0.26	<0.001
Gender						<0.001
Male	45.95(44.63–47.27)	32.51(30.00–35.13)	41.42(38.78–44.11)	49.41(46.79–52.02)	57.71(55.21–60.17)	
Female	54.05(52.73–55.37)	67.49(64.87–70.00)	58.58(55.89–61.22)	50.59(47.98–53.21)	42.29(39.83–44.79)	
Race						<0.001
Mexican American	4.41(4.13–4.71)	5.52(4.83–6.30)	4.54(4.00–5.15)	4.32(3.81–4.90)	3.48(3.01–4.02)	
Hispanic	3.86(3.59–4.14)	4.63(4.04–5.29)	4.03(3.52–4.62)	3.59(3.09–4.17)	3.33(2.84–3.90)	
Non-Hispanic White	76.87(76.02–77.69)	62.44(60.09–64.73)	77.76(76.07–79.37)	80.43(78.86–81.91)	83.87(82.52–85.15)	
Non-Hispanic Black	9.15(8.72–9.60)	19.40(17.97–20.93)	8.27(7.49–9.13)	6.17(5.53–6.88)	4.86(4.28–5.50)	
Other race	5.72(5.22–6.27)	8.02(6.82–9.41)	5.39(4.42–6.55)	5.49(4.53–6.64)	4.46(3.69–5.39)	
Education						0.010
< High school	17.66(16.86–18.49)	19.21(17.53–21.02)	15.73(14.26–17.33)	17.49(15.96–19.13)	18.53(16.91–20.27)	
High school	25.38(24.25–26.55)	24.56(22.28–26.99)	25.10(22.83–27.52)	25.40(23.16–27.78)	26.30(24.16–28.55)	
> High school	56.96(55.67–58.23)	56.23(53.54–58.88)	59.16(56.57–61.71)	57.11(54.56–59.63)	55.18(52.70–57.62)	
Marital status						0.003
Married/living with a partner	62.53(61.29–63.76)	61.06(58.44–63.61)	63.50(60.98–65.95)	63.27(60.78–65.68)	62.00(59.61–64.33)	
Never married	6.33(5.74–6.98)	8.21(6.91–9.74)	5.53(4.53–6.72)	5.86(4.81–7.13)	6.11(4.94–7.55)	
Separated/divorced/widowed	31.14(29.99–32.31)	30.73(28.41–33.15)	30.98(28.67–33.39)	30.87(28.60–33.24)	31.89(29.73–34.12)	
Income poverty ratio						<0.001
< 1.3	22.10(21.20–23.03)	25.54(23.56–27.63)	20.46(18.72–22.31)	21.27(19.57–23.07)	21.85(20.11–23.70)	
(1.3–3.5)	38.41(37.15–39.68)	37.34(34.73–40.02)	35.97(33.51–38.51)	37.64(35.19–40.15)	42.47(40.03–44.94)	
≥3.5	39.49(38.13–40.86)	37.12(34.31–40.02)	43.57(40.83–46.35)	41.09(38.42–43.82)	35.68(33.15–38.29)	
Smoke						<0.001
Yes	52.84(51.52–54.16)	45.96(43.23–48.72)	49.30(46.62–51.99)	55.08(52.45–57.68)	59.60(57.11–62.05)	
No	47.16(45.84–48.48)	54.04(51.28–56.77)	50.70(48.01–53.38)	44.92(42.32–47.55)	40.40(37.95–42.89)	
Alcohol use						<0.001
Yes	75.92(74.86–76.94)	71.09(68.66–73.41)	76.16(74.03–78.16)	77.10(75.07–79.01)	78.32(76.34–80.18)	
No	24.08(23.06–25.14)	28.91(26.59–31.34)	23.84(21.84–25.97)	22.90(20.99–24.93)	21.68(19.82–23.66)	
Frailty						<0.001
No	63.54(62.3–64.76)	65.04(62.45–67.53)	70.52(68.13–72.80)	65.57(63.15–67.92)	53.31(50.82–55.79)	
Yes	36.46(35.24–37.7)	34.96(32.47–37.55)	29.48(27.20–31.87)	34.43(32.08–36.85)	46.69(44.21–49.18)	

three models. The impact of lnSII on frailty was as follows: Model 1 (OR = 1.34, 95% CI: 1.21–1.48), Model 2 (OR = 1.41, 95% CI: 1.26–1.57), Model 3 (OR = 1.38, 95% CI: 1.24–1.54). When assessing different levels of lnSII, compared to the second quartile of lnSII, the first and third quartiles did not show a significant difference in the probability of frailty. At the same time, the likelihood significantly increased in the fourth quartile: Model 1 (OR = 1.84, 95% CI: 1.58–2.13), Model 2 (OR = 1.86, 95% CI: 1.59–2.17), Model 3 (OR = 1.82, 95% CI: 1.55–2.12). Furthermore, the trend *p*-values for all three models were below 0.001.

The impact of lnSIRI on frailty was as follows: Model 1 (OR = 1.45, 95% CI: 1.32–1.58), Model 2 (OR = 1.73, 95% CI: 1.56–1.91), and Model 3 (OR = 1.69, 95% CI: 1.53–1.88). When assessing different levels of lnSIRI, compared to the second quartile of lnSIRI, the first quartile did not show a significant difference in the probability of frailty. In contrast, the probabilities significantly increased in the third and fourth quartiles. For the third quartile: Model 1 (OR = 1.26, 95% CI: 1.08–1.47), Model 2 (OR = 1.32, 95% CI: 1.12–1.55), Model 3 (OR = 1.30, 95% CI: 1.10–1.53); For the fourth quartile: Model 1 (OR = 2.09, 95% CI: 1.80–2.44), Model 2 (OR = 2.34, 95% CI: 1.99–2.76), Model 3 (OR = 2.29, 95% CI: 1.95–2.70). Furthermore, the trend *p*-values for all three models were below 0.001.

TABLE 3 Baseline characteristics of the study population stratified by quartiles of lnSII value.

	lnSII total	Q1(≤5.78)	Q2(5.78–6.14)	Q3(6.14–6.5)	Q4(≥6.5)	*p*-value
Sample size	11,234	2,808	2,808	2,808	2,810	
Year	64.75 ± 0.13	64.54 ± 0.26	64.50 ± 0.26	64.91 ± 0.26	65.00 ± 0.26	0.170
Gender						0.924
Male	45.95(44.63–47.27)	46.39(43.64–49.15)	46.17(43.52–48.85)	45.80(43.18–48.44)	45.53(43.04–48.05)	
Female	54.05(52.73–55.37)	53.61(50.85–56.36)	53.83(51.15–56.48)	54.20(51.56–56.82)	54.47(51.95–56.96)	
Race						<0.001
Mexican American	4.41(4.13–4.71)	4.65(4.05–5.33)	4.83(4.25–5.49)	4.40(3.88–4.98)	3.81(3.31–4.37)	
Hispanic	3.86(3.59–4.14)	4.12(3.57–4.74)	4.32(3.76–4.95)	3.48(3.02–4.01)	3.57(3.06–4.18)	
Non-Hispanic White	76.87(76.02–77.69)	67.51(65.32–69.62)	76.17(74.46–77.81)	79.91(78.35–81.39)	82.10(80.65–83.47)	
Non-Hispanic Black	9.15(8.72–9.60)	16.92(15.62–18.31)	8.68(7.87–9.57)	6.89(6.19–7.67)	5.53(4.92–6.20)	
Other race	5.72(5.22–6.27)	6.80(5.57–8.28)	6.00(5.08–7.06)	5.32(4.40–6.41)	4.99(4.14–6.00)	
Education						0.013
< High school	17.66(16.86–18.49)	19.18(17.49–20.99)	16.47(14.96–18.10)	17.19(15.64–18.87)	18.03(16.47–19.70)	
High school	25.38(24.25–26.55)	25.49(23.14–28.00)	23.95(21.80–26.23)	26.88(24.55–29.35)	25.20(23.09–27.42)	
> High school	56.96(55.67–58.23)	55.33(52.62–58.01)	59.58(57.04–62.07)	55.92(53.33–58.49)	56.77(54.31–59.21)	
Marital status						<0.001
Married/living with a partner	62.53(61.29–63.76)	61.91(59.32–64.43)	66.82(64.41–69.15)	61.57(59.05–64.04)	59.87(57.42–62.27)	
Never married	6.33(5.74–6.98)	7.86(6.58–9.37)	4.98(4.02–6.15)	5.96(4.90–7.23)	6.75(5.55–8.19)	
Separated/divorced/ widowed	31.14(29.99–32.31)	30.23(27.94–32.62)	28.20(26.02–30.49)	32.46(30.13–34.89)	33.38(31.14–35.69)	
Income poverty ratio						0.002
< 1.3	22.10(21.20–23.03)	24.25(22.32–26.30)	21.14(19.37–23.02)	20.52(18.84–22.30)	22.84(21.08–24.71)	
(1.3–3.5)	38.41(37.15–39.68)	37.69(35.09–40.36)	37.17(34.71–39.70)	39.01(36.51–41.57)	39.58(37.16–42.04)	
≥3.5	39.49(38.13–40.86)	38.06(35.24–40.96)	41.69(38.97–44.47)	40.47(37.79–43.21)	37.58(35.00–40.23)	
Smoke						<0.001
Yes	52.84(51.52–54.16)	50.00(47.24–52.76)	49.35(46.69–52.01)	53.61(50.97–56.24)	57.72(55.20–60.21)	
No	47.16(45.84–48.48)	50.00(47.24–52.76)	50.65(47.99–53.31)	46.39(43.76–49.03)	42.28(39.79–44.80)	
Alcohol use						0.311
Yes	75.92(74.86–76.94)	74.71(72.45–76.84)	75.63(73.43–77.71)	76.27(74.17–78.24)	76.82(74.83–78.69)	
No	24.08(23.06–25.14)	25.29(23.16–27.55)	24.37(22.29–26.57)	23.73(21.76–25.83)	23.18(21.31–25.17)	
Frailty						<0.001
No	63.54(62.3–64.76)	64.09(61.44–66.65)	68.88(66.49–71.18)	66.95(64.56–69.27)	54.65(52.15–57.13)	
Yes	36.46(35.24–37.7)	35.91(33.35–38.56)	31.12(28.82–33.51)	33.05(30.73–35.44)	45.35(42.87–47.85)	

We also used RCS to visualize the association between lnSII, lnSIRI, and frailty. After adjusting for all covariates in the primary analysis Model 3 mentioned above, we observed a non-linear correlation between lnSII, lnSIRI, and frailty (Figure 2).

3.3 Stratified analyses and interaction test

The interaction tests in the subgroup analysis revealed that the impact of lnSIRI on frailty varied with age (p for interaction = 0.007) and income-to-poverty ratio (p for interaction <0.001). However, gender, race, education, marital status, smoking, and alcohol consumption did not influence this positive correlation (p for interaction >0.05), as illustrated in Figure 3.

The relationship between lnSII and frailty showed no statistically significant differences across different strata, indicating that age, gender, race, education, marital status, income-to-poverty ratio, smoking, and alcohol consumption did not significantly affect this positive correlation (p for interaction >0.05), as depicted in Figure 4.

4 Discussion

This cross-sectional study investigated the relationship between lnSII, lnSIRI, and frailty using weighted logistic regression. We included 11,234 adults aged 40 years and older. The study's results indicated a positive correlation between lnSII and lnSIRI with frailty. This finding aligns with previous research, which suggested that individuals with

TABLE 4 Association between lnSII, lnSIRI and frailty.

	Model 1 OR (95% CI)	*p*-value	Model 2 OR (95% CI)	*p*-value	Model 3 OR (95% CI)	*p*-value
lnSII	1.34(1.21–1.48)	<0.0001	1.41(1.26–1.57)	<0.0001	1.38(1.24–1.54)	<0.0001
lnSII quartiles						
Q1(≤5.78)	1.24(1.06–1.45)	0.0073	1.16(0.98–1.36)	0.0787	1.16(0.99–1.37)	0.071
Q2(5.78–6.14)	Reference	Reference	Reference	Reference	Reference	Reference
Q3(6.14–6.5)	1.09(0.94–1.27)	0.2562	1.09(0.93–1.27)	0.309	1.07(0.92–1.26)	0.3854
Q4(≥6.5)	1.84(1.58–2.13)	<0.0001	1.86(1.59–2.17)	<0.0001	1.82(1.55–2.12)	<0.0001
p trend	<0.001		<0.001		<0.001	
lnSIRI	1.45(1.32–1.58)	<0.0001	1.73(1.56–1.91)	<0.0001	1.69(1.53–1.88)	<0.0001
lnSIRI quartiles						
Q1(≥ − 0.29)	1.29(1.10–1.51)	0.0019	1.09(0.93–1.29)	0.2897	1.10(0.94–1.30)	0.2367
Q2(−0.29 to 0.11)	Reference	Reference	Reference	Reference	Reference	Reference
Q3(0.11–0.52)	1.26(1.08–1.47)	0.0038	1.32(1.12–1.55)	0.0008	1.30(1.10–1.53)	0.0016
Q4(≥0.52)	2.09(1.80–2.44)	<0.0001	2.34(1.99–2.76)	<0.0001	2.29(1.95–2.70)	<0.0001
p trend	<0.001		<0.001		<0.001	

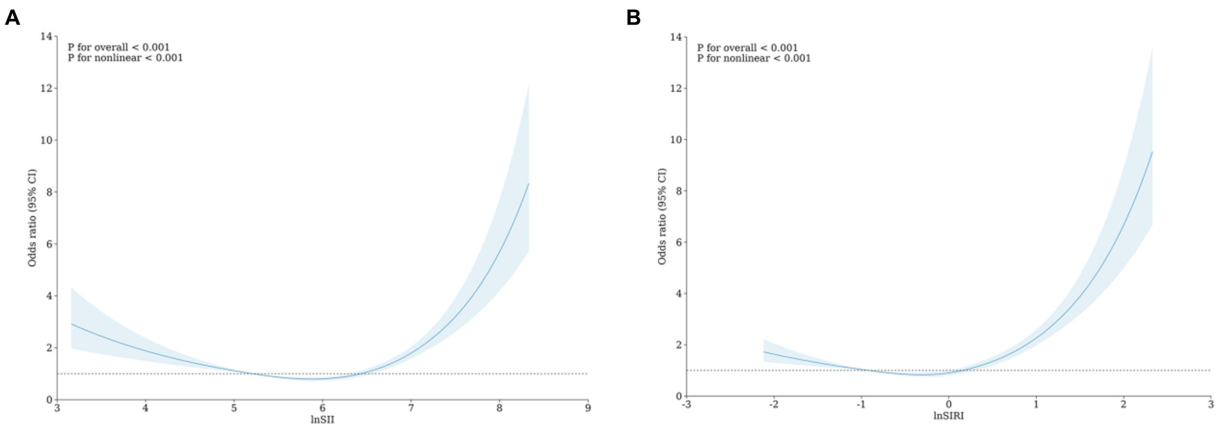

FIGURE 2
RCS analysis of lnSII **(A)** and lnSIRI **(B)** with the odds ratio of frailty.

higher neutrophil-to-lymphocyte ratio and higher SII levels have an increased risk of frailty events (17). Furthermore, our study revealed that age and income poverty ratio influence the association between lnSIRI and frailty. In contrast, the association between lnSII and frailty is relatively unaffected by other factors. We also observed several differences between frail and non-frail individuals. Frail individuals were more likely to be female, have lower educational attainment, lower income poverty ratio, less likely to be married/cohabiting, smokers, and had higher levels of lnSII and lnSIRI. Previous studies have also shown that the frail group is more likely to be female, have lower educational attainment, and have lower income (31, 32).

Research indicates that the prevalence of frailty among older adults is between 12 and 24% in 62 countries and regions (33). Frailty has been shown to have varying degrees of impact on the prognosis of older adults with cardiovascular diseases, increasing the incidence and mortality rates of cardiovascular disease patients (34). It becomes an independent risk factor for various major adverse cardiovascular events, including death, stroke, readmission for heart failure, and postoperative cardiac complications (35). Additionally, frail patients are at a higher risk of developing sepsis, pneumonia, and kidney failure compared to non-frail individuals (36). However, the pathological mechanisms leading to frailty remain unclear, and there is a lack of recognized, accurate, and reliable biological markers for frailty (37–39). Future research efforts should focus on understanding the pathogenesis of frailty to improve early diagnosis and intervention, thereby alleviating the burden on global healthcare systems.

The study points out that elevated levels of inflammatory markers are commonly found in older adults, and inflammation may be a primary factor leading to frailty (40, 41). The association between changes in the immune system and frailty involves multiple pathways, with neutrophils being a crucial biomarker for innate immunity, platelets potentially contributing to immune function, and lymphocytes providing rich information about adaptive immunity (42, 43). SII and SIRI have demonstrated exceptional validity as

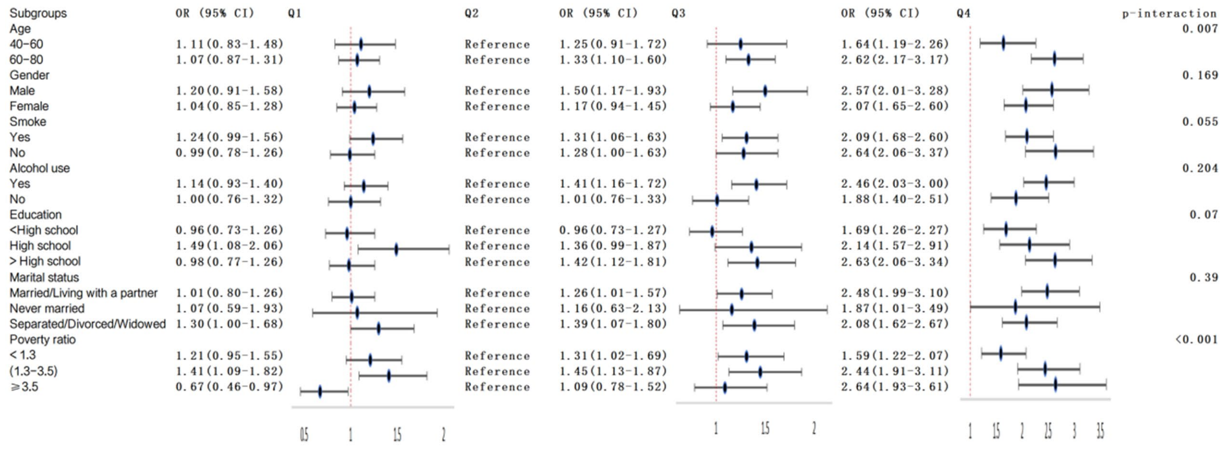

FIGURE 3
Subgroup analysis and interaction of the association between lnSIRI and frailty.

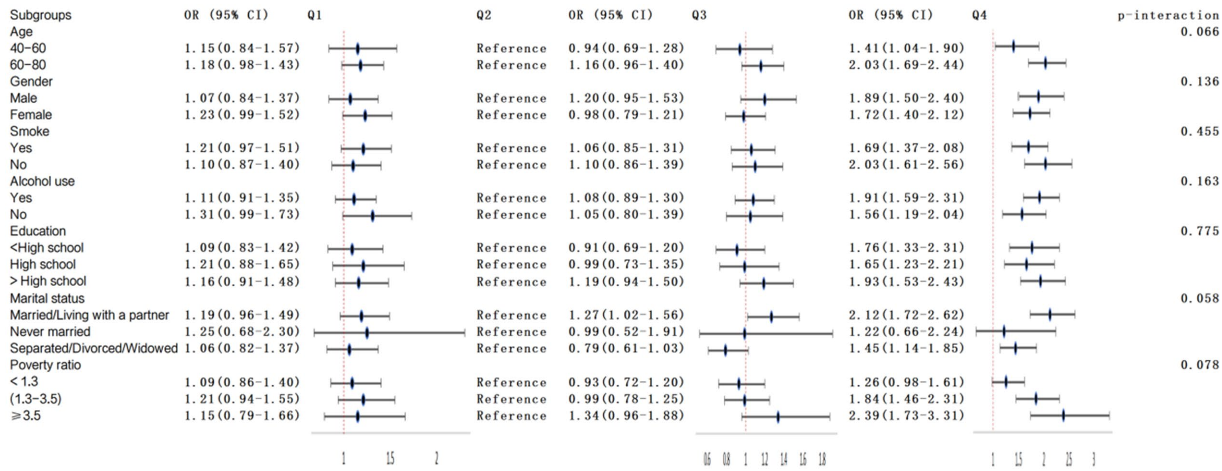

FIGURE 4
Subgroup analysis and interaction of the association between lnSII and frailty.

emerging biomarkers in various diseases (44). SII's predictive ability for major cardiovascular events in coronary heart disease patients undergoing coronary intervention surpasses traditional risk factors (45). Both SII and SIRI are closely correlated with cardiovascular and all-cause mortality. These studies emphasize the role of managing inflammatory markers in frailty among middle-aged and older adults and suggest that emerging biomarkers like SII and SIRI could be powerful tools for assessing and managing the health of middle-aged and older individuals (46, 47).

The findings of this study reveal a positive correlation between SII and SIRI with frailty, especially with SIRI exhibiting a more significant association. The study holds general significance due to its large sample size and representative sample selection. However, it is essential to note some limitations. Firstly, the study adopts a cross-sectional design, thus preventing the establishment of a causal relationship between SII, SIRI, and frailty. Secondly, some unaccounted confounding factors could impact the accurate assessment of the genuine associations.

5 Conclusion

This cross-sectional study provides compelling evidence indicating a positive correlation between systemic inflammatory biomarkers (SIRI and SII) and frailty. Given the ease of assessment of SIRI and SII in the laboratory, they can serve as cost-effective predictive factors for future frailty occurrences. This offers feasibility and guiding information for further interventions targeting the immune system to reduce the incidence 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.

Author contributions

HZ: Conceptualization, Data curation, Methodology, Software, Visualization, Writing – original draft. XL: Supervision, Writing – review & editing. XW: Data curation, Visualization, Writing – original draft. YJ: Conceptualization, Supervision, Validation, Visualization, Writing – review & editing.

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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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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2024.1377408/full#supplementary-material

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Association between complete blood count-derived inflammatory markers and the risk of frailty and mortality in middle-aged and older adults

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Objective: This study aimed to evaluate the association between six complete blood count (CBC)-derived inflammatory markers [neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammatory index (SII), systemic inflammatory response index (SIRI), and pan-immune inflammation value (PIV)] and the risk of frailty and mortality.

Methods: Data were obtained from the National Health and Nutrition Examination Survey (NHANES) 1999–2018. Mortality was identified using the National Death Index until December 31, 2019. Multiple logistic regression analysis was conducted to evaluate the association between six CBC-derived inflammatory markers and frailty. The Cox regression model assessed the association between six CBC-derived inflammatory markers and mortality in frail populations. Restricted cubic spline (RCS) was used to visualize the association of the six CBC-derived inflammatory markers with mortality risk. The predictive value of CBC-derived inflammatory markers for mortality was further assessed using a random survival forest (RSF) approach.

Results: This study analyzed data from a total of 16,705 middle-aged and older participants. Among them, 6,503 participants were frail, with a mortality rate of 41.47%. Multiple logistic regression analysis showed that NLR, MLR, PLR, SII, SIRI, and PIV were positively associated with frailty risk. The Cox regression model revealed that participants in the highest quartile had a significantly increased risk of death compared to those in the lowest quartile: NLR (HR=1.73, 95% CI:1.54, 1.94), MLR (HR=1.71, 95% CI:1.51, 1.93), PLR (HR=1.28, 95%CI: 1.15, 1.43), SII (HR=1.50, 95%CI:1.34, 1.68), SIRI (HR=1.88, CI 95%:1.67, 2.12), PIV (HR=1.55, 95%CI:1.38, 1.73). Random survival forest (RSF) analyses demonstrated that MLR had the highest predictive value for mortality risk in middle-aged and older adult frail participants.

Conclusion: The results suggest that CBC-derived inflammatory markers are associated with a higher risk of frailty as well as mortality in the middle and old-aged population of the United States.

KEYWORDS

CBC-derived inflammatory markers, frailty, mortality, RSF, NHANES

1 Introduction

Frailty represents a burgeoning global health concern (1). Studies have shown that frailty is prevalent in the aging population, and its incidence escalates with age (2). This age-related syndrome disrupts bodily homeostasis, resulting in the loss of physiological functions and immune system abnormalities (3, 4). Frail patients exhibit diminished resilience to both external and internal stressors, leading to acute health fluctuations in response to minor perturbations (5). Frail older adults face substantially heightened susceptibility to various adverse outcomes, such as falls, disability, hospitalization, and mortality (6).

Studies have shown that even in the absence of infection, frail older adults develop chronic low-grade inflammation over time (7, 8). This chronic inflammation, which leaves the organism in a protracted state of inflammation, ultimately accumulates, and exacerbates damage (9). Chronic inflammation, characterized by elevated levels of inflammatory cytokines, can play a role in the development of frailty, and is strongly associated with frailty and premature death (10, 11). With the understanding of the mechanisms of frailty, there is a need for improved markers to assess the prognosis of frailty.

CBC-derived inflammatory markers are composed of neutrophils, lymphocytes, platelets, and monocytes. These markers are utilized in the predictive assessment of various inflammation-related diseases (12, 13). Recent studies have shown that the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and pan-immuno-inflammatory value (PIV) can serve as indicators of inflammation associated with frailty (14, 15). Additionally, the Systemic Immunoinflammatory Index (SII), derived from CBC, has been shown to have the potential to predict the risk of frailty and mortality in middle-aged and older adult frail patients (16). However, the association between other CBC-derived inflammatory markers and the risk of frailty as well as mortality in frail patients remains incompletely assessed. Therefore, this study aimed to investigate the prognostic significance of inflammatory markers derived from complete blood counts in frail individuals.

2 Materials and methods

2.1 Study population

All participants in the National Health and Nutrition Examination Survey (NHANES) provided written consent to voluntarily participate in the study, and the NHANES study protocol was approved by the Research Ethics Review Board of the National Center for Health Statistics. We examined participant information for 10 cycles from 1999 to 2018. The study excluded participants aged below 45 years, with unavailable CBC data, and lacking follow-up information. A frailty index (FI) was utilized to categorize the remaining participants into frail participants ($n = 6{,}503$) and non-frail participants ($n = 10{,}202$), as depicted in Supplementary Figure S1.

Referring to previous related studies using the NHANES, a set of 36 variables was utilized to construct the FI, encompassing domains of disease, physical functioning, and laboratory tests (17, 18). Each variable was scored as either dichotomous (taking 0 or 1) or continuous (ranging from 0 to 1). A higher score for each item indicates greater impairment. The total score for all items is divided by 36 (the total number of items) to derive the FI. Finally, participants were categorized as non-frail (FI < 0.25) and frail (FI ≥ 0.25) according to their FI scores (19, 20). Supplementary Table S1 demonstrates the deficiency items and scoring criteria for inclusion in the FI.

2.2 Definition of CBC-derived inflammatory markers

The methods used to derive complete blood count (CBC) parameters utilize the Beckman Coulter method of counting and sizing, along with an automatic diluting and mixing device for sample processing. Indicators were computed using the following formulas: MLR = monocytes/lymphocytes, NLR = neutrophils/lymphocytes, PLR = platelets/lymphocytes, SII = platelets × neutrophils/lymphocytes, SIRI = neutrophils × monocytes/lymphocytes, PIV = neutrophils × monocytes × platelets/lymphocytes (12, 15). Since platelets are available only as absolute counts and not as percentages, to ensure the uniformity of the data, all CBC-derived inflammatory indices in this study were obtained by calculating the absolute counts of complete blood cells.

2.3 Covariates

To assess the impact of underlying factors, several covariates obtained through questionnaires and physical examinations are utilized. These variables encompass gender, age, race, education, marital status, family poverty income ratio (PIR), body mass index (BMI), smoking status, and drinking status. Race was classified as Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, or Other Race. Educational level is classified into below high school, high school, or equivalent, and above high school. Marital status is divided into two categories: married (including cohabitation with a partner) and unmarried (including widowed, separated, and divorced). Smoking status was classified into three categories: never smokers (<100 cigarettes before the survey), former smokers (>100 cigarettes before the survey, currently quitting), and current smokers (>100 cigarettes before the survey, currently smoking). Drinking status was divided into two categories: heavy drinker (≥2 drinks/day for men and ≥1 drink/day for women) and non-heavy drinker (<2 drinks/day for men and <1 drink/day for women) (21).

2.4 Assessment of mortality

This study considers all-cause mortality as the endpoint, with causes of death encompassing heart disease, malignancy, chronic lower respiratory tract disease, cerebrovascular disease, and other causes. Survival time was determined from the NHANES mobile examination center (MEC) date, with follow-up ending on December 31, 2019. Death data were acquired from the National Center for Health Statistics.

2.5 Statistical analysis

Participants' basic characteristics were expressed as median (interquartile range [IQR]) for continuous variables and as number (percentage) for categorical variables. The Kruskal-Wallis rank sum test was used for comparisons of continuous variables, and the chi-square test was used for comparisons of categorical variables. For missing data on covariates, the MissForest R package was employed to fill in.

The CBC-derived inflammatory markers were divided into quartiles, with the lowest quartile serving as the reference. Multivariate logistic regression models were employed to assess the odds ratios (OR) and 95% confidence intervals (95% CI) for the association between CBC-derived inflammatory markers and frailty. Hazard ratios (HR) and 95% confidence intervals (95% CI) for all-cause mortality in frail patients were determined using COX regression analysis. Model 2 adjusted for age, gender, and race. Model 3 adjusted for age, gender, race, marital status, education level, family poverty income ratio, body mass index, smoking status, and alcohol status. To further explore the relationship between CBC-derived inflammatory markers and the risk of death in frail patients, restricted cubic spline regression analyses were additionally conducted. The knots were placed at each exposure variable's 5th, 35th, 65th, and 95th percentiles.

Additionally, the odds ratio (OR) and 95% confidence interval (95% CI) between CBC parameters and frailty were calculated using the same method. The hazard ratio (HR) and 95% confidence interval (95% CI) between CBC parameters and death in frail patients were further analyzed. A random survival forest approach was employed to compare the predictive value of CBC-derived inflammatory markers and CBC parameters for all-cause mortality in frail patients.

Sensitivity analyses were conducted to evaluate the robustness of the results. Due to the controversy surrounding the FI critical value defining the frailty state, an alternative critical value was used to redefine the frailty state. Frailty was defined as FI > 0.21, while non-frailty was defined as FI ≤ 0.21. Consequently, the FI was reconstructed after excluding platelet counts from the original FI, and the main analyses were conducted. R (version 4.3.3) performed all analyses.

3 Results

3.1 Characteristics of the study population

Table 1 displays the baseline characteristics of middle-aged and older adult populations with frailty in NHANES 1999–2018. Among the 16,705 middle-aged and older adult participants included, the median age 67 (61.75) years, with 49.40% being male. Among them, 6,503 (38.93%) were identified as frail, the median age 69 (61.78) years, with 45.19% being male. Compared to non-frail participants, frail participants were more likely to be older, non-Hispanic black females, have lower levels of education and income, be unmarried, smoke, consume alcohol lightly, and have a higher BMI ($p < 0.05$). Neutrophil, monocyte and lymphocyte counts were significantly higher and platelet counts were significantly lower in frail patients ($p < 0.05$). Among all CBC-derived inflammatory markers, NLR, MLR, SII, SIRI, and PIV showed significant differences between frail and non-frail participants.

3.2 Association between CBC-derived inflammatory markers and frailty risk

The correlations between CBC-derived inflammatory markers and frailty are presented in Table 2. We found that NLR, MLR, SII, SIRI, and PIV showed positive associations with the risk of frailty in the crude model. The results remained statistically significant after adjusting for gender, age, and race.

In Model 2, higher levels of NLR, MLR, PLR, SII, SIRI, and PIV were found to be associated with an increased risk of frailty. Using the lowest quartile as a reference, the odds ratios (OR) and 95% confidence intervals (95% CI) at the highest quartile were NLR (OR = 1.96, 95% CI: 1.77, 2.16), MLR (OR = 1.81, 95% CI: 1.64, 2.01), PLR (OR = 1.13, 95% CI:1.03, 1.24), SII (OR = 1.56, 95% CI:1.42, 1.71), SIRI (OR = 2.03, 95% CI:1.84, 2.25), PIV (OR = 1.71, 95% CI:1.55, 1.89). Notably, lower levels of PLR were nevertheless associated with a decreased frailty risk. Compared with the lowest quartile, the odds ratios for participants in quartile 2 and quartile 3 were (OR = 0.86, 95% CI:0.78, 0.94) and (OR = 0.91, 95% CI:0.83, 0.99), respectively.

Additionally, the relationship between CBC parameters and the risk of frailty was analyzed (Supplementary Table S2). After adjusting for all confounders, we found that higher levels of neutrophil and monocyte counts were positively associated with the risk of frailty, while lymphocyte and platelet counts were negatively associated with the risk of frailty, with statistically significant results ($p < 0.05$).

3.3 Relationship between CBC-derived inflammatory markers and risk of death

The median follow-up period was 82.3 months (range: 1–249 months), with 2,697 deaths (41.47%). CBC-derived inflammatory markers (NLR, MLR, PLR, SII, SIRI, and PIV) exhibited a significantly higher risk of death in frail patients in the highest quartile compared to the lowest quartile. In model 2, the hazard ratios (HR) and 95% confidence intervals (95% CI) of death for the CBC-derived inflammatory markers were as follows: NLR (HR = 1.73, 95% CI: 1.54, 1.94), MLR (HR = 1.71, 95% CI: 1.51, 1.93), PLR (HR = 1.28, CI: 1.15, 1.43), SII (HR = 1.50, 95% CI:1.34, 1.68), SIRI (HR = 1.88, 95% CI: 1.67, 2.12), PIV (HR = 1.55, 95% CI: 1.38, 1.73) (Table 3).

CBC-derived inflammatory markers exhibited non-linear correlations with all-cause mortality in frail participants (P for non-linearity < 0.05, Figure 1). Additionally, we examined the relationship between CBC parameters and the risk of death in frail patients. We found that elevated neutrophil and monocyte counts were linked with an elevated risk of death in frail individuals, while increased lymphocyte and platelet counts were linked with a reduced risk of death in frail individuals (Supplementary Table S3).

3.4 Additional surveys of pre-frail participants

We conducted additional analyses involving 7,446 pre-frail participants (0.1 < FI < 0.25) to investigate the relationship between CBC parameters, their derived inflammatory markers, and all-cause mortality in pre-frail patients. In fully adjusted models, NLR, MLR, SII, SIRI, PIV, and neutrophil counts showed associations with an increased risk of all-cause mortality, while lymphocyte counts showed an association with a decreased risk of all-cause mortality. Their hazard ratios (HR) and 95% confidence intervals (95% CI) for death in the highest quartile compared with those in the lowest quartile of pre-frail participants were as follows: NLR (HR = 1.36, 95% CI: 1.19, 1.55), MLR (HR = 1.33, 95% CI: 1.16, 1.52), SII (HR = 1.24, 95% CI: 1.10, 1.41), SIRI (HR = 1.36, 95% CI: 1.18, 1.56), PIV (HR = 1.29, 95% CI: 1.13, 1.48), neutrophils (HR = 1.36, 95% CI: 1.19, 1.55), lymphocyte (HR = 0.80, 95% CI: 0.71, 0.91) (Table 4; Supplementary Table S4). A non-linear association was observed between all-cause mortality and CBC-derived inflammatory markers in pre-frail participants (P for non-linear <0.05, Figure 2).

TABLE 1 Baseline characteristics of middle-aged and older adult populations with frailty.

Variable	Total (N = 16,705)	Non-frail (N = 10,202)	Frail (N = 6,503)	p-value
Age (years)	67.00 (61.00, 75.00)	66.00 (61.00, 73.00)	69.00 (61.00, 78.00)	<0.001
Gender				<0.001
Male	8,252 (49.40%)	5,313 (52.08%)	2,939 (45.19%)	
Female	8,453 (50.60%)	4,889 (47.92%)	3,564 (54.81%)	
Race				<0.001
Mexican American	2,405 (14.40%)	1,477 (14.48%)	928 (14.27%)	
Other Hispanic	1,386 (8.30%)	862 (8.45%)	524 (8.06%)	
Non-Hispanic White	8,529 (51.06%)	5,284 (51.79%)	3,245 (49.90%)	
Non-Hispanic Black	3,231 (19.34%)	1,840 (18.04%)	1,391 (21.39%)	
Other race	1,154 (6.91%)	739 (7.24%)	415 (6.38%)	
Education level				<0.001
Below high school	5,501 (32.93%)	2,925 (28.67%)	2,576 (39.61%)	
High school	3,954 (23.67%)	2,382 (23.35%)	1,572 (24.17%)	
Above high school	7,250 (43.40%)	4,895 (47.98%)	2,355 (36.21%)	
Marital status				<0.001
Unmarried	6,971 (41.73%)	3,783 (37.08%)	3,188 (49.02%)	
Married	9,734 (58.27%)	6,419 (62.92%)	3,315 (50.98%)	
Family PIR	2.04 (1.18,3.62)	2.39 (1.34,4.13)	1.61 (1.01,2.75)	<0.001
Smoking status				<0.001
Never smoker	7,853 (47.01%)	5,029 (49.29%)	2,824 (43.43%)	
Former smoker	6,109 (36.57%)	3,602 (35.31%)	2,507 (38.55%)	
Current smoker	2,743 (16.42%)	1,571 (15.40%)	1,172 (18.02%)	
Drinking status				<0.001
Non-heavy drinker	13,627 (81.57%)	8,150 (79.89%)	5,477 (84.22%)	
Heavy drinker	3,078 (18.43%)	2052 (20.11%)	1,026 (15.78%)	
BMI (Kg/m^2)	28.30 (25.00, 32.36)	27.80 (24.70, 31.34)	29.40 (25.62, 34.24)	<0.001
Neutrophils (10^3/μL)	4.00 (3.10, 5.10)	3.90 (3.00, 4.80)	4.30 (3.30, 5.40)	<0.001
Monocyte (10^3/μL)	0.60 (0.40, 0.70)	0.50 (0.40, 0.70)	0.60 (0.50, 0.70)	<0.001
Lymphocyte (10^3/μL)	1.90 (1.50, 2.40)	1.90 (1.50, 2.40)	1.90 (1.50, 2.40)	0.015
Platelet (10^3/μL)	232.00 (195.00, 276.00)	233.00 (197.00, 275.00)	232.00 (190.00, 279.00)	0.028
NLR	2.06 (1.52, 2.82)	2.00 (1.48, 2.67)	2.22 (1.60, 3.08)	<0.001
MLR	0.29 (0.22, 0.38)	0.28 (0.21, 0.36)	0.30 (0.22, 0.40)	<0.001
PLR	120.69 (94.14, 156.07)	120.80 (95.29, 154.38)	120.53 (91.97, 159.09)	0.931
SII (10^3/μL)	477.83 (336.00, 684.00)	461.16 (328.25, 647.31)	508.30 (347.49, 745.32)	<0.001
SIRI (10^3/μL)	1.13 (0.76, 1.69)	1.06 (0.72, 1.56)	1.27 (0.82, 1.91)	<0.001
PIV (10^6/μL)	259.92 (166.44, 409.60)	243.42 (159.39, 381.25)	290.00 (179.25, 455.91)	<0.001

Family PIR, Family poverty income ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; SIRI, systemic inflammatory response index; SII, systemic immune-inflammation index; PIV, pan-immune inflammation value; CBC, complete blood cell. The continuous variables are expressed as medians (interquartile spacing). Categorical variables are presented as numbers (percentages). N reflects the study sample.

3.5 Prognostic value of CBC-derived inflammatory markers

We utilized the random survival forest (RSF) method to compare the predictive value of CBC parameters and their derived inflammatory markers for all-cause mortality in the frail middle-aged and older adult population. Our findings indicate that the monocyte-to-lymphocyte ratio (MLR) exhibits the highest prognostic value for predicting all-cause mortality in both frailty and pre-frailty populations (Figure 3). Therefore, MLR may serve as a valuable clinical indicator for predicting the risk of death in frail populations.

TABLE 2 Associations between CBC-derived inflammatory markers and frailty risk in middle-aged and older adult populations.

	Crude		Model 1		Model 2	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value	OR (95%CI)	*p* value
NLR						
Quartile1	1 (Reference)		1 (Reference)		1 (Reference)	
Quartile2	1.01 (0.92, 1.11)	0.8317	1.08 (0.98, 1.18)	0.1242	1.07 (0.97, 1.18)	0.1610
Quartile3	1.19 (1.09, 1.30)	0.0001	1.31 (1.19, 1.43)	<0.0001	1.26 (1.15, 1.39)	0.0001
Quartile4	1.80 (1.65, 1.96)	<0.0001	2.01 (1.84, 2.21)	<0.0001	1.96 (1.77, 2.16)	<0.0001
P for trend	1.30 (1.26, 1.35)	<0.0001	1.36 (1.31, 1.42)	<0.0001	1.34 (1.29, 1.40)	<0.0001
MLR						
Quartile1	1 (Reference)		1 (Reference)		1 (Reference)	
Quartile2	0.93 (0.85, 1.02)	0.1209	0.98 (0.89, 1.07)	0.6382	1.04 (0.94, 1.14)	0.4343
Quartile3	1.07 (0.98, 1.17)	0.1190	1.16 (1.06, 1.27)	0.0017	1.23 (1.11, 1.35)	<0.0001
Quartile4	1.48 (1.36, 1.62)	<0.0001	1.65 (1.50, 1.82)	<0.0001	1.81 (1.64, 2.01)	<0.0001
P for trend	5.00 (3.69, 6.78)	<0.0001	7.33 (5.25, 10.23)	<0.0001	9.89 (6.96, 14.04)	<0.0001
PLR						
Quartile1	1 (Reference)		1 (Reference)		1 (Reference)	
Quartile2	0.83 (0.76, 0.90)	<0.0001	0.81 (0.74, 0.89)	<0.0001	0.86 (0.78, 0.94)	0.0013
Quartile3	0.82 (0.75, 0.89)	<0.0001	0.81 (0.74, 0.88)	<0.0001	0.91 (0.83, 0.99)	0.0499
Quartile4	0.99 (0.91, 1.08)	0.8343	0.95 (0.87, 1.04)	0.2517	1.13 (1.03, 1.24)	0.0115
P for trend	1.00 (1.00, 1.00)	0.5243	1.00 (1.00, 1.00)	0.7798	1.00 (1.00, 1.00)	0.0005
SII						
Quartile1	1 (Reference)		1 (Reference)		1 (Reference)	
Quartile2	0.95 (0.87, 1.04)	0.2654	0.98 (0.90, 1.08)	0.7040	0.95 (0.86, 1.05)	0.2928
Quartile3	1.10 (1.01, 1.20)	0.0312	1.15 (1.05, 1.26)	0.0033	1.09 (0.99, 1.20)	0.0646
Quartile4	1.57 (1.44, 1.72)	<0.0001	1.66 (1.51, 1.82)	<0.0001	1.56 (1.42, 1.71)	<0.0001
P for trend	1.00 (1.00, 1.00)	<0.0001	1.00 (1.00, 1.00)	<0.0001	1.00 (1.00, 1.00)	<0.0001
SIRI						
Quartile1	1 (Reference)		1 (Reference)		1 (Reference)	
Quartile2	1.03 (0.94, 1.13)	0.4997	1.12 (1.02, 1.23)	0.0143	1.06 (0.96, 1.17)	0.2503
Quartile3	1.42 (1.30, 1.55)	<0.0001	1.62 (1.48, 1.78)	<0.0001	1.49 (1.35, 1.64)	<0.0001
Quartile4	1.95 (1.79, 2.13)	<0.0001	2.32 (2.11, 2.55)	<0.0001	2.03 (1.84, 2.25)	<0.0001
P for trend	1.51 (1.44, 1.59)	<0.0001	1.65 (1.57, 1.74)	<0.0001	1.54 (1.46, 1.63)	<0.0001
PIV						
Quartile1	1 (Reference)		1 (Reference)		1 (Reference)	
Quartile2	1.04 (0.95, 1.14)	0.3685	1.09 (1.00, 1.20)	0.0614	1.03 (0.94, 1.14)	0.4839
Quartile3	1.30 (1.19, 1.42)	<0.0001	1.40 (1.27, 1.53)	<0.0001	1.28 (1.17, 1.41)	<0.0001
Quartile4	1.76 (1.62, 1.93)	<0.0001	1.94 (1.77, 2.13)	<0.0001	1.71 (1.55, 1.89)	<0.0001
P for trend	1.00 (1.00, 1.00)	<0.0001	1.00 (1.00, 1.00)	<0.0001	1.00 (1.00, 1.00)	<0.0001

Data are presented as OR (95% CI). Crude adjusts for none. Model 1 adjust for age, gender, and race. Model 2 adjust for Model 1 plus marital status, education level, family poverty income ratio, body mass index, smoking status, and alcohol status.

3.6 Sensitivity analyses

After we adjusted the FI threshold and redefined frailty, the association of CBC parameters and their derived inflammatory markers with the risk of frailty and death remained unchanged (Supplementary Tables S5, S6). A new FI was constructed after excluding platelet counts, and reclassify the frail population. We observed similar results in the adjusted full model (Supplementary Tables S7, S8).

4 Discussion

CBC-derived inflammatory markers integrate multiple parameters, which have the advantage of their ability to capture the complex interactions between different cell types in the blood, which is more informative than any single measurement. Therefore, in this study of a nationally representative population in the United States, we focused on the relationship of CBC-derived inflammatory

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TABLE 3 Associations of CBC-derived inflammatory markers with mortality in middle-aged and older adult populations with frailty.

	Crude		Model 1		Model 2	
	HR (95%CI)	*p* value	HR (95%CI)	*p* value	HR (95%CI)	*p* value
NLR						
Quartile1	1 (Reference)		1 (Reference)		1 (Reference)	
Quartile2	1.21 (1.08, 1.37)	0.0015	1.07 (0.95, 1.20)	0.2915	1.06 (0.94, 1.19)	0.3791
Quartile3	1.51 (1.35, 1.70)	<0.0001	1.22 (1.08, 1.37)	0.0010	1.22 (1.08, 1.37)	0.0010
Quartile4	2.34 (2.09, 2.61)	<0.0001	1.72 (1.53, 1.93)	<0.0001	1.73 (1.54, 1.94)	<0.0001
P for trend	1.38 (1.32, 1.43)	<0.0001	1.24 (1.19, 1.29)	<0.0001	1.24 (1.20, 1.29)	<0.0001
MLR						
Quartile1	1 (Reference)		1 (Reference)		1 (Reference)	
Quartile2	1.23 (1.09, 1.39)	0.0007	1.00 (0.88, 1.13)	0.9609	1.03 (0.91, 1.16)	0.6923
Quartile3	1.78 (1.58, 2.00)	<0.0001	1.27 (1.12, 1.43)	<0.0001	1.33 (1.17, 1.50)	<0.0001
Quartile4	2.76 (2.47, 3.09)	<0.0001	1.61 (1.43, 1.82)	<0.0001	1.71 (1.51, 1.93)	<0.0001
P for trend	24.01 (17.66, 32.65)	<0.0001	5.26 (3.77, 7.34)	<0.0001	6.10 (4.37, 8.53)	<0.0001
PLR						
Quartile1	1 (Reference)		1 (Reference)		1 (Reference)	
Quartile2	1.01 (0.90, 1.13)	0.9197	0.97 (0.87, 1.09)	0.6130	0.99 (0.89, 1.12)	0.9188
Quartile3	1.07 (0.96, 1.20)	0.2281	1.00 (0.89, 1.11)	0.9320	1.05 (0.94, 1.18)	0.3950
Quartile4	1.47 (1.32, 1.63)	<0.0001	1.23 (1.11, 1.37)	0.0002	1.28 (1.15, 1.43)	<0.0001
P for trend	1.00 (1.00, 1.00)	<0.0001	1.00 (1.00, 1.00)	<0.0001	1.00 (1.00, 1.00)	<0.0001
SII						
Quartile1	1 (Reference)		1 (Reference)		1 (Reference)	
Quartile2	1.17 (1.04, 1.31)	0.0078	1.10 (0.98, 1.24)	0.1041	1.10 (0.97, 1.23)	0.1266
Quartile3	1.22 (1.09, 1.37)	0.0005	1.17 (1.04, 1.31)	0.0085	1.16 (1.03, 1.30)	0.0119
Quartile4	1.64 (1.47, 1.83)	<0.0001	1.52 (1.36, 1.69)	<0.0001	1.50 (1.34, 1.68)	<0.0001
P for trend	1.00 (1.00, 1.00)	<0.0001	1.00 (1.00, 1.00)	<0.0001	1.00 (1.00, 1.00)	<0.0001
SIRI						
Quartile1	1 (Reference)		1 (Reference)		1 (Reference)	
Quartile2	1.43 (1.27, 1.61)	<0.0001	1.29 (1.15, 1.46)	<0.0001	1.25 (1.11, 1.41)	0.0002
Quartile3	1.61 (1.44, 1.81)	<0.0001	1.30 (1.15, 1.46)	<0.0001	1.28 (1.14, 1.45)	<0.0001
Quartile4	2.56 (2.29, 2.86)	<0.0001	1.92 (1.71, 2.16)	<0.0001	1.88 (1.67, 2.12)	<0.0001
P for trend	1.56 (1.48, 1.64)	<0.0001	1.36 (1.29, 1.43)	<0.0001	1.35 (1.28, 1.43)	<0.0001
PIV						
Quartile1	1 (Reference)		1 (Reference)		1 (Reference)	
Quartile2	1.14 (1.01, 1.28)	0.0301	1.11 (0.98, 1.24)	0.0908	1.10 (0.98, 1.23)	0.1139
Quartile3	1.30 (1.16, 1.46)	<0.0001	1.22 (1.08, 1.36)	0.0009	1.20 (1.07, 1.35)	0.0015
Quartile4	1.77 (1.59, 1.97)	<0.0001	1.58 (1.41, 1.76)	<0.0001	1.55 (1.38, 1.73)	<0.0001
P for trend	1.00 (1.00, 1.00)	<0.0001	1.00 (1.00, 1.00)	<0.0001	1.00 (1.00, 1.00)	<0.0001

Data are presented as HR (95% CI). Crude adjusts for none. Model 1 adjust for age, gender, and race. Model 2 adjust for Model 1 plus marital status, education level, family poverty income ratio, body mass index, smoking status, and alcohol status.

markers to the risk of frailty and mortality in middle-aged and older adults. We found that elevated levels of NLR, MLR, PLR, SII, SIRI, and PIV were positively associated with frailty risk, whereas lower levels of PLR were negatively associated with frailty risk. Among frail patients, higher levels of NLR, MLR, PLR, SII, SIRI, and PIV were found to be associated with an increased risk of death. Additionally, the results of our survival prediction modeling analyses indicated that MLR was the most predictive inflammatory marker for mortality risk in this population. These findings suggest that CBC-derived inflammatory markers, especially MLR, may serve as useful clinical indicators for assessing mortality risk in frail patients. In conclusion, our study demonstrates the potential utility of CBC-derived inflammatory markers as indicators for assessing both frailty and mortality risk.

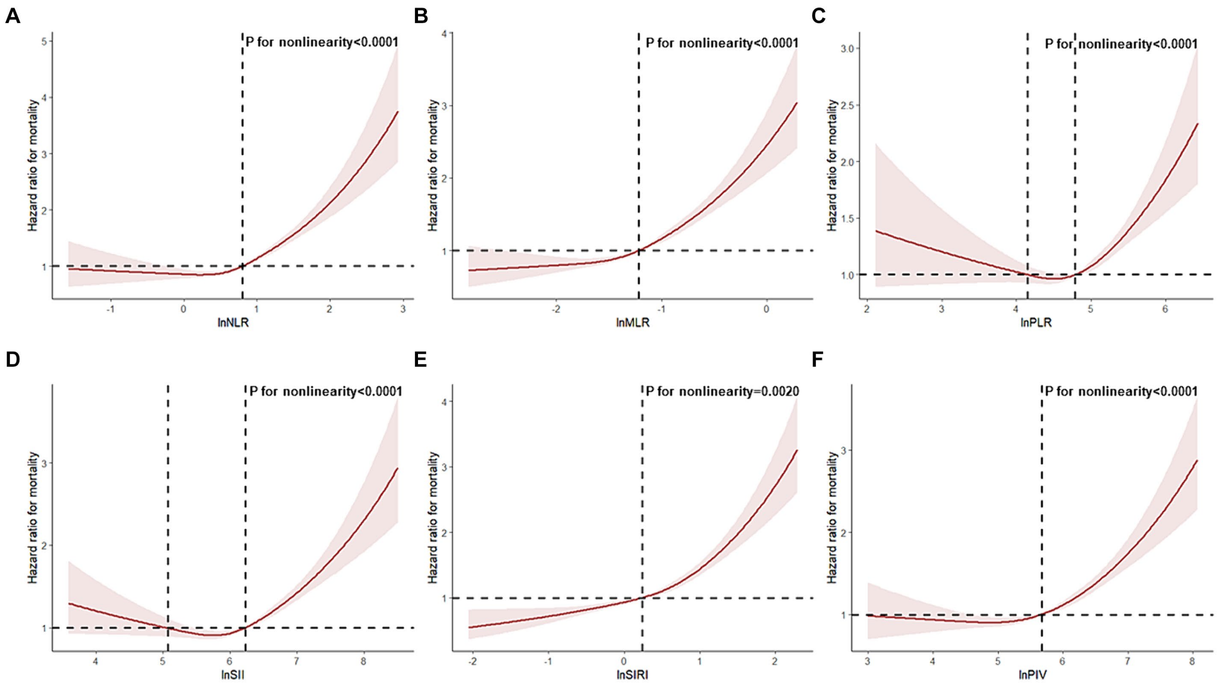

FIGURE 1
Restricted cubic spline analyses the association of complete blood cell count (CBC)-derived indicators (**A**: NLR; **B**: MLR; **C**: PLR; **D**: SII; **E**: SIRI; **F**: PIV) with all-cause mortality in middle-aged and older adult populations with frailty. Adjusted for adjusted for age, gender, race, marital status, education level, family poverty income ratio, body mass index, smoking status, and alcohol status.

The development of frailty is linked to various physiological alterations, including chronic inflammation and age-related changes (22). Previously, several studies have demonstrated that levels of inflammatory markers such as IL-6, CRP (C-reactive protein), and TNF-α are markedly elevated in older and frail individuals (23–25). Recently, several studies have investigated the association between CBC-derived inflammatory markers and frailty, finding significant associations with NLR, PLR, SII, and PIV (15, 26, 27). However, most of these studies had small sample sizes and focused on individuals with specific diseases and hospitalizations. This study targeted a broad population to comprehensively assess the association of multiple CBC-derived inflammatory markers with frailty risk and prognosis.

In our investigation, we observed a u-shaped association between PLR and SII levels and mortality in frail patients. This suggests that elevated and reduced levels of PLR and SII may both increase the risk of death. However, in the non-linear association between NLR, MLR, SIRI, and PIV and mortality, an increased risk of death was observed only at high levels. These results suggest that excessive immune-inflammatory responses in frail populations pose significant health risks. Research has indicated that excessive inflammation promotes chronic inflammation and may serve as a potential etiologic factor of sarcopenia associated with frailty (28, 29). Chronic inflammation contributes to cardiovascular risk events and is a major driver of cancer-related frailty (30, 31). Considering the risk of an inflammatory state, maintaining appropriate levels of CBC-derived inflammatory markers is crucial for reducing mortality in frail patients.

In our additional analysis focused on pre-frail patients, we found that elevated levels of NLR, MLR, SII, SIRI, PIV, and neutrophil counts were associated with an elevated risk of all-cause mortality, while increased levels of lymphocyte counts were associated with a reduced risk of all-cause mortality. We observed a u-shaped association between all six CBC-derived inflammatory markers and the risk of all-cause mortality in pre-frail participants. In contrast to the frail population, pre-frail participants with excessively low levels of NLR, MLR, SIRI, and PIV may also face an increased risk of mortality. Notably, excessive levels of CBC-derived inflammatory markers may have a more profound effect on increased mortality in frail patients compared to pre-frail patients.

Among the four CBC parameters and six CBC-derived markers of inflammation, MLR stands out as the most valuable predictor of the risk of death in both frailty and pre-frail individuals. MLR is the ratio of monocytes to lymphocytes; elevated MLR indicates either an increase in monocytes or a decrease in lymphocytes. Research has shown that monocytes and macrophages mediate molecular inflammatory pathways in frail patients (32, 33). Additionally, frailty is associated with elevated monocyte counts (34). Frailty is associated with the aging of multiple physiological structures and functions, particularly immune senescence (35). Changes in lymphocyte numbers and function characterize immune senescence and contribute to the development of frailty (36). A study found a negative correlation between lymphocyte counts and frailty and that lymphocyte counts were lower in frail older adults (37). This is likely because the thymus undergoes atrophy due to aging, resulting in reduced lymphocyte production and functional changes (38). Thus, elevated MLR reflects an increased inflammatory response and the progression of frailty, indicating an elevated risk of death in frail patients (39). These findings suggest that MLR may be associated with the underlying biological mechanisms of frailty. Therefore, MLR is valuable for predicting the risk of death in frail patients.

TABLE 4 Associations of CBC-derived inflammatory markers with mortality in middle-aged and older adult populations with pre-frailty.

	Crude		Model 1		Model 2	
	HR (95%CI)	*p* value	HR (95%CI)	*p* value	HR (95%CI)	*p* value
NLR						
Quartile1	1 (Reference)		1 (Reference)		1 (Reference)	
Quartile2	1.02 (0.89, 1.17)	0.7895	0.96 (0.84, 1.11)	0.6099	0.97 (0.84, 1.12)	0.6582
Quartile3	1.31 (1.15, 1.49)	<0.0001	1.12 (0.98, 1.28)	0.0855	1.10 (0.96, 1.26)	0.1553
Quartile4	1.92 (1.70, 2.18)	<0.0001	1.39 (1.22, 1.59)	<0.0001	1.36 (1.19, 1.55)	<0.0001
P for trend	1.38 (1.31, 1.45)	<0.0001	1.19 (1.13, 1.25)	<0.0001	1.17 (1.11, 1.24)	<0.0001
MLR						
Quartile1	1 (Reference)		1 (Reference)		1 (Reference)	
Quartile2	1.17 (1.02, 1.34)	0.0291	0.98 (0.85, 1.13)	0.8080	1.01 (0.88, 1.16)	0.9051
Quartile3	1.49 (1.31, 1.70)	<0.0001	1.03 (0.90, 1.18)	0.6583	1.07 (0.93, 1.22)	0.3542
Quartile4	2.35 (2.08, 2.67)	<0.0001	1.29 (1.12, 1.47)	0.0003	1.33 (1.16, 1.52)	<0.0001
P for trend	28.11 (18.18, 43.47)	<0.0001	3.01 (1.87, 4.86)	<0.0001	3.27 (2.03, 5.27)	<0.0001
PLR						
Quartile1	1 (Reference)		1 (Reference)		1 (Reference)	
Quartile2	0.86 (0.75, 0.98)	0.0229	0.88 (0.77, 1.00)	0.0491	0.89 (0.78, 1.01)	0.0806
Quartile3	0.89 (0.78, 1.01)	0.0714	0.87 (0.76, 0.99)	0.0315	0.90 (0.79, 1.02)	0.0987
Quartile4	1.18 (1.05, 1.33)	0.0061	1.03 (0.91, 1.16)	0.6578	1.07 (0.95, 1.21)	0.2656
P for trend	1.00 (1.00, 1.00)	<0.0001	1.00 (1.00, 1.00)	0.2009	1.00 (1.00, 1.00)	0.0520
SII						
Quartile1	1 (Reference)		1 (Reference)		1 (Reference)	
Quartile2	0.90 (0.79, 1.04)	0.1471	0.96 (0.84, 1.11)	0.5939	0.94 (0.82, 1.07)	0.3548
Quartile3	1.11 (0.98, 1.26)	0.1083	1.08 (0.95, 1.24)	0.2322	1.04 (0.91, 1.18)	0.6028
Quartile4	1.47 (1.30, 1.66)	<0.0001	1.30 (1.15, 1.47)	<0.0001	1.24 (1.10, 1.41)	0.0007
P for trend	1.00 (1.00, 1.00)	<0.0001	1.00 (1.00, 1.00)	<0.0001	1.00 (1.00, 1.00)	<0.0001
SIRI						
Quartile1	1 (Reference)		1 (Reference)		1 (Reference)	
Quartile2	1.25 (1.09, 1.44)	0.0013	1.04 (0.90, 1.19)	0.6022	1.04 (0.90, 1.19)	0.6074
Quartile3	1.53 (1.34, 1.74)	<0.0001	1.19 (1.04, 1.37)	0.0138	1.16 (1.01, 1.34)	0.0323
Quartile4	2.25 (1.98, 2.55)	<0.0001	1.42 (1.24, 1.63)	<0.0001	1.36 (1.18, 1.56)	<0.0001
P for trend	1.62 (1.51, 1.74)	<0.0001	1.26 (1.17, 1.35)	<0.0001	1.22 (1.13, 1.31)	<0.0001
PIV						
Quartile1	1 (Reference)		1 (Reference)		1 (Reference)	
Quartile2	1.15 (1.00, 1.32)	0.0458	1.06 (0.92, 1.22)	0.4263	1.02 (0.89, 1.18)	0.7343
Quartile3	1.43 (1.25, 1.63)	<0.0001	1.20 (1.05, 1.38)	0.0083	1.16 (1.01, 1.33)	0.0372
Quartile4	1.83 (1.61, 2.08)	<0.0001	1.40 (1.22, 1.60)	<0.0001	1.29 (1.13, 1.48)	0.0002
P for trend	1.00 (1.00, 1.00)	<0.0001	1.00 (1.00, 1.00)	<0.0001	1.00 (1.00, 1.00)	<0.0001

Data are presented as HR (95% CI). Crude adjusts for none. Model 1 adjust for age, gender, and race. Model 2 adjust for Model 1 plus marital status, education level, family poverty income ratio, body mass index, smoking status, and alcohol status.

Our research has several strengths. First, our study population is derived from a large, nationally representative health survey, resulting in findings that are more reliable and representative. Second, CBC-derived inflammatory markers comprise multiple parameters, potentially offering a more comprehensive assessment of immune and inflammatory responses than a single indicator. Third, we employed a restricted cubic spline to investigate the nonlinear relationship between CBC-derived inflammatory markers and mortality risk. Fourth, we conducted several sensitivity analyses to mitigate bias resulting from constructing FI and determining thresholds. Finally, we examined the association of multiple CBC parameters and their derived inflammatory markers with the risk of frailty and mortality. Using the RSF method, we identified MLR as the most valuable predictor of all-cause mortality in the frail middle-aged and older adult population.

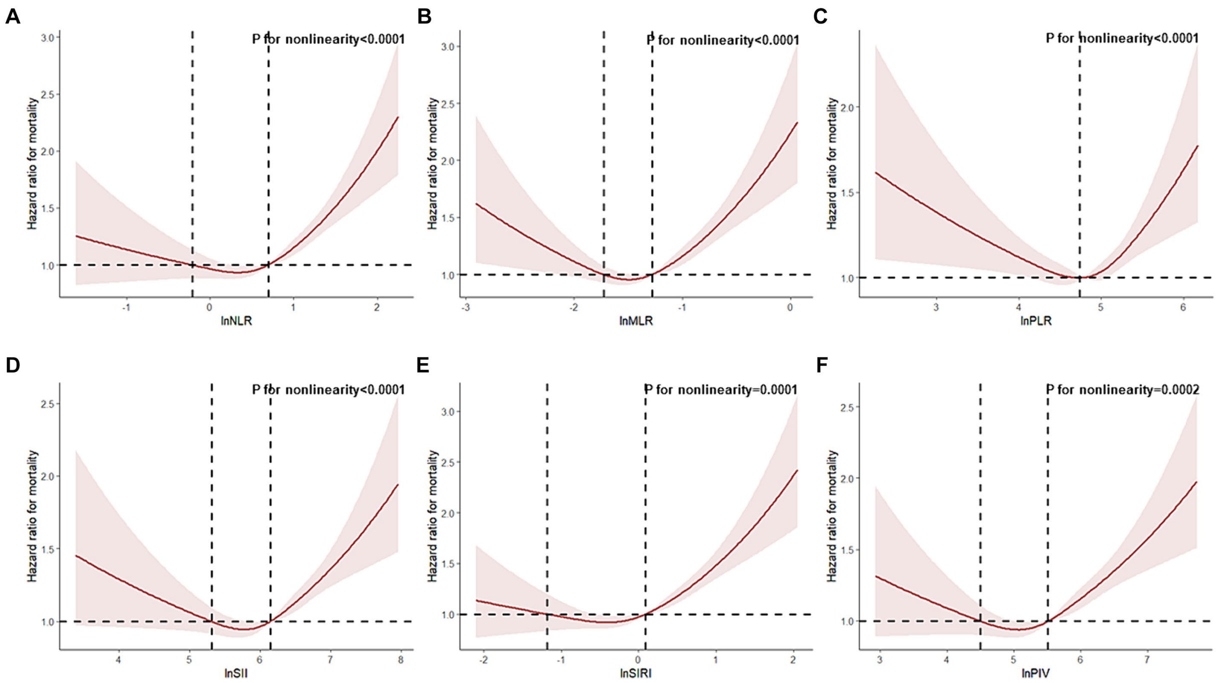

FIGURE 2
Restricted cubic spline analyses the association of complete blood cell count (CBC)-derived indicators (**A**: NLR; **B**: MLR; **C**: PLR; **D**: SII; **E**: SIRI; **F**: PIV) with all-cause mortality in middle-aged and older adult populations with pre-frailty. Adjusted for adjusted for age, gender, race, marital status, education level, family poverty income ratio, body mass index, smoking status, and alcohol status.

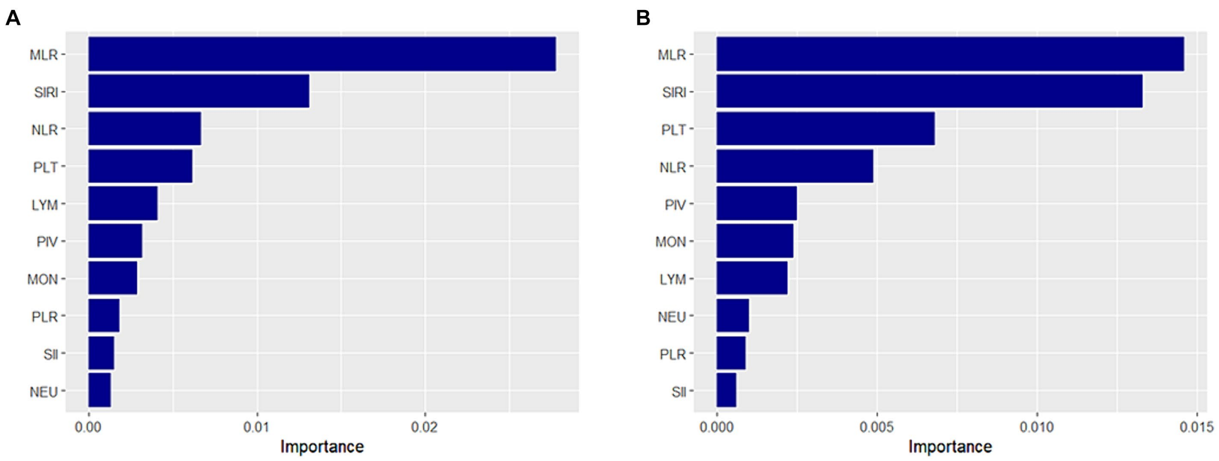

FIGURE 3
Prognostic value of complete blood cell count (CBC)-derived indicators. A random survival forest method was used to compare the value of CBC parameters and CBC-derived inflammatory markers in predicting all-cause mortality in middle-aged and older adult populations with frailty **(A)** and pre-frailty **(B)**.

However, this study also has several limitations. First, the construction of the frailty index lacks uniformity, and the threshold values for frailty are arbitrarily determined, potentially biasing the selection of frail populations. Second, although this study adjusted for multiple confounders, potential confounding factors may still exist. Third, the use of one-time CBC parameters to calculate CBC-derived inflammatory markers may lead to bias. Fourth, we failed to account for differences in the nonlinear relationship between CBC-derived inflammatory markers and the risk of death in frail and pre-frail populations.

5 Conclusion

The findings of this study indicate that elevated levels of six CBC-derived inflammatory markers are correlated with increased all-cause mortality in middle-aged and older adult individuals with frailty. Elevated levels of MLR, NLR, SIRI, SII, and PIV were linked to increased all-cause mortality in middle-aged and older adult individuals in a pre-frail state. MLR aids in identifying high-risk individuals in frail populations and is a cost-effective and readily accessible marker. Our study offers further evidence supporting the potential utility of CBC-derived inflammatory markers in predicting frailty prognosis.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://www.cdc.gov/nchs/nhanes.

Ethics statement

The studies involving humans were approved by NCHS Research Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YT: Writing – original draft, Writing – review & editing. YZ: Writing – original draft, Writing – review & editing. WS: Writing – review & editing. TZ: Writing – review & editing. ZX: Writing – review & editing. LJ: Writing – review & editing. LL: Writing – review & editing. DL: Writing – review & editing. QW: Writing – review & editing.

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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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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2024.1427546/full#supplementary-material

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Dual trajectories of social participation and frailty in Chinese older adults: a longitudinal study based on CLHLS from 2008 to 2018

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Introduction: This study aimed to identify the dual trajectories of social participation (SP) and frailty index (FI) among Chinese older adults, and investigate common influential factors of both trajectories.

Methods: Utilizing data from the Chinese Longitudinal Healthy Longevity Survey (CLHLS) 2008–2018 surveys, 1,645 individuals were analyzed. A group-based dual trajectory model and logistic regression were used to examine trajectories, their interrelations and shared influencing factors.

Results: This study identified three SP, two FI trajectories and six distinct sub-groups of individuals. The study confirmed a long-term, interrelated relationship between two outcomes and identified some common factors. Compared to participants in the lower SP trajectory, those who followed the middle SP trajectory and higher SP trajectory had increased probabilities of belonging to the slow-growth FI trajectory (90.28 and 99.71%, respectively). And the participants in the slow-growth FI exhibited higher probabilities of belonging to the middle SP and the higher SP trajectory (37.64 and 25.34% higher, respectively) compared with those in the rapid-growth FI trajectory. Age, marital status, and drinking status were mutual factors associated with the dual trajectories.

Discussion: The results showed significant associations between higher levels of frailty and lower levels of social participation. Related intervention policies should consider the dual trajectories and the common factors that underlie these trajectories of SP and FI.

KEYWORDS

social participation, frailty, aged, longitudinal studies, group-based trajectory modeling

1 Introduction

China has become an ageing society with the largest aging population globally (1). Achieving a healthy ageing society requires prioritizing the health needs of older persons and establishing optimal preparations for health care. Frailty, a critical indicator of treatment needs and its research have increased rapidly in Asia (2–4). It is strongly associated with the occurrence of depression (5), dementia (6), as well as overall and cause-specific mortality (7). Given the dynamic nature and varied developmental pathways of frailty (8), understanding its longitudinal change and influencing factors is essential for effective and timely intervention aimed at reducing risk. Several studies in Korea and Japan have explored the diverse trajectories of frailty among older adults, revealing the influence of factors like educational attainment, smoking, alcohol consumption, sleep, and marital status, while older adults who developed frailty and who remained frail were more likely to have cognitive impairment (9–12).

Social participation (SP), a central component of the World Health Organization's approach to achieving healthy ageing (13), significantly impacts the mental and physical well-being of older adults (14) such as reducing the likelihood of dementia episodes (15) and depression (16). SP may follow distinct paths among different subgroups of older adults. Kawai et al. observed two trajectory patterns of the social interaction scores using large-scale longitudinal data from a cohort of older adults in Japan (17), and similar findings have been reported in China (18). Several studies in Asian countries have shown that age, sex, activities of daily living (ADL), having a chronic disease have an impact on social participation (17, 19, 20). Moreover, a study from Iran reported that educational level, income level and marital status influence the social participation of older people.

The majority of the current investigations have revealed a unidirectional relationship between social participation and frailty. An observational study conducted among older people in Japan revealed that ongoing engagement in social activities may lower the risk of frailty, specifically in oral function and depressive mood (21). Xie et al. (22) showed that promoting diverse forms of social interaction is a promising strategy to mitigating the burden associated with frailty in older individuals. Furthermore, embracing healthy habits and actively participating in social activities can help counteract the detrimental effects of declining health on overall life expectancy (23). While both cross-sectional and lagged social participation-frailty relationships have been observed (24), research exploring the potential direction of frailty level on social participation among Chinese older people remains limited.

Both frailty and social engagement status are instable that influence each other. Notably, the bidirectional, dynamic relationship between social participation and frailty remained under-explored in developing nations (25, 26). Hence, investigating the potential correlation between their paths and protective and risk variables can yield insights for healthcare and social services for older adults.

The current study investigated the trajectories of social participation and frailty index in a cohort of older Chinese adults from 2008 and 2018. We conducted a comprehensive analysis of the long-term and interconnected patterns between SP (social participation) and FI (frailty index) trajectories over a certain period. Additionally, we defined distinct sub-groups based on the combined trajectories of SP and FI. Ultimately, we examined the factors influencing the later dual trajectories of SP and FI. Figure 1 illustrates our conceptual framework and three hypotheses derived from the above review:

> *H1:* We hypothesized that there will be distinct trajectories of both social participation and frailty index. Lower SP trajectories is associated with higher FI trajectories within each subgroup, and vice versa.
>
> *H2:* We hypothesized the existence of a minimum of four sub-groups, determined by the dual trajectories.
>
> *H3:* We hypothesized that age, education, marital status, co-residence, economic income and drinking status were shared risk factors that could impact the dual trajectories of SP and FI among older adults.

2 Materials and methods

2.1 Data and participants

The Chinese Longitudinal Healthy Longevity Survey (CLHLS) is a nationwide repeated cross-sectional survey applying a multistage, stratified cluster sampling between 1998 and 2018 which covers 631 randomly selected cities of 23 provinces in mainland China. The survey began in 1998, with subsequent surveys being conducted every 3–4 years. Ethical approval for the study was obtained from the ethics committees of Peking University. All participants or their proxy respondents provided informed consent.

Data from four waves of CLHLS from 2008 to 2018 were utilized in our study. Firstly, participants older than 65 years old at the 2008 baseline were included, following the definition of older adults (27). Of those, we excluded individuals with missing in 2011/2014/2018 wave, missing SP, missing frailty, missing covariates. Finally, we included 1,645 individuals for complete cases analysis. More details on participant inclusion and exclusion can be found in Supplementary Figure S1.

2.2 Measures

2.2.1 Assessment of social participation

The assessment of social involvement required utilizing a thorough questionnaire consisting of 10 items encompassing cognitive, physical, and social activities. This questionnaire has been widely utilized and has demonstrated its validity (25, 28). House work, growing vegetables or doing other field work, garden work, reading newspapers or books, raise domestic animals or pets, playing cards or mah-jongg, watching tv or listening to radio, participating in some social activities, traveling and exercising are all part of these activities. The specifics about the selection and allocation of the indicators can be found in Supplementary Table S1. The social involvement indicator has a cumulative score of 34, with higher scores indicating greater levels of social participation.

2.2.2 Assessment of frailty

The phenotypic approach and the frailty index (FI) are the predominant methodologies employed for evaluating an individual's frailty status. The frailty level of participants was determined using the Frailty Index (FI) based on the Rockwood technique in this study (29). There exists 38 variables concerning chronic diseases, cognitive and

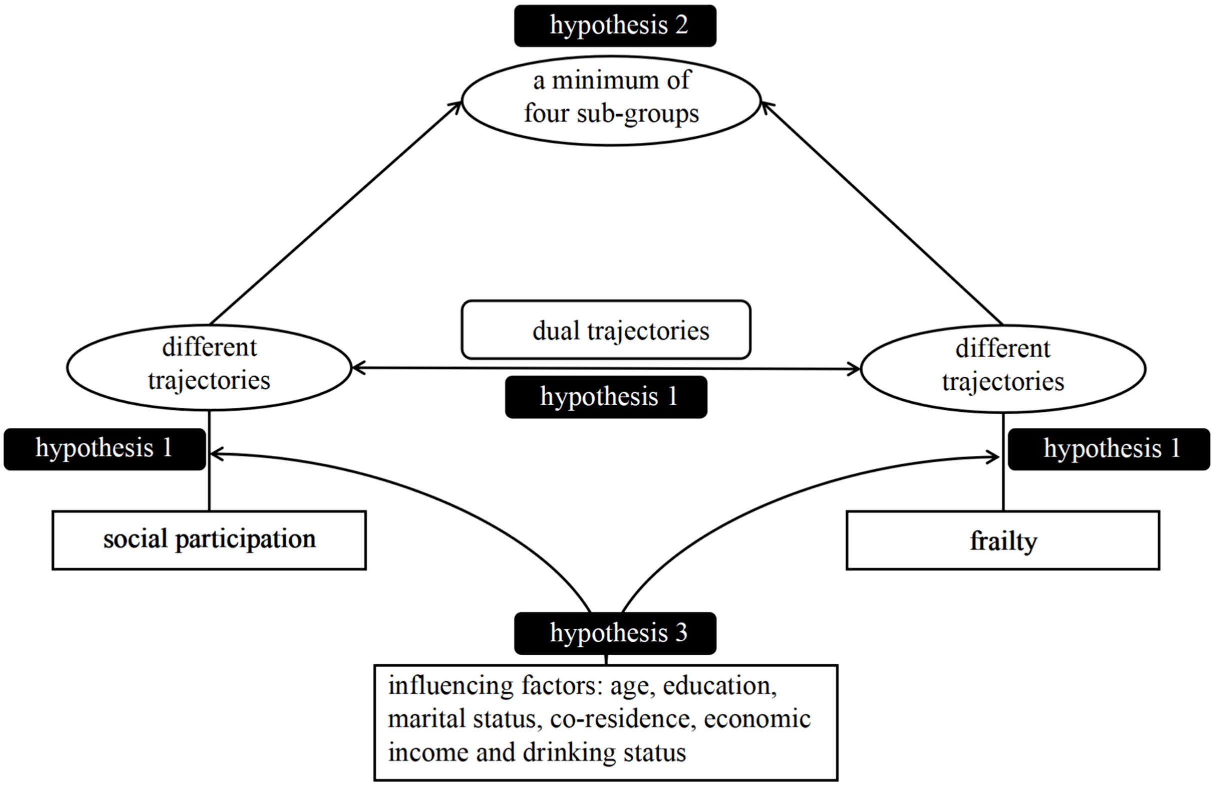

FIGURE 1
Conceptual framework of hypothetical model.

physical function, activities of daily life, visual and hearing status, as well as the number of illnesses suffered in the past 2 years. Of those, we utilized the validated Chinese version of the Mini Mental State Examination (MMSE) to measure cognitive function (30). The score of each deficit was quantified into the 0 to 1 interval that was shown in Supplementary Table S2. Particularly, if the number of illnesses suffered in the past 2 years is more than 2, the variable has a score of 2. This method of calculation was established based on earlier studies conducted by CLHLS, and its validity and reliability has been demonstrated in these studies (31, 32). Reliability and validity tests of the FI and MMSE questionnaires were also conducted, using Cronbach's alpha and KMO values as measures, respectively. The baseline data was employed for these calculations, revealing a Cronbach's alpha value of 0.785 and a KMO value of 0.838 for FI. As for MMSE, both the Cronbach's alpha value and the KMO value stood at 0.920. Consequently, the reliability and validity of the questionnaire are acceptable. In our study, each participant's total FI score, ranging from 0 to 1, was determined by the ratio of the total sum of scores to the number of deficits included. A Frailty Index (FI) with less than 30 elements was classified as missing (33), while a FI more than 0.25 indicates frailty (34).

2.2.3 Covariates

Building upon the existing extensive literature concerning the social engagement patterns and vulnerability of older Chinese individuals as previously documented (9–12, 17–20, 25, 32, 35), various covariates were assessed at baseline, encompassing sociodemographic characteristics [age, gender, residence, education, marital status, economic income], lifestyle behaviors [drinking, smoking, sleep duration], co-residence (alone, not alone). The age groups were categorized into 65–75 and ≥ 75 years and residence were defined as city and non-city. The levels of education were specified as uneducated (never being educated), primary school (being educated for 1–6 years), and middle school or above (being educated for 7 years or more). Current marital status included married, separation after marriage (separated, divorced, widowed) and unmarried. Low economic income was defined as the total household income of the previous year falling below the third quartile of all participants'. The smoking and drinking habits were categorized as never, previous, and current. We defined sleep as normal (5–10 h/day and no sleep disorder), excessive (>10 h/day) and insufficient (<5 h/day or having sleep disorder) (35).

2.2.4 Analytic strategy

Similar to earlier research (18, 36), our analytical approach comprised three main components. Initially, group-based trajectory modeling (GBTM) was employed to ascertain trajectory patterns for two outcomes. Furthermore, both binary and multivariate logistic regression models were utilized to investigate the shared factors influencing their trajectories. Furthermore, a dual-trajectory model was employed to establish a connection between the complete longitudinal progression of social participation and frailty.

GBTM represents a specific implementation of finite mixture models that relies on non-parametric and semi-parametric statistical technique. This model assumes the existence of heterogeneity and explore the development trends of different groups over time. The optimal trajectory groups are expected to exhibit the following characteristics to the greatest extent possible (37): the smaller absolute Bayesian Information Criteria (BIC) value; the bigger change in BIC; the value of the Average Posterior Probability (APP) > 0.7; Odds of Correct Classification (OCC) > 5; Proportions per class≥5%; Relative entropy (E_k) is close to 1; parsimony; interpretability of groups. The "PROC TRAJ" command of SAS 9.4 was used.

The dual trajectory model offers a clear and simply comprehensive statistical description of the developmental connections between two desired outcomes. It can further be employed to uncover hidden groups of individuals who follow similar patterns across two indicators of interest (37). The dual model also offers the conditional and joint probabilities of belonging to each trajectory group, illustrating the combination or interaction between these two developmental variables (38). Additionally, the quantity of optional trajectory groups in the dual model commonly corresponds to those identified in the univariate models (38).

A two-tailed p value < 0.05 was used to determine statistical significance. The analyses were performed using SAS 9.4 version and SPSS 27 for Windows.

3 Results

3.1 Sample characteristics at baseline

Supplementary Table S3 shows the characteristics of the study sample. A total of 1,645 older adults had the mean (standard deviation, SD) of 74.73 (7.45) years at baseline, of which 48% were men and 52% were women. 13.71 (5.60) and 0.12 (0.06) were separately the mean (SD) social participation score and the mean (SD) FI score. Approximately 13% participants lived in the city but 87% did not. There were 59% of individuals with no education and 38% of them had primary education. Nearly 59% older adults among the participants were in current married status and 40% had separated after marriage. Most of them did not reside alone (85%), had low or middle economic income (75%), never drank (64%), never smoked (62%), and had normal sleep (80%).

3.2 Trajectories of social participation among older adults

We used four sequential models, varying from two-class to five-class models, with zero-order, linear, and quadratic specifications to determine the most appropriate model. The fitness information of different models is displayed in Supplementary Tables S4, S5. While the absolute BIC values of the four-class and five-class models were lower than that of the three-class model, the proportion of one group in the four-class and five-class models did not meet the 5% criterion. Consequently, considering the model's interpretability and simplicity, we opted for the three-class model as the most suitable base model. Figure 2 illustrates the three paths of social engagement. As time progressed, it was observed that 15.8% of the older individuals exhibited a lower SP with a declining trajectory, whereas 64.5% displayed a middle SP with a declining trajectory, and 19.6% showed a higher SP with a declining trajectory.

3.3 Multivariate logistic regression of SP trajectories

The results of the multivariate logistic regression analysis, as presented in Table 1, indicate that individuals aged over 75 years demonstrated a reduced likelihood of 71.1 and 85.1% to be part of the middle SP group and higher SP group, respectively, when compared to the middle SP group. Individuals residing in either urban or rural areas exhibited considerably reduced likelihood of engaging in medium and higher levels of social participation. When comparing older people without education to those being educated for 1 ~ 6 years, the probabilities of belonging to the higher SP group were 3.17 times greater. And for those who received education of 7 years or more, the probability of belonging to the higher SP group was 6.809 times greater. Divorced older adults had a 49% lower probability of being in the medium SP trajectory and a 55.2% lower probability of being in the higher SP trajectory compared to the lower SP trajectory. Unmarried older adults were 77.7% less likely to be in the middle SP group than in the lower SP group. Participants who did not live alone were unlikely to be in the higher SP, in contrast with the lower SP. Middle or high income, drinking at present made older adults 107 and 85.7% more likely to be in the higher SP groups, respectively, than in the lower SP group.

3.4 Trajectories of frailty index among older adults

Model fitting was conducted through a systematic adjustment of the number of groups pertaining to the frailty index, ranging from two to five. The fitting parameters obtained from these analyses are presented in Supplementary Tables S6, S7. The two-class model exhibited the lowest absolute BIC value, satisfying additional criteria as well. Therefore, the two-class model was selected as the ultimate FI model. Figure 3 displays two paths of the frailty index. The initial category, characterized by a gradual increase in FI, comprised 81.5% of the total sample size (N = 1,341). The second class exhibited a swiftly expanding FI trend, encompassing 18.5% of the sample (N = 304).

3.5 Logistic regression of FI trajectories

The Logistic regression analysis of various FI trajectories is presented in Table 2. A higher likelihood of older women belonging to the rapid-growth FI group, compared to the slow-growth FI group, was observed to be 1.905 times. Similarly, participants aged over 75 had a 3.691 times greater likelihood of being in the rapid-growth FI category compared to those with slow-growing FI. Older people with only primary education and a current drinking habit had a likelihood of 34.7 and 35% lower, respectively, to be in the rapid growth FI trajectory compared to the slow-growth FI trajectory. Furthermore, post-marital separation and inadequate sleep were associated with a 46.1 and 48.4% higher likelihood, respectively, of older people being included in the rapid-growth FI groups compared to the slow-growth FI group.

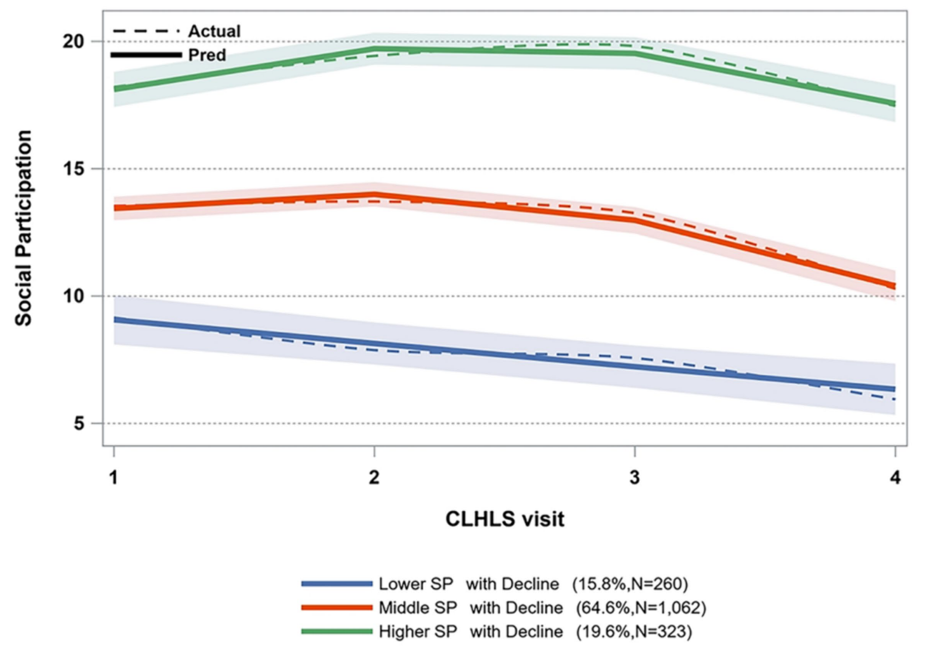

FIGURE 2
Trajectories of social participation.

3.6 Dual trajectories of social participation and frailty index

Panel A of Table 3 displays the conditional probability for each FI trajectory. The probabilities for the lower SP, middle SP, and higher SP groups collectively sum up to 100%. Older adults in the lower SP trajectory were most likely to belong to the rapid-growth FI trajectory (77.29%) and least likely to belong to the slow-growth trajectory (22.71%). Compared to participants in the lower SP trajectory, those who followed the middle SP trajectory and the higher SP trajectory had increased probabilities of belonging to the slow-growth FI trajectory (90.28 and 99.71%, respectively).

The conditional probabilities of belonging to each of the SP groups, given the frailty index groups, are displayed in Panel B. The probabilities for the slow-growth FI and rapid-growth FI groups each added up to 100%. When compared with older adults in the rapid-growth FI trajectory, those in the slow-growth FI exhibited higher probabilities of belonging to the middle SP and the higher SP trajectory (37.64 and 25.34% higher, respectively). These results suggest that rapid FI is associated with lower levels of SP within each SP subgroup.

Panel C illustrates the dual probabilities of participants in each of the SP and FI trajectories, where the six probabilities all added up to 100%. The group with slow-growth FI reporting middle SP had the highest probability (53.98%), followed by the group with slow-growth FI reporting higher SP (19.27%). The probability of the group with rapid-growth FI and higher SP was the lowest (0.36%).

4 Discussion

Our study investigated different trajectories of social participation and frailty state and the dynamic links between these trajectories of two outcomes. It was revealed that higher levels of frailty and lower levels of social participation exhibited significant bidirectional relationships, with age, education level, marital status, and drinking status potentially influencing the dual trajectories among Chinese older adults.

We have classified three unique trajectories of social participation (SP) among Chinese older people, each corresponding to different levels. A significant proportion of individuals (64.5%) aligns with the trajectory of medium SP with decline, spanning from 10 to 15, which is less than half of the total score. This suggests that a large portion of the older people in China exhibit a low level of social participation, potentially stemming from inadequate pension benefits. The Chinese government should encourage older adults to take part in social activities more frequently while providing more social resources. While the studies conducted in other Asian countries, such as Japan (17) and Korea (39), identified different numbers of SP trajectories, the trend observed in each trajectory closely mirrored our results, showing a gradual decline over time. At the same time, the two studies with larger sample sizes facilitated a more detailed grouping based on different levels of social participation, resulting in differences in the number of trajectories. Consistent with previous studies (26), this study identified two distinct FI trajectories.

Moreover, bidirectional longitudinal relationships between SP and FI were examined, a relationship that has not been thoroughly investigated in previous literature. Within each grouping, older people following a trajectory of decreasing lower SP were more likely to be included in the rapid-growth FI trajectory. Similarly, those involved in the rapid-growth FI trajectory had a higher likelihood of being in the lower SP with a decline. And these results confirm existing one-way evidence from studies in other East Asian countries. For example, Abe et al. reported that participating in social activities could improve the frailty status of older adults in Japan (40). A

TABLE 1 The logistic regression of SP trajectories.

Variables	Middle SP with Decline vs. Lower SP with decline			Higher SP with Decline vs. Lower SP with decline		
	OR		95% CI	OR		95% CI
		Lower	Upper		Lower	Upper
Gender (ref.=Male)						
Female	0.779	0.515	1.178	0.827	0.488	1.400
Age, years (ref.=65~75)						
>75	0.289***	0.211	0.396	0.149***	0.098	0.228
Residence (ref. = City)						
Town or Rural	0.554*	0.312	0.982	0.164***	0.088	0.307
Education level, years (ref.=0)						
1 ~ 6	1.226	0.872	1.724	3.170***	2.014	4.990
≥7	1.275	0.675	2.408	6.809***	3.360	13.800
Marital status (ref.=In marriage)						
Separation after marriage	0.510***	0.362	0.719	0.448***	0.280	0.714
Not in marriage	0.223*	0.068	0.735	0.230	0.044	1.199
Co-residence (ref.=Alone)						
Not alone	0.733	0.487	1.104	0.467*	0.258	0.845
Economic income (ref.=Low)						
Middle or high	1.292	0.894	1.868	2.070**	1.323	3.241
Drinking status (ref.=Never)						
Past	1.406	0.855	2.310	1.276	0.675	2.410
Present	1.226	0.801	1.878	1.857*	1.109	3.109
Smoking status (ref.=Never)						
Past	0.754	0.455	1.249	1.136	0.611	2.111
Present	1.130	0.707	1.806	1.393	0.792	2.451
Sleep duration (ref.=Normal)						
Excessive	0.704	0.339	1.464	1.205	0.466	3.115
Insufficient	1.670	1.670	1.670	1.670	1.670	1.670

OR, odds ratio; CI, confidence interval; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

subsequent study involving older people found an association between functional disability and the number and types of social participation activities (41). Therefore, a strong correlation exists between decreased social participation (SP) and higher frailty status, consistent with prior research on the simultaneous and delayed connections between SP and frailty in older individuals (24). These results may be attributed to various factors. Social involvement offers social connections, increased possibilities for physical activity (42) and access to role-based support (43), which can enhance both physical and psychological well-being, thereby alleviating the negative effects of frailty. Simultaneously, the frailty index encompasses several aspects such as chronic illness, cognitive impairments, and functional restrictions, indicating that individuals with a high level of frailty are likely to have restricted participation in social activities (44). The above results partially validated our first supposition.

The present study identified six discrete subgroups of individuals displaying a combination of SP and FI trajectories, partially validating our initial hypothesis 2. Each of those groupings should be implemented with targeted intervention strategies in order to enhance their health status and overall quality of life. In the case of the rapid-growth of FI combined with higher SP trajectory group, there is a need to strongly emphasize interventions aimed at decreasing FI. A progressive exercise program combined with nutrition intervention led to enhancements in frailty status (45), indicating the necessity for increased vigilance from the community and family members toward the psychological well-being of older people to reduce adverse emotions (46). However, for the slow-growing FI with the lower or middle SP trajectory groups, enhancing the SP level is essential. Our suggestion is to focus on SP interventions, such as raise awareness regarding the importance of social engagement, providing multiple channels of social activities, conducting lectures on social etiquette,

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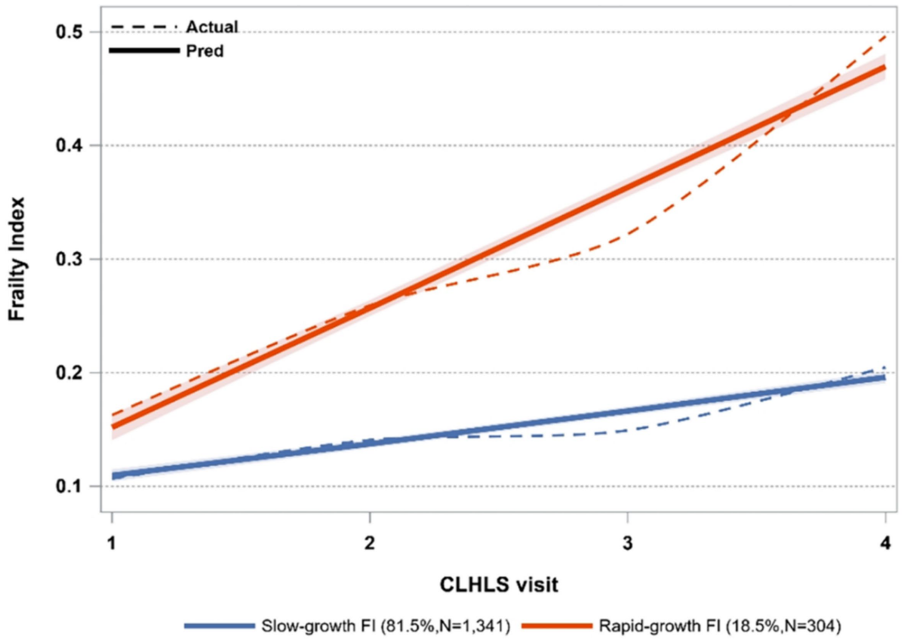

FIGURE 3
Trajectories of frailty index.

and enhancing expression skills for older adults (47). Individuals in the lower or middle SP who are experiencing rapid growing in frailty require more attention, which necessitates the integration of SP and interventions targeting frailty.

It is imperative to explore the influential factors, as clinical practice could focus on addressing risk factors and leveraging protective factors to create a supportive environment that caters to the diverse needs of older adults with varying trajectories of SP and FI. In our study, we explored the influencing factors of both SP and FI utilizing logistic regression, where the results partially confirmed hypothesis 3. Age emerges as a risk factor for lower SP and high FI, aligning with findings from previous studies (20, 48), underscoring the importance of focusing on the situation of older seniors (75+). Our research, in alignment with prior studies (48), indicated that older adults with primary education are more likely to belong to the slow-growth FI and higher SP trajectory. This could be attributed to the fact that low education could relate to worse choices regarding unhealthy behaviors, which leads to an increasing risk of frailty (49) and having less resources to take part in SP activities (18). A study conducted by Jung et al. found similar results indicating that older individuals in Korea with limited educational attainment exhibited a higher probability of belonging to the frailty trajectory characterized by escalating levels, potentially due to the impact of education on health behaviors (10). Furthermore, our study aligns with prior studies (50, 51) by demonstrating that individuals experiencing marital separation were more inclined to fall into the rapid-growth FI and lower SP trajectory. In a longitudinal study database developed by Nagai et al., it was evidenced that individuals who were widowed and faced economic stress were less likely to engage in regular activities, consequently displaying overall poorer health (51). China possesses a long history of alcohol culture, where drinking serves as a social lubricant associated with various social activities (52). Therefore, wine is the medium of socialization at the Chinese dinner table, which may be related to the level of social participation. Our findings indicated a heightened level of SP and lower frailty among older adults who currently consume alcohol, but the association between drinking and frailty exhibited inconsistencies compared to previous studies that documented various levels of frailty. One Mendelian randomization study indicated that there is no causal relationship between alcohol consumption and frailty (12). However, another analysis, including participants older than 55 years, revealed that people with heavier alcohol consumption had a reduced likelihood of frailty compared to non-drinkers (53). The volume of alcohol consumed or other confounding factors could potentially provide an explanation. Our study solely considered current or past drinking status, but the types of alcohol and drinking context may influence the results as well. Ortolá et al. reported that certain drinking patterns, especially drinking only with meals and the Mediterranean drinking pattern, are associated with a lower risk of frailty in older adults (54). Limited research exists in developing nations investigating the association between drinking patterns, frailty, and social engagement, aspects that will be addressed in our next plan.

This study had several strengths. Firstly, by utilizing nationally representative data on older adults in China, our findings provided valuable insights into the long-term patterns and associations between them. Secondly, this study explored common influencing factors associated with the dual trajectories of two variables which can give clinical practice to improve SP and frailty in older adults. However, it is important to acknowledge the study's limitations. Firstly, selection bias may be present. Participants in the current study tended to be healthier than those excluded because our study spanned a decade.

TABLE 2 The logistic regression of FI trajectories.

Variables	Rapid-growth FI vs. Slow-growth FI		
	OR	95% CI	
		Lower	Upper
Gender (ref.=Male)			
Female	1.905**	1.282	2.829
Age, years (ref.=65~75)			
>75	3.691***	2.757	4.941
Residence (ref.=City)			
Town or Rural	0.675	0.455	1.002
Education level, years (ref.=0)			
1~6	0.653**	0.473	0.901
≥7	0.705	0.420	1.185
Marital status (ref.=In marriage)			
Separation after marriage	1.461*	1.060	2.013
Not in marriage	1.157	0.246	5.444
Co-residence (ref.=Alone)			
Not alone	1.264	0.854	1.870
Economic income (ref.=Low)			
Middle or high	0.754	0.540	1.052
Drinking status (ref.=Never)			
Past	0.996	0.639	1.551
Present	0.650*	0.428	0.987
Smoking status (ref.=Never)			
Past	1.550	0.976	2.462
Present	0.950	0.607	1.487
Sleep duration (ref.=Normal)			
Excessive	1.434	0.713	2.883
Insufficient	1.484*	1.060	2.078

OR, odds ratio; CI, confidence interval; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

TABLE 3 Dual trajectory model for social participation and frailty index.

Social Participation	A: Probability of social participation conditional on frailty index	
	Frailty index	Conditional probability
Lower SP with decline	Slow-growth FI	22.71%
	Rapid-growth FI	77.29%
Middle SP with decline	Slow-growth FI	90.28%
	Rapid-growth FI	9.72%
Higher SP with decline	Slow-growth FI	99.71%
	Rapid-growth FI	0.29%

	B: Probability of frailty index conditional on social participation	
	Social participation	Conditional probability
Slow-growth FI	Lower SP with decline	4.65%
	Middle SP with decline	69.69%
	Higher SP with decline	25.66%
Rapid-growth FI	Lower SP with decline	67.63%
	Middle SP with decline	32.05%
	Higher SP with decline	0.32%

	C: Joint probability of social participation and frailty index	
Social participation	Slow-growth FI	Rapid-growth FI
Lower SP with decline	8.27%	7.54%
Middle SP with decline	53.98%	10.58%
Higher SP with decline	19.27%	0.36%

Secondly, our analysis focused on related baseline factors and did not encompass all indicators that may be associated with SP and FI trajectories. Thirdly, although we found the relation between the trajectories of the two outcomes, we should not interpret it as causality. Finally, the exploration of the dual trajectories of social participation and frailty in the older population is currently in its initial stage, and further researches should delve into the deeper mechanism of the two and the existence of unknown superimposed effects. Studies about the influence of lifestyle factors such as drinking patterns, dietary patterns on frailty and social participation are also of interest.

5 Conclusion

This study investigated significant connections between increased frailty levels and reduced social engagement, offering insights into healthcare and social services. To address the global ageing situation, intervention policies aiming at the dual trajectories and common underlying factors of SP and FI should be considered to enhance their effectiveness.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: https://opendata.pku.edu.cn/dataverse/CHADS.

Ethics statement

The studies involving humans were approved by the Biomedical Ethics Committee of Peking University, Beijing, China. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YB: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. JH: Data curation, Methodology, Writing – original draft. YM: Supervision, Writing – review & editing. PY: Funding acquisition, Methodology, Writing – review & editing. PW: Supervision, Writing – review & editing.

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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.

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2024.1401145/full#supplementary-material

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Case study: lessons learned from a community-based early frailty intervention programme in Singapore

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Frailty is a dynamic and evolving state of health which involves the gradual loss of physiological in-built reserves. In Singapore, there is growing interest in delivering frailty intervention programmes at scale in the community to meet the demands of an ageing population. New methods of programme delivery such as community-led models that do not rely on healthcare professional manpower are critical to address this unmet need. In this paper, we describe our experience and some lessons learned from the implementation of a community-based early frailty intervention programme for older adults, delivered for the first time by trained laypersons. From August to September 2022, "Steady Lah," a community-based early frailty intervention programme with physical activity and nutrition-based elements, was conducted at an Active Ageing Centre in Singapore. A total of 23 participants with mean age of 73.8 years were enrolled in the 12-session programme comprising of progressive strength and balance-based exercises and workshop-based learning focusing on nutrition. In the implementation of this run of "Steady Lah," modifications were made from a healthcare professional-led model to a trained layperson-led model with additional steps taken to ensure participant safety and assess overall effectiveness when delivered by trained laypersons. Good collaboration between stakeholders in healthcare institutions and the community is necessary to co-develop a model that prioritises the needs of the frail older adults.

KEYWORDS

frailty, older adults, early frailty intervention, community-based programmes, strength and balance

1 Introduction

Frailty is defined as a dynamic and evolving state of health which involves the gradual loss of physiological in-built reserves leading to losses in one or more domains of human function (physical, cognitive, psychological and/or social) and increases the vulnerability of older adults to adverse health-related outcomes (1).It is associated with adverse outcomes such as mortality, increased hospitalisation, disability, and falls (2).

In Singapore, frailty is an area of focus at the national level. With a rapidly ageing population and an estimated prevalence of pre-frailty and frailty at 30% and 5% respectively, there is growing interest in enhancing nationwide efforts to address the needs of this specific population of older adults (3, 4). In May 2023, the Singapore Ministry of Health published a "National Frailty Strategy Report" (1). One of the key recommendations in the report was for

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the community to play a bigger role in both identification of older adults with frailty, and management of older adults with early frailty through interventions such as exercise, nutritional support and falls prevention.

Current evidence shows that frailty can be prevented, reversed or delayed in the early stages and managed in later stages, through early detection and interventions to optimise functional ability, activity participation and quality of life (1). Examples of effective interventions include multicomponent exercises that incorporate elements of strength, resistance, balance, and aerobic capacity, and multi-domain interventions focusing on other areas such as nutrition (5–8).

Various frailty intervention programmes have been developed and implemented by healthcare institutions in Singapore. One example is a programme named "Steady Lah," loosely named after a local Singlish expression that is typically used to praise someone. "Steady Lah" was first conceptualised in 2018 by healthcare professionals from Tan Tock Seng Hospital (TTSH), one of the largest multi-disciplinary hospitals in Singapore. The programme aimed to improve participants' overall physical function, delay the progression of frailty, and was delivered by healthcare professionals such as physiotherapists and dieticians. Initial runs of "Steady Lah" conducted at selected community sites in 2019 showed positive results. However, the programme design and healthcare professional-dependent model of delivery meant that there were challenges with scaling up the programme to more sites to meet the overall demand in the community. In November 2021, the Health Promotion Board (HPB), a statutory board under the Ministry of Health with the vision of building "A Nation of Healthy People," partnered TTSH to jointly review the curriculum and programme design of "Steady Lah" with intent to scale up nationwide. A revised model of this community-based early frailty intervention programme delivered for the first time by trained laypersons, was implemented in 2022. This case study documents the experience of our team and shares lessons learned for future applications.

2 Context

2.1 Setting

The revised model of "Steady Lah" was implemented at an Active Ageing Centre (AAC) in the central region of Singapore from August to September 2022. AACs are drop-in social recreational centres managed by not-for-profit organisations, which extend support to older adults living nearby in the community (9). There are currently 157 AACs located across the island in Singapore, and this is planned to increase to 220 by 2025 (10).This would ensure that 8 in 10 older adults would have an AAC near their homes and be able to benefit from the activities offered (10). Examples of activities in an AAC include physical activity programmes, social events like singing and games, communal meals, and organised excursions to cater to the wide range of interests of older adults. Traditionally the activities are catered to older adults with varying functional abilities rather than specifically designed for sub-groups such as older adults with early frailty. For our programme, interested participants at the AAC were referred to attend the programme registration day by AAC managers based on a description of the programme objectives and target population of older adults with early frailty. The final assessment on eligibility was conducted by the team from the HPB's Healthy Ageing Division prior to enrolment.

2.2 Population

The target population for the programme was community-dwelling older adults aged 50 and above who were at-risk or showing early signs of frailty. We used gait speed as a proxy measure for early frailty and participants with gait speeds between 0.9 m/s to 1.2 m/s were assessed to be eligible for the programme. This cut-off range was decided in reference to proposed cut-offs and gait speed norms available in regional and local literature, and identified older adults with average or lower gait speeds.

For reference, the lowest quintile of gait speed in the local population was reported to be 0.9 m/s (11). This is slightly lower but close to the recommendation of the 2019 Asian Working Group for Sarcopenia where a gait speed cut-off of 1.0 m/s is used to identify low physical performance (12). The upper range of eligibility of the programme was set at 1.2 m/s. This was referenced from the same local study which found that the average gait speed for older adults aged 51 to 80 ranged from 0.9 m to 1.14 m/s (11). In a similar study conducted among older Japanese adults aged 65 and above, the 3rd quintile for usual gait speed in men was 1.25–1.34 m/s while that in women was 1.20–1.31 m/s (13). The upper limit of 1.20 m/s was set to exclude more robust older adults who may not benefit as much from the "Steady Lah" programme.

In addition, participants were excluded if they required assistance to ambulate at home, were undergoing chemotherapy or radiotherapy, were undergoing dialysis, or were diagnosed with kidney disease or Parkinson's disease. This was because certain physical exercises in the programme curriculum were unsuitable for participants with these conditions or because the general nutritional advice provided during workshops was not appropriate for participants on restricted diets or specific medications.

A total of 34 older adults were assessed on registration day. Of these, 23 were identified to be eligible for the programme. An overview of the age range and gender distribution of the participants is described in Table 1.

3 Programme description

"Steady Lah" is a community-based early frailty intervention programme with physical activity and nutrition-based elements conducted across 12 sessions. It was conducted two times a week on Mondays and Thursdays for 2 h. Each session comprises of 60 min of physical activity and 60 min of workshop-based learning. The revised model was delivered by trained laypersons including fitness trainers and workshop facilitators from August to September 2022. The 60-min physical activity element was of low to moderate intensity and focused on progressive strength and balance exercises. Some examples of exercises in the programme curriculum include sit to stand, heel raises, and side steps. The difficulty of the exercises was adjusted according to the performance of the participants by varying the number of repetitions, the range of motion or the level of hand support used during the exercises. Taking the example of heel raises, the participants are first introduced to six repetitions of bilateral heel raises with hand support on a chair placed in front. When the instructor assesses that most of the class can perform the required number of repetitions of this exercise, the number of repetitions

TABLE 1 Baseline characteristics of participants

Variable	Participants assessed and recruited		Participants assessed to be unsuitable		All participants assessed	
	Mean +/− SD or %	*N*	Mean +/− SD or %	*N*	Mean +/− SD or %	*N*
Age	73.8 +/− 7.52	23	73.5 +/− 7.20	11	73.7 +/−7.41	34
Gender						
Male	8.7%	2	9.1%	1	8.8%	3
Female	91.3%	21	90.9%	10	91.2%	31

is then increased to eight or 10. The subsequent increase in difficulty for this exercise type is when participants perform bilateral heel raises without hand support and then, unilateral heel raises with hand support.

The workshop component included short presentations and interactive activities to educate older adults on tips for a healthy diet with emphasis on adequate protein and calcium intake. This was conducted by a bilingual trainer in both English and Mandarin. For the message of ensuring adequate protein intake, the presentation component included material on the definition of protein, the importance of protein to maintain physical function and reduce muscle loss, the recommendation to consume protein at each meal, and common protein-rich foods. In the interactive activities, participants would identify which food item was rich in protein among the images flashed or identify which serving size of a particular protein-rich food item was equivalent to one serving of protein. Some examples of the material shared during the workshops on protein serving size and modifying meals to increase protein content are as illustrated in Figures 1, 2. A modified food frequency questionnaire developed by TTSH to capture food groups relevant in the local setting among older adults was also introduced as a tool for older adults to understand their protein and calcium intake and make incremental changes.

Lastly, the programme included a homework component where participants were provided with a set of instructions on how to continue with the exercises at home. Figure 3 is an example of a set of homework exercises that participants can perform and track during the days between the "Steady Lah" sessions. For each exercise prescribed, additional material is provided with step-by-step pictorial instructions on how to perform the movements correctly and safely. Figures 4, 5 are illustrative examples of how participants can perform a sit to stand with hand support in English and Mandarin. Certain homework tasks were also assigned to participants as part of the workshop curriculum. This was deliberately designed to encourage participants to apply lessons learnt during the session to their daily lifestyle and be more aware of their dietary choices. Figure 6 is an example of a simple take-home activity where participants identify protein-rich food items in their meals and are subsequently given the opportunity to share this during the session.

As part of the programme, a functional assessment test was administered at the first and last session for participants to better understand their baseline functional ability and appreciate any changes over the course of the programme. The test comprised of three assessments namely, gait speed, number of repetitions of sit to stand in 30 s and time to complete the four-square step test. These assessments are commonly used in both clinical and research settings.

4 Discussion

4.1 Modifying the programme for delivery by trained laypersons

The concept of general community-based physical activity programmes for well older adults conducted by fitness trainers is not new in Singapore. However, the unmet need that our programme aims to address is that of delivering an intervention specifically for older adults with early frailty. The profile of older adults with early frailty is notably different from the general older population and fitness trainers are less familiar with engaging this population as compared to healthcare professionals. However, in Singapore's context, a model anchored on delivery by specialised healthcare professional manpower would not be scalable due to both cost and scarcity.

To address this gap between fitness trainers' competencies and the higher level of needs among older adults with early frailty, we adopted the following modifications, in consultation with the experts from TTSH. The overall principle was to identify and retain the core elements of the programme and remove or simplify other elements that were more challenging to administer. We reduced the complexity of both the physical activity and nutrition-based components to remove any highly technical movements and content that could not be delivered by individuals without formal healthcare training. A defined curriculum with a fixed number of exercises and adjustment of the difficulty tiering of the exercises such that fitness instructors could offer progression or regression based on the participants' profiles and progress was developed. In addition, a standardised set of educational material for the workshop was also developed with emphasis on pegging the difficulty level of the content to that of a non-healthcare professional.

4.2 Assessing effectiveness

The follow-up question that comes with making any modifications to a previously proven intervention is that of sufficient fidelity and the ability for the modified programme to still realise the intended outcomes. Given that the overall objective of this pilot was to test out a modified model of programme delivery and assess if the processes were feasible to scale, the ability of this study design to offer robust effectiveness evaluation data was limited. The overall approach adopted involved comparison of participant assessment scores before and after completion of the programme to assess if the participants recruited in this pilot saw any benefits and improvements at the individual level. A paired *t*-test was used to assess the statistical

FIGURE 1
Example of "Steady Lah" workshop content—protein serving size.

FIGURE 2
Example of "Steady Lah" workshop content—incorporating protein in meals.

significance at a p-value of 0.05, and all statistical analysis was run on STATA 13.0.

Overall, statistically significant improvements were observed among participants for both functional assessment test scores and protein and calcium intake after completion of the programme. Given the earlier limitations mentioned, these results serve to provide an initial sensing of the potential effectiveness of the programme and will need to be triangulated with more data, when available.

Figures 7–9 illustrate the observed change in the average functional assessment scores before and after completion of the programme. Out of the 23 participants enrolled, 22 participants attended the follow-up session where the functional assessment tests were repeated. Out of the 22 participants, one declined to participate in the 30 s sit to stand and the four-square step test.

Figures 10–12 show the changes in average protein and calcium intake at baseline and after completion of the programme. The data was available for 21 participants.

4.3 Addressing safety considerations

Another important consideration specific to programmes involving physical activity and special populations like older adults is safety. In the shift from a healthcare professional-led model of

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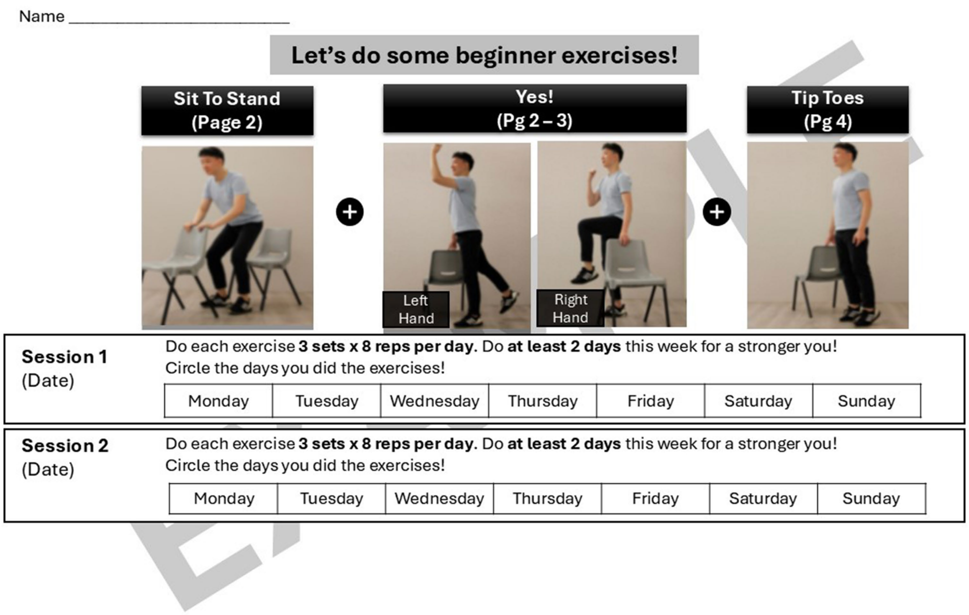

FIGURE 3
Example of "Steady Lah" homework exercises—tracking sheet.

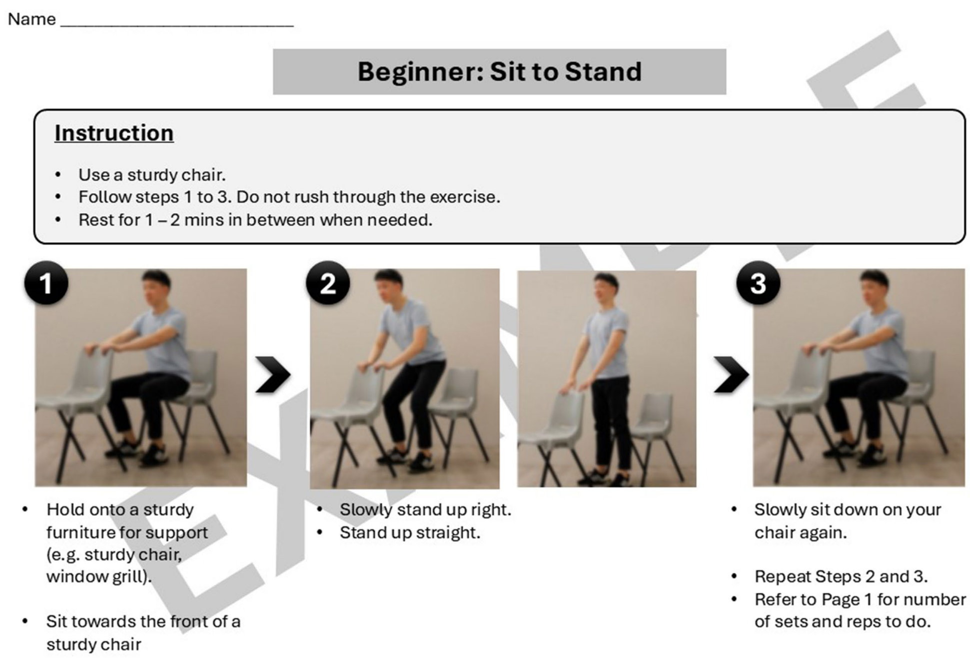

FIGURE 4
Example of "Steady Lah" homework exercises—English translation.

delivery to a trained layperson-led model, we noted that additional measures would have to be taken to address participants' safety considerations. Some of the measures that we adopted include placing significant emphasis on safety during instructor training, restricting the class size to support a high instructor to participant ratio and performing pre-participation suitability checks to ensure that participants can perform the exercises in the programme curriculum. For example, participants who report any signs and symptoms suggestive of cardiovascular disease are advised to proceed for a medical consultation prior to joining the programme. During the set-up and administration of the four-square step test used to assess dynamic balance, additional emphasis is placed on safety as participants are required to change direction and walk backwards. At any point in time, two fitness instructors are required at this test station to ensure that participants perform the test safely. In addition, participants who require the use of walking aids or have unsteady gait

FIGURE 5
Example of "Steady Lah" homework exercises—Mandarin translation.

FIGURE 6
Example of "Steady Lah" homework activity on nutrition.

are exempted from this test. In the pre-programme training, our fitness instructor was also equipped with the knowledge on how to recognise participants who were unwell or unsteady when performing exercises such that he could intervene early before any potential incidents.

Throughout our planning, conduct and review of the pilot run, the team had frequent discussions related to optimising the safety processes of the trained layperson-led model of "Steady Lah." While we acknowledge the need to deliver the programme safely, we noted that a balance needed to be struck between introducing multiple new safety processes, minimising complexity of programme administration from the instructor's perspective and ensuring that the barrier to entry to the programme from the older adults' perspective was not too high that they would be put off from enrolling in "Steady Lah." In the absence of clear guidelines on recommended safety processes for community-based early frailty interventions, our experience suggested

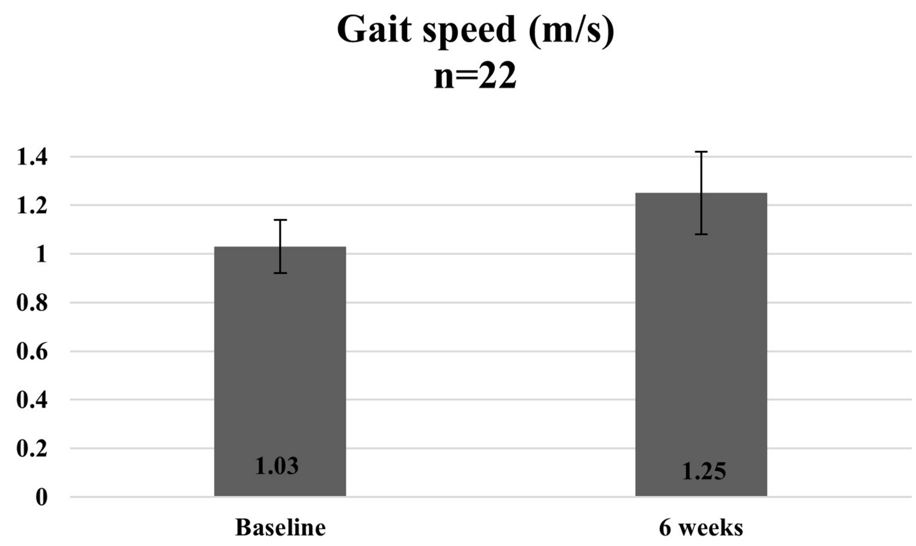

FIGURE 7
Average gait speed of participants at baseline and 6 weeks.

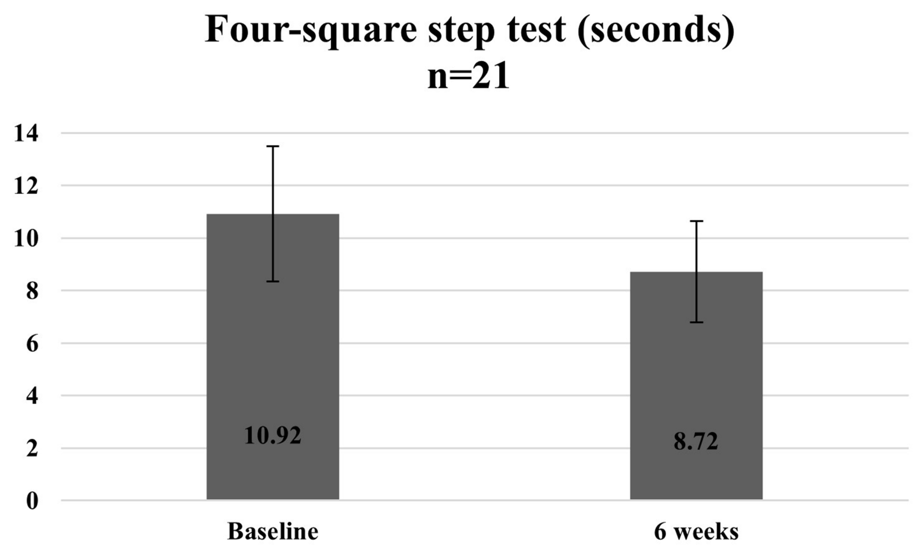

FIGURE 8
Average time taken to complete the four-square step test at baseline and 6 weeks.

the need for constant iteration to best address the competing interests of the stakeholders involved in any programme.

4.4 Reaching the target population adequately

The overall aim of our programme is to address the unmet needs of community dwelling older adults with early frailty. For this run of "Steady Lah," we tapped on the Active Ageing Centre and its existing clientele to identify suitable older adults. This was an opportunistic group of participants. However, from our experience we observed that it was challenging to identify more potential participants with early frailty who may benefit from the programme based on this outreach approach. Out of 34 older adults shortlisted by the AAC manager, only about two-thirds met the programme inclusion criteria. Also, the participants were predominantly female. One of our hypotheses are that older adults with early frailty may not have found the previous general physical activity programmes suitable for them and hence may not be regular participants in the AAC activities. Hence, there is a need to diversify the recruitment strategy for "Steady Lah" to truly reach out to all potential participants who could benefit. For example, future iterations may need to work with the Silver Generation Office, a national volunteer outreach group that engages with older adults or engage healthcare institutions to receive referrals from healthcare providers such as general practitioners and community nurses (14).

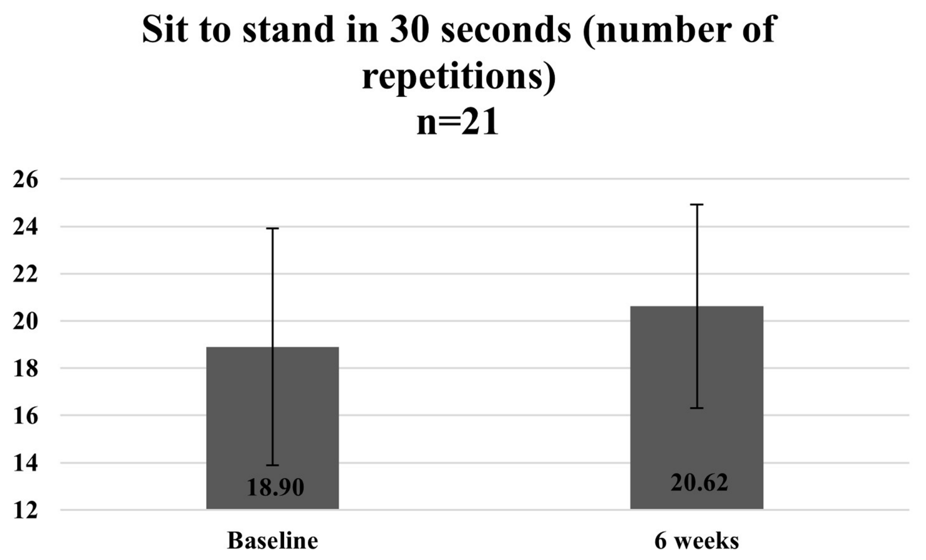

FIGURE 9
Average number of repetitions of sit to stand in 30 s at baseline and 6 weeks.

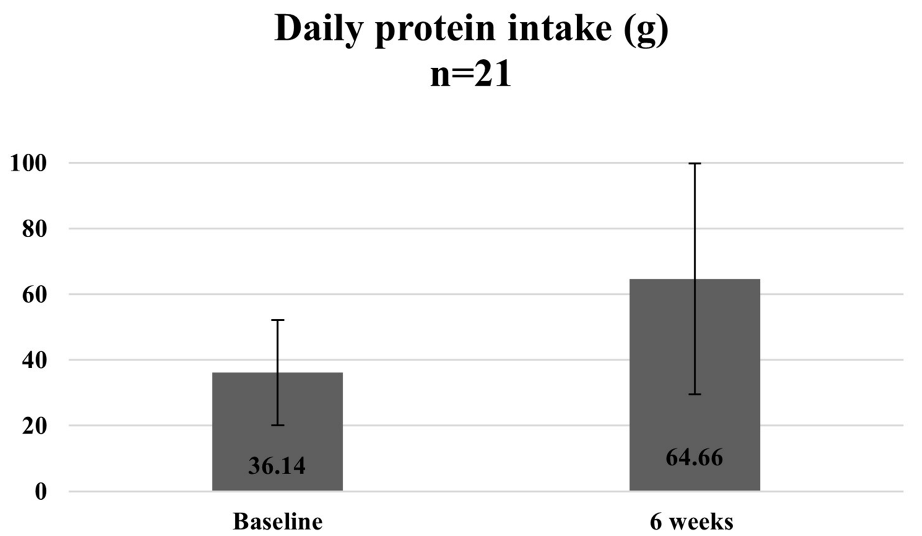

FIGURE 10
Average daily protein intake at baseline and 6 weeks.

5 Limitations

The focus of the experience documented in this paper was to modify and implement a community-based frailty intervention programme that was previously delivered, solely by healthcare professionals. The emphasis was on understanding if the modified programme could be implemented by trained laypersons and if there were any additional considerations that needed to be addressed to ensure that the programme benefitted older adults with early frailty in the community. The overall intent in the long run is to run "Steady Lah" at multiple sites throughout Singapore. As such, this was not intended to be a robust programme evaluation and lacks the methodological rigour to do so. The absence of a control group makes it harder to fully appreciate and size the impact of the intervention on the outcomes. Also, the convenience sample of participants from the Active Ageing Centre was not representative of the broader population of older adults with early frailty. As our team iterates and implements the programme at more sites, conducts systematic training for cohorts of fitness instructors conducting the programme and reviews the experiences from those runs, additional data and lessons can be assessed to offer more insights. As of August 2023, "Steady Lah" has been progressively implemented at more community sites throughout Singapore with the support of community partners and a growing pool of fitness instructors with special training in managing older adults with early frailty (15). The evaluation of these additional runs is ongoing.

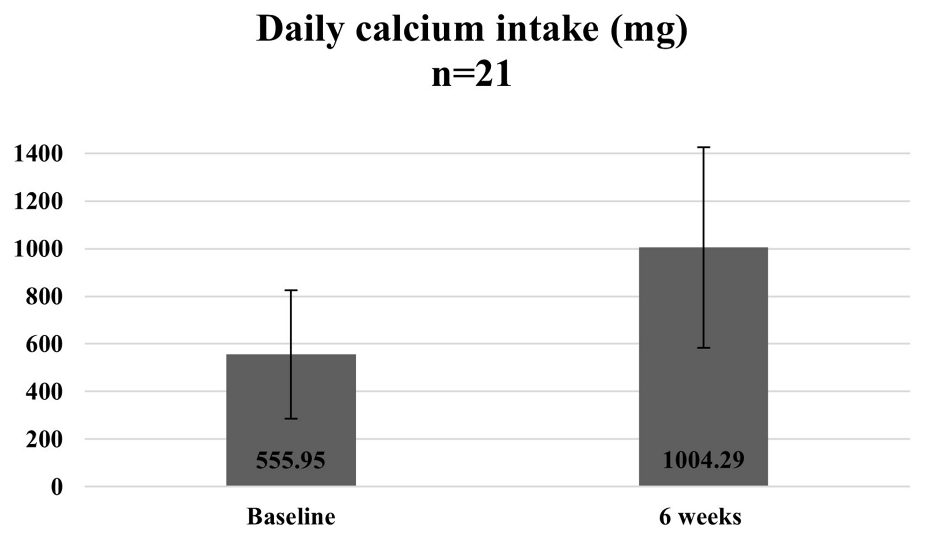

FIGURE 11
Average daily calcium intake at baseline and 6 weeks.

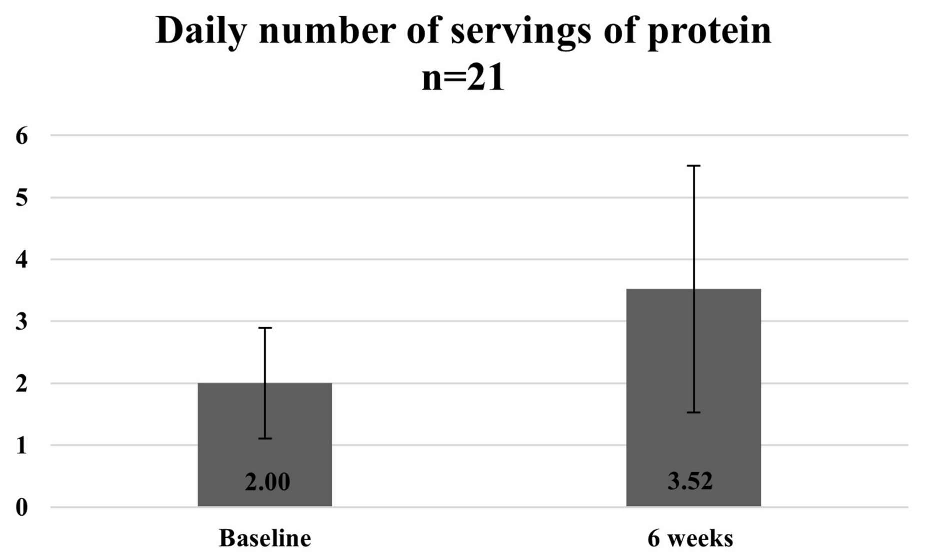

FIGURE 12
Average number of servings of protein at baseline and 6 weeks.

6 Conclusion

In conclusion, our experience from this inaugural run of a community-based frailty intervention programme for older adults with early frailty, delivered by trained laypersons, demonstrates that this sub population of older adults can indeed be better supported in the community by non-healthcare professionals. In Singapore, evidence-based programmes targeting this sub population are initially developed in healthcare institutions but subsequently require support and resources from the community to expand the programme reach. This requires good collaboration between stakeholders in healthcare institutions and the community to co-develop a model that ultimately prioritises the needs of frail older adults without compromising on the quality of the intervention. Other communities embarking on a similar journey to support older adults with frailty in the community can consider taking reference from this case study to design and implement community-based interventions.

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 review was not required for this case study as it is a service evaluation to assess and improve the delivery of a public benefit programme. This is in accordance with the guidelines issued by the Ministry of Health (Singapore) with reference to local legislation governing human biomedical research, i.e., the Human Biomedical Research Act (HBRA). Written informed consent to participate in the Steady Lah programme was provided by all participants via consent form on the programme registration day. For further details, please refer to the following published guidelines: Ministry of Health (Singapore) Human Biomedical Research Act Overview: https://www.moh.gov.sg/policies-and-legislation/human-biomedical-research-act.

Author contributions

KJ: Writing – original draft. RN: Writing – review & editing. EL: Writing – review & editing. PC: Writing – review & editing. HL: Writing – review & editing. SC: Writing – review & editing. DL: Writing – review & editing. CW: Writing – review & editing. VS: Writing – review & editing.

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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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Effects of activities participation on frailty of older adults in China

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Objective: Frailty represents a significant health challenge among older adults, necessitating effective interventions to enhance their overall wellbeing. This study aims to investigate the impact of various types of activity participation on frailty in older adults and to elucidate their intrinsic associations, thereby providing a basis for targeted interventions.

Methods: This study constructed a classification of activities based on the framework proposed by the WHO regarding functional ability in healthy aging, innovatively dividing activities into five categories: physical activity, social activity, economic activity, information activity and sleep activity. Utilizing data from the China Health and Retirement Longitudinal Study (CHARLS 2020), the research employed multiple linear regression and mediation analysis to explore the effects of these activities on the frailty status of older adults and their underlying mechanisms. Furthermore, propensity score matching was conducted to robustly test the regression results.

Results: The study found that physical activity ($\beta = -0.006$, $p < 0.01$), social activity ($\beta = -0.007$, $p < 0.01$), economic activity ($\beta = -0.017$, $p < 0.01$), information activity ($\beta = -0.040$, $p < 0.01$) and sleep activity ($\beta = -0.044$, $p < 0.01$) all had significant positive effects on the frailty status of older adults. Additionally, sleep activity mediated the relationship between physical activity and frailty status, accounting for 4.819%. Social activity mediated the relationship between information activity and frailty status, accounting for 7.692%.

Conclusion: Older adults should enhance their participation in various activities to alleviate frailty. This can be further improved through the following three aspects: engaging in moderate physical exercise, fostering and promoting awareness of volunteer services, and popularizing the use of information technology.

KEYWORDS

frailty, physical activity, social activity, economic activity, information activity, sleep activity, older adults

1 Introduction

With the intensification of the aging population process, frailty among the older adults is becoming an increasingly prominent health challenge. Frailty is a common and complex geriatric condition, often defined as a decrease in physiological reserve and reduced resistance to stressors caused by cumulative declines in multiple physiological systems (1–3). Frailty is considered to be a dynamic process that worsens with age (4), leading to adverse consequences for the physical and mental health of older adults. During the period of frailty, the probability of older adults developing other diseases is 12%—24%, with a incidence rate as high as 46% to 49% in the early stage of frailty (5). Besides, frailty is closely associated with adverse health outcomes such as cognitive impairment (6), disabilities (7), hospitalization (8), and death (9). Fortunately, frailty is a reversible process, and early identification of risk factors as well as proactive interventions can delay the progression of older adults from pre-frailty to frailty (10). Among these factors, participation in activities stands out as a particularly significant influence on frailty in older adults (11–13). Activity theory posits that older adults with higher levels of activity tend to exhibit greater life satisfaction (14) and stronger social adaptation compared to those with lower activity levels. This positive effect can be attributed to the supportive roles provided by engagement in activities (14), which help older adults maintain a positive self-concept, prevent brain degeneration, reduce dysfunction, enhance positive emotions, and improve quality of life. Additionally, these activities bolster the ability to cope with environmental changes and organic frailty (14–16). Existing research indicates that, even after controlling for demographic variables, engagement in activities significantly elevates the overall health status of older individuals and mitigate the onset of frailty (17–19). However, the impact of different types of activities on frailty in older adults may vary (18). Therefore, it is essential to further delineate the types of activities and investigate the specific effects and underlying mechanisms of these activities on frailty in older adults.

The World Health Organization (WHO) states that healthy aging is the process of developing and maintaining the functional ability that enables wellbeing in older individuals. Functional ability encompasses a person's capacity to move independently, build and maintain relationships, contribute to society, make decisions, learn and grow, as well as meet their basic needs (20). Older individuals demonstrate their functional ability through activity participation, which in turn affects their health status (21). Based on the WHO's framework for functional ability in older individuals, we categorize their activities into five types: physical activities, social activities, economic activities, information activities and sleep activities, as illustrated in Figure 1.

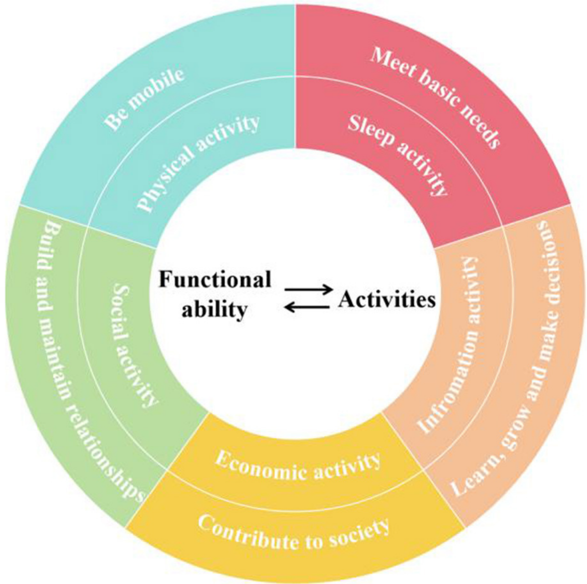

FIGURE 1
Framework of activities of older adults.

Physical activity refers to activities that require energy expenditure, muscle movement, and physical labor. It is commonly classified into three categories: vigorous physical activities (VPA), moderate physical activities (MPA), and low-intensity physical activities (LPA) (22). Physical activity can mitigate and delay several adverse health outcomes associated with frailty in older individuals, such as cognitive impairment, muscle loss, and depression (23). Consequently, it is considered one of the most effective methods for improving the quality of life and functional abilities in older individuals (24), and it may even serve as a predictor of frailty (25). Higher levels of moderate-to-vigorous physical activity (MVPA) are effective in improving frailty (26), reducing its incidence (27), preventing mobility disorders in frail older individuals (28), and counteracting the negative effects of sedentary behavior (29). However, despite the positive impacts of physical activity on the health of older individuals, it also increases the risk of falls and fractures due to decreased bone mineral density associated with aging (30). Therefore, Kwok et al. encouraged retirees to engage in physical activities following health activity guidelines to minimize these risks (31).

Social activity refers to various communication and interaction behaviors in social life that older adults participate in, involving visiting or socializing with friends, playing mahjong and chess, etc. After retirement, older adults are freed from the constraints of work schedules and social activities, providing them more leisure time. In this new stage of life, they can meet their needs for fulfillment through active social engagement, facilitating a smooth transition from work to retirement (10). Social activities are capable of promoting older adults to establish social networks, receive emotional support and recognition, enhance self-efficacy and enhance stress resistance, thereby reducing the risk of illness as well as improving quality of life (32). Conversely, insufficient engagement in social activities may lead to feelings of loneliness and social isolation among older adults, increasing their risk of frailty. Existing researches have indicated that living in socially active neighborhood is related to lower levels of frailty, highlighting the crucial role of enhancing social activity participation in frailty prevention (33). Most researchers suggested that social activities may impact the frailty status of older adults and researches primarily focused on impacts of different categories of activities (34). Some existing researches indicate that engaging in group games, joining sports clubs and participating in voluntary work can effectively reduce the risk of frailty among older adults. However, some basic social interactions, such as interacting with friends and joining community organizations, have not been proved to have a positive impact on alleviating frailty in older adults (35). Takatori et al. suggested that social factors have no significant improvement effect on frailty in older adults, but social activities based on the promotion of exercise could improve the status of older adults before frailty (36).

Economic activity means various behaviors undertaken by older adults for surviving and developing. Engaging in economic activities may lead to two distinctly different living conditions for older individuals, thereby affecting their physiological and psychological status in different ways. Academic researches on work and frailty in older adults has yielded mixed findings. Research by Jung et al. in the field of productive activities (including volunteer service, paid work, and childcare) showed that after controlling for age, disability, and cognition, work was irrelevant with the likelihood of accumulating frailty (37). However, another research showed that both shift work and low payment have negative effects on the frailty status of older adults. The disruption of circadian rhythms caused by shift work can exacerbate frailty in older adults (38). Retirement may have a protective effect on the health of the older adults who are engaged in low-paid work because of their negative social psychology, which in turn increases their frailty (39). A longitudinal study in the UK supported the aforementioned views, indicating that leaving paid employment before reaching retirement age is beneficial for slowing the progression of frailty in men, and continuing to work does not provide long-term health benefits (40). Furthermore, another study classified work frequency into light, moderate, and vigorous, analyzing their impacts on frail older adults. The results showed that moderate work significantly decreased the pre-frailty rate in older adults (41). What's more, work can also be categorized into intellectual and physical work, both of which have been shown to have positive effects on frailty in older adults (18).

Information activity means utilizing information and communication technologies by older adults. The choice of whether or not to use the internet can reflect the degree of social adaptation and attitude toward societal changes among older adults, which can further influence their living conditions and mindset. The rapid development of information and communication technology (ICT) provides opportunities for users to connect with society, and has become an important mean to help older adults improve frailty status. The use of ICT by older adults can facilitate connections with family members, potentially improving their psychological wellbeing. The lifting effect may be more pronounced in frail older adults (42). Meanwhile, A cross-sectional study indicated a negative correlation between frailty and the use of ICT, with non-use of ICT being a predictor of frailty, and concluded that older women who did not use ICT were more likely to be frail (43).

Sleep activity pertains to the sleeping behavior of older adults. Research on the impact of sleep activity on frailty in older adults can be divided into two categories: sleep quality and sleep duration. Older adults with poor sleep quality are at a higher risk of physical frailty (44). Specifically, sleep-related insomnia can lead to decreased physical performance in older adults (45), resulting in a 66% higher likelihood of frailty compared to peers (46). Additionally, after controlling for covariates such as demographic information, lifestyle, and health-related conditions, poor sleep quality is highly associated with the probability of cognitive frailty (47). Existing studies of sleep duration on frailty in older adults have shown a non-significant association between short sleep duration and risk of frailty (48), with only excessive sleep duration being significantly associated with a high risk of cognitive frailty (49). This may be attributable to the U-shaped relationship observed between sleep duration and all-cause mortality, wherein the lowest risk is associated with a sleep duration of 5.8 h from sleep onset (50).

Different types of activities may interact with each other, thereby influencing frailty in older adults. Regular physical activity promotes relaxation and energy consumption (51), and has been proposed as an effective non-pharmacological treatment option to improve sleep in older adults (52). Existing studies have shown that physical activity is associated with sleep quality in older adults (53), with those engaging in higher levels of physical activity exhibiting better sleep quality (54) and regularity (55). Regular moderate-intensity physical activity in older adults significantly improves sleep outcomes such as sleep quality, sleep disorders, and sleep duration (56). Improved sleep conditions may further slow down the progression of frailty in older adults. Therefore, it is hypothesized that sleep activity may have a mediating effect between physical activity and frailty in older adults. The emergence of ICT has created new possibilities for older people to stay socially connected (57). The use of ICT by older adults can enhance communication efficiency and frequency with family members and friends, facilitating closer connections between them (58). Furthermore, ICT can help older adults overcome spatial limitations, enabling them to connect with strangers online and even develop offline relationships, thereby expanding their social circles (59). Given that participation in social activities, both online and offline may influence frailty in older adults, it is hypothesized that social activity may mediate the relationship between information activity and frailty in older individuals.

All in all, academic researches on the effects of different activity types on frailty in older adults remain inconclusive. There might be variations in the effects of different activity types on frailty among older adults, and may exist correlations between different types of activities that subsequently influence frailty. However, current academic researches on the impact of various activities on frailty primarily focuses on the effects of single or limited categories of activities (18, 60), which has resulted in a fragmented body of studies. There is a lack of comprehensive and systematic research examining the influence of the main activities that older adults frequently engage in during their daily life on frailty. Therefore, this study constructed a classification of activities based on the framework proposed by the WHO regarding functional ability in healthy aging, innovatively dividing activities into five categories: physical activity, social activity, economic activity, information activity and sleep activity. In addition, this study differs from the majority of previous research that concentrates on the mechanisms of alleviating frailty in older adults by improving physiological and psychological factors (61, 62). The findings will clarify the individual and interactive effects of various activities on frailty, deepening and expanding existing academic researches on this topic. Furthermore, based on the results of this research, the study will further provide practical recommendations for improving frailty in the daily lives of older adults, ultimately enhancing their overall wellbeing. Based on the analysis above, this study proposes the following hypotheses:

H1: Physical activity can effectively mitigate the frailty in older adults, but participation in physical activities of different intensities has varying impacts on frailty.

H2: Social activity can effectively mitigate the frailty in older adults and participation in different social activities also has varying effects on frailty conditions.
H3: Economic activity can effectively mitigate the frailty in older adults.
H4: Information activity can effectively mitigate the frailty in older adults.
H5: Sleep activity can effectively mitigate the frailty in older adults.
H6: Sleep activity mediates the impact of physical activity on frailty in older adults.
H7: Social activity mediates the impact of information activity on frailty in older adults.

2 Methods

2.1 Data and participants

The study utilized the data from the fifth phase (2020) of the China Health and Retirement Longitudinal Survey (CHARLS), which is an ongoing longitudinal cohort study. The aim of CHARLS is to collect a high-quality set of micro data representing Chinese households and individuals aged 45 and above, investigating 150 counties and 450 communities (villages) across 28 provinces (autonomous regions, and municipalities) in China. The CHARLS National Baseline Survey was launched in 2011 and was tracked 2 to 3 years. In order to guarantee the unbiased and representativeness of the survey, CHARLS set a filtering section that can exclude invalid samples. CHARLS also conducted the sample through four phases at the county (district)-village (residential)-household-individual level. CHARLS used the Probability Proportional to Size (PPS) method for sampling at two levels: county (districts)-village (residential). By the completion of the follow-up in 2020, the sample has covered a total of 19,000 respondents from 11,400 households, making it a good-quality dataset that includes individual basic information, family structure, health status, economic conditions, social security, and other aspects. All participants in the study signed informed consent forms, and the protocol has been approved by the Ethics Committee of Peking University.

Since the research object was the older adults in this study, 8,741 respondents under the age of 60 were excluded. Among the remaining respondents, 12 were missing information on physical activity, 16 were missing information for social activity, 339 were missing information for economic activity, 18 were missing information for sleep activity, 3,305 were missing information on frailty index and 8 were missing information for covariates. Six thousand nine hundred and forty three respondents were finally included in our research and the sample selection process is depicted in Figure 2.

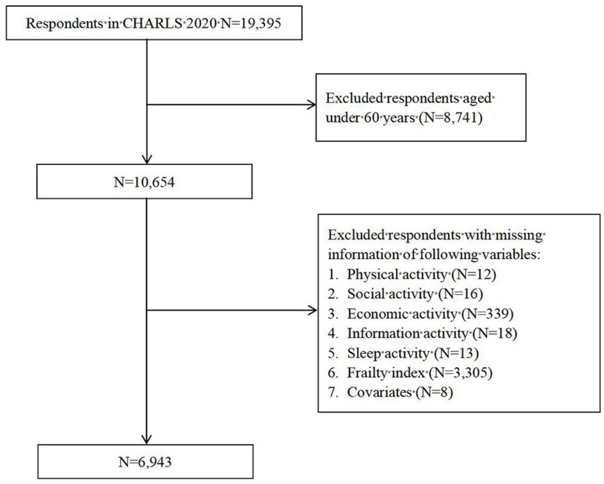

FIGURE 2
Respondents' flow in the study.

2.2 Dependent variable

The dependent variable in this study was frailty, which was measured by frailty index (FI). The index was consistent with previous studies (63, 64). It encompassed 8 domains, including chronic diseases, self-reported health, ADL, IADL, depression, and cognitive, comprising a total of 37 indicators, which were derived from self-report and objective measurement of the study participants. The specific items were shown in Table 1. FI was calculated by dividing the sum of scores by the total number of items, with scores ranging from 0 to 1, and a higher score indicated a higher level of frailty among older adults.

2.3 Independent variables

This study selected different types of activities as independent variables, including physical activity, social activity, economic activity, information activity, and sleep activity. For physical activity, the study evaluated its impact on frailty based on varying intensity levels. The research also explored the impact of different types of social activities on frailty. For economic and informational activities, the study measured their impact on frailty based on participation status. Regarding sleep activities, the research evaluated the impact on frailty based on the duration of sleep.

Referring to previous literature (22), physical activity among older adults was categorized into three levels based on intensity: low-intensity physical activity (LPA) such as walking, including walking for work or from one place to another at home, as well as walk for leisure, exercise, or entertainment. Moderate physical activity (MPA), such as carrying light objects, regular-speed cycling, mopping, brisk walking, etc., leading to faster breathing than usual. Vigorous physical activity (VPA) that cause rapid breathing, such as lifting heavy objects, farming, aerobics, fast cycling, etc. Participants were asked to report the intensity, frequency, and duration of their physical activity per week. The frequency ranged from 0 to 7 days per week, and the daily duration of physical activity was divided into five categories, i.e., no physical activity physical activity = 0 min, physical activity <30 min, 30–119 min, 120–239 min, and >240 min. The total of physical activity (TPA) was calculated by multiplying the daily duration of each type of physical activity

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TABLE 1 Construction of frailty index indicator system.

Domains		Description of the items	Cut-off value
Chronic diseases	1	Self-reported physician diagnosed hypertension	Yes = 1, No = 0
	2	Self-reported physician diagnosed dyslipidemia	Yes = 1, No = 0
	3	Self-reported physician diagnosed diabetes	Yes = 1, No = 0
	4	Self-reported physician diagnosed cancer	Yes = 1, No = 0
	5	Self-reported physician diagnosed chronic lung diseases	Yes = 1, No = 0
	6	Self-reported physician diagnosed liver disease	Yes = 1, No = 0
	7	Self-reported physician diagnosed heart attack	Yes = 1, No = 0
	8	Self-reported physician diagnosed stroke	Yes = 1, No = 0
	9	Self-reported physician diagnosed kidney disease	Yes = 1, No = 0
	10	Self-reported physician diagnosed stomach or other digestive diseases	Yes = 1, No = 0
	11	Self-reported physician diagnosed any emotional, nervous, or psychiatric problems	Yes = 1, No = 0
	12	Self-reported physician diagnosed memory-related disease	Yes = 1, No = 0
	13	Self-reported physician diagnosed arthritis or rheumatism	Yes = 1, No = 0
	14	Self-reported physician diagnosed asthma	Yes = 1, No = 0
Self-reported health	15	Self-reported rating of health status	Poor/very poor=1, fair/good/very good=0
ADL	16	Difficulty with dressing	Yes = 1, No = 0
	17	Difficulty with bathing or showering	Yes = 1, No = 0
	18	Difficulty with eating	Yes = 1, No = 0
	19	Difficulty with getting into or out of bed	Yes = 1, No = 0
	20	Difficulty with using the toilet	Yes = 1, No = 0
	21	Difficulty with controlling urination and defecation	Yes = 1, No = 0
IADL	22	Difficulty with doing household chores	Yes = 1, No = 0
	23	Difficulty with preparing hot meals	Yes = 1, No = 0
	24	Difficulty with shopping for groceries	Yes = 1, No = 0
	25	Difficulty with taking medications	Yes = 1, No = 0
	26	Difficulty with managing money	Yes = 1, No = 0
Depression	27	Bothering by things much of time	Yes = 1, No = 0
	28	Having trouble keeping mind on things much of time	Yes = 1, No = 0
	29	Feeling depressed much of time	Yes = 1, No = 0
	30	Feeling that everything is an effort much of time	Yes = 1, No = 0
	31	Feeling hopeful about the future much of time	No = 1, Yes=0
	32	Feeling fearful much of time	Yes = 1, No = 0
	33	Sleeping is restless much of time	Yes = 1, No = 0
	34	Feeling happy much of time	No = 1, Yes=0
	35	Feeling lonely much of time	Yes = 1, No = 0
	36	Feeling that could not get going much of time	Yes = 1, No = 0
Cognition	37	Sum of orientation test score, memory test score and calculating test score/30	Continuous, ranging from 0 to 1

by its weekly frequency. To further standardize the measurement of physical activity, the study utilized metabolic equivalent value (MET). Based on previous research, 1 MET represents resting oxygen consumption, while VPA corresponds to 8 MET, MPA to 4 MET, and LPA can be expressed as 3.3 MET. Total physical activity (TPA) was calculated by the sum of MET of VPA, MPA and LPA. For statistical convenience, the TPA was divided by 60 to calculate the MET hours per week and presented in the final data form using the LN (TPA+1).

Social activity among older adults included seven categories: (1) visiting or socializing with friends, (2) playing mahjong, chess, cards, or attending community activities, (3) providing unpaid help to non-cohabiting relatives, friends, or neighbors, (4) participating in sports, social, or other types of clubs, (5) participating in community-related organizations, (6) participating in volunteer or charity activities or caring for non-cohabiting patients or disabled persons, (7) attending school or training courses. The study measured the dimension of social activity by calculating the number of social activities older adults participated in. According to previous research, the study further categorized social activity into four types (65): item (1) was categorized as simple interpersonal activities (SIA), items (2) and (7) as intellectual activities (INA), items (3) and (6) as volunteer activities (VOA), and items (4) and (5) as club activities (CLA).

The economic activity of older adults was measured by their participation in work, including farm work, wage labor, business activities, and assisting with family businesses. It was assigned to 1 if engaged in work, and 0 otherwise.

In this study, information activity participation among older adults was measured by their internet usage, which was assigned to 1 if older adults used the internet and 0 otherwise.

Sleep activity status among older adults was measured by their sleep duration. Based on previous research, older adults' sleep duration was categorized into three classes (66): short sleep duration (≤5 h), moderate sleep duration (5 h ∼ 9 h), and long sleep duration (≥9 h), and assigned values of 0, 1, and 2, respectively.

2.4 Mediators

This study included two mediating variables, analyzing the mediating effect of sleep activity between physical activity and frailty status among older adults, and the mediating effect of social activity between information activity and frailty status among older adults.

2.5 Covariates

The control variables selected for this study encompassed gender (0 = female, 1 = male), age (in years), hukou (0 = agricultural, 1 = non-agricultural), education level (0 = low level of education, including elementary school and below; 1 = medium level of education, including middle school graduation to vocational school; 2 = high level of education, including 2-/3-Year College/Associate degree and above) and marital status (0 = married, 1 = separated/divorced/widowed/never married).

2.6 Statistical analysis

Stata18.0 and SPSS26.0 were used for statistical analysis. Descriptive statistics and multiple linear regression analysis were initially conducted using SPSS 26.0. Frequency and standard deviation were used to represent categorical data, while mean and standard deviation were used for continuous data. Further mediation analysis was conducted using SPSS 26.0, employing the SPSS macro developed by Hayes (Model 4). Bias-corrected percentile Bootstrap method was utilized to estimate the 95% confidence interval of the mediating effects, with 5,000 samples extracted after controlling for gender, age, hukou, education level, and marital status. The mediating effect was considered significant if the 95% confidence interval did not include 0 (67). Lastly, the study concluded with a robustness test of the analysis results using propensity score matching (PSM) via Stata 18.0.

TABLE 2 Descriptive statistics of variables ($N = 6,943$).

Variables	Mean/%	SD	Minimum	Maximum
Frailty index	0.374	0.128	0.061	0.879
Gender				
Male	50.151%			
Female	49.849%			
Age	69.097	6.274	60	110
Hukou				
Agricultural	75.400%			
Non-Agricultural	24.600%			
Education level				
Low level of education	70.575%			
Medium level of education	28.201%			
High level of education	1.224%			
Marital status				
Separated/divorced/widowed/never married	22.685%			
Married	77.315%			
Total physical activity	3.726	1.641	0	6.062
Social activity	0.683	0.909	0	6
Economic activity				
Participation	38.355%			
Non-participation	61.645%			
Information activity				
Participation	75.313%			
Non-participation	24.687%			
Sleep activity	0.817	0.476	0	2

3 Results

3.1 Descriptive analysis

The descriptive results of the data are presented in Table 2. A total of 6,943 older participants were included in the study, with an average age of 69.1 years. Additionally, the gender proportion was balanced, with males and females accounting for 49.8% and 50.2% respectively. Moreover, the education level of the older adults was generally low, with 70.6% having the degree of primary school or below. Furthermore, a high proportion of older adults

TABLE 3 Effects of PA on frailty status in older adults.

Variables	Frailty index of older adults			
	Model 1	Model 2	Model 3	Model 4
Gender	−0.044*** (0.003)	−0.035*** (0.003)	−0.036*** (0.003)	−0.033*** (0.003)
Age	0.003*** (0.000)	0.001*** (0.000)	0.002*** (0.000)	0.001*** (0.000)
Hukou	−0.041*** (0.003)	−0.039*** (0.003)	−0.038*** (0.003)	−0.038*** (0.003)
Education level	−0.063*** (0.003)	−0.052*** (0.003)	−0.051*** (0.003)	−0.052*** (0.003)
Marriage	−0.022*** (0.003)	−0.019*** (0.003)	−0.019*** (0.003)	−0.019*** (0.003)
Total physical activity		−0.006*** (0.001)		−0.006*** (0.001)
Low-intensity physical activity			−0.005*** (0.001)	
Moderate physical activity			−0.003*** (0.001)	
Vigorous physical activity			0.002** (0.001)	
Social activity		−0.007*** (0.002)	−0.007*** (0.002)	
Simple interpersonal activities				−0.001 (0.003)
Intellectual activities				−0.027*** (0.004)
Volunteer activities				0.006 (0.004)
Club activities				−0.013** (0.005)
Economic activity		−0.017*** (0.003)	−0.022*** (0.003)	−0.018*** (0.003)
Information activity		−0.040*** (0.004)	−0.038*** (0.004)	−0.039*** (0.004)
Sleep activity		−0.044*** (0.003)	−0.044*** (0.003)	−0.043*** (0.003)
Adjustment R^2	0.190	0.248	0.249	0.252
F-value	327.512***	230.009***	192.829***	181.224***

Standard errors in parentheses. **, and *** indicate significant at the 5%, and 1% levels, respectively.

had agricultural hukou, accounting for 75.4%, and the majority of older adults were in a state of marriage, comprising approximately 77.3% of the total. The average FI of the older adults included in this study was 0.37, indicating that the overall frailty status of older adults was in the lower middle level. There were significant differences in the participation of older adults in different activities. For instance, the average MET for older adults was 3.73, with a standard deviation of 1.64, indicating that the TPA participation among older adults was moderate, but there were considerable individual differences. Moreover, older adults had a low frequency of participation in social activity, with 54.1% not participating in any social activity, 29.4% participating in one social activity, and only 16.5% participating in two or more social activities. What's more, most older adults were still involved in economic activity, accounting for approximately 61.6%. However, the participation in information activity was not ideal, with only 24.7% of older adults reporting the use of the internet in their daily lives. Lastly, the sleep duration of the older participants included in the study was relatively moderate, while 22.1% of older adults had insufficient sleep duration, and 3.85% had excessive sleep duration.

3.2 Effects of different activity types on frailty status of older adults

Table 3 presented the effects of different types of activities on the frailty status of older adults. Model 1 included only the

TABLE 4 Mediating effect of sleep activity.

	Effect value	Boot SE	Boot LL CI	Boot UL CI	Relative mediation effect
Total effect	−0.0083	0.0009	−0.0100	−0.0066	
Direct effect	−0.0079	0.0008	−0.0095	−0.0062	95.181%
Indirect effect	−0.0004	0.0002	−0.0008	−0.0001	4.819%

TABLE 5 Mediating effect of social activity.

	Effect value	Boot SE	Boot LL CI	Boot UL CI	Relative mediation effect
Total effect	−0.0429	0.0035	−0.0498	−0.0360	
Direct effect	−0.0396	0.0036	−0.0467	−0.0326	92.308%
Indirect effect	−0.0033	0.0006	−0.0045	−0.0021	7.692%

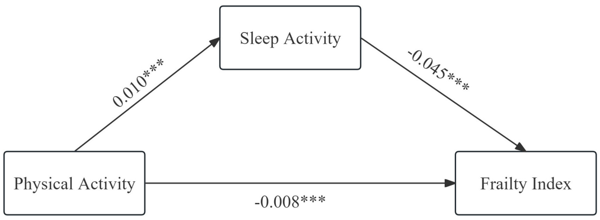

FIGURE 3
Mediating effect of sleep activity.

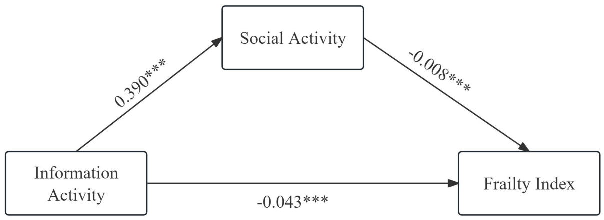

FIGURE 4
Mediating effect of social activity.

control variables, while Model 2 added various activity variables based on Model 1. Model 3 and 4 further analyzed the impacts of different physical activity intensities and types of social activities on frailty in older adults respectively based on the foundation. After controlling for relevant covariates, TPA exhibited a significant negative effect on the frailty status of older adults ($\beta = -0.006$, $p < 0.01$). Further exploration revealed that LPA and MPA significantly predicted lower frailty status among older adults ($\beta = -0.005$, $p < 0.01$; $\beta = -0.003$, $p < 0.01$), whereas engaging in VPA could exacerbate frailty in older adults ($\beta = 0.002$, $p < 0.05$). The statistical results verified hypotheses H1. Overall participation in social activity showed a significant negative impact on the FI of older adults ($\beta = -0.007$, $p < 0.01$). Based on this, the study further investigated the influence of different categories of social activity participation on FI. The results indicated that engaging in INA and CLA significantly contributed to lower FI among older adults ($\beta = -0.027$, $p < 0.01$; $\beta = -0.013$, $p < 0.05$), while participating in SIA and VOA did not affect frailty status. The data analysis results showed that Hypothesis 2 is partially supported. Additionally, the study findings revealed that engaging in economic activity, information activity, and sleep activity all significantly predicted lower frailty status among older adults ($\beta = -0.017$, $p < 0.01$; $\beta = -0.040$, $p < 0.01$; $\beta = -0.044$, $p < 0.01$). These findings validated hypotheses H3, H4, and H5.

3.3 Mediation analysis

Regression analysis indicated that participation in physical, social, economic, information, and sleep activities all had varying degrees of negative effects on frailty status in older adults. However, previous studies have shown that there were also mutual influences among these activities. Therefore, further exploring the mechanisms of how different types of activities affect frailty status in older adults is of significant importance. In this study, sleep activity and social activity were selected as mediating variables to investigate the influence mechanisms of physical activity and informational activity on frailty status respectively. The results were presented in Tables 4, 5 and Figures 3, 4. Sleep activity was found to partially mediate the relationship between physical activity and the FI in older adults. The direct effect coefficient between physical activity and frailty index was −0.0083, and the mediating effect coefficient of sleep activity was −0.0004. The mediating effect accounted for 4.8% of the total effect. The mediation indicated that physical activity influenced frailty status in older adults by extending their sleep duration. Social activity partially mediated the relationship between information activity and frailty. The coefficient of direct effect between information activity and frailty was −0.0429, and the mediating effect coefficient of social activity was −0.0033. The mediating effect accounted for 7.7% of the total effect. The mediation suggested that information activity alleviated frailty status in older adults by promoting their participation in social activity. The statistical analysis results confirmed H6 and H7.

3.4 Robust test

We used two propensity score matching methods, including nearest neighbor matching and kernel matching in this study.

The results were presented in Table 6. After controlling gender, age, hukou, education level as well as marital status, the effects of five different types of activities on frailty among older adults were all significant, suggesting that the baseline regression results were robust.

4 Discussion

This study investigated the effects of physical activity, social activity, economic activity, information activity, and sleep activity on frailty in older adults and explored the potential mechanisms underlying these effects. Our findings indicated that all five activity types have significant negative effects on frailty of older adults. Specifically, physical activity can alleviate frailty by extending sleep duration, and information activity can reduce frailty by enhancing social engagement.

Initially, participation in different types of activities had a significant negative impact on frailty in older adults. First of all, the effectiveness of PA interventions in coping with frailty in older adults has been documented (25, 68). PA is defined as all movements in daily life, including occupational, commuting, and leisure activities (69). It is closely associated with maintaining and improving physiological function and physical health, and the impact of different intensity of physical activity on frailty varies. LPA such as walking, climbing stairs, and rising from the floor or chair can improve muscle strength, enhance balance and flexibility, reduce the risk of chronic diseases and musculoskeletal issues, as well as improve cognitive function and mental health in older adults (70). The improvement is closely related to the functional capacity of older adults and can significantly alleviate frailty with aging (71). MPA such as cycling and brisk walking has been shown to be relevant to lower resting blood pressure, improved lipid and lipoprotein profiles, enhanced glucose homeostasis, reduced abdominal fat deposition, as well as extended active life expectancy (72). In addition, MPA can also induce rapid expansion of the mitochondrial compartment in muscle cells, which can alleviate the frailty outcomes caused by years of sedentary habits in older adults (73, 74). However, as intensity increases, PA may not necessarily have a sustained positive impact on older adults, since VPA often increases the risk of injury and sudden death in older adults (72). VPA can also lead to fatigue, respiratory difficulties, restricted mobility, anxiety, etc. (75). As a result, moderate exercise is beneficial for the physical and mental health of older adults.

Secondly, high level of social activity participation can alleviate frailty in older adults. Social activity participation is a broad concept, including involvement in volunteering, recreational activities, interpersonal interactions, etc. (76). Activity theory suggests that social engagement can provide role support for older adults and build social relationships (77), reduce feelings of loneliness (78), as well as encourage older adults to adopt healthy behaviors, thereby improving frailty. The effects of different social activities on frailty various. As individuals age, older adults may experience the loss of friends and partners (78), which may increase their risk of social isolation and loneliness, further leading to frailty (79) and increased risk of early death (80). However, CLA can create a friendly and sociable environment. Participating in these activities can enhance social contact and interaction, enhance their sense of belonging, address their social and psychological needs (81), improve their mental health and cognitive function (82), thus further alleviating frailty. Additionally, cognition decline, as an inevitable result of aging (83), further contributes to frailty in older adults (84). While participating in INA can significantly improve older adults' memory, attention, processing speed, and enhance cognitive reserve. It is an effective intervention to improve older adults' cognitive abilities (85), which can further inhibit the progression of functional decline and reduce the likelihood of disability in older adults (86). Interestingly, this study found that SIA and VOA did not have a significant impact on frailty in older adults. This may because simple interpersonal activities, which only involve visiting or communicating with others, are unlikely to affect the physiological functions and capabilities of older adults, thus having an insignificant impact on frailty conditions. Meanwhile, the volunteering awareness among older adults in China are not enough, leading to lower participation in volunteer work, thus not significantly affecting their frailty.

Thirdly, engaging in economic activity can positively influence the health of older adults. Participating in intellectual economic activities can provide cognitive stimulation, strengthen synaptic transmission (neural plasticity), and increase cognitive reserve, thus positively affecting the maintenance or improvement of cognitive function (87). This positive impact does not diminish with age, as older employees often have experienced more cognitively challenging, allowing for more cognitive exercises. Even older adults who want to take on new tasks after retirement can enhance the function of the prefrontal cortex and further improve the cognitive function through working (88). While engaging in physical economic activities as well as physical activities generated on the way to work, such as walking and cycling, all strengthen mobility and reduce the risk of disability and physical decline in older adults, thereby alleviating frailty status (88).

Fourthly, active engagement in information activity can have beneficial effects on both the physical and mental health of older adults, thereby alleviating frailty. As age increases, the prevalence of neurocognitive disorders (such as mild cognitive impairment or dementia) continues to rise (89). These cognitive impairments often lead to disability and dependence, thus exacerbating the overall frailty condition in older adults (90). However, the Internet, as an increasingly popular information technology, can provide older adults with a new source of positive stimulation. With the deep integration of Internet-based technologies (such as smartphones, wearable devices, etc.) into daily cognitive processing, older adults using the Internet can gradually develop various forms of online cognition in their aging brains and can leverage emerging online functions to achieve cognitive abilities (91). Furthermore, using the Internet can also improve the mental health of older adults. The emergence of the Internet has brought about many new types of online activities, such as playing online games, watching videos, online shopping, social interaction, etc., all of which can help older adults achieve the purpose of entertainment and leisure, thereby improving their negative emotions (92). Additionally, as the Internet provides abundant information, some older adults

TABLE 6 Robust test.

	Physical activity	Social activity	Economic activity	Information activity	Sleep activity
Nearest neighbor matching	−0.047***	−0.020***	−0.024***	−0.043***	−0.062***
Kernel matching	−0.048***	−0.020***	−0.023***	−0.043***	−0.062***
Covariates	Control	Control	Control	Control	Control

***indicates significant at the 1% level.

can regularly search for health-related information to manage their physical and mental health, so as to improving frailty condition (93).

Fifthly, extension of sleep duration can also effectively improve the frailty condition in older adults. In recent years, sleep disorders, as a risk factor for physical frailty in older adults, have gradually attracted widespread attention (94). This is mainly because sleep disorders may over activate the HPA axis, leading to increased secretion of cortisol, thereby accelerating the degradation of muscle protein (95). Sleep disorders may also lead to dysfunction of the hypothalamic-pituitary-gonadal (HPG) axis, reducing the secretion of testosterone, thereby inhibiting the synthesis of muscle protein. These imbalanced processes of degradation and synthesis lead to the deterioration of muscle mass, which in turn leads to the core of physical weakness, namely muscle weakness (96, 97). Other possible mechanisms include chronic inflammation (IL-6, TNF-α, and CRP) (98) and imbalance in growth hormone (GH) secretion (99). According to statistics, the prevalence of sleep disorders in people over 60 years old is 42.3% (100). Sleep is a modifiable lifestyle factor, which can effectively improve the overall health of older adults, reduce frailty risks, and decrease their late-stage consequences through early adoption of effective intervention measures (101).

This study found that the above five categories of activities can indirectly alleviate their frailty status through interaction. The results indicated that sleep activity played a partial mediating role in the influence of PA on frailty in older adults. Previous research has shown that regular PA can improve the sleep quality of older adults (102). This is mainly because regular PA promotes relaxation and energy consumption in older adults, which is conducive to initiating and maintaining sleep (103, 104). However, the frequency and intensity of PA among older adults need special attention. Research has found that a three times per week exercise program predicts beneficial sleep outcomes (105, 106). Specific types of activities such as Ba Duan Jin, Tai Qi, and yoga as well as combinations of different types of exercises are known to positively affect sleep in older adults (107). Improved sleep quality further enhances older adults' cognitive abilities and reduces the risk of dementia (108), alleviating physical and mental health problems, thus positively impacting the overall frailty status of older adults (109).

Moreover, social activities play a mediating role between information activity and frailty in older adults. Putnam defined social capital as "the connections between personal social networks and the norms of reciprocity and trust that arise from them" (110). Further research has divided social capital into psychological/cognitive dimensions and network/structural dimensions (111). Network social capital includes resources obtained through social networks (111) and can be measured through social participation and informatization (112). As an "network" itself, the Internet provides older adults with effective and convenient communication channels (113). In addition to enhancing communication with family and friends, the Internet also assists older adults to establish contact with strangers, conduct in-depth online communication and offline social activities (59). Simultaneously, as a platform carrying a large amount of information, the Internet hosts online and offline organizations classified according to interests and hobbies. Older adults can accumulate social capital, alleviate loneliness and enhance their sense of belonging by joining clubs of interest and participating in activities (114). Furthermore, active social participation also helps further enhance cognitive function, curb the progression of functional decline, and reduce the likelihood of disability, thereby alleviating the overall frailty status.

Above all, we believe that in the future, older adults should seize opportunities to engage in various activities according to their own circumstances. However, it is worth noting that engaging in activities with excessively high intensity may not alleviate the frailty status. The reasons of engaging in VPA in this study were for exercise partly, while others do so out of economic necessity. For older adults exercising for health, it is advisable to reduce the intensity appropriately to enhance individual safety and physical health. For those engaged in physical labor due to economic necessity, the government should enact relevant social security policies such as providing financial assistance to relieve the financial pressure. Currently, the participation of older adults in volunteer services is not satisfactory. Consequently, the communities and related organizations should strengthen advocacy and publicity of volunteer services among older adults (115). Moreover, the proportion of older adults participating in information activities is relatively low. It is necessary to rely on family members and communities to further improve the digital literacy of older adults, promote them to integrate into the information society and empower older adults (116). For rural and remote areas having issues of the digital divide (117), government departments should increase investment in communication infrastructure construction, and mobilize enterprises actively participate in promoting the popularization and application of communication technology.

This study differs from previous single or limited researches by innovatively constructing an activity classification based on the functional capability framework for healthy aging proposed by the WHO. The classification includes five categories: physical activity, social activity, economic activity, information activity, and sleep activity. The research explores the impact of these activities on frailty and further investigates the mediating roles of sleep activity and social activity in the relationship between physical activity, information activity, and frailty. The findings not only provide a detailed overview of how various daily activities affect frailty in older adults but also offer practical pathways for preventing and mitigating frailty in daily life, aligning closely with the current promotion of healthy aging concepts. However, this study has some limitations, including the use of cross-sectional data, which may not capture the dynamic relationship between activity participation and frailty. Future research should explore these relationships longitudinally to verify the temporal effects.

5 Conclusion

Frailty, as a medical syndrome characterized by specific physical symptoms, significantly impacts the wellbeing of older adults and imposed considerable economic and psychological burdens on their caregivers. To explore the effective mechanisms for mitigating frailty in older adults, this study summarized previous research and utilized microdata from the CHARLS 2020, combining it with the functional capability framework for healthy aging proposed by the WHO to construct a classification of different activities. The study empirically investigated the impact of participation in these activities on frailty in older adults. The results indicated that physical, social, economic, information, and sleep activities can effectively alleviate frailty. Additionally, the study examined how physical activity and information activity improved frailty status through their effects on sleep activity and social activity respectively. These findings will enrich the existing research on frailty in older adults and provide new perspectives on improving frailty status. They will enable older adults to identify clear pathways for enhancing their health in daily life and suggest that simple, feasible activity options can significantly improve their health, which holds important practical implications for enhancing the overall wellbeing of older populations.

Data availability statement

Data are available from the China Health and Retirement Longitudinal Study (CHARLS) (http://charls.pku.edu.cn/) for researchers who meet the criteria for access to CHARLS data.

Ethics statement

The studies involving humans were approved by the Institutional Review Board of Peking University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

ZN: Conceptualization, Formal analysis, Investigation, Writing – original draft. XiuZ: Formal analysis, Methodology, Software, Writing – original draft. YS: Formal analysis, Writing – original draft. XiaZ: Writing – review & editing. SX: Conceptualization, Supervision, Validation, Writing – review & editing. XY: Funding acquisition, Project administration, Writing – review & editing.

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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.

Publisher's note

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Nomogram model for screening the risk of frailty in older adult atrial fibrillation patients: a cross-sectional study

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Background: Frailty is common in atrial fibrillation (AF) patients, but the specific risk factors contributing to frailty need further investigation. There is an urgent need for a risk prediction model to identify individuals at high risk of frailty.

Aims and objectives: This cross-sectional study aims to explore the multiple risk factors of frailty in older adult patients with AF and then construct a nomogram model to predict frailty risk.

Methods: We recruited 337 hospitalized patients over the age of 60 (average age: 69, 53.1% male) with AF between November 2021 and August 2022. Data collected included patient demographics, disease characteristics, sleep patterns, mental health status, and frailty measures. We used LASSO and ordinal regression to identify independent risk factors. These factors were then incorporated into a nomogram model to predict frailty risk. The model's performance was assessed using the concordance index (C-index) and calibration curves.

Results: Among the AF patients, 23.1% were classified as frail and 52.2% as pre-frail. Six risk factors were identified: age, gender, history of coronary heart disease, number of chronic conditions, sleep disruption, and mental health status. The internal validation C-index was 0.821 (95% CI: 0.778–0.864; bias-corrected C-index: 0.795), and the external validation C-index was 0.819 (95% CI: 0.762–0.876; bias-corrected C-index: 0.819), demonstrating strong discriminative ability. Calibration charts for both internal and external validations closely matched the ideal curve, indicating robust predictive performance.

Conclusion: The nomogram developed in this study is a promising and practical tool for assessing frailty risk in AF patients, aiding clinicians in identifying those at high risk.

Relevance to clinical practice: This study demonstrates the utility of a comprehensive predictive model based on frailty risk factors in AF patients, offering clinicians a practical tool for personalized risk assessment and management strategies.

KEYWORDS

frailty, atrial fibrillation, nomogram, sleep disruption, mental health status, chronic diseases

1 Introduction

Atrial fibrillation (AF) is the most common arrhythmia, affecting 2 to 4% of adults and approximately 37.57 million individuals worldwide (1). AF significantly heightens the risk of ischemic stroke by 4 to 5 times (2), doubles the likelihood of myocardial infarction (3), and greatly increases the risk of vascular dementia and Alzheimer's disease (4). Frailty, a geriatric syndrome caused by the decline of physical function and physiological reserves, renders individuals more vulnerable to adverse events and stressors (5). Research indicates that neuroendocrine disorders, chronic inflammation, impaired energy metabolism, social environment, and psychological factors are involved in the occurrence and regression of frailty (6). Given that frailty and AF share similar pathogenic pathways like chronic inflammation and neuromodulation (3) the prevalence of frailty is notably high among AF patients (7). Meanwhile, frailty is strongly linked to increased stroke and bleeding risks in these patients (8), in addition, to reducing the possibility of maintaining sinus rhythm (9). Frailty progresses dynamically and is reversible, thus, early detection of risk factors and targeted interventions can help reverse pre-frailty and slow its advancement. Previous studies have highlighted various sociodemographic and clinical risk factors, covering age, polypharmacy, loneliness, and sleep status (10, 11). However, studies focusing on integrated risk factors for frailty specifically in AF patients are scarce. A prediction model based on these risk factors could more effectively identify high-risk individuals compared to existing diagnostic tools like the FRAIL scale which only provides broad categorizations (12). This model enables more precise and personalized prediction of frailty occurrence. Currently, frailty risk prediction models are widely used in many diseases (13). However, to our knowledge, there has not been a frailty risk predictive tool in the AF field. Among the many tools for visualization of the results of prediction models, the nomogram has simple and intuitive advantages it can quickly and personally calculate risk probabilities (14). Therefore, we aim to construct and validate a nomogram model to predict the risk of frailty in AF patients by combining multi-dimensional risk factors from socio-demographic, behavioral, and mental dimensions, to provide clinicians with a valuable tool to assess frailty risk more accurately in this population.

2 Methods

2.1 Study participants

This study employed a cross-sectional survey design and included 337 older adult patients diagnosed with AF who were admitted to the Affiliated Hospital of Teaching in Tianjin between November 2021 and August 2022. Among them, 242 patients enrolled from November 2021 to April 2022 were assigned to the training group, while the remaining 95 patients constituted the testing group.

Participants were selected based on the following criteria: (1) a diagnosis of AF according to the European Society of Cardiology guidelines (15); (2) age 60 years and older, in line with Chinese geriatric criteria; (3) ability to communicate effectively and willingness to participate in the study. Exclusion criteria included patients with (1) severe mental illness that would impede cooperation, and (2) reversible AF caused by hyperthyroidism or electrolyte disorders.

2.2 Baseline data collection

2.2.1 Baseline data

Baseline characteristics included a range of variables: (1) demographic variables such as age, gender, and education level; (2) clinical parameters including AF type, Body Mass Index (BMI), AF duration, number of chronic ailments, and a history of diabetes, hypertension, coronary heart disease, heart failure, and ischemic stroke; (3) lifestyle factors such as smoking status and alcohol consumption; and (4) laboratory indices comprising low-density lipoprotein (LDL), high-density lipoprotein (HDL), high-sensitivity C-reactive protein (Hs-CRP), brain natriuretic peptide (BNP), left atrial diameter (LA), left ventricular end-diastolic diameter (LVEDD), and left ventricular ejection fraction (LVEF).

2.2.2 Ethics approval and consent

This study received approval from the Ethics Committee for Clinical Research of Tianjin Medical University General Hospital (approval number IRB2022-WZ-053). All procedures adhered to relevant guidelines and regulations. Informed consent was obtained from all participants.

2.2.3 Data collection method

Clinical and biochemical data were retrieved from hospital medical records, while general information was obtained through interviews and questionnaire surveys. Researchers explained the study's goals and procedures to participants to secure informed consent. Out of 350 distributed questionnaires, 337 were completed and valid, resulting in a high response rate of 96.2%.

2.3 Assessment of frailty, mental health status, and sleep status

Frailty was evaluated using the Chinese version of the FRAIL scale, which incorporates five components: fatigue (over the past month), resistance, ambulation (ability to climb stairs or walk 200 meters unassisted), illness (presence of $\geq$5 chronic conditions), and weight changes (weight loss>3 kg in the past 3 months). Each component is scored between 0 and 1Scores are classified as follows: robust (score of 0), pre-frail (scores of 1–2), and frail (scores of 3–5). The scale demonstrated strong reliability and validity, with a Cronbach's α coefficient of 0.826 (12). Mental health was evaluated using the Mental Health Inventory-5 scale (MHI-5), a validated 5-item subscale of the SF-36 questionnaire which assesses both negative emotions such as anxiety and depression, and positive emotions like happiness and peace experienced over the past month (16). Scores were recorded using a Likert scale from 1 ("All the time") to 5 ("None"), with total scores ranging from 0 to 100. Previous studies categorized patients into four groups based on their MHI-5 scores: 86–100, 76–85, 53–75, and 0–52, with the86-100 serving as the reference group and scores $\leq$52 indicating severe depressive symptoms (17). The reliability and applicability of the MHI-5 in AF populations have been extensively demonstrated and utilized (18). Sleep status was assessed across three fronts: sleep duration, sleep disruption, and difficulty falling asleep within the past month. Sleep duration quantifies actual nighttime sleep, sleep disruption tracks the frequency of awakenings not related to nocturia, and difficulty falling asleep assesses the inability to initiate sleep after more than 30 min of preparation.

2.4 Statistical analysis

Statistical analysis was performed using SPSS 23.0 and R version 4.1.3. Additional data processing utilized software packages including "MASS," "Brant," "RMS," and "GLMNet." These tools facilitated comprehensive exploration and interpretation of the collected data. Continuous variables were described using mean ± standard deviation or median (range), while categorical variables were presented as proportions and percentages. Descriptive analysis focused on elucidating the frailty status and socio-demographic characteristics of older adult AF patients. Lasso regression was employed to select variables, addressing multicollinearity and reducing the risk of model overfitting. Variables with a non-zero penalty coefficients were retained as candidates. Ordinal regression was then applied to identify the most significant candidates, which were integrated into a nomogram model for frailty prediction in AF patients. Ultimately, the C-index and the calibration curve were considered to appraise the discrimination and predictive ability of the model, respectively. The C-index is a measure used to assess the discriminative ability of a predictive model, specifically evaluating how well the model can accurately determine the likelihood of an event occurring for a patient. The C-index ranges from 0.5 to 1, where 0.5 indicates that the model's predictive ability is no better than random guessing, and 1 signifies perfect predictive accuracy. A higher C-index reflects better predictive performance of the model. The C-index>0.7 indicated good discrimination.

The calibration curve is used to evaluate the calibration performance of the predictive model, specifically the consistency between the predicted probabilities and the actual probabilities of the events. Ideally, the calibration curve should be a straight line passing through (0,0) and (1), indicating that the model's predicted probabilities perfectly align with the actual probabilities. Deviations from this straight line indicate discrepancies between the predicted and actual probabilities. If the curve falls below the line in a certain range, it suggests that the model underestimates the probability of the event occurring in that range; conversely, if the curve is above the line, it indicates that the model overestimates the event probability. $p < 0.05$ was considered to be statistically significant.

3 Results

3.1 Patient characteristics and baseline comparison

The average age of the patients was 69 ± 6 years. A total 179 were male (53.1%), 30.5% had a smoking history, and 20.7% had a history of alcohol consumption. Among the AF patients, the prevalence rates were 24.7% for robust, 52.2% for pre-frail, and 23.1% for frail individuals (Table 1).

3.2 Screening variables

Variable selection utilized lasso regression with fourfold cross-validation, identifying six key predictors from an initial pool of 25 variables. The selected predictors included age, gender, history of coronary heart disease, number of chronic diseases, sleep disruption frequency, and mental health status (Figure 1). The parallel line test confirmed the suitability of ordinal regression with a. p-value of 0.69. The ordinal regression results revealed significant associations with frailty for the following predictors: age (66–70 years: OR, 1.0 [95% CI, 0.51–1.92]; 71–75 years: OR, 2.28 [95% CI, 1.02–5.19]; 76–80 years: OR, 3.91 [95% CI, 1.43–15.86]; ≥80 years: OR, 4.13 [95% CI, 1.14–15.86]; $p = 0.005$), gender (female: OR, 1.86 [95% CI, 1.06–3.31]; $p = 0.029$), history of coronary heart disease (OR, 2.46 [95% CI, 1.31–4.67]; $p = 0.004$), number of chronic diseases (>4: OR, 5.08 [95% CI, 2.57–10.36]; $P < 0.001$), sleep disruption <3 times/week: OR, 1.50 [95% CI, 0.71–3.19]; ≥3 times/week: OR, 2.59 [95% CI, 1.36–4.98]; $p = 0.012$), and mental health status (76–85 points: OR, 1.45 [95% CI, 0.74–2.86]; 53–75 points: OR, 3.00 [95% CI, 1.39–6.57]; 0–52 points: OR, 6.98 [95% CI, 2.40–21.30]; $P < 0.001$) were significantly associated with frailty (Table 2).

3.3 Development of a nomogram model for frailty prediction in AF patients

Based on the ordinal regression results, we developed a nomogram model to predict frailty risk among AF patients (Figure 2). Each predictor in the nomogram is assigned a specific score displayed at the top. Clinicians can calculate a patient's total score by summing these values and then estimate the probability of pre-frailty and frailty by drawing a line from the total score to the risk axis. For instance, a 74-year-old male with a history of coronary heart disease, a mental health status score of 52, more than four chronic diseases, and sleep disruption exceeding three times per week, would have a total score of 323.5, indicating a 0.99% risk for pre-frailty and an 85% risk for frailty.

3.4 Performance of the nomogram model

The nomogram model's performance was assessed through discrimination and calibration plots. Calibration plots (Figure 3) demonstrated a high degree of alignment between actual and ideal curves, reflecting strong predictive accuracy. The C-index for the training group (0.821, 95% CI: 0.778–0.864; bias-corrected C-index: 0.795) and testing group (0.819, 95% CI: 0.762–0.876; bias-corrected C-index: 0.819) underscored the model's strong discriminatory power.

4 Discussion

4.1 Improved risk prediction with multidimensional predictors

The study developed and validated a nomogram model to predict the risk of frailty in AF patients. Key predictors included age, gender, history of coronary heart disease, number of chronic illnesses, sleep

TABLE 1 Basic characteristics of older adult AF patients.

Item	Characteristic	All patients (n = 337)	Training group (n = 242)	Testing group (n = 95)
Frail status	Robust	83 (24.7%)	55 (22.7%)	28 (29.5%)
	Pre-frail	176 (52.2%)	130 (53.7%)	46 (48.4%)
	Frail	78 (23.1%)	57 (23.6%)	21 (22.1%)
Age (year)	—	69 ± 6	69 ± 6	68 ± 7
BMI (Kg/m^2)	—	25.56 ± 3.38	25.8 ± 3.4	24.85 ± 2.91
Duration (month)	—	20 (7.65)	29 (9.77)	12 (3.36)
Number of chronic diseases	—	3.68 ± 1.79	3.83 ± 1.78	3.32 ± 1.78
Gender	Male	179 (53.1%)	135 (55.8%)	44 (46.3%)
	Female	158 (46.9%)	107 (44.2%)	51 (53.7%)
AF type	Paroxysmal	208 (61.7%)	150 (62.0%)	58 (61.1%)
	Persistent	129 (38.3%)	92 (38.0%)	37 (38.9%)
Education	Primary school	49 (14.5%)	35 (14.5%)	14 (14.7%)
	Junior high school	118 (35.0%)	89 (36.8%)	29 (30.5%)
	Senior high school	92 (27.3%)	63 (26.0%)	29 (30.5%)
	Junior college	78 (30.2%)	55 (22.7%)	23 (24.2%)
Diabetes	Yes	73 (21.7%)	48 (19.8%)	25 (26.3%)
Hypertension	Yes	217 (64.4%)	166 (68.6%)	51 (53.7%)
Coronary heart disease	Yes	133 (39.5%)	93 (38.4%)	40 (42.1%)
Heart failure	Yes	37 (11.0%)	18 (7.4%)	19 (20.0%)
Ischemic stroke	Yes	88 (26.1%)	60 (24.8%)	28 (29.5%)
Smoking	No	234 (69.4%)	165 (68.1%)	69 (72.6%)
	Smoking cessation	51 (15.1%)	42 (17.4%)	9 (9.5%)
	Yes	52 (15.4%)	35 (14.5%)	17 (17.9%)
Drinking	No	267 (79.2%)	184 (76.0%)	83 (87.4%)
	Abstinence	23 (6.8%)	22 (9.1%)	1 (1.1%)
	Yes	47 (13.9%)	36 (14.9%)	11 (11.6%)
Sleep duration	>7 h	97 (28.8%)	71 (29.3%)	26 (27.4%)
	5–7 h	195 (57.9%)	137 (56.7%)	58 (61.1%)
	<5 h	45 (1345%)	34 (14.0%)	11 (11.6%)
Sleep disruption	None	102 (30.3%)	67 (27.7%)	35 (36.8%)
	<3 times/week	81 (24.1%)	125 (51.7%)	23 (24.2%)
	≥3 times/week	154 (45.7%)	117 (48.3%)	37 (38.9%)
Difficulty falling asleep	No	132 (39.2%)	85 (35.1%)	47 (49.5%)
	Yes	205 (60.8%)	157 (64.9%)	48 (50.5%)
LDL (mmol/L)	–	2.68 ± 0.86	2.66 ± 0.89	2.74 ± 0.79
HDL (mmol/L)	–	1.12 (1.01, 1.30)	1.12 (1.02, 1.29)	1.13 (0.96, 1.35)
Hs-crp (mg/L)	–	1.42 (0.75, 2.80)	1.42 (0.73, 2.54)	1.43 (0.82, 3.67)
BNP (pg/ml)	–	143 (71,282)	139 (70,273)	164 (76,314)
LA (mm)	–	42.21 ± 5.55	42.11 ± 5.43	42.48 ± 5.90
LVEDD (mm)	–	48.08 ± 4.16	48.08 ± 4.03	48.06 ± 4.53
LVEF (%)	–	62 (60.63)	62 (60.63)	62 (59.63)
Mental health status (points)	–	74.60 ± 16.62	75.68 ± 15.62	72.75 ± 16.87

Basic data are expressed as Mean ± SD or Median (IQR) or Number (%). *$p < 0.05$. LA, left atrial diameter; LV, left ventricular end-diastolic diameter; LVEF, Left ventricular ejection fraction; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; Hs-crp, high-sensitivity c-reactive protein; BNP, brain natriuretic peptide, troponin.

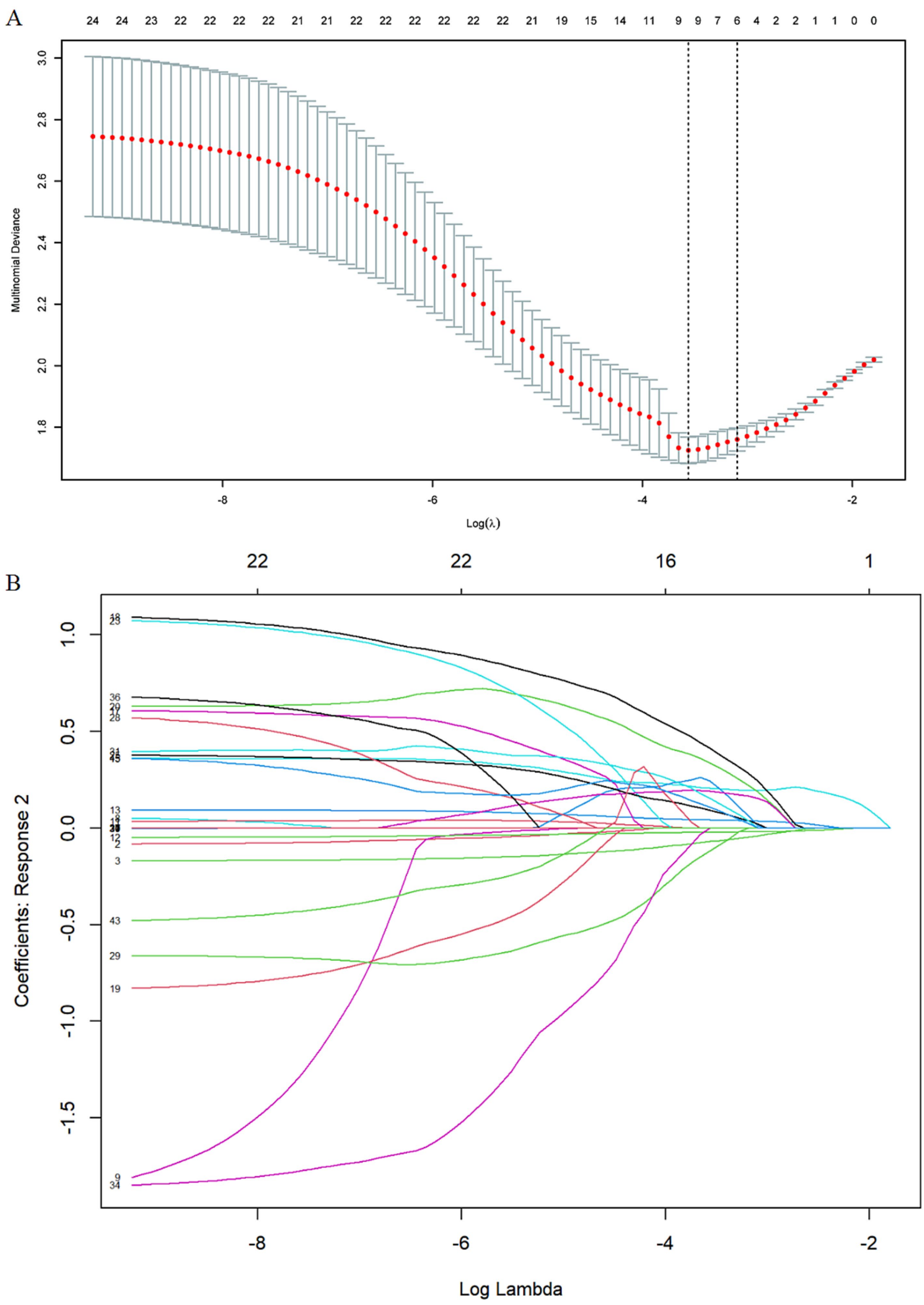

FIGURE 1
Variables selection by using least absolute shrinkage and LASSO regression. (A) Cross-validation plot for the penalty term: The 2 dashed lines correspond to two special lambda values: lambda. Min(left) and lambda. l SE (right). We ultimately selected the six variables associated with the lambda.1 SE value. (B) Values of the penalty parameter: The curve in the figure represents the change trajectory of each independent variable coefficient, the vertical coordinate is the value of the corresponding coefficient of the independent variable, the lower abscissa is log(λ), and the upper abscissa is the number of variables with non-zero coefficients in the model at this time.

TABLE 2 Ordinal regression analysis of frailty in older adult AF patients.

Item	*P*	*OR*	OR (95%CI)	
			Lower limit	Upper limit
Age				
60–65	0.005*	–	–	–
66–70		1	0.51	1.92
71–75		2.28	1.02	5.19
76–80		3.91	1.43	15.86
≥80		4.13	1.14	15.86
Gender				
Male	0.029*	–	–	–
Female		1.86	1.06	3.31
History of coronary heart disease				
No	0.004*	–	–	–
Yes		2.46	1.31	4.67
Number of chronic diseases				
≤4	<0.001*	–	–	–
>4		5.08	2.57	10.36
Sleep disruption				
No	0.012*	–	–	–
<3 times/week		1.5	0.71	3.19
≥ 3 times/week		2.59	1.36	4.98
MHI-5 score				
86–100	<0.001*	–	–	–
76–85		1.45	0.74	2.86
53–75		3	1.39	6.57
0–52		6.98	2.4	21.3

*$P < 0.05$. OR, odds ratio.

disturbances, and mental health status emerged as independent predictors. Both internal and external validations consistently affirmed the model's robust discriminatory and calibration capabilities. The prevalence of pre-frailty and frailty in our AF cohort were 52.2 and 23.1%, respectively—aligned closely with meta-analytic findings (pre-frailty: 39.7%, range: 29.9–50.5%; frailty: 35.0%, range: 26.1–45.1%) (19). Comparatively, the prevalence of frailty in Chinese community residents is lower, reported at 9.9%, with a range of 2.3 to 12.7% (20). The higher frailty rates in the AF cohort could be attributed to shared underlying pathogenic mechanisms (3). Frail AF patients exhibited elevated risks of all-cause mortality, ischemic stroke, and bleeding (19). Hence, identifying risk factors and constructing predictive models are imperative for assessing frailty risk in the AF population. Prior studies enrolled diversiform factors such as dietary habits, age, exercise habits, and social support into frailty risk models, which demonstrated that incorporating comprehensive predictors is more effective than relying solely on physiological indicators, given that frailty results from multi-systems working together (21).

Our study's innovation lies in integrating diverse risk factors encompassing demographic, sociological, lifestyle, mental health, and sleep-related parameters. This nomogram model is user-friendly, enabling clinicians to swiftly compute patient frailty risks with intuitive ease.

4.2 AF patients with advanced age, female, and various chronic diseases are more prone to frailty

Aging leads to differential declines in physiological systems, notably marked changes in skeletal muscle. Firstly, there is a reduction in muscle contractile tissue and an increase in non-contractile tissue, such as fat and connective tissues (22). Secondly, skeletal muscle experiences a decrease in capillary density and oxidative capacity (23). Even with high-protein diets or physical exercise, muscle protein synthesis rates decline (24). Concurrently, degeneration of the basal ganglia affects motor planning, thereby compromising motor control (22). These changes contribute to decreased muscle quantity and mass, culminating in reduced muscle strength (24). Physical activity has been shown to enhance muscle strength and attenuate frailty progression (25). However, the relationship between AF and exercise is nuanced; long-term endurance exercise may increase AF risk in a J-shaped pattern, while mild to moderate physical activity provides protection against AF (26). Gender differences exist in the association between exercise and AF; moderate to vigorous exercise reduces AF risk in women, whereas vigorous exercise increases risk in men (27). Clinicians should tailor exercise recommendations to the type, intensity, and duration of activity and address psychological barriers like kinesiophobia that hinder physical activity (28). Older adult AF patients are particularly vulnerable to multimorbidity including heart failure, stroke, and coronary artery disease. In our study, 30.2% of older adult AF patients exhibited four or more concurrent diseases, exacerbating frailty progression under chronic stress. Notably, AF patients with coronary artery disease demonstrated a 2.4-fold higher frailty risk.

The challenge of managing multiple chronic conditions often leads to polypharmacy, which increases the risk of adverse drug effects and, consequently, frailty (29). Frailty itself also increases the risk of drug-related harm (30). Thus, careful medication management, including appropriate dosages and schedules, is essential for older adult AF patients.

Furthermore, we identified that women had a 1.86-fold higher frailty risk compared to men. Older women exhibit lower skeletal muscle mass and higher fat mass relative to older men (31), partly due to postmenopausal estrogen depletion (32). Cultural and lifestyle choices, such as engaging in high-intensity household activities without sufficient structured exercise, may also contribute to functional impairments and frailty progression among older women, particularly in Chinese populations (33).

4.3 AF patients with sleep disruption are more prone to frailty

Studies indicate a high prevalence of sleep issues among AF patients (34). Our research demonstrates a positive correlation between sleep disruption and increased frailty, possibly exacerbated by the symptom burden associated with AF (35). During the night, with the activation of the vagus nerve, the

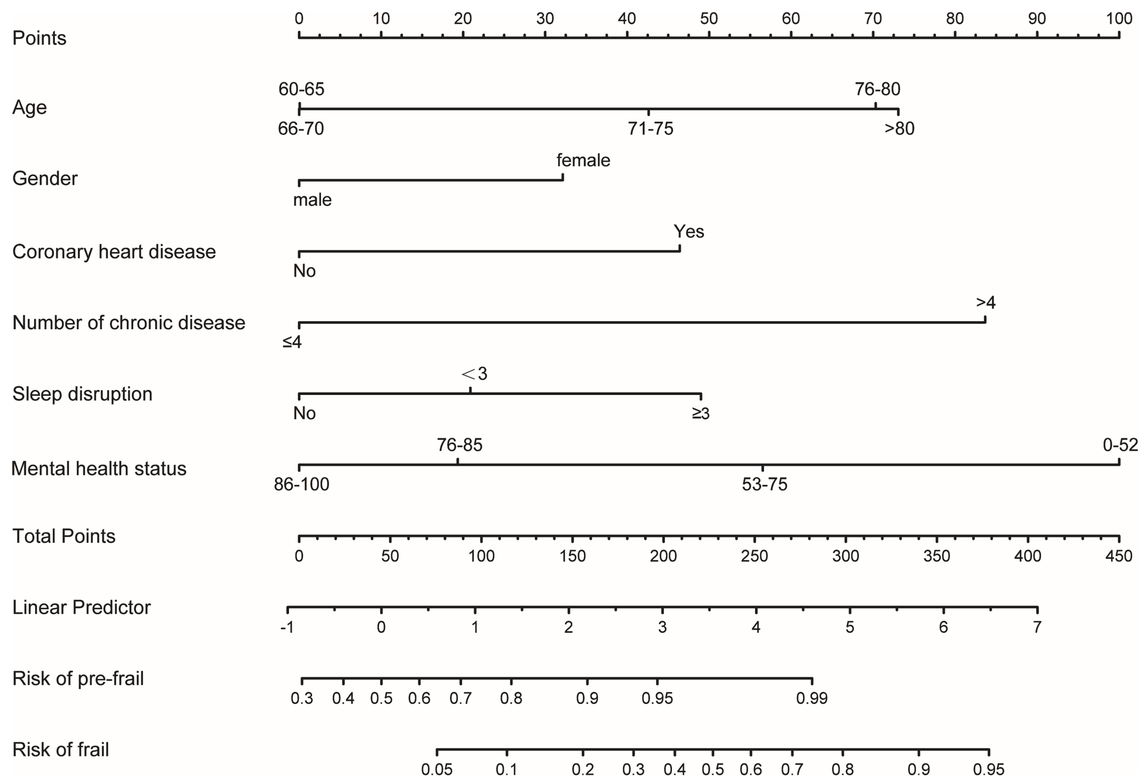

FIGURE 2
Nomogram for estimating frailty probability in older adult patients with AF. This nomogram includes age, gender, number of chronic diseases, history of coronary heart disease, sleep disruption, and mental health status. The horizontal scale labeled "Points" reflects the impact of each variable. Draw a line up to the points axis for each variable, The total score was calculated by summing all the variables. Then, the probability of pre-frail and frail was acquired by drawing a line down from the total points axis to the horizontal axis "Risk of pre-frail" and "Risk of frail" below.

incidence of symptoms such as palpitations and dyspnea increases. In addition, reduced sensory stimulation from the environment leads patients to be more sensitive to symptoms. These effects stack up, leading to an increased risk of sleep disruption. Sleep disruption causes dysfunction of the hypothalamic–pituitary–adrenal axis and gonadal axis, decreased cortisol responsiveness, and decreased levels of growth hormone and insulin-like growth factor-1 (36), which are crucial in frailty development. Another study noted a significant association between sleep duration and frailty (37). However, this study did not obtain the same effect which may be related to only considering the night sleep time and ignoring the factors like napping. To mitigate these effects, healthcare providers should advise patients to reduce electronic device use before bedtime, use relaxing music, and optimize their sleep environment.

4.4 AF patients with negative mental health status are more prone to frailty

Our investigation underscores a negative correlation between mental health status and frailty in AF patients. Those scoring ≤52 on the MHI-5 scale faced a 6.4-fold higher frailty risk, echoing findings by Uchmanowicz I (38). Negative mental states trigger neuroimmune responses that increase inflammatory cytokine release, leading to muscle mass and strength decline and thus promoting frailty. These inflammatory processes additionally impact brain regions managing emotions like fear and anxiety, exacerbating conditions such as anxiety and depression (39). A meta-analysis confirmed that depression increased frailty prevalence by fourfold, while frailty also significantly raised depression incidence. (40). Clinical strategies should prioritize assessing mental health in older adult AF patients and recommending interventions such as aromatherapy and meditation for emotional stabilization.

4.5 Strengths and limitations

This study offers valuable insights into the factors influencing frailty in AF patients and has developed a predictive model for frailty risk. This model enables healthcare providers to assess frailty risk more accurately. However, the study has limitations, including a small sample size and the absence of large-scale multicenter trials. Furthermore, frailty was assessed using subjective Frail scales rather than objective measures such as grip strength and stride length. The focus on hospitalized patients also introduces potential selection bias.

5 Conclusion

Frailty emerges as a prevalent condition among older adult patients with AF. Factors such as age, gender, history of coronary

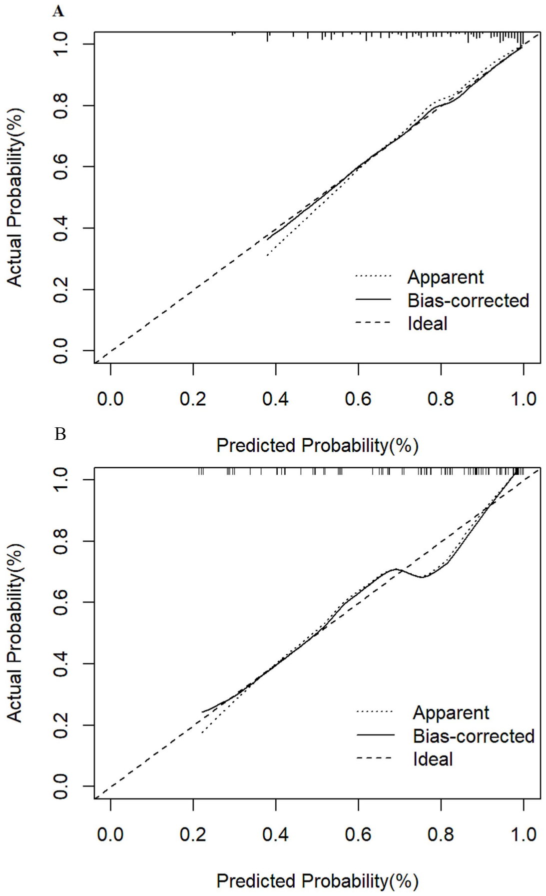

FIGURE 3
Calibration curves for frailty risk prediction model. (A) Calibration curves of the training group show that the apparent curve closely matches the ideal curve, indicating excellent predictive probability. (B) Calibration curves of the testing group also demonstrate that the apparent curve aligns well with the ideal curve, confirming the model's strong predictive performance.

heart disease, comorbidity burden, sleep disturbances, and mental health status significantly influence frailty development in AF patients. A nomogram model incorporating these significant risk factors demonstrates robust predictive and discriminative capabilities.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author.

Ethics statement

The studies involving humans were approved by Ethics Committee for Clinical Research of the Tianjin Medical University General Hospital with approval number (IRB2022-WZ-053). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

HaL: Conceptualization, Data curation, Investigation, Project administration, Supervision, Writing – original draft, Writing – review & editing. ML: Conceptualization, Project administration, Supervision, Validation, Writing – original draft. ZX: Methodology, Data collection, Project administration, Investigation, Writing – original draft, Writing – review & editing, Visualization. HoL: Conceptualization, Formal analysis, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. DS: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing.

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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.

Publisher's note

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Exploring the impact of vitamin D-related genetic variants on muscular fitness changes in middle-aged and older adults in Kosovo

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Introduction: Age-related decline in muscle strength and performance significantly impact morbidity and mortality. Various factors including genetics have been investigated to better understand this decline. This study aimed to investigate longitudinal changes in physical performance and strength and their association with genetic variants in genes involved in the vitamin D pathway.

Methods: This longitudinal study was conducted in the Prishtina region, Kosovo, with community-dwelling adults over 40 years of age. Genomic DNA was extracted from saliva samples to assess single nucleotide polymorphisms in the vitamin D receptor (VDR) gene (rs7975232, rs2228570, rs731236, also referred to as ApaI, FokI, and TaqI, respectively) and the vitamin D binding protein (GC) gene (rs4588, rs2282679). Physical performance was assessed by isometric handgrip strength, 30-s chair stand, timed up and go and 6-min walk test. Vitamin D levels were assessed from blood samples only at follow-up.

Results: A total of 138 participants (65.1 ± 9.0 years, 52.2% female) were included. Over a 2.7-year period, significant declines in the 30-s chair stand test ($p < 0.001$) and timed up and go performance ($p < 0.001$) were observed, whereas BMI increased. Only female participants experienced a decrease in handgrip strength ($p < 0.001$). Genotyping showed significant associations of the ApaI variant with changes in BMI and handgrip strength. Participants with the minor CC genotype showed a greater increase in BMI and a greater decrease in absolute and relative handgrip strength. No significant interactions were observed for FokI and TaqI in the VDR gene, or rs4588 and rs2282679 in the GC gene. Vitamin D deficiency (<50 nmol/L) was prevalent in 47.5% of participants, with significant differences in 25(OH)D levels observed between genotypes of the GC gene (rs4588, $p = 0.039$; rs2282679, $p = 0.036$).

Conclusion: Physical fitness declined significantly over time, with female participants experiencing a greater decline in handgrip strength. The ApaI variant in the VDR gene was associated with changes in muscle strength, while variants in the GC gene were associated with vitamin D levels. These findings suggest that genetic factors related to the vitamin D pathway may contribute to the age-related decline in muscle strength. Therefore, genetic predisposition should be considered when developing individual interventions for healthy aging.

KEYWORDS
physical performance, 25-hydroxyvitamin D, GC, VDR, polymorphism, aging

1 Introduction

The aging process is characterized by numerous physiological changes throughout an individual's life. A noteworthy aspect of this process is the decline in muscle strength, which is reported to commence as early as the third or fourth decade of life (1). Muscle strength and physical performance are often considered the most reliable indicators of age-related muscle alterations (2). The revised consensus criteria for defining and diagnosing sarcopenia by the European Working Group in Sarcopenia for Older People (EWGSOP2) have suggested to focus on low muscle strength as a key feature of sarcopenia, followed by low muscle quantity and quality for confirming the sarcopenia diagnosis, and poor physical performance for establishing the severity of sarcopenia (3).

Numerous factors and patterns are being investigated for their potential association with the aging process, particularly about muscle strength and function (4). Genetics stands out as an area of interest in exploring its potential influence on age-related muscle strength and function. One specific focus has been on the impact of gene polymorphisms related to the vitamin D pathway, their potential effects on vitamin D status, as well as muscular characteristics (5).

Some of these studies have focused specifically on the VDR gene, which encodes the vitamin D receptor and whose muscular expression has been shown to decline with age (6). In the VDR gene, the rs2228570 (FokI) polymorphism produces a protein that is three amino acids shorter, while rs731236 (TaqI) and rs7975232 (ApaI) are in a high linkage disequilibrium with 3` UTR polymorphisms (7). These polymorphisms are not involved in protein coding but may influence mRNA stability due to their proximity to the poly (A) tail (8). Another interesting gene within the vitamin D/muscle axis is the group-specific component (GC) gene encoding the vitamin D binding protein, which binds nearly all 25-hydroxyvitamin D (25(OH)D) in the blood and has a high affinity for actin in skeletal muscle cells (9). Carriers of the variant A allele of the commonly studied rs4588 polymorphism in the vitamin D binding protein not only show a lower affinity of the vitamin D binding protein to 25(OH)D, but also lower levels of both, vitamin D binding protein and 25(OH)D (10). Another variation within the GC gene, rs2282679, which is in strong linkage disequilibrium with rs4588, is associated with vitamin D status (5).

In a first cross-sectional study conducted in community-dwelling adults from the Prishtina region (Kosovo), we showed that the prevalence of probable sarcopenia, sarcopenia and severe sarcopenia was dependent on the specific cut points used, but was 5.5, 5.5, and 2.4% in men, respectively, according to the EWGSOP2 criteria. Possibly masked by the high prevalence of overweight and obesity, no cases of sarcopenia and severe sarcopenia were detected in women (11). A common ACTN3 polymorphism (rs1815739), frequently associated with muscle phenotypes, was not convincingly associated with muscle mass, strength and performance (12, 13). Three years later, we performed a second study focusing on vitamin D status. Vitamin D deficiency [25(OH)D concentration < 50 nmol/L] was observed in 47.5% of middle-aged and older adults, and low serum 25(OH)D was associated with low muscle strength (14). As a sub-sample of the first study participants also enrolled in the second study, this secondary analysis aimed to investigate whether longitudinal changes in muscle characteristics would be related to the frequently reported polymorphisms across the VDR gene (rs7975232 (ApaI), rs2228570 (FokI) and rs731236 (TaqI)) and the GC gene (rs4588 and rs2282679). By examining the relationship between these genetic variants and longitudinal changes in muscle characteristics, the study hopes to contribute to our understanding of how genetic predisposition may affect muscle health in older adults. We hypothesized that unfavorable variants in the VDR or GC genes would be associated with a greater decline in muscle mass, strength, and performance.

2 Methods

2.1 Study population

This longitudinal observation used data from two cross-sectional studies conducted in two different time periods: August 2016 – June 2017 and December 2019 – February 2020 (Figure 1). From the 308 subjects participating in the first study, 138 agreed and were eligible to participate in the second follow-up study. The recruitment strategy and inclusion criteria for the initial studies were described in detail in a previous publication (12). The participants were initially selected through purposive sampling, with the aim of ensuring that they met the specific criteria that were relevant to the study objectives. Additionally, we used snowball sampling, where existing participants referred others from their networks who met the study criteria. This approach allowed us to leverage the close-knit relationships common in the area, which helped us to expand our participant pool and enhance the relevance of the insights gathered. The criteria ensured that male and female participants were over 40 years of age, with no upper limit, had no acute illnesses or conditions that would directly affect their ability to participate in the physical performance tests, and belonged to the specified region and age group. The distribution of male and female participants was based on the natural availability and eligibility of volunteers within the target demographic, rather than a strict quota. By prioritizing eligibility criteria, we aimed to ensure that our sample accurately reflected the demographic characteristics of the population, thereby increasing the validity of our findings.

The first measurements took place at the Sports Medicine Laboratory of the Universi College in Prishtina (Kosovo), while the second measurements took place at the Laboratory for Human Biomarkers of the University "Fehmi Agani" in Gjakova (Kosovo). Both studies were conducted by the same research group, strictly following the initially set order (personal health, behaviors and socio-economic data collection, anthropometric measurements, body composition, short 30–60 min lunch break with a standardized light meal and physical performance assessments). At the second assessment, blood samples were taken by licensed health professionals in the morning immediately after the personal data collection.

Each participant followed a specified protocol, which began the day before with abstinence from alcohol and overnight fasting, as well as

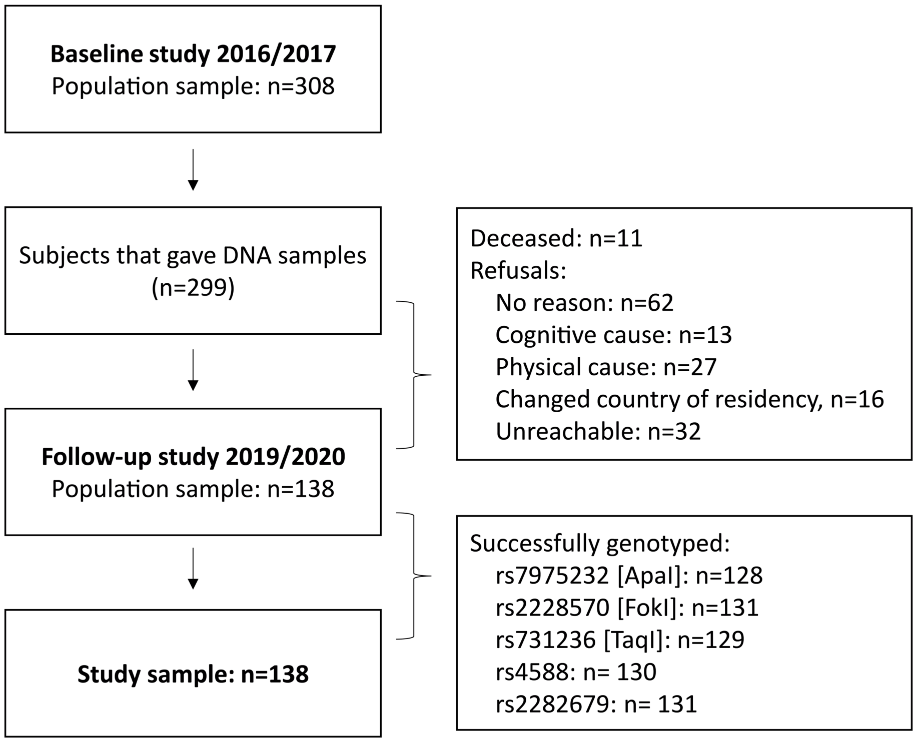

FIGURE 1
Participant flow.

wearing light indoor clothing during the assessments, in accordance with the International Standards for Anthropometric Assessments (15). Measurements started with personal data collection, saliva (study 1) or blood (study 2) sampling, anthropometry, body composition, a short break with a light standardized meal, and concluded with physical performance assessments. Nutritional status score was assessed using the long form of the Mini Nutritional Assessment (MNA) questionnaire (16).

2.2 Anthropometric and physical fitness assessments

Anthropometric and physical fitness assessments have been described previously (11, 14). Briefly, body height was measured to the nearest 0.5 cm using a portable stadiometer (DT05L, Kinlee, Zhongshan Jinli Electronic Weighing Equipment Co. Ltd., China and Seca, Hamburg, Germany at the 1st and 2nd assessment, respectively), while body weight was measured to the nearest 0.1 kg using a digital scale (Inbody 720, Biospace Co., Seoul, Korea and Seca, Hamburg, Germany, respectively). Body weight was divided by the squared height to obtain the body mass index (BMI), expressed in kg/m^2. We did not include body composition in these analyses as the devices were different at the two-time points, making a direct comparison difficult.

At both time points, isometric handgrip strength was recorded by assessing the maximum force (two trials of 3–4 s, the better recorded) on an adaptable dynamometer (JAMAR, Petterson Medical, Warrenville, IL, United States) using the self-reported dominant hand while seated (17). Physical performance was assessed by the 30-s chair-stand (for lower body), timed up-and-go (functional mobility) and 6-min walk (aerobic endurance) tests (18). The test–retest reliability of isometric handgrip strength and all physical performance assessments was found to be acceptable (ICC > 0.7) in the Kosovo population (19).

2.3 Genotyping and vitamin D status

The detailed methodology of the genotyping process was described in our previous study (12). Briefly, the saliva samples were collected and stored at −20°C in Kosovo, and then sent for further analyses to the Laboratory of Molecular Exercise Physiology at the Centre for Sport Science and University Sports, University of Vienna (Austria), where the samples were stored at −80°C. Genomic DNA was extracted from participants' saliva samples using the GeneFiX™ Saliva-Prep DNA Isolation Kit (Isohelix, Kent, United Kingdom) following the manufacturer's instructions. SNP genotyping was performed using commercially available genotyping assays for real-time quantitative PCR (Applied Biosystems/Thermo Fisher Scientific, Vienna, Austria). Specifically, for this study, genotyping of three candidate single nucleotide polymorphisms (SNPs) located in the VDR gene (rs7975232 [ApaI], rs2228570 [FokI] and rs731236 [TaqI]) and two in the GC gene (rs4588 and rs2282679) was performed.

Unfortunately, blood samples were only collected during the second assessment period. To minimize the impact of seasonal variations, measurements were carried out during the winter months, when the lowest values are expected due to the geographical location of Kosovo (42°40′N, 21°10′E). In order to minimize diurnal variations samples were taken in the morning and processed as described previously (14). Briefly, serum samples were first processed (centrifuged at 2,000 g for 10 min at room temperature) and stored (at −20°C) in Kosovo, and then shipped frozen to the laboratory in Vienna for measurement of total 25-(OH)D (including 25-OH vitamin D_2 and 25-OH vitamin D_3). Total serum 25-(OH)D was measured using a commercially available enzyme-linked immunosorbent assay kit (EUROIMMUN Medizinische Labordiagnostika AG, Lübeck, Germany). The assay demonstrated strong correlations with other methods: HPLC ($r^2 = 0.91$, $n = 80$), LC–MS/MS ($r^2 = 0.93$, $n = 100$), and the IDS 25-OH Vitamin D Direct EIA ($r^2 = 0.93$, $n = 231$), consistent with the rigorous standards outlined by the Vitamin D Standardization Program. In this study, the intra-assay variability (CV) was 5.22% from 40 measurements per sample, and inter-assay variability (CV) was 7.82% from four measurements across 10 test runs.

2.4 Statistical analysis

All data analyses were performed using the SPSS 27 Windows statistical package (SPSS, Inc., Chicago, IL, United States). The significance level was set at $p < 0.05$. Descriptive data were presented as mean and standard deviation for continuous variables and relative frequencies for categorical variables. Two-way mixed ANOVA was used to determine the main effects of time (using the simple main effect for time) and group (using the simple main effect for groups), as well as time*group interactions. In the case of significant interactions, longitudinal changes were detected by dependent *t*-tests conducted separately for men and women. A non-parametric Kruskal–Wallis test followed by a Bonferroni-corrected *post hoc* test was used to determine differences in 25(OH)D concentrations between genotypes. Hardy–Weinberg equilibrium (HWE) was calculated by using a one-degree-of-freedom chi-squared test (χ^2), comparing the observed distribution of genotypes with the distribution of genotypes expected from applying the Hardy–Weinberg equilibrium assumption [performed using the online application: http://www.ihh.kvl.dk/htm/kc/popgen/genetik/applets/kitest.htm (accessed on 2024-01-27)].

3 Results

3.1 Participants characteristics

A total of 308 participants were recruited in the first study, of whom 299 people provided saliva DNA samples (12). From this initial study population, 138 community-dwelling male and female participants aged ≥40 years from the Prishtina region agreed to participate in the second follow-up study. Age at baseline was 65.1 ± 9.0 years (63.7 ± 9.2 in female and 66.6 ± 8.7 in male participants). The time gap between the first and second assessments was 2.7 ± 0.3 years (2.9 ± 0.4 in female and 2.8 ± 0.3 in male participants). Figure 1 illustrates the participant flow and provides information on the reasons for attrition.

The overall and sex-specific characteristics of the study participants at baseline and follow-up are described in Table 1, whereby time, group (sex) and time*group interactions were reported. Male participants were significantly taller ($p < 0.001$) and had a greater body mass ($p = 0.010$), higher absolute handgrip and relative handgrip strength ($p < 0.01$), 6-min walk performance ($p < 0.01$) and nutritional status score ($p < 0.05$). Female participants were observed to have a significantly higher BMI ($p < 0.01$), a longer time to complete the timed up-and-go test ($p < 0.010$) and took a higher number of medications ($p < 0.001$).

Height decreased significantly over time ($p < 0.001$), whereas BMI ($p = 0.004$), nutritional status score, number of medications taken ($p < 0.001$) increased. A McNemar test showed that the prevalence of chronic diseases, particularly cardiovascular diseases (including hypertension), increased, whereas the prevalence of metabolic diseases like diabetes and osteoporosis stayed stable over the observation period. Regarding physical performance, absolute and relative handgrip strength ($p < 0.001$), timed up and go test ($p = 0.002$) and 6-min walk test ($p = 0.001$) worsened, whereas the 30-s chair stand test remained unchanged ($p = 0.158$). A time*sex interaction was observed for handgrip strength and timed up and go test. Follow-up analyses showed that a significant decrease in handgrip strength and handgrip strength relative to individual body mass was observed in women ($p < 0.001$), but the opposite occurred in men ($p < 0.05$). The time taken to complete the timed up-and-go test increased significantly over time only in female participants ($p < 0.001$), whereas the increase in men was smaller and did not reach significance. Interestingly, the mini nutritional status score increased only in women ($p < 0.001$). The increase in BMI observed in both women and men did not correlate with the changes in any of the fitness parameters ($p > 0.05$).

3.2 Genotyping and vitamin D levels (at time point 2)

The genotype distribution for ApaI (rs7975232), FokI (rs2228570), TaqI (rs731236), rs4588 and rs2282679 and the Hardy–Weinberg equilibrium (HWE) of these genotypes are shown in Table 2. All SNPs investigated were in Hardy–Weinberg equilibrium (HWE), except for FokI (rs2228570).

A Kruskal-Wallis test revealed significantly different 25(OH)D levels between genotypes of the GC gene for rs4588 [$\chi^2(2) = 6.509$, $p = 0.039$] and rs2282679 [$\chi^2(2) = 6.648$, $p = 0.036$]. For rs4588, median 25(OH)D levels were lower in individuals with the AA genotype (40.2 [26.2–45.5] nmol/L) compared with those with the CC genotype (53.6 [17.7–120.6] nmol/L), although a Bonferroni-corrected *post hoc* analysis did not reach significance between the two groups ($p = 0.076$). In contrast, for rs2282679, median 25(OH)D levels were lower in individuals with the CC genotype (42.9 [26.2–49.5] nmol/L) compared with those with the AA genotype (53.6 [17.7–120.6] nmol/L). Again, a Bonferroni-corrected *post hoc* test did not reach significance ($p = 0.076$). Differences in 25(OH)D levels between GC genotypes are shown in Figure 2. No differences were found for the genotypes in the VDR gene, with ApaI [$\chi^2(2) = 1.769$, $p = 0.413$], FokI [$\chi^2(2) = 4.897$, $p = 0.086$] and TaqI [$\chi^2(2) = 0.393$, $p = 0.822$].

3.3 Impact of VDR genotypes on longitudinal changes in physical performance

Baseline data and longitudinal changes in physical performance health-related parameters are shown in Table 3 separately for ApaI (rs7975232), FokI (rs2228570), and TaqI (rs731236).

TABLE 1 Longitudinal changes in anthropometric and physical fitness tests.

Variable	Overall baseline (n = 138)	Female baseline (n = 72)	Male baseline (n = 66)	Change to follow-up (overall) (n = 138)	Change to follow-up (female) (n = 72)	Change to follow-up (male) (n = 66)	Time	Sex	Time * sex
Height [m]	1.65 ± 0.09	1.59 ± 0.07	1.71 ± 0.07###	−0.010 ± 0.023°°°	−0.012 ± 0.026	−0.007 ± 0.019	**<0.001**	**<0.001**	0.246
Body mass [kg]	80.1 ± 14.0	77.1 ± 11.4	83.4 ± 15.9##	0.17 ± 4.25	0.16 ± 4.41	0.19 ± 4.10	0.631	**0.007**	0.975
BMI [kg/m²]	29.6 ± 4.9	30.7 ± 4.6	28.3 ± 4.9##	0.43 ± 1.70°°	0.55 ± 1.94	0.31 ± 1.38	**0.004**	**0.002**	0.397
Handgrip strength [kg]	31.7 ± 9.7	26.0 ± 6.1	38.0 ± 9.0###	−0.6 ± 5.2	−2.6 ± 4.6***	1.5 ± 4.9*	0.208	**<0.001**	**<0.001**
Handgrip strength relative [kg/kg]	0.40 ± 0.11	0.34 ± 0.09	0.46 ± 0.11###	−0.009 ± 0.070	−0.036 ± 0.062***	0.020 ± 0.067*	0.151	**<0.001**	**<0.001**
Timed up and go test [s]	6.66 ± 1.55	6.82 ± 1.56	6.49 ± 1.53##	0.95 ± 2.06°°°	1.43 ± 2.20***	0.42 ± 1.77	**<0.001**	**0.002**	**0.004**
30-s chair stand test [repetitions]	12 ± 3	12 ± 3	12 ± 3	−1 ± 3°°°	−1 ± 3	−1 ± 3	**<0.001**	0.158	0.729
6-min walk test [m]	451.0 ± 138.8	422.4 ± 129.4	481.8 ± 142.9##	−6.5 ± 88.7	−13.9 ± 89.1	1.4 ± 88.2	0.411	**0.001**	0.316
Mini nutritional status score [−]	24.8 ± 3.1	24.0 ± 3.4	25.8 ± 2.5#	1.2 ± 2.9°°°	2.1 ± 3.1***	0.3 ± 2.4	**<0.001**	**0.017**	**<0.001**
Number of medications [n]	1.8 ± 1.9	2.3 ± 1.9	1.3 ± 1.7##	0.55 ± 1.56°°°	0.45 ± 1.79	0.66 ± 1.27	**<0.001**	**0.003**	0.433

BMI (body mass index); Data are expressed as mean ± standard deviation for the total population and separately for men and women; two-way mixed ANOVA was used to determine main time and sex effects and time*sex interactions; ***p < 0.001, *p < 0.05 for simple main effects (change over time separated by sex), °°°p < 0.001, °°p < 0.01 for main time effects, ###p < 0.001, ##p < 0.001, #p < 0.05 for main differences between males and females. Bold values indicate statistically significant p-values (p < 0.05).

For ApaI, there was a statistically significant interaction between ApaI and time on BMI [F(2,125) = 3.870, p = 0.023, partial η^2 = 0.058], handgrip strength [F(2,125) = 6.141, p = 0.003, partial η^2 = 0.089] and handgrip strength related to body mass [F(2,125) = 7,528, p < 0.001, partial η^2 = 0.108]. BMI increased, but absolute and relative handgrip strength decreased in CC carriers, whereas these parameters remained unchanged in the AA genotype group. The interaction between ApaI genotype and change in handgrip strength remained significant when controlled for age, change in BMI, and 25(OH)D level [F(2,121) = 7.733, p < 0.001, partial η^2 = 0.113].

There was no statistically significant interaction for the 30-s chair stand test [F(2,124) = 0.447, p = 0.641, partial η^2 = 0.007], but the main effect of group showed that there was an overall significant difference in mean 30-s chair stand repetitions between genotype groups [F(2,124) = 5.006, p = 0.008, partial η^2 = 0.075]. Interestingly, CC carriers had significantly higher values than AA carriers (p = 0.035). Results for the 6-min walk test showed no effect of the ApaI genotype, either at baseline or with respect to changes over time.

For FokI and TaqI, no genotype*time interactions or main group effects were detected (Table 3).

3.4 Impact of GC genotypes on longitudinal changes in physical performance

Similar to FokI and TaqI, no genotype*time interactions or main group effects were found for rs4588 and rs2282679 in the GC gene (Table 4).

In detail, there was no interaction for the rs4588 genotypes and time with respect to BMI [F(2, 127) = 0.526, p = 0.592, partial η^2 = 0.008], handgrip strength [F(2,127) = 2.017, p = 0.137, partial η^2 = 0.031], timed up and go [F(2,127) = 0.100, p = 0.905, partial η^2 = 0.002], 30-s chair stand test [F(2,126) = 1.134, p = 0.325, partial η^2 = 0.018] and 6-min walk test [F(2,126) = 0.070, p = 0.933, partial η^2 = 0.001]. However, simple main effects for time revealed that only CC and CA carriers were significantly slower during the timed up and go test (p < 0.05) hinting to an unfavorable AA genotype.

For the rs2282679, there was no interaction effect with time for BMI [F(2,128) = 0.505, p = 0.604, partial η^2 = 0.008], handgrip strength [F(2,128) = 2.052, p = 0.133, partial η^2 = 0.031], timed up and go [F(2,128) = 0.143, p = 0.867, partial η^2 = 0.002], 30-s chair stand test [F(2,127) = 0.846, p = 0.432, partial η^2 = 0.013] and 6-min walk test [F(2,127) = 0.079, p = 0.924, partial η^2 = 0.001]. Similar to the findings above, simple main effects for time showed that time needed for the timed up and go test only increased in CA and AA carriers (p < 0.05) hinting to an unfavorable CC genotype.

4 Discussion

This study shows that muscle strength and physical performance decline over approximately 3 years, regardless of biological sex, although isometric strength and functional mobility decline at a higher rate in female participants. In addition, vitamin D-related gene polymorphisms may play a role in this decline, with rs7975232 (ApaI) emerging as a promising candidate regarding its influence on

TABLE 2 Genotype frequencies.

SNP	Aliases	Chr	Gene	Major/ Minor alleles	Subjects (n)	Genotype frequency, *n* (%)	Allele frequency, *n* (%)	HWE
rs7975232	ApaI	12	VDR	A/C	128	AA 42 (32.8) AC 67 (52.3) CC 19 (14.9)	A 74.5 (58.98) C 52.5 (41.02)	0.652
rs2228570	FokI	12	VDR	G/A	131	AA 19 (14.5) AG 44 (33.6) GG 68 (51.9)	A 41 (31.30) G 90 (68.70)	0.043*
rs731236	TaqI	12	VDR	A/G	129	AA 51 (39.5) AG 55 (42.6) GG 23 (17.8)	A 78.5 (60.85) G 50.5 (39.15)	0.490
rs4588	–	4	GC	C/A	130	CC 82 (63.1) CA 40 (30.7) AA 8 (6.2)	C 102 (78.5) A 28 (21.5)	0.593
rs2282679	–	4	GC	A/C	131	CC 9 (6.9) CA 40 (30.5) AA 82 (62.6)	C 29 (22.14) A 102 (77.86)	0.425

SNP (single nucleotide polymorphism), Chr (chromosome), HWE (Hardy–Weinberg Equilibrium); *Distribution not consistent with Hardy Weinberg's law at $p < 0.05$.

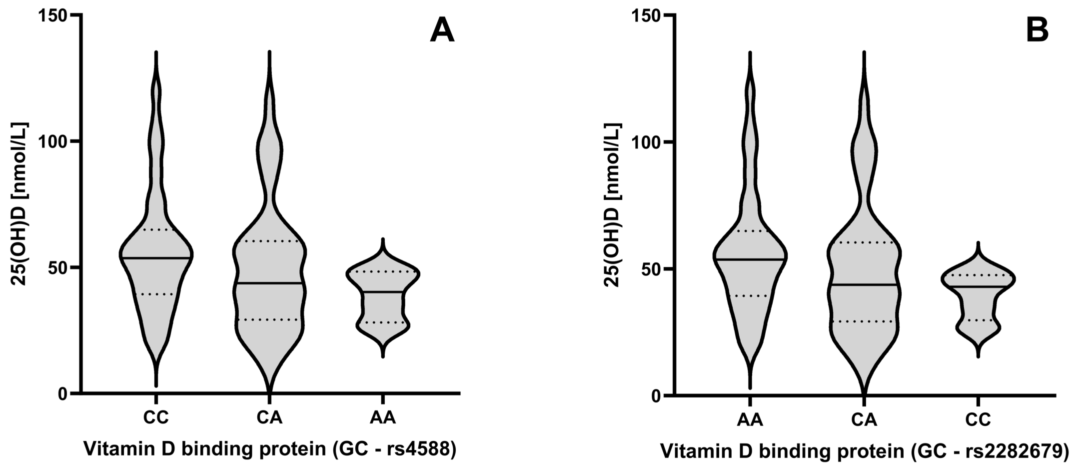

FIGURE 2
Impact of the rs4588 **(A)** and rs2282679 **(B)** genotypes across GC genes on 25-hydroxyvitamin D (25(OH)D) levels. Violine plots are shown to visualize the distribution of the data with 25th, 50th and 75th percentile shown as lines.

strength-related traits. Beyond this observation, 25(OH)D concentration at time point 2 was significantly lower in AA carriers of the rs4588 and in CC carriers of the rs2282679 SNPs, both located in the vitamin D binding GC gene.

It has been suggested that the age-related decline in muscle strength should not necessarily be viewed as a singular process but rather as a more comprehensive multifactorial one (e.g., inability of the nervous systems to fully activate skeletal muscles, differences between biological sexes, etc.). Furthermore, a significant association between low levels of muscle strength and poor physical performance and/or physical disability has been reported (20), with potential implications for morbidity and mortality. The results of this study confirm the age-related decline in isometric muscle strength relative to the individual's body mass, but only in female participants. It is noteworthy that a very wide age range was included in this study (40 years and older) with 8.7% of the participants under 50 years of age, 60.1% of the participants between 50 and 70 years of age, and 31.2% of the participants being over 70 years of age. The distribution of women and men between the age groups is similar and not statistically different. Therefore, the observed difference between men and women could be explained by an earlier onset of handgrip strength decline in women, as shown in the Copenhagen Sarcopenia Study, where handgrip strength declined in women from the age of 50 and in men from the age of 60 years (21). It has been suggested that poorer physical function in women compared with men can be explained predominantly by differences in body composition. The higher proportion of body fat in women may put them at a significant biomechanical disadvantage resulting in greater disability in old age (22). As BMI is significantly higher in our female cohort this could be a further factor for the observed differences.

TABLE 3 Influence of vitamin D receptor (VDR) genetic variants on changes in physical performance and health-related parameters up to follow-up.

Variable	Baseline			Change to follow-up			p-values		
rs7975232 [ApaI]	AA (n = 42)	AC (n = 67)	CC (n = 19)	AA (n = 42)	AC (n = 67)	CC (n = 19)	Time	Group	Time * ApaI
BMI [kg/m²]	31.4 ± 5.9[a]	28.9 ± 4.3[a,b]	28.5 ± 3.7[b]	−0.05 ± 1.65	0.50 ± 1.65°	1.23 ± 1.92°	**0.001**	**0.043**	**0.023**
Handgrip strength [kg]	29.5 ± 11.6	32.1 ± 8.4	30.3 ± 5.9	−1.26 ± 5.5	0.47 ± 4.93	−3.98 ± 4.06°°°	**0.002**	0.106	**0.003**
Handgrip strength relative [kg/kg]	0.36 ± 0.14[a]	0.41 ± 0.10[b]	0.40 ± 0.09[a,b]	−0.01 ± 0.07	0.00 ± 0.07	−0.06 ± 0.06°°°	**<0.001**	**0.011**	**<0.001**
Timed up and go test [s]	6.78 ± 1.77	6.60 ± 1.52	6.58 ± 1.49	1.47 ± 2.65°°	0.73 ± 1.86°°	0.96 ± 1.46°	**<0.001**	0.219	0.200
30-s chair stand test [repetitions]	11 ± 3[a]	12 ± 2[a,b]	13 ± 3[b]	−1 ± 3°°	−1 ± 3	−1 ± 3	**0.005**	**0.008**	0.641
6-min walk test [m]	425.4 ± 153.2	453.6 ± 132.0	469.5 ± 116.5	−8.8 ± 98.8	0.4 ± 86.0	−25.9 ± 90.2	0.217	0.343	0.530
Mini nutritional status score [−]	24.6 ± 3.4	24.8 ± 3.0	25.4 ± 2.5	0.85 ± 3.24	1.48 ± 2.76°°°	1.05 ± 2.36	**<0.001**	0.234	0.520
Number of medications [n]	2.1 ± 1.8	1.8 ± 1.8	1.7 ± 1.9	0.42 ± 1.70	0.63 ± 1.58°°	0.61 ± 1.42	**0.001**	0.764	0.790

Variable	Baseline			Change to follow-up			p-values		
rs2228570 [FokI]	AA (n = 19)	AG (n = 44)	GG (n = 68)	AA (n = 19)	AG (n = 44)	GG (n = 68)	Time	Group	Time * FokI
BMI [kg/m²]	30.3 ± 4.7	29.8 ± 5.2	29.2 ± 4.9	0.04 ± 1.82	0.38 ± 1.56	0.60 ± 1.81	0.052	0.786	0.430
Hand grip strength [kg]	30.0 ± 10.4	32.9 ± 10.0	30.5 ± 8.6	−0.81 ± 5.56	0.27 ± 4.76	−1.08 ± 5.51	0.310	0.222	0.412
Hand grip strength relative [kg/kg]	0.37 ± 0.12	0.41 ± 0.12	0.39 ± 0.11	−0.00 ± 0.07	0.00 ± 0.06	−0.02 ± 0.07	0.308	0.363	0.303
Timed up and go test [s]	6.13 ± 1.78	6.86 ± 1.64	6.69 ± 1.46	1.41 ± 1.90°°	0.48 ± 1.89	1.20 ± 2.25°°°	**<0.001**	0.552	0.136
30-s chair stand test [repetitions]	12 ± 2	12 ± 3	11 ± 3	−0 ± 3	−1 ± 3	−1 ± 3°	**0.024**	0.164	0.647
6-min walk test [m]	444.0 ± 103.8	481.8 ± 156.8	429.0 ± 129.0	6.9 ± 75.1	−15.8 ± 84.8	−4.0 ± 97.8	0.637	0.133	0.631
Mini nutritional status score [−]	25.2 ± 2.4	25.0 ± 3.4	24.5 ± 3.1	0.97 ± 2.42	1.48 ± 3.04°°	1.15 ± 3.02°°	**<0.001**	0.288	0.776
Number of medications [n]	1.8 ± 1.7	1.4 ± 1.7	1.9 ± 1.8	0.79 ± 1.75	0.52 ± 1.41°	0.55 ± 1.67°	**<0.001**	0.217	0.814

Variable	Baseline			Change to follow-up			p-values		
rs731236 [TaqI]	AA (n = 51)	AG (n = 55)	GG (n = 23)	AA (n = 51)	AG (n = 55)	GG (n = 23)	Time	Group	Time * TaqI
BMI [kg/m²]	28.6 ± 3.9	29.9 ± 5.2	31.6 ± 5.6	0.82 ± 1.80°°	0.44 ± 1.48°	−0.23 ± 2.05	**0.038**	0.096	0.055
Hand grip strength [kg]	30.2 ± 8.0	32.5 ± 9.6	29.3 ± 11.3	−1.33 ± 5.21	−0.02 ± 5.54	−0.95 ± 4.62	0.127	0.180	0.429
Hand grip strength relative [kg/kg2]	0.39 ± 0.10	0.40 ± 0.11	0.36 ± 0.14	−0.28 ± 0.07	0.00 ± 0.07	−0.01 ± 0.06	0.109	0.232	0.099

(Continued)

TABLE 3 (Continued)

Variable	Baseline			Change to follow-up			*p*-values		
rs731236 [TaqI]	AA (*n* = 51)	AG (*n* = 55)	GG (*n* = 23)	AA (*n* = 51)	AG (*n* = 55)	GG (*n* = 23)	Time	Group	Time * TaqI
Timed up and go test [s]	6.59 ± 1.42	6.71 ± 1.61	6.74 ± 1.92	0.78 ± 1.55°°	0.87 ± 1.89°°	1.92 ± 3.26°	**<0.001**	0.209	0.074
30-s chair stand test [repetitions]	12 ± 3	11 ± 3	11 ± 3	−1 ± 3°	−0 ± 3	−2 ± 2°°	**0.001**	0.099	0.196
6-min walk test [m]	450.2 ± 131.9	449.4 ± 138.1	422.6 ± 142.9	2.8 ± 89.0	−20.6 ± 92.8	8.5 ± 85.2	0.721	0.702	0.290
Mini nutritional status score [−]	25.1 ± 3.5	24.5 ± 2.6	24.8 ± 3.7	1.16 ± 3.01°°	1.56 ± 2.75°°°	0.65 ± 3.34	**<0.001**	0.514	0.460
Number of medications [n]	1.6 ± 1.8	1.8 ± 1.8	2.3 ± 2.0	0.72 ± 1.39°°	0.49 ± 1.60°	0.36 ± 2.04	**0.001**	0.461	0.629

BMI (body mass index). Data are expressed as means ± standard deviations for the participants separated based on the genotypes; Mixed two-way ANOVA was used to determine main time and group effects as well as time*group interactions; °°°$p < 0.001$, °°$p < 0.01$ for main time effects, different superscript letters ("a" and "b") indicate the statistically significant differences for simple main effects between groups. Bold values indicate statistically significant p-values ($p < 0.05$).

However, the primary aim of this study was to investigate the potential influence of SNPs from vitamin D pathway-related candidate genes (VDR and GC) on decline in physical performance and strength. The selection of the genotypes was based on a previous systematic review showing some evidence for their association with vitamin D levels and some extent also to muscular performance (5). The VDR gene encodes the vitamin D receptor, which is a member of the nuclear receptor superfamily and is a genomic and non-genomic mediator of the effects of vitamin D in the organism, whereas the GC gene encodes the vitamin D binding protein, which is a multifunctional protein that also has a role as a transporter of vitamin D metabolites (23).

In the VDR gene, rs7975232 (ApaI), an intron variant, emerged as a promising candidate in this regard, with time and group effects and time*group interactions observed for grip strength. A significant decline was seen in homozygous recessive (CC) genotype carriers for handgrip strength and relative handgrip strength, and in homozygous dominant (AA) genotype carriers for the 30-s chair stand test. Consistent with these findings, cross-sectional studies have reported that carriers of the homozygous dominant genotype have a significantly higher handgrip strength (24), but also that homozygous recessive carriers have significantly higher knee and elbow peak torque (25). As observed, both upper and lower body strength were inversely affected by ApaI genotypes, suggesting a beneficial role of the major allele in upper strength and the minor allele in lower body strength. However, these findings warrant further mechanistic investigation. Among carriers of rs2228570 [FokI] genotypes (initiator codon variant), subjects homozygous for the major allele (GG) showed a trend for a decreased chair stand performance, suggesting that the minor allele could be the beneficial one for lower body strength. This would be in line with previous studies observing that carriers of the major homozygous genotype had significantly lower quadriceps strength (26) or significantly lower peak and average isometric quadriceps strength (27). However, other studies found no significant associations between these genotypes and muscle properties (28, 29). Finally, the rs731236 [TaqI] polymorphism, a synonymous variant, showed no effect on changes in physical performance in our study. Studies in this area also remain controversial, as studies showing no association between TaqI genotypes and muscular performance (25, 28) contrast with others observing higher isometric quadriceps strength in homozygous recessive genotypes compared with homozygous dominant and heterozygous genotypes (27) or higher handgrip strength in centenarians with dominant genotypes compared with the other genotypes (24).

For the GC-investigated SNPs, our study shows that the decline in TUG performance and chair-stand test was pronounced in carriers of homozygous dominant genotypes in both rs4588 and rs2282679 polymorphisms. This suggests that the beneficiary allele in this population is the minor allele, T allele for rs4588 and G allele for rs2282679, respectively. To the best of our knowledge, the literature investigating the direct impact of these polymorphisms across GC gene in muscle traits is sparse, and our results seem promising although these findings need to be validated in larger study populations, especially as carriers of the rare genotype comprised only 8 (rs4588) and 9 (rs2282679) participants.

In our previous systematic review, we demonstrated that certain genetic variants within genes involved in the vitamin D pathway influence vitamin D levels (5). Vitamin D deficiency is considered to be a widespread global health problem, particularly in older populations (30). A potential association between vitamin D levels and muscle strength and/or performance is of great interest not only to the scientific community but also to public health professionals, although direct positive effects of vitamin D supplementation on sarcopenia indices remain controversial (31). Individual genetic makeup may add to this equation. In this study, carriers of the major alleles for rs4588 and rs2282679 (located within the GC gene) were observed to have slightly higher serum 25(OH)D levels, although the significance did not persist after Bonferroni-correction of *post hoc* analyses. It is unlikely that BMI, weight, or age have driven this observation, as these parameters were not different between the genotype groups. Furthermore, these results are consistent with many

TABLE 4 Influence of vitamin D binding protein (GC) genetic variants on changes to follow-up.

Variable	Baseline			Change to follow-up			*P*-values		
rs4588	CC (*n* = 82)	CA (*n* = 40)	AA (*n* = 8)	CC (*n* = 82)	CA (*n* = 40)	AA (*n* = 8)	Time	Group	Time * GC1
BMI [kg/m²]	29.6 ± 4.9	29.8 ± 5.1	30.3 ± 4.6	0.34 ± 1.83	0.68 ± 1.56°°	0.60 ± 1.75	**0.023**	0.833	0.592
Handgrip strength [kg]	31.3 ± 9.5	30.7 ± 9.7	31.1 ± 6.1	−1.33 ± 5.02	0.66 ± 5.75	−1.20 ± 3.70	0.374	0.978	0.137
Handgrip strength relative [kg/kg]	0.39 ± 0.11	0.39 ± 0.12	0.39 ± 0.08	−0.02 ± 0.07	0.00 ± 0.08	−0.02 ± 0.05	0.193	0.921	0.288
Timed up and go test [s]	6.63 ± 1.52	6.82 ± 1.68	6.19 ± 1.79	1.06 ± 2.31°°°	0.92 ± 1.72°°	0.80 ± 1.84	**0.001**	0.551	0.905
30-s chair stand test [repetitions]	12 ± 3	11 ± 3	12 ± 2	−1 ± 3°°	−0 ± 3	−2 ± 3	**0.004**	0.307	0.325
6-min walk test [m]	454.3 ± 128.4	425.3 ± 161.5	476.8 ± 79.4	−8.7 ± 93.2	−4.6 ± 87.2	2.3 ± 79.4	0.762	0.366	0.933
Mini nutritional status score [−]	24.7 ± 3.2	24.9 ± 3.3	24.1 ± 2.6	1.24 ± 2.92°°°	1.15 ± 2.99°	1.75 ± 3.40	**0.001**	0.822	0.873
Number of medications [n]	1.7 ± 1.8	2.1 ± 1.9	1.75 ± 1.39	0.71 ± 1.63°°°	0.18 ± 1.48	1.13 ± 1.55	**0.002**	0.795	0.131

Variable	Baseline			Change to follow-up			*P*-values		
rs2282679	CC (*n* = 9)	CA (*n* = 40)	AA (*n* = 82)	CC (*n* = 9)	CA (*n* = 40)	AA (*n* = 82)	Time	Group	Time * GC2
BMI [kg/m²]	30.8 ± 4.5	29.8 ± 5.1	29.6 ± 4.9	0.50 ± 1.67	0.68 ± 1.56°°	0.34 ± 1.83	**0.026**	0.705	0.604
Hand grip strength [kg]	34.6 ± 11.8	30.7 ± 9.7	31.3 ± 9.5	−1.29 ± 3.47	0.66 ± 5.75	−1.33 ± 5.02	0.329	0.658	0.133
Hand grip strength relative [kg/kg]	0.41 ± 0.09	0.39 ± 0.12	0.39 ± 0.11	−0.02 ± 0.04	0.00 ± 0.08	−0.02 ± 0.07	0.170	0.906	0.281
Timed up and go test [s]	6.42 ± 1.82	6.82 ± 1.68	6.63 ± 1.52	0.72 ± 1.73	0.92 ± 1.72°°	1.06 ± 2.31°°°	**0.001**	0.712	0.867
30-s chair stand test [repetitions]	11 ± 3	11 ± 3	12 ± 3	−2 ± 3	0 ± 3	−1 ± 3°°	**0.007**	0.208	0.432
6-min walk test [m]	454.9 ± 99.1	425.3 ± 161.5	454.3 ± 128.4	2.6 ± 74.2	−4.6 ± 87.2	−8.7 ± 93.2	0.758	0.488	0.924
Mini nutritional status score [−]	24.6 ± 2.7	24.9 ± 3.3	24.7 ± 3.2	1.67 ± 3.19	1.15 ± 2.99°	1.24 ± 2.92°°°	**0.001**	0.931	0.894
Number of medications [n]	1.7 ± 1.3	2.1 ± 1.9	1.7 ± 1.8	1.11 ± 1.45	0.18 ± 1.48	0.71 ± 1.63°°°	**0.001**	0.832	0.125

BMI (body mass index). Data are expressed as means ± standard deviations for the participants separated based on the genotypes; Mixed two-way ANOVA was used to determine main time and group effects as well as time*group interactions; °°°$p < 0.001$, °°$p < 0.01$ for simple main time effects. Bold values indicate statistically significant p-values ($p < 0.05$).

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of those included in our systematic review (5), where 73 and 77% of the conducted studies selected (respectively) showed an association of rs4588 and rs2282679 with vitamin D levels, and the major alleles were the beneficiary ones in both cases. This was not evident between selected SNPs across the VDR gene, with conflicting results already reported (5). However, other factors should be taken into consideration when comparing such data between the different studies, including the heterogeneity in measurements of vitamin D status or levels and participant characteristics.

The decline in age-related muscle strength is recognized as a multifactorial process influenced by genetics, but also lifestyle factors (such as nutritional and physical behaviors) as well as metabolic processes that may have impacted the study outcomes. Regarding vitamin D supplementation, data collected and reported for the studied population (14), revealed that 87.6% of participants did not take vitamin D supplements, despite their very low daily dietary vitamin D intake (1.89 ± 0.67 μg/day). It further appears from the evidence from systematic reviews and meta-analyses that physical activity alone may not be sufficient to increase 25(OH)D levels, regardless of the amount of time spent outdoors (32). As no specific data on physical activity levels were recorded, it was assumed that participants did not significantly alter their physical activity behaviors over time. To address potential confounding factors, the Physical Readiness Questionnaire (PAR-Q) was used to exclude severe cases, along with the original study's specific exclusion criteria (14), which included acute illness preventing exercise testing and serious chronic illnesses requiring continuous medical care. Additionally, a comparison of the two measurement time points showed no changes in the prevalence of self-reported medical conditions such as osteoporosis, hypertension, or diabetes.

To further investigate these effects, we performed correlations between BMI and 25(OH)D levels, as well as between longitudinal changes in BMI and muscle strength. However, no significant associations were found. This lack of association may reflect the complex interplay of factors influencing vitamin D status, including the known role of adiposity in the sequestration of vitamin D, which can reduce its bioavailability. While body fat is an important factor in aging, and not BMI alone, our study did not find any significant correlation between BMI, weight, or body composition with vitamin D levels. Despite the recognized influence of adiposity on vitamin D metabolism (33, 34), our findings suggest that other factors may be at play in this cohort. In addition, in contrast to height, which declined significantly from the first to the second measurement, weight did not change, thus resulting in an overall increase in BMI over time. This reflected in the increased prevalence of overweight and obesity in the study population over time (from 40.6 to 42.0% in the overweight group and from 42.0 to 44.9% in the obese group), particularly in women (from 38.9 to 40.3% and from 50.0 to 55.6%, respectively). The number of participants with normal weight decreased from 16.7 to 12.3% compared to the baseline measurements, which raises the alarm about the seriousness of this problem for the public health of Kosovo (11, 12). It should be noted that the optimal BMI levels may be higher for older adults as compared to young adults (35), and that body composition may be a better indicator of health (36). Future studies need to address this issue in the region in more detail. A recent review of the global burden of metabolic diseases for the period 2000–2019 found that the prevalence of metabolic diseases (including obesity) is increasing worldwide, regardless of socio-demographic index (37). This, along with the low expected life expectancy observed in Kosovo (70.3 years for men and 74.8 years for women) (38) may reflect the impact of increasing overweight and obesity rates.

Given that the expected life expectancy and the proportion of older people are higher in high-income countries, most age-related studies are conducted in these parts of the world. Nevertheless, the expected growth of the older population from developing countries is estimated to outstrip that from high-income countries by a ratio of 2 to 1 by 2050 (39), raising many concerns about what the future holds. This is particularly worrying given the lack of data on aging and age-related decline in muscle phenotypes in low-and-middle income countries, and the prevalence of age-related diseases that are expected to increase as an inevitable burden of the future (40).

Although this study was designed, planned, and conducted to the best of our knowledge, there are certain limitations. Firstly, the number of participants included in the study is rather low. Of the 308 subjects initially recruited for the genotype analyses (12), only 138 were able or wanted to participate in the follow up study. This limitation could have been influenced by the generally lower number of mature adults (8.1%), a lower life expectancy at birth (41) and the low socio-economic level of this age group in Kosovo (42). Secondly, the focus was on middle-aged to older adults, given the significant and visible decline in physical performance that is observed in these age groups. While this demographic provided a valuable opportunity to study the early and more pronounced stages of muscle strength decline, which aligns with our core research aims, it could be considered a limitation. Future long-term studies should examine the effects of genetic variants in vitamin D pathway-related genes on muscle characteristics from young adulthood into later life.

In conclusion, this study provides valuable insights into the age-related decline in muscle strength and physical performance in a developing European country. On of the key strengths of this research is its focus on a diverse cohort, including a broad age range of middle-aged and older adults, which enabled the examination of the early stages of muscle strength decline. Furthermore, the inclusion of participants from a lower socio-economic background and a developing country context provides unique insights and emphasizes the necessity for region-specific interventions. Additionally, the implication and interaction of genotypes across vitamin D-related genes, specifically rs7975232 (Apal) in the VDR gene and rs4588 and rs2282679 in the GC gene, along with vitamin D status (alone and in combination) should help prevent future complications by paving the way for tailored-based individual and population-specific intervention strategies. These findings represent one of the few follow-up data sets on the age-related effects of muscle phenotypes and the genetic background within the population of Kosovo, highlighting the importance of incorporating genetic, socio-economic, and regional factors into public health strategies aimed at improving the well-being of aging populations.

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: https://data.mendeley.com/datasets/jcfjfh8ybk/1, doi: 10.17632/jcfjfh8ybk.1.

Ethics statement

The studies involving humans were approved by Ethical-Professional Committee of the University Clinical Center of Kosovo (no 1695/22.11.2018). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

EK: Conceptualization, Data curation, Investigation, Project administration, Resources, Writing – original draft. AB: Funding acquisition, Data curation, Investigation, Writing – original draft. K-HW: Writing – review & editing, Validation. BW: Conceptualization, Formal analysis, Funding acquisition, Resources, Supervision, Writing – review & editing.

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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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Impact of preoperative frailty on new disability or death after cardiac surgery in elderly patients: a prospective cohort study

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Background: Disability may be a potential adverse outcome of exposure to stressors in frail patients, and assessment of frailty may provide additional information for preoperative decision-making, but there is a lack of research on the impact of preoperative frailty on death or new disability after cardiac surgery. The main objective of this study was to evaluate the effect of preoperative frailty on short-term death or new disability after cardiac surgery in elderly individuals.

Patients and methods: This prospective cohort study included 351 patients aged ≥60 years who were scheduled to undergo elective open heart surgery at the Affiliated Hospital of Xuzhou Medical University from March 2023 to March 2024. Patients were examined prospectively using the Comprehensive Assessment of Frailty (CAF) score, which separated patients into frail and non-frail groups. The primary outcome was 90-day disability or death. Multivariate logistic regression models were used to estimate the association between frailty and 90-day new disability or death.

Results: An assessment of frailty was performed on 351 patients, and 325 patients were included in the final analysis. The prevalence of frailty was found to be 23.08%. New disability or death occurred within 90 days after surgery in 41 (12.6%) of our patients. In multivariate analysis, frailty [OR, 3.31; 95% CI, 1.43–7.62] was independently associated with 90-day new disability or death. Empirical ROC analysis showed that CAF (AUC = 0.762) predicted 90-day new disability or death postoperatively more reliably than the traditional risk assessment tools ASA + age (AUC = 0.656) and EuroSCORE II (AUC = 0.643).

Conclusion: The study demonstrates that preoperative frailty, bypass time, diabetes, BMI and EuroSCORE II are independent risk factors for 90-day new disability or death after cardiac surgery in elderly patients. Notably, frailty was a more effective predictor of 90-day new disability or death than the traditional risk predictors EuroSCORE II and ASA + age.

KEYWORDS

aging, frailty, disability, cardiac surgery, patient-centered outcome

Introduction

Compared to other surgeries, cardiac surgery is characterized by high risk and difficulty and is a highly volatile event. Patients undergoing cardiac surgery are often exposed to strong external stressors, such as extracorporeal circulation, sternotomy, hypothermia, and prolonged anesthesia and operating time, which deal a severe blow to the body's overall homeostasis and cause damage to vital organs. However, in recent years, with the advances in surgical techniques, anesthesia management and postoperative rehabilitation care, appropriate conditions have been created to improve the prognosis of cardiac surgery. Therefore, perioperative physicians should do an excellent job of preoperative risk assessment and take effective measures in all aspects of the perioperative period to mitigate the stress injury suffered by cardiac surgery patients. Common preoperative risk assessment tools for cardiac surgery include the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II), the Society of Thoracic Surgeons score (STS), and the ASA class. Still, these tools lack physiological assessment (1, 2).

Frailty is defined as a clinical condition in older people in which physiological reserves decline, resulting in increased vulnerability, decreased resistance to stress, and impaired ability to maintain or restore homeostasis after stress (3, 4). Previous studies have shown that the prevalence of frailty in elderly patients undergoing major surgery is approximately 20–40% (5, 6) and that elderly patients with preoperative comorbidities of frailty have higher rates of postoperative complications and mortality (7). However, it is reassuring to know that frailty is not a reversible functional state like age and comorbidities and that preoperative physiologic reserve can be increased with appropriate nutritional support and rehabilitation (8).

Due to the increasing standard of living, people are no longer only concerned with whether the surgery can be successful or not but rather with good independent mobility and quality of life after the surgery, and the desire to avoid a new disability is especially urgent. Disability is defined by the difficulty in performing activities of daily living or the development of various limitations. Currently, disability is often assessed using the standard sets of Activities of Daily Living (ADLs) and Instrumental Activities of Daily Living (IADLs) (9, 10), but both lack an assessment of social participation, which is included in the World Health Organization Disability Assessment Scale, second edition (WHODAS 2.0) (11, 12). Recent prospective studies have shown that preoperative disability is associated with patient self-reported death or new disability after surgery in non-cardiac patients (13, 14). Thus, disability may be a potential adverse outcome of exposure to stressors in frail patients, and assessment of frailty may provide additional information for preoperative decision-making, but there is a lack of research on the impact of preoperative frailty on death or new disability after cardiac surgery.

The main objective of this study was to evaluate the effect of preoperative frailty on short-term death or new disability after cardiac surgery in elderly individuals, to provide some reference value for perioperative risk assessment and decision-making, and to achieve the goal of improving patients' postoperative recovery.

Materials and methods

Study design and study population

The study was approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (XYFY2023-KL044-01) and registered in the Chinese Clinical Trials Registry (ChiCTR2300069382). We adhered to the reporting requirements established by the Strengthening the Reporting of Observational Studies in Epidemiology (15). Written informed consent was obtained from each participant prior to enrollment. Patients were recruited between March 2023 and March 2024.

Elderly (≥60 years) patients undergoing elective open heart surgery were eligible for enrollment. The exclusion criteria were as follows: Preoperative refusal to participate in this study or communication difficulties; inability to complete a frailty assessment due to absolute bed rest; preoperative comorbidities of severe hepatic and renal dysfunction; preoperative history of IABP (Intra-Aortic-Balloon-Pump), mechanical ventilation, or pacemaker implantation; those who are unable to be reached or refuse to cooperate with postoperative telephone follow-up.

Frailty and disability assessment

During the preoperative assessment, in addition to routine examinations, all consenting participants underwent an assessment of the CAF and the WHO Disability Assessment Scale 2.0 (WHODAS) by a researcher who was unaware of the content of the postoperative follow-up; the methodology of the CAF assessment is described in the study by Sündermann et al. (16). The CAF can be broadly viewed as a composite of three frailty assessment scales [FP (Frailty Phenotype) (17), CFS (Canadian Clinical Frailty Scale) (18), and MPPT (Modified Physical Performance Test)], consisting primarily of biomarker assessments (serum albumin level, serum creatinine level, BMI, and FEV1), physical tests of fatigue, activity level, gait speed, grip strength, and balance stability, and including measures of the CFS. The total score of the CAF was 35 points, with patients scoring ≥11 being frail and those scoring <11 being non-frail.

The baseline assessment of preoperative disability was determined using the WHO Disability Assessment Scale 2.0 (WHODAS) (11–13). The WHODAS 2.0 consists of six main domains: mobility, self-care, getting by, cognition, and social participation. The 12 items of the WHODAS are scored as described in previous studies, with each item having a numerical value: none = 0; mild = 1; moderate = 2; severe = 3; and extreme = 4. The total score ranges from 0 (no disability) to 48 (total disability or death) and is then divided by 48 and multiplied by 100 to give a disability score of 0 (no disability or death). mild = 2; severe = 3; extreme = 4. The total score ranged from 0 (no disability) to 48 (total disability or death), then divided by 48 and multiplied by 100 to convert to a percentage of the disability score. Preoperative disability was defined as a WHODAS 2.0 total score percentage greater than or equal to 25%.

Definition of outcomes

The primary outcome was the relationship between preoperative frailty and new disability or death at 3 months postoperatively.

Postoperative patient follow-up was performed by an anesthesiologist who was unaware of the results of the preoperative evaluation. Telephone follow-up and electronic medical record documentation were the primary means of determining patients' postoperative survival status. New disability at 90 days was defined as the occurrence of a WHODAS 2.0 ≥ 25% postoperatively in patients who were not disabled preoperatively; if the patient had a preoperative comorbid disability (WHODAS ≥ 25%), an increase in the percentage of WHODAS scores by 8 at 90 days postoperatively indicated the occurrence of new disability (11–13).

Secondary outcomes included (1) 90-day disability-free survival (DFS), (2) ICU length of stay, (3) postoperative non-hospital discharge, (4) postoperative length of stay, (5) major morbidity (19, 20) (Supplementary Table S1), (6) incidence of PPCs (21), (7) 90-day readmission rate, and (8) 90-day mortality.

We conducted a *post hoc* study to compare the validity of the CAF with the commonly used FP and CFS in predicting 90-day new disability or death. We asked whether the predictive validity of the traditional and rapidly assessable preoperative frailty scales (FP and CFS) would achieve the same categorical properties as the CAF, because the preoperative assessment of the CAF is time-consuming.

Other variables

All patients were managed according to standard cardiac surgery protocols, with pre-operative perioperative risk assessment followed by anesthesia for surgery, post-operative transfer to the surgical intensive care unit, and after stabilization of vital signs, transfer to the general surgical ward for further management and routine post-operative rehabilitation for all patients.

Baseline clinical and demographic data were collected according to the protocol, including sex, age, smoking and alcohol consumption, comorbidities (diabetes, hypertension, myocardial infarction, etc.), ASA class, EuroSCORE II, pulmonary function (FEV1, FVC, and FEV1/FVC), type of surgery, and left ventricular ejection fraction (LVEF). Operating time, Cross-clamp time, bypass time, urine volume, blood loss, total fluid intake, and total fluid output were recorded during surgery. Data on ICU stay, postoperative hospital stay, non-hospital discharge, 90-day Major Morbidity, and readmission within 90 days were collected.

Statistical analysis

Data normality was tested by visual inspection of histograms and Shapiro–Wilk's W test. All normally distributed and skewed continuous variables were expressed as mean (SD) or median (interquartile range [IQR]). Categorical variables were indicated as frequencies (%). Comparison of continuous variables among groups was performed with the use of the Student's *t*-test or Mann–Whitney U-test, depending on the normality of the distribution. In contrast, the Fisher's Exact test was used to compare categorical variables.

A Least Absolute Shrinkage and Selection Operator regression analysis was conducted with statistically significant risk factors included in the univariable study to remove non-zero characteristic components. After that, a multivariate logistic regression analysis (stepwise regression method) was used to identify the 90-day new disability or death risk variables. Internal validation was carried out using the bootstrap self-sampling technique (1,000 bootstrap samples repeatedly sampled), and the model's discrimination was tested using the relatively adjusted C-index (concordance index). The calibration curve was drawn to evaluate the model's consistency. In addition, the inverse probability treatment weighting (IPTW) approach was used for two groups to adjust for observed possible confounding factors. Multivariable logistic regression analyses were used to obtain the IPTW-adjusted odds ratio (OR) in the IPTW-adjusted cohort. The predictive validity was assessed using the area under the receiver operating characteristic (ROC) curve (AUC). An AUC of 0.5–0.7 implies poor prediction accuracy, whereas an AUC of 0.7–0.9 suggests high prediction performance. The DeLong test compared the AUC of different models.

p-value < 0.05 (two-sided) was considered statistically significant. R4.1.2 and MedCalc 20.0. Statistical software was used for analysis.

Sample size calculation

Based on the pre-test, the incidence of death or new disability at 90 days after cardiac surgery in elderly individuals is about 10%, the multivariate regression model includes at least 5 outcome events for each variable (22), a total sample size of 250 is required (5*5/10% = 250), and considering the 15% dropout rate, 250/(1–15%) = 295 patients are proposed to be included in this study.

Missing data

We used complete cases for the initial analysis, and preoperative baseline data were complete for all participants. A total of 351 individuals were included in the study, and final data were complete for 325 individuals. Our overall proportion of missing values was small, our analysis was based on all available data without imputation.

Results

Baseline characteristics

An assessment of frailty was performed on 351 patients, and 325 patients were included in the final analysis (Figure 1). The prevalence of frailty was found to be 23.08%. Table 1 shows that age, proportion of female, NT-ProBNP, hsTnT, stroke/TIA, myocardial infarction, diabetes, proportion of preoperative disability, NYHA class, ASA class, EuroSCORE II, and duration of surgery were higher in patients in the frail group compared with those in the non-frail group. The rates of alcohol consumption, hemoglobin, albumin, FEV1, and FVC were lower ($p < 0.05$), while all other factors were not statistically different ($p > 0.05$).

Associations of frailty with post-operative outcomes

New disability or death occurred within 90 days after surgery in 41 (12.6%) of our patients, including 23 (33.1%) in the frail

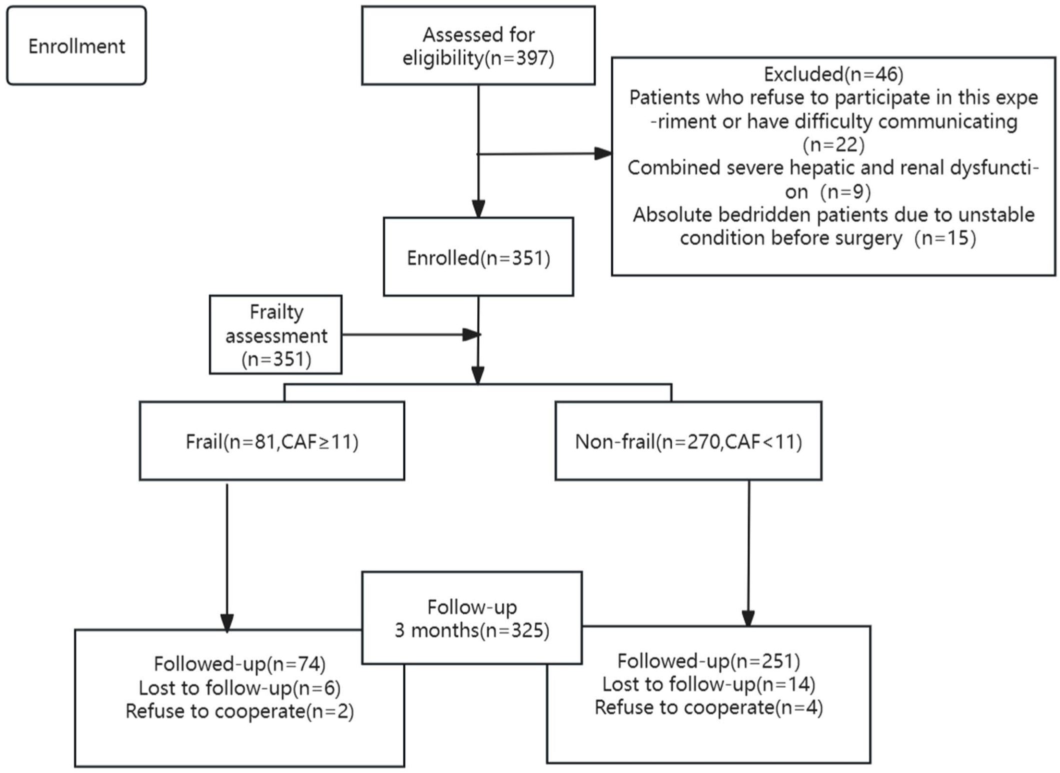

FIGURE 1
Study participant flow diagram (CAF: Comprehensive assessment of frailty score).

group and 18 (7.2%) in the non-frail group of patients; there was a significant difference in new disability or death at 90 days between the groups (Table 2, $p < 0.05$). Table 2 shows that patients in the frail group had higher WHODAS scores, postoperative pulmonary complications, major morbidity at 90 days, ICU stay, postoperative hospitalization, in-hospital mortality, mortality within 90 days, and incidence of readmission within 90 days ($p < 0.05$), while disability-free survival (DFS) at 90 days postoperatively was lower ($p < 0.05$).

Risk factors associated with 90-day new disability or death

According to the Least Absolute Shrinkage and Selection Operator regression analysis (Figure 2), we selected eight non-zero characteristic variables including frailty, EuroSCORE II, diabetes, Creatinine, ASA class, BMI, time of operation and bypass time (Table 3). Then, taking these eight predictors and conducting a multifactor logistic regression using a stepwise regression method approach, five meaningful variables were finally identified (Figure 2). In multivariate analysis, frailty [OR, 3.31; 95% CI, 1.43–7.62], bypass time (OR, 1.01; 95% CI, 1.00–1.01), BMI (OR, 0.87; 95% CI, 0.77–0. 98), diabetes (OR, 3.47; 95% CI, 1.40–8.55), and EuroSCORE II (OR, 1.75; 95% CI, 1.20–2.57) were independently associated with 90-day new disability or death (Figure 3). Frailty (OR, 3.15; 95% CI, 1.55–6.43) was also independently associated with 90-day new disability or death in a multivariate analysis of the inverse probability weighted adjusted cohort (Table 4).

Model validation: We reported a bias-corrected concordance statistic to verify the internal validity of our primary model utilizing calibration and discrimination with a 1,000-sample bootstrapping approach. Our calibration curve revealed that our model was well-calibrated (Supplementary Figure S1). With a C-statistic of 0.824 and an optimism-corrected C-statistic of 0.810, the discriminative ability demonstrated strong model performance in predicting 90-day new disability or death.

Predictability of postoperative 90-day new disability or death， DFS, PPCs and 90-day major morbidity by different risk assessment tools

Empirical ROC analysis showed that CAF (AUC = 0.762) predicted 90-day new disability or death postoperatively more reliably than the traditional risk assessment tools ASA + age (AUC = 0.656), EuroSCORE II (AUC = 0.643), and WHODAS (AUC = 0. 662). The difference in the area under the curve between the first three methods and CAF was significant (p values of 0.039, 0.019, and 0.029, corresponding to z values of 2.064, 2.350, and 2.190, respectively). It can also be seen that the CAF was also a better predictor of DFS among the four risk assessment tools (AUC = 0.799), but was a poorer predictor of PPCs and 90-day major morbidity for all four risk assessment tools (AUC < 0.700) (Figure 4).

TABLE 1 Clinical characteristics of study participants.

Variables	Total (*n* = 351)	Non-frail (*n* = 270)	Frail (*n* = 81)	*p*
Age (year)	66.8 ± 5.2	66.2 ± 5.1	68.7 ± 5.1	<0.001
Sex (female)	119 (33.9)	77 (28.5)	42 (51.9)	<0.001
BMI (kg/m^2)	24.4 ± 3.5	24.4 ± 3.4	24.6 ± 3.7	0.704
Smoke	135 (38.5)	110 (40.7)	25 (30.9)	0.109
Alcohol	100 (28.5)	85 (31.5)	15 (18.5)	0.023
LVEF (%)	58.0 ± 7.9	58.4 ± 8.0	56.6 ± 7.4	0.082
FEV1 (L)	2.3 ± 0.7	2.4 ± 0.7	1.9 ± 0.7	<0.001
FVC (L)	2.6 ± 0.9	2.7 ± 0.9	2.2 ± 0.8	<0.001
FEV_1/FVC (%)	86.6 ± 13.6	87.1 ± 12.4	84.6 ± 17.2	0.164
NT-ProBNP (pg/mL)	742.9 ± 978.8	677.8 ± 927.6	963.3 ± 1113.8	0.023
hsTnT (ng/L)	26.5 ± 54.0	22.8 ± 51.8	38.6 ± 59.4	0.022
Hemoglobin (g/L)	134.9 ± 16.0	138.2 ± 14.4	123.8 ± 16.1	<0.001
Albumin (g/L)	41.9 ± 3.7	42.3 ± 3.7	40.5 ± 3.4	<0.001
Stroke/TIA	155 (44.2)	111 (41.1)	44 (54.3)	0.036
PAH	83 (23.6)	63 (23.3)	20 (24.7)	0.801
Bronchial disease	22 (6.3)	14 (5.2)	8 (9.9)	0.127
Myocardial infarction	49 (14.0)	31 (11.5)	18 (22.2)	0.014
Atrial fibrillation	44 (12.5)	35 (13)	9 (11.1)	0.659
Sleep apnea	36 (10.3)	24 (8.9)	12 (14.8)	0.123
Diabetes	84 (23.9)	55 (20.4)	29 (35.8)	0.004
Hypertension	184 (52.4)	138 (51.1)	46 (56.8)	0.369
Cough and sputum	73 (20.8)	51 (18.9)	22 (27.2)	0.108
CKD	21 (6.0)	14 (5.2)	7 (8.8)	0.283
Type of operation				0.925
CABG	195 (55.6)	151 (55.9)	44 (54.3)	
Valve	127 (36.2)	97 (35.9)	30 (37)	
CABG + Valve	26 (7.4)	20 (7.4)	6 (7.4)	
Other	3 (0.9)	2 (0.7)	1 (1.2)	
CAF	8.6 ± 5.4	6.2 ± 2.1	16.8 ± 5.1	<0.001
FP	1.0 (0.0, 2.0)	1.0 (0.0, 1.0)	3.0 (2.0, 4.0)	<0.001
CFS	3.0 (3.0, 4.0)	3.0 (3.0, 3.0)	4.0 (4.0, 5.0)	<0.001
EuroSCORE II (%)	1.2 (0.9, 1.7)	1.1 (0.8, 1.5)	2.0 (1.4, 2.8)	<0.001
WHODAS	5.0 (2.0, 9.0)	4.0 (1.0, 7.0)	14.0 (9.0, 20.0)	<0.001
Preoperative disability (WHODAS ≥ 25%)	70 (20.1)	17 (6.3)	53 (66.2)	<0.001
ASA class				<0.001
2	8 (2.3)	8 (3)	0 (0)	
3	286 (81.5)	243 (90)	43 (53.1)	
4	57 (16.2)	19 (7)	38 (46.9)	
NYHA ≥ 3	110 (31.5)	54 (20.1)	56 (69.1)	<0.001
Off-pump surgery	146 (41.6)	110 (40.7)	36 (44.4)	0.553
Cross-clamp time (min)	42.0 (0.0, 86.0)	42.0 (0.0, 82.0)	45.0 (0.0, 94.0)	0.794
Bypass time (min)	70.0 (0.0, 122.0)	71.0 (0.0, 119.0)	60.0 (0.0, 130.0)	0.807
Time of operation (h)	5.2 ± 1.5	5.1 ± 1.4	5.5 ± 1.5	0.044
Total liquid output (L)	2.00 (1.46, 2.345)	2.00 (1.40, 2.315)	2.02 (1.60, 2.40)	0.916

(Continued)

TABLE 1 (Continued)

Variables	Total (n = 351)	Non-frail (n = 270)	Frail (n = 81)	p
Total fluid intake (L)	3.15 (2.75, 3.909)	3.150 (2.70, 3.90)	3.20 (2.80, 3.953)	0.376
Urine output (L)	1.50 (1.00, 2.00)	1.50 (1.00, 2.00)	1.50 (1.00, 2.00)	0.695
Blood loss (L)	0.50 (0.35, 0.70)	0.485 (0.342, 0.60)	0.50 (0.40, 0.80)	0.212

Data: Means ± standard deviations, absolute rate, and percentage. Statistical significance was defined as $p < 0.05$. BMI, Body Mass Index; LVEF, Left Ventricular Ejection Fraction; FVC, Forced Vital Capacity; FEV1, Forced Expiratory Volume In 1 s; TIA, Transient Ischemic Attacks; PAH, Pulmonary Arterial Hypertension; CKD, Chronic Kidney Diseases; CABG, Coronary Artery Bypass Graft; CAF, Comprehensive Assessment of Frailty; FP, Frailty Phenotype; CFS, Clinical Frailty Scale; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; WHODAS, WHO Disability Assessment Schedule; ASA, American Society of Anesthesiologists; NYHA, New York Heart Association.

TABLE 2 Postoperative outcomes.

Variables	Total (n = 325)	Non-frail (n = 251)	Frail (n = 74)	p
WHODAS in 90 day	3.0 (1.0, 7.0)	2.0 (0.0, 4.5)	12.0 (4.0, 33.5)	<0.001
New disability or death	41 (12.6)	18 (7.2)	23 (31.1)	<0.001
Disability-free survival (DFS)	262 (80.6)	226 (90)	36 (48.6)	<0.001
90-day major morbidity	80 (24.6)	47 (18.7)	33 (44.6)	<0.001
PPCs in 90 day	111 (34.2)	66 (26.3)	45 (60.8)	<0.001
Pulmonary infection	48 (14.8)	26 (10.4)	22 (29.7)	<0.001
Prolonged mechanical ventilation	32 (9.8)	13 (5.2)	19 (25.7)	<0.001
Deep sternal wound infection	17 (5.2)	11 (4.4)	6 (8.1)	0.234
New stroke	3 (0.9)	1 (0.4)	2 (2.7)	0.131
Delirium	42 (12.9)	22 (8.8)	20 (27)	<0.001
AKI	52 (16.0)	36 (14.3)	16 (21.6)	0.133
Sepsis	10 (3.1)	5 (2)	5 (6.8)	0.052
Re-exploration for bleeding	12 (3.7)	8 (3.2)	4 (5.4)	0.480
Postoperative hospital stay	10.0 (8.0, 12.0)	9.0 (8.0, 11.0)	11.0 (9.0, 14.0)	0.003
ICU stay	17.0 (17.0, 19.0)	17.0 (17.0, 19.0)	18.0 (17.0, 48.0)	<0.001
In hospital mortality	15 (4.6)	6 (2.4)	9 (12.2)	0.002
Death of 3 month	24 (7.4)	10 (4)	14 (18.9)	<0.001
Readmission in 90 days	40 (12.3)	24 (9.6)	16 (21.6)	0.006

Data: Means ± standard deviations, absolute rate, and percentage. Statistical significance was defined as $p < 0.05$. WHODAS, WHO Disability Assessment Schedule; PPCs, Postoperative Pulmonary Complications; AKI, Acute Kidney Injury; ICU, Intensive Care Unit.

Post hoc outcomes

Compared to the common clinical frailty assessment scales (CFS and FP), the CAF (AUC = 0.762) had superior predictive efficacy compared to CFS (AUC = 0.696) and FP (AUC = 0.686) (p-values of 0.036 and 0.005, corresponding to z-values of 2.096 and 2.819, respectively, Supplementary Figure S2).

Discussion

The study demonstrates that preoperative frailty, bypass time, diabetes, BMI, and EuroSCORE II are independent risk factors for 90-day new disability or death after cardiac surgery in elderly patients. Notably, frailty was a more effective predictor of 90-day new disability or death than the traditional risk predictors EuroSCORE II and ASA + age.

The study indicates that frailty is an independent risk factor for new disability or death after cardiac surgery in the elderly, which is consistent with other studies. In a multicenter cohort study of 702 patients undergoing elective noncardiac surgery, frail patients had statistically significantly higher rates of new 90-day disability or death, longer hospital stays, and need for institutional discharge compared to other patient groups (13). However, this study's surgical procedures did not include cardiac surgery. Therefore, the results cannot be applied to patients undergoing cardiac surgery. Another single-center cohort study (6) of 146 adult patients undergoing elective open-heart surgery also found that preoperative frailty significantly reduced patients' disability-free survival at 90 days postoperatively, leading to a decrease in postoperative functional recovery and quality of life. This study, while insightful about the relationship between preoperative frailty and disability-free survival at 90 days postoperatively in patients undergoing cardiac surgery, did not have sufficient efficacy (the sample size was only 145) to explore whether frailty was an independent risk factor for new disability or death at 90 days postoperatively and to rule out the effect of preoperative patients' comorbid disability on their postoperative functional status. The mechanisms behind frailty and postoperative self-reported disability in elderly cardiac surgery patients are unclear. These issues may be related to chronic inflammation, aging of the immune system, and endocrine dysregulation (23–25).

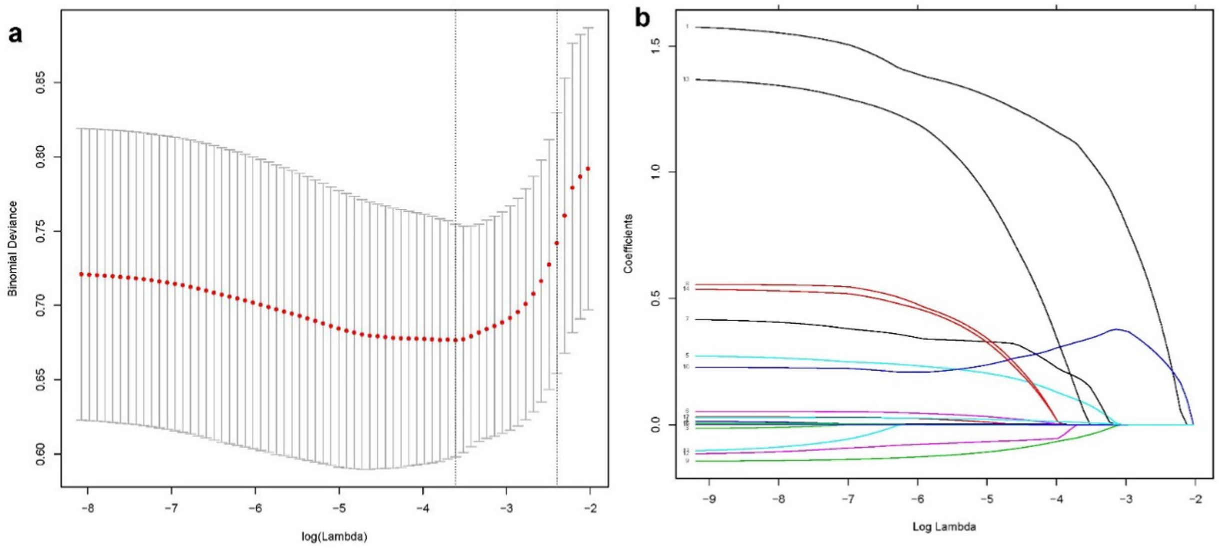

FIGURE 2
The LASSO binary logistic regression model is used to select variables. A coefficient profile plot **(A)** was used to display the log (lambda) series. Eight variables with nonzero coefficients were chosen using optimal lambda. To confirm the optimal parameter (lambda) in the LASSO model, the partial likelihood deviance (binomial deviance) curve was plotted against log (lambda), and dotted vertical lines were drawn based on a min criteria **(B)**.

TABLE 3 Coefficients and Lambda.min value of the LASSO regression.

Variable num	Variable name	Coefficient	lambda. type	lambda. value
1	Frailty	1.08	lambda.min	0.027
10	EuroSCORE II	0.334	lambda.min	0.027
13	Diabetes	0.055	lambda.min	0.027
17	Creatinine	0.008	lambda.min	0.027
4	Bypass time	0.001	lambda.min	0.027
5	Time of operation	0.088	lambda.min	0.027
7	ASA class	0.172	lambda.min	0.027
9	BMI	−0.046	lambda.min	0.027

EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; ASA, American Society of Anesthesiologists; BMI, Body Mass Index.

This study showed that the prevalence of preoperative frailty in elderly patients was 23.08%, which is consistent with previous reports in the literature (6, 16). The clinical significance of assessing preoperative frailty is to assist the perioperative physician in recognizing the patient's preoperative risk level and making rational clinical decisions. Overall, in order to improve the prognosis of frail patients, multidisciplinary collaboration is more important (26). In frail patients at higher risk for poor functional outcomes, the cardiac surgeon decides whether minimally invasive treatment is possible (27, 28), the anesthesiologist enhances intraoperative monitoring of the patient's vital organs (e.g., enhanced cerebral oximetry monitoring, lung-protective ventilation, and ultrasound-guided goal-directed fluid therapy) (29) and the nursing team initiates an early tailored Customized functional recovery programs (intensive pulmonary physiotherapy, early ambulation, resistance training, and nutritional support) should be initiated early by the nursing team (30). If frail patients are more stable preoperatively, we believe it is also essential to delay surgery appropriately, and studies have shown that preoperative functional rehabilitation led by the rehabilitation department can increase the patient's physiologic reserve, thereby increasing stress resistance (30). The study also discovered that conventional risk assessment metrics, such as EuroSCORE II and ASA + age, were inadequate predictors of patient-centered outcomes, such as new disability or death. The ROC analysis clearly showed that frailty, as defined by CAF, is a

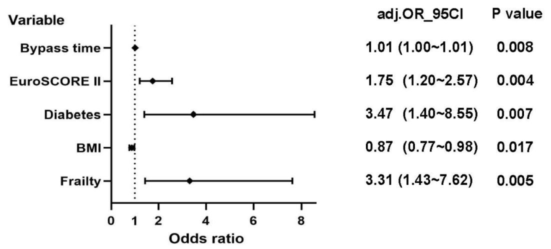

FIGURE 3
Logistic regression analysis of 90-day new disability or death (EuroSCORE II: European System for Cardiac Operative Risk Evaluation II; BMI: Body Mass Index).

TABLE 4 Associations between frailty and 90-day new disability or death in the crude analysis, multivariable analysis, and propensity-score analyses.

Analysis	Odds ratio (95%CI)
Crude analysis	5.84 (2.94 ~ 11.61)
Multivariable analysis	3.31 (1.43 ~ 7.62)
Propensity-score analysis with inverse probability weighting	3.15 (1.55 ~ 6.43)

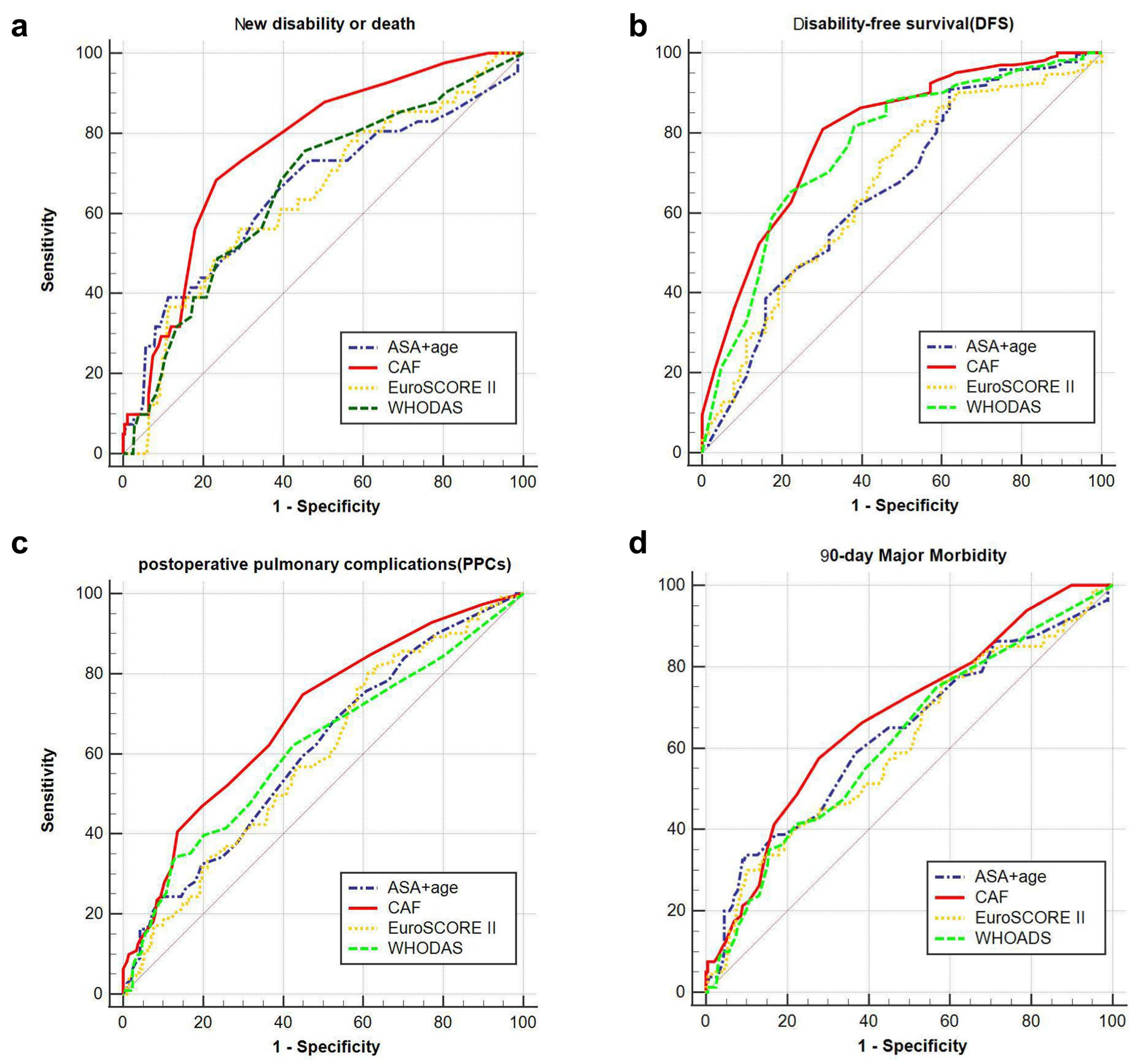

FIGURE 4
Prediction of different risk indices at different complications and 90-day new disability or death. **(A)** The area under the curve of chart-derived CAF, ASA + age, EuroSCORE II and WHODAS for DFS was 0.762 (95% CI, 0.712–0.807), 0.656 (95% CI, 0.602–0.708), 0.643 (95% CI, 0.588–0.695), and 0.662 (95% CI, 0.608–0.714), respectively. **(B)** The area under the curve of chart-derived CAF, ASA + age, EuroSCORE II and WHODAS for 90-day new disability or death was 0.799 (95% CI, 0.752–0.841), 0.668 (95% CI, 0.614–0.719), 0.668 (95% CI, 0.614–0.719), and 0.765 (95% CI, 0.715–0.810), respectively. **(C)** The area under the curve of chart-derived CAF, ASA + age, EuroSCORE II and WHODAS for PPCs was 0.694 (95% CI, 0.641–0.744), 0.608 (95% CI, 0.553–0.662), 0.594 (95% CI, 0.538–0.647), and 0.614 (95% CI, 0.559–0.668), respectively. **(D)** The area under the curve of chart-derived CAF, ASA + age, EuroSCORE II and WHODAS for 90-day Major Morbidity was 0.678 (95% CI, 0.624–0.728), 0.634 (95% CI, 0.579–0.687), 0.608 (95% CI, 0.552–0.661), and 0.619 (95% CI, 0.563–0.672), respectively (EuroSCORE II: European System for Cardiac Operative Risk Evaluation II; WHODAS WHO Disability Assessment Schedule; ASA American Society of Anesthesiologists; CAF: Comprehensive assessment of frailty score).

more reliable predictor of adverse postoperative outcomes in elderly cardiac patients than EuroSCORE and ASA + age. Therefore, adding frailty measures, particularly CAF, to the traditional perioperative risk scoring system may improve the ability of perioperative physicians to predict relevant clinical outcomes in patients.

The present study also demonstrated that bypass time, BMI, diabetes, and EuroSCORE II were independent risk factors for 90 days after cardiac surgery in elderly patients. Longer bypass time are known to be more fatal for elderly and frail cardiac surgery patients. Previous studies (31) have shown that prolonged bypass time reflects the complexity of the surgical maneuver and may exacerbate damage to vital organs, with adverse prognostic consequences for elderly patients. In this study, only 4.9% of elderly patients were obese (BMI ≥ 30 kg/m^2). On this basis, we found that higher BMI was associated with lower disability or death. Previous studies (32) have shown that lower body weight and obesity are associated with poor prognosis after cardiac surgery (U-shaped relationship between BMI and all-cause mortality). That said, in the present study, there were fewer obese patients whose positive association with poor outcome was masked, thus showing overall that a slightly higher BMI may contribute to survival. Diabetes is characterized by long-term insulin resistance, compensatory hyperinsulinemia, and varying degrees of hyperglycemia (33). Previous studies (34) have confirmed that diabetes is associated with patient prognosis. Patients with hyperglycemia are at increased risk for surgical site infection, pneumonia, delirium, and mortality.

There are some limitations to our study. First, the present study was a single-center, small-sample observational study with only a short-term postoperative follow-up, and a large multicenter sample is needed in the future to validate the conclusions and explore the relationship between frailty and long-term postoperative disability trajectory. Second, the CAF involves several aspects and may be time-consuming to assess preoperatively, but the *post hoc* analysis of the present study demonstrated that the CAF, although time-consuming, is a better predictor of postoperative outcomes than conventional frailty assessment scales (FP and CFS), so the CAF is recommended for the very high-risk elderly cardiac surgery population. Third, this study excluded patients who were completely bedridden preoperatively. Fourth, this study's predictors and outcome indicators were human-rated scales, both of which are somewhat subjective. In addition, due to the nature of observational studies, there may be confounding factors that cannot be assessed.

Conclusion

In conclusion, we found that preoperative frailty, prolonged bypass time, diabetes, BMI, and EuroSCORE II were independent risk factors for 90-day new disability or death after cardiac surgery in elderly patients. Frailty was more effective in predicting 90-day new disability or death than the traditional risk predictors EuroSCORE II and ASA + age. Preoperative assessment of frailty can assist the perioperative team in preoperative clinical decision making and provide medical support throughout the course of an elderly frail patient scheduled for cardiac surgery.

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 humans were approved by Ethics Committee of Affiliated Hospital of Xuzhou Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

WM: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. WS: Conceptualization, Data curation, Funding acquisition, Resources, Visualization, Writing – review & editing. QP: Project administration, Resources, Software, Writing – review & editing. CZ: Investigation, Resources, Software, Writing – review & editing. WZ: Data curation, Formal analysis, Investigation, Writing – review & editing. GF: Conceptualization, Formal analysis, Funding acquisition, Methodology, Software, Supervision, Visualization, Writing – review & editing. SZ: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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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.

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2025.1526896/full#supplementary-material

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Comparison of characteristics of bimanual coordinated movements in older adults with frailty, pre-frailty, and robust health

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Introduction: Despite the growing concern regarding a potential increase in the number of older adults with frailty owing to an aging global population, the characteristics of bimanual coordination in such older adults remain unclear. This study aimed to compare bimanual coordinated movements among community-dwelling older adults with frailty, pre-frailty, and robust health and identify the specific characteristics of these movements in older adults with frailty.

Methods: Participants were categorized into frail, pre-frail, and robust groups based on Kihon Checklist scores. They performed bimanual coordination tasks in-phase (tapping the thumb and index finger together as fast as possible) and anti-phase (alternating the movement between the left and right fingers), and the task parameters were compared among the groups.

Results: The total travel distance during the anti-phase task in the frail group was significantly shorter than that in the robust group. However, all three groups showed lower finger dexterity during the anti-phase task than in the in-phase task and the left hand than in the right hand.

Conclusion: Older adults with frailty exhibit less movement during bimanual coordination tasks than robust older adults, suggesting that such tasks may be useful tools for assessing frailty.

KEYWORDS

bimanual coordination, finger-tapping, older adults, frailty, pre-frailty, robust health

1 Introduction

The percentage of older adults in the population is increasing annually worldwide. According to the World Health Organization, between 2020 and 2050, the population of individuals aged ≥60 years is estimated to double to 2.1 billion, and the population of those aged ≥80 years is projected to triple to 426 million (World Health Organization, 2022). The rapid aging of the global population has driven interest in improving the understanding of healthy aging and identifying assessment methods for it (Beard et al., 2016; Behr et al., 2023). Healthy aging is a complex multidimensional concept that encompasses biological, functional, lifestyle, and psychosocial factors (Behr et al., 2023). Additionally, achieving healthy aging requires early interventions to prevent significant declines in physical and cognitive functions (Silva et al., 2023). The number of older adults with frailty is also expected to increase as the older adult population grows. Frailty is defined as "a medical syndrome caused by multiple factors and triggers, characterized by a decline in muscle strength and endurance, a decrease in physiological function, and an increased vulnerability to needing care or facing death" (Morley et al., 2013). However, physical function in individuals with frailty has been reported to improve with appropriate interventions (de Labra et al., 2015). Furthermore, the prevention of frailty has been identified as a key future project in public health (Liotta et al., 2018) and holds significant social importance. Therefore, establishing a method for assessing frailty is crucial for maintaining the health of older adults.

In daily life, hands are the most frequently used body part (Lee and Jung, 2015), and healthy older adults have been found to engage in activities involving both hands more frequently than those involving only one hand (Kilbreath and Heard, 2005). Upper limb function in humans has been shown to change with age. Ingram et al. compared upper limb muscle strength, positional and superficial sensations, one-handed dexterity, bimanual coordination, muscle power stability, and functional performance in healthy participants aged 20–95 years (Ingram et al., 2019). Their results showed that the participant's performance on all the parameters decreased with age, and the decline in bimanual coordination was particularly significant. Additionally, studies have reported that bimanual movements exhibit decreased accuracy, increased variability, and prolonged motor execution times with age (Kang et al., 2022). These results indicate that bimanual coordinated movements play an important role in the daily lives of older adults and that the coordination underlying these movements declines with age.

Although older adults with frailty have been reported to exhibit lower dexterity in one-handed movements than healthy older adults (Lammers et al., 2020; Schmidle et al., 2022), the characteristics of bimanual coordinated movements in older adults with frailty have not been clarified. Frailty in older adults has also been reported to result in less independence in activities of daily living than healthy older adults (Tornero-Quiñones et al., 2020), a higher risk of falling (Anders et al., 2007), and sarcopenia (Cruz-Jentoft and Sayer, 2019). In contrast, higher finger dexterity has been reported to be associated with better predictive postural control ability in stepping movements (Sun and Shea, 2016), and improved upper limb function has been reported to enhance gait ability and overall quality of life (Leblebici et al., 2024). Furthermore, sensory stimulation from the fingertips resulting from light contact has been shown to reduce ankle joint and body sway in the standing posture of older adults (Barela et al., 2018), suggesting that upper limb function, including finger function, can compensate for the decline in gait ability and standing balance. These findings indicate that bimanual coordination characteristics differ depending on the degree of frailty. Elucidating these differences could lead to the development of an assessment tool for the early detection of frailty.

Therefore, this study aimed to compare the bimanual coordinated movements of community-dwelling older adults with frailty, pre-frailty, and robust health and determine the characteristics of bimanual coordinated movements in older adults with frailty. We hypothesized that the degree of frailty affects bimanual coordination, with bimanual coordination declining progressively from robust older adults to pre-frail older adults and then to frail older adults.

2 Methods

2.1 Participants

This cross-sectional study was conducted with 358 community-dwelling older adults who participated in physical fitness assessment sessions held in two cities in September 2023. The exclusion criteria for participants were: (i) age < 65 years; (ii) Mini-Mental State Examination (MMSE) scores < 24, based on previous studies (Mitchell, 2009; Ideno et al., 2012; Lin et al., 2014; Jin et al., 2019); (iii) presence of hand dexterity impairments due to musculoskeletal or central nervous system diseases; (iv) left-handedness; (v) inability to undergo measurements; and (vi) a maximum distance amplitude ≥ 300 mm in the bimanual coordination task (Enokizono et al., 2020). After applying these exclusion criteria, the remaining 312 participants were included in the analysis (Supplementary Figure S1).

2.2 Ethics declarations

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Research Ethics Committee of Kyoto Tachibana University (Approval number 24–30). Informed consent was obtained from all the participants in the study.

2.3 Measures

First, we assessed the frailty of the participants using the Kihon Checklist (KCL). The KCL is a questionnaire developed in Japan to identify older adults at high risk of needing care in the near future (Arai and Satake, 2015; Satake et al., 2017). In recent years, the KCL has been widely used as a tool for assessing frailty. It has shown high sensitivity when validated against the Cardiovascular Health Study criteria and is regarded as the gold standard for frailty assessment (Satake et al., 2016). Accordingly, the KCL is recommended as a validated tool in international clinical guidelines for frailty assessment (Dent et al., 2017; Sentandreu-Mañó et al., 2021). The KCL is a self-administered questionnaire with "yes/no" responses that consists of 25 questions covering seven domains: activities of daily living, physical function, nutritional status, oral function, social withdrawal, cognitive function, and depressive mood. In the KCL, higher scores indicate a greater risk of needing care in daily life. In this study, participants with scores of 0–3, 4–7, and ≥8 were categorized into robust, pre-frail, and frail groups, respectively (Satake et al., 2016).

TABLE 1 Characteristics of the bimanual coordinated task.

	Parameter	Description	Assessment
Distance	Total travel distance (mm)	The sum of the distances moved by the thumb and index finger. The overall amount of movement.	Higher values indicate higher finger dexterity.
	Ave of local max distance (mm)	Average amplitude of the distance waveform.	Values closer to 40 mm indicate higher finger dexterity.
	SD of local max distance (mm)	Variation in the amplitude of the distance waveform.	Lower values indicate higher finger dexterity.
	Slope of approximate line of local max points (mm/s)	The slope is a linear regression of the relationship between the maximum point of each tap and time. As the tap amplitude decreases due to fatigue, the slope increases in the negative direction. When there is no effect of fatigue, the slope is 0.	Lower values indicate higher finger dexterity.
Tap interval	Number of taps (taps)	Number of taps during the measurement time.	Higher values indicate higher finger dexterity.
	Ave of tap intervals (s)	Average in time difference between two consecutive taps.	Lower values indicate higher finger dexterity.
	Frequency of taps (Hz)	Inverse to the mean of the tap interval.	Higher values indicate higher finger dexterity.
	SD of inter-tap interval (s)	Variations in time difference between two consecutive taps.	Lower values indicate higher finger dexterity.
Phase difference	SD of phase difference (degree)	Assuming the interval between one tap is 360°, the time lag between the left and right hands is expressed as an angle. This parameter is the variation of its value.	Lower values indicate higher finger dexterity.

Ave, average; Max, maximum; SD, standard deviation.

Next, all participants performed a bimanual coordination task. Participants sat on chairs with backrests and placed their forearms on a platform. During each task, the forearms were positioned in neutral rotation with the third, fourth, and fifth fingers slightly flexed, and the participants underwent measurements with their eyes closed (Supplementary Figure S2). The bimanual coordination task consisted of two tasks: the in-phase task, in which tapping movements of the thumb and index finger were performed simultaneously as quickly as possible with both hands, and the anti-phase task, in which tapping movements alternated between the left and right hands (Supplementary Figure S3) (Sano et al., 2011; Sugioka et al., 2020). The measurement process began with the in-phase task. Participants performed a 15-s practice session before the measurement, followed by a 15-s measurement for each task. Adequate rest was provided between tasks to prevent participants from becoming fatigued. All measurements were completed in approximately 5 min. We instructed all participants to "perform as fast as possible and maintain the same rhythm" during the bimanual coordination tasks. During the practice session, we confirmed that participants had no communication problems, fully understood the task content, and were able to perform the task accurately, as explained by the experimenter.

Finger movements during bimanual coordination tasks were measured using a magnetic sensor finger-tapping device (UB-2, Maxell Ltd. Tokyo, Japan) (Sugioka et al., 2020). This device comprises a magnetic induction coil, a sensing coil, and a circuit unit (Kandori et al., 2004). The sensors are attached to the participant's thumb and index finger using sensor attachment bands, and voltage is induced between them based on electromagnetic induction. Since the induced voltage has a nonlinear relationship with the distance between the coils, the distance between the fingertips where the sensors are attached can be estimated from the voltage (Shima et al., 2008). Therefore, the magnetic sensor finger-tapping device provides highly reproducible and reliable measurements across periods, devices, and examiners (Sano et al., 2011). During the bimanual coordination task, the participants were instructed to open their fingers to a width of 40 mm to minimize amplitude variations across participants (Suzumura et al., 2021; Sugioka et al., 2022). The parameters of the bimanual coordination task (distance, tap interval, and phase difference) were obtained from the recorded data (Table 1) (Sano et al., 2011). Four parameters of "Distance" were used to evaluate the distance and movement amplitude of the thumb and index finger during the task; four parameters of "Tap interval" were used to evaluate the average speed of movement and variability of tapping; and one parameter of "Phase difference" was used to evaluate the timing discrepancy of tapping between the hands.

2.4 Statistical analysis

Participants were categorized into frail, pre-frail, and robust groups based on the KCL results. First, a chi-square test was conducted to compare the male/female ratios among the groups. Participants' age, height, weight, and MMSE and KCL scores were compared between the groups using one-way analysis of variance (ANOVA). Next, three-way ANOVA with a mixed design was conducted to compare the total travel distance, average of local maximum distance, standard deviation (SD) of local maximum distance, slope of the approximate line of local maximum points, number of taps, average of tap intervals, frequency of taps, and SD of

TABLE 2 Characteristics of the participants.

	Frail (n = 47)	Pre-frail (n = 136)	Robust (n = 129)	F	Post-hoc test
Age (years)	78.38 (5.73)	77.94 (6.25)	76.85 (6.04)	1.57	
Height (cm)	152.09 (8.77)	152.92 (7.60)	154.07 (8.32)	1.26	
Body weight (kg)	50.41 (8.27)	52.48 (9.87)	53.70 (9.46)	2.13	
MMSE (score)	27.74 (1.99)	28.35 (1.76)	28.46 (1.85)	2.68	
KCL (score)	9.47 (1.70)	5.10 (1.07)	1.91 (0.99)	772.14*	Robust < Pre-frail < Frail

MMSE, mini-mental state examination; KCL, kihon checklist; *$p < 0.05$.

inter-tap interval during the bimanual coordination task, considering hand (left, right), task (in-phase task, anti-phase task), and group (frail, pre-frail, robust) as factors. Additionally, a two-way ANOVA with a mixed design was used to compare the SD of the phase difference between left- and right-hand tapping, considering task (in-phase task, anti-phase task) and group (frail, pre-frail, robust) as factors. Bonferroni *post hoc* tests were performed for parameters showing significant interactions or main effects in all ANOVAs. Finally, Pearson correlation analysis was conducted to examine the relationship between the bimanual coordination tasks and the MMSE, assessing whether participants' cognitive function influenced bimanual coordination. Statistical analyses were performed using SPSS version 29.0 (IBM, Armonk, NY, United States), with the significance level set at 5%.

3 Results

3.1 Characteristics of the participants

Based on the KCL assessment of frailty, we categorized the participants into three groups: frail (47 participants; 8 males, 39 females; aged 69–90 years), pre-frail (136 participants; 27 males, 109 females; aged 65–91 years), and robust (129 participants; 33 males, 96 females; aged 65–93 years). The results of the chi-square test showed no significant differences among male/female ratios in each group ($\chi^2 = 2.10$, $p = 0.37$). One-way ANOVA revealed no significant intergroup differences in age, height, weight, or MMSE score ($p > 0.05$) but showed significant differences in the KCL score ($p < 0.05$). Post-hoc tests showed that the KCL scores in the pre-frail and frail groups were significantly higher than that of the robust group, and the score in the frail group was significantly higher than that in the pre-frail group ($p < 0.05$; Table 2).

3.2 Results of three-way ANOVA with hand, task, and group as factors

The three-way ANOVA results showed no significant interactions among the three factors (hand × task × group) for the total travel distance, average of local maximum distance, SD of local maximum distance, slope of the approximate line of local maximum points, number of taps, average of tap intervals, frequency of taps, and SD of the inter-tap interval ($p > 0.05$). Additionally, no significant hand × group and task × group interactions were observed. Conversely, the slope of the approximate line of local maximum points and the SD of the inter-tap interval showed significant hand × task interactions ($p < 0.05$). Post-hoc test results indicated that in the in-phase task, the slope of the approximate line of local maximum points was significantly higher in the right hand than in the left hand ($p < 0.05$). Additionally, the slope of the approximate line of the local maximum points in the right hand was significantly higher in the in-phase task than in the anti-phase task ($p < 0.05$). The SD of the inter-tap interval was significantly higher in the left hand than in the right hand in both the in-phase and anti-phase tasks ($p < 0.05$). In addition, the SD of the inter-tap interval was significantly higher in the anti-phase task than in the in-phase task for both the left and right hands ($p < 0.05$).

The total travel distance showed a significant main effect of the group factor ($p < 0.05$). Post-hoc test results indicated that the total travel distance was significantly longer in the robust group compared to the frail group ($p < 0.05$) (Supplementary Figure S4). The total travel distance, average of the local maximum distance, SD of the local maximum distance, slope of the approximate line of local maximum points, number of taps, average tap intervals, frequency of taps, and SD of the inter-tap interval had significant main effects of the task factor ($p < 0.05$). The *post hoc* test results showed that the total travel distance, number of taps, and frequency of taps showed significant main effects of the task factor ($p < 0.05$). The frequency of taps was significantly higher in the in-phase task than in the anti-phase task ($p < 0.05$). The average of the local maximum distance, SD of the local maximum distance, and average tap intervals were significantly higher in the anti-phase task than in the in-phase task ($p < 0.05$). The total travel distance, SD of the local maximum distance, number of taps, average tap intervals, frequency of taps, and SD of the inter-tap interval showed significant main effects of the hand factor ($p < 0.05$). According to the *post hoc* tests, the total travel distance, number of taps, and frequency of taps were significantly higher for the right hand than for the left hand ($p < 0.05$). In contrast, the SD of the local maximum distance and average tap intervals were significantly higher for the left hand than for the right hand ($p < 0.05$; Table 3).

3.3 Results of two-way ANOVA with task and group as factors

In the two-way ANOVA, the SD of the phase difference showed no significant interaction between the task and group factors nor a main effect of the group factor. However, a significant main effect of

TABLE 3 Results of three-way ANOVA with hand, task, and group as factors.

	Task	Hand	Frail (n = 47)	Pre-frail (n = 136)	Robust (n = 129)	IE	IE	IE	IE	ME	ME	ME	Post-hoc test		
						Hand × group	Task × group	Hand × task	Hand × group × task	Hand	Task	Group			
						F	F	F	F	F	F	F	Hand	Task	Group
Total traveling distance (mm)	IP	L	3,857.11	4,125.05	4,599.64	2.48	0.46	0.71	1.02	6.99*	105.45*	3.78*	L < R[b]	AP < IP[b]	Frail < Robust[b]
			(1,491.55)	(1,550.39)	(1,658.75)										
		R	4,145.72	4,339.03	4,565.60										
			(1,301.58)	(1,506.82)	(1,555.99)										
	AP	L	3,342.03	3,475.23	3,820.00										
			(1,221.67)	(1,099.30)	(1,269.37)										
		R	3,478.85	3,637.13	3,842.62										
			(1,345.38)	(1,218.38)	(1,259.59)										
Ave of local max distance (mm)	IP	L	44.59	48.02	48.49	1.24	1.20	0.52	0.55	0.61	296.09*	0.37		IP < AP[b]	
			(14.92)	(17.47)	(16.69)										
		R	46.64	49.35	47.59										
			(10.78)	(16.78)	(15.84)										
	AP	L	61.17	60.83	63.15										
			(18.47)	(16.07)	(17.13)										
		R	61.34	62.08	62.54										
			(16.40)	(16.84)	(16.27)										
SD of local max distance (mm)	IP	L	6.07	6.83	6.72	0.23	0.84	0.39	1.49	33.41*	50.52*	2.14	R < L[b]	IP < AP[b]	
			(1.71)	(2.40)	(2.22)										
		R	5.64	5.66	5.64										
			(1.62)	(2.06)	(2.09)										
	AP	L	7.16	7.97	7.78										
			(3.48)	(3.46)	(2.96)										
		R	6.27	7.35	7.03										
			(3.11)	(3.34)	(2.80)										

(Continued on following page)

TABLE 3 (*Continued*) Results of three-way ANOVA with hand, task, and group as factors.

	Task	Hand	Frail (n = 47)	Pre-frail (n = 136)	Robust (n = 129)	IE	IE	IE	IE	ME	ME	ME	Post-hoc test		
						Hand × group	Task × group	Hand × task	Hand × group × task	Hand	Task	Group			
						F	F	F	F	F	F	F	Hand	Task	Group
Slope of approximate line of local max points (mm/s)	IP	L	−0.09	−0.08	−0.16	0.69	0.21	7.49*	0.78	3.25	4.33*	0.06	IP: L < R[a]	R: AP < IP[a]	
			(0.48)	(0.71)	(0.68)										
		R	0.03	0.06	0.05										
			(0.61)	(0.67)	(0.58)										
	AP	L	−0.05	−0.18	−0.13										
			(0.77)	(0.75)	(0.81)										
		R	−0.18	−0.11	−0.13										
			(0.55)	(0.75)	(0.72)										
Number of taps	IP	L	43.32	43.79	46.94	0.53	0.46	0.32	0.13	20.05*	590.79*	2.74	L < R[b]	AP < IP[b]	
			(12.57)	(14.58)	(13.32)										
		R	43.72	44.77	47.81										
			(12.67)	(15.54)	(14.11)										
	AP	L	26.64	27.69	29.60										
			(8.37)	(7.77)	(9.36)										
		R	27.13	28.40	30.13										
			(9.10)	(8.15)	(9.79)										
Ave of intervals (s)	IP	L	0.37	0.39	0.35	0.12	1.88	0.52	0.05	4.52*	339.70*	1.50	R < L[b]	IP < AP[b]	
			(0.12)	(0.17)	(0.13)										
		R	0.37	0.38	0.34										
			(0.12)	(0.17)	(0.13)										
	AP	L	0.61	0.57	0.56										
			(0.24)	(0.17)	(0.23)										
		R	0.60	0.56	0.55										
			(0.21)	(0.17)	(0.24)										

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TABLE 3 (*Continued*) Results of three-way ANOVA with hand, task, and group as factors.

	Task	Hand	Frail (n = 47)	Pre-frail (n = 136)	Robust (n = 129)	IE	IE	IE	IE	ME	ME	ME	Post-hoc test		
						Hand × group	Task × group	Hand × task	Hand × group × task	Hand	Task	Group			
						F	F	F	F	F	F	F	Hand	Task	Group
Frequency of taps (Hz)	IP	L	2.93	2.96	3.17	0.76	0.52	0.80	0.06	17.43*	583.26*	2.73	L < R[b]	AP < IP[b]	
			(0.84)	(0.97)	(0.89)										
		R	2.95	3.03	3.23										
			(0.84)	(1.04)	(0.95)										
	AP	L	1.83	1.90	2.02										
			(0.56)	(0.52)	(0.62)										
		R	1.84	1.94	2.05										
			(0.61)	(0.54)	(0.66)										
SD of inter-tapping interval (s)	IP	L	0.04	0.04	0.04	0.02	0.27	5.48*	0.53	36.49*	129.20*	0.03	IP: R < L[a] AP: R < L[a]	L: IP < AP[a] R: IP < AP[a]	
			(0.03)	(0.03)	(0.03)										
		R	0.03	0.04	0.04										
			(0.02)	(0.02)	(0.03)										
	AP	L	0.09	0.09	0.10										
			(0.07)	(0.07)	(0.08)										
		R	0.08	0.07	0.08										
			(0.08)	(0.05)	(0.08)										

Ave, average; Max, maximum; SD, standard deviation; IP, in-phase task; AP, anti-phase task; L, left; R, right, IE, interaction effect; ME, main effect; *a*, *post hoc* test of interaction effect; *b*, *post hoc* test of main effect; * $p < 0.05$.

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TABLE 4 Results of two-way ANOVA with task and group as factors.

	Task	Frail (n = 47)	Pre-frail (n = 136)	Robust (n = 129)	IE	ME	ME	Post-hoc test	
					Task × group	Task	Group		
					F	F	F	Task	Group
SD of phase difference (degree)	IP	26.46	27.99	29.68	0.12	36.99*	0.41	IP < AP[b]	
		(18.70)	(17.26)	(25.57)					
	AP	37.87	37.59	38.93					
		(24.32)	(21.15)	(18.86)					

SD, standard deviation; IP, in-phase task; AP, anti-phase task; L, left; R, right; IE, interaction effect; ME, main effect; *b*, *post hoc* test of main effect; * $p < 0.05$.

the task factor was observed ($p < 0.05$). The *post hoc* test results showed that the SD of the phase difference was significantly higher for the anti-phase task than for the in-phase task ($p < 0.05$; Table 4).

3.4 Results of correlation analysis between the bimanual coordination task and the MMSE

The results of the correlation analysis showed that the total traveling distance, the slope of the approximate line of local maximum points, number of taps, average tap intervals, frequency of taps, and SD of inter-tapping intervals in the in-phase and anti-phase tasks were significantly correlated with the MMSE; however, the correlations were very weak ($p < 0.05$; Supplementary Table S1).

4 Discussion

This study compared the characteristics of bimanual coordinated movements in community-dwelling older adults with frailty, pre-frailty, and robust health. The results showed that the total distance of the bimanual coordinated movements was shorter in the frail group than in the robust group. Additionally, regardless of the degree of frailty, finger dexterity during the bimanual coordination task was lower in the anti-phase task than in the in-phase task and lower in the left hand than in the right hand. These results suggest that older adults with and without frailty exhibit similar levels of bimanual coordination. However, the amount of movement in bimanual coordination tasks was lower in older adults with frailty than in robust older adults. Bimanual coordination tasks are simple, non-invasive, and can be performed without placing an excessive burden on older adults. These characteristics make bimanual coordination tasks suitable as an assessment method for older adults living in the community or those with limited mobility, enabling evaluations to be conducted at home or in caregiving settings. Based on these points, assessing the total traveling distance during bimanual coordination tasks holds potential as a screening method to identify frail older adults.

4.1 Relationship between bimanual coordination and frailty

In this study, older adults were categorized into pre-frail, frail, and robust groups and asked to perform a bimanual coordination task consisting of in-phase and anti-phase tasks. The results showed that the total travel distance was shorter in the frail group than in the robust group. The total travel distance is influenced by the velocity and number of movement taps (Tomita et al., 2020), which represent the amount of finger movement. In a study evaluating the relationship between frailty and finger movement control while performing unilateral movements using the dominant hand, agility, smoothness of movement, and strength were reported to be lower in older adults with frailty than in healthy older adults (Schmidle et al., 2022). Frailty is characterized by a decline in muscle strength and endurance, and reduced muscle strength results in slower movement speeds (Morley et al., 2013; Alcazar et al., 2019). Therefore, it is likely that the frail group performed bimanual coordination tasks more slowly than the robust group. Consequently, the total traveling distance in the frail group may have been shorter than that of the robust group in this study. Although the difference in the amount of movement between the frail and robust groups could also be attributed to reduced endurance in the frail group (Morley et al., 2013; Angulo et al., 2020), the slope of the approximate line of the local maximum points, which reflects the effect of fatigue based on the relationship between the maximum distance between two fingers per tap and time, showed no significant difference between the frail and robust groups in this study. Therefore, the reduced movement in the bimanual coordination task was likely owing to decreased muscle strength and slower movement speed rather than a decline in endurance.

4.2 Comparison of in-phase and anti-phase tasks

Our findings also showed that the total travel distance, number of taps, and frequency of taps were higher in the in-phase task than in the anti-phase task. The average of the local maximum distance, SD of the local maximum distance, average tap intervals, and SD of the phase difference were higher in the anti-phase task than in the in-phase task. The slope of the approximate line of the local maximum points is suspected to be influenced by fatigue because the distance between the two fingers becomes narrower over time if the slope has a negative value. In the present study, the slope of the approximate line of the local maximum points was negative for the anti-phase task and positive for the in-phase task for the right hand. Therefore, the anti-phase task may have been affected by fatigue. Additionally, the SD of the inter-tap interval showed that the rhythm of movement was more variable in the anti-phase task. The number of taps, average tap interval, and frequency of taps indicated that the anti-phase task involved fewer taps, a lower frequency, and longer periods than the in-phase task. The total travel distance and the average and SD of the local maximum distance revealed that the amount of movement was smaller in the anti-phase task than in the in-phase task and that the distance between two fingers per tap and its variation were larger in the anti-phase task than in the in-phase task. The SD of the phase difference showed that the anti-phase task had more timing deviations than the in-phase task for both tasks. Therefore, in this study, the performance of the anti-phase task was lower than that of the in-phase task for all parameters of finger dexterity. The anti-phase task requires specific muscle activity with continuous timing to maintain alternating bimanual movements, and this timing is asymmetric between the left and right hands (Tian et al., 2020). Additionally, maintaining attention is necessary to preserve the phase relationship between hands. For anti-phase tasks and cognitive function, research involving community-dwelling older adults with declining cognitive function has shown a correlation between tapping velocity in the anti-phase task and a decline in working memory and attention (Suzumura et al., 2021). Therefore, the anti-phase task, which requires independent alternating movements of both hands, is suggested to be more challenging than the in-phase task or unilateral motor tasks and is prone to differences in finger function (Sugioka et al., 2022). Therefore, similar to robust older adults, older adults with frailty in this study may have experienced higher difficulty in the anti-phase task than in the in-phase task and showed characteristics of reduced finger dexterity for each parameter.

4.3 Comparison of left and right hand in bimanual coordinated movement

Since the participants performed the same finger-tapping task with their left and right hands, we expected no significant differences between the parameters for each hand. However, the total travel distance was significantly longer with the right hand than with the left. Additionally, the SD of the local maximum distance was lower for the right hand than for the left hand. The right hand showed a higher number and frequency of taps as well as longer intervals than the left hand. Furthermore, the SD of the inter-tap interval was smaller for the right hand than for the left hand. If the thumb is repeatedly moved in a specific direction, the trained movement increases cortical excitability (Classen et al., 1998). Therefore, repetitive movements induce plastic reorganization in the primary motor cortex, and this phenomenon is called use-dependent plasticity (Mawase et al., 2017; Raffin and Siebner, 2019). This use-dependent plasticity has been found to inhibit motor errors and reduce motor planning time, even in complex daily activities (Spampinato and Celnik, 2021). The dominant hand is used more frequently than the non-dominant hand in daily life, and older adults are trained to use the dominant hand in their daily activities (Suzumura et al., 2016). These findings suggest that the primary motor cortex innervating the dominant hand enables spatially and temporally efficient movements through use-dependent plasticity (Shin et al., 2009). In the present study, the right hand may have had higher finger dexterity than the left hand for all parameters, regardless of other factors. Therefore, older adults with frailty, such as robust older adults, have higher finger dexterity during bimanual coordination tasks with their right hand than with their left hand.

4.4 Limitations

This study had a few limitations. First, the KCL consists of seven domains: activities of daily living, motor function, nutritional status, oral function, social withdrawal, cognitive function, and depressive mood. It provides a simple and multidimensional approach to evaluating frailty. However, this study did not clarify how bimanual coordination is related to the physical, social, and psychological aspects of frailty. This point requires further investigation. Second, in this study, the cutoff value for the MMSE was set at less than 24 points, which means the study may have also included older adults with mild cognitive impairment. In the future, it will be necessary to clarify the characteristics of bilateral coordination in older adults with mild cognitive impairment or cognitive frailty, which is a combination of mild cognitive impairment and physical frailty. Third, this study did not examine in detail whether the participants were able to perform the bimanual coordination task accurately. In the future, it will be necessary to examine the accuracy of the bimanual coordination task, including reliability and reproducibility. Fourth, this study investigated the characteristics of bimanual coordination only at the behavioral level and did not examine the neural mechanisms underlying bimanual coordination. Previous studies comparing unilateral movements across a wide range of ages, from children to healthy older adults, have demonstrated that immature or degenerated motor systems may maintain or improve performance by bilaterally mobilizing brain regions, as opposed to normal motor systems (Addamo et al., 2013; Fujiyama et al., 2016). Moreover, structural changes in the corpus callosum have been observed in older adults with frailty (Sugioka et al., 2022), suggesting that a decline in bimanual coordination may be attributed to alterations in interhemispheric interaction. Future studies should investigate interhemispheric interactions and functional and structural changes in the corpus callosum among frail older adults using transcranial magnetic stimulation or functional magnetic resonance imaging. Fifth, while the magnetic sensor-based finger-tapping device used in this study enables precise measurements, it is costly and may be difficult to implement in certain settings. This limitation, particularly in resource-constrained environments, may hinder the wider application of this method. It is important to explore and develop alternative, more cost-effective methods capable of measuring similar parameters to address this limitation. Such efforts could enhance the practicality and accessibility of frailty assessments across diverse environments.

5 Conclusion

This study characterized bimanual coordinated movements in older adults with frailty, pre-frailty, and robust health. Based on the bimanual coordination task, the total traveling distance was shorter in the frail group than in the robust group. Regardless of the severity of frailty, participants showed lower bimanual coordination in the anti-phase task than in the in-phase task, and finger dexterity during the bimanual coordination tasks was lower in the left hand than in the right hand. Therefore, while older adults with frailty exhibit bimanual coordination similar to that of robust older adults, the amount of movement in the bimanual coordination task by those with frailty is lower than that of robust older adults. The results of this study suggest that bimanual coordination tasks may be applicable as an assessment tool for frailty.

Data availability statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available because they contain information that could compromise the privacy of research participants.

Ethics statement

The studies involving humans were approved by the Research Ethics Committee of Kyoto Tachibana University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

SF: Data curation, Formal analysis, Investigation, Visualization, Writing–original draft, Writing–review and editing. SM: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing–review & editing. AG: Investigation, Writing–review & editing. SS: Investigation, Writing–review & editing. RY: Writing–review & editing. YS: Investigation, Writing–review & editing. TM: Funding acquisition, Writing–review & editing. KN: Funding acquisition, Writing–review & editing. HN: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing–review & editing.

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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.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fragi.2025.1519129/full#supplementary-material

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The impact of age and frailty on hospitalization and survival in older liver transplant recipients: a longitudinal cohort study

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Purpose: Frailty is a well-established risk factor for adverse outcomes, particularly in liver transplant candidates. This study investigates the impact of age and frailty on key clinical outcomes—hospitalizations, waitlist survival, and post-transplant mortality—in cirrhotic patients evaluated for liver transplantation.

Methods: This study included older adults with chronic liver disease under consideration for transplantation. Data collected encompassed medical history, Model for End-Stage Liver Disease (MELD) and Child-Turcotte-Pugh (CTP) scores, Mini-Mental State Examination (MMSE), Mini Nutritional Assessment (MNA), and frailty status, assessed using both the Liver Frailty Index (LFI) and the Survey of Health, Ageing, and Retirement in Europe Frailty Index (SHARE-FI). Clinical outcomes, including mortality and hospitalizations, were tracked over a 24-month period.

Results: Among 100 patients (67% male), those under 70 exhibited higher MNA, MMSE, and SHARE-FI scores. Based on frailty classification, 25 patients were frail, 28 pre-frail, and 47 robust. Younger patients experienced more hospitalizations during follow-up ($p = 0.03$) and had a higher probability of hospitalization within 24 months ($p = 0.002$). Although transplant-free survival did not differ significantly across groups, frail patients had a significantly higher mortality rate ($p = 0.04$). Overall, 24 patients underwent transplantation, while 26 died, including six post-transplant deaths. MELD and CTP scores were strong predictors of mortality, while among frailty measures, only SHARE-FI demonstrated significant predictive value. In multivariate Cox models, MELD [HR = 1.17, $p = 0.001$; HR = 1.11, $p = 0.002$], CTP [HR = 1.43, $p = 0.003$; HR = 1.41, $p = 0.006$], and LFI (HR = 1.69, $p = 0.04$) were significantly associated with mortality.

Conclusion: Frailty, rather than age, emerges as a key predictor of mortality in liver transplant candidates. Further research is needed to validate these findings and enhance frailty assessment, ultimately improving candidate selection for transplantation.

KEYWORDS

older adults, liver transplantation, MELD, frailty, CTP

Introduction

Liver disease is a major global health concern, affecting approximately 800 million people annually and contributing to nearly 2 million deaths each year (Marcellin and Kutala, 2018). The primary causes include viral infections, excessive alcohol consumption, and non-alcoholic fatty liver disease (NAFLD), while less common etiologies involve autoimmune disorders (e.g., primary sclerosing cholangitis, primary biliary cirrhosis, autoimmune hepatitis) and genetic conditions (e.g., hemochromatosis, α1-antitrypsin deficiency, Wilson's disease) (Marcellin and Kutala, 2018; Huang et al., 2023). Without appropriate treatment, these conditions can progress to cirrhosis, which initially manifests in a compensated phase before advancing to decompensated cirrhosis, characterized by severe complications and, ultimately, end-stage liver disease (D'Amico et al., 2006). The European Association for the Study of the Liver (EASL) recommends liver transplantation for patients with end-stage disease when it is expected to improve survival or quality of life (European Association for the Study of the Liver, 2016).

With advancements in surgical techniques, liver transplantation criteria have broadened, and age is no longer considered a strict limitation for inclusion on the transplant list (Su et al., 2016). While the benefits of restoring liver function through transplantation are well established, the impact of frailty on pre-transplant evaluation and outcomes remains a subject of ongoing debate (Chen et al., 2014). Frailty is a clinical geriatric syndrome characterized by age-related declines in physiological reserves and an increased vulnerability to stressors. Its prevalence rises with age, affecting more than 25% of individuals aged 85 and older (Fried et al., 2021). In chronic liver disease, frailty arises not only as a consequence of aging but also as a direct result of the systemic alterations induced by the disease—including progressive loss of physiological reserves, sarcopenia, malnutrition, and cognitive decline. These factors, compounded by comorbidities, often impair a patient's ability to withstand major surgery and recover from postoperative complications, even in relatively young individuals with cirrhosis. Consequently, assessing frailty in liver transplant candidates is essential because it provides a comprehensive evaluation of overall health beyond liver function alone. Frailty is known to be associated with adverse outcomes, including falls, disability, hospitalization, and mortality (Hurria et al., 2014). In the context of liver transplantation, it has been linked to higher in-hospital mortality, increased perioperative complications, and greater post-transplant healthcare costs (Lai et al., 2022; Porter et al., 2024). Notably, previous studies have demonstrated that frailty—independent of age—doubles the risk of mortality for patients on the transplant waitlist (Haugen et al., 2020), underscoring its critical role in waitlist outcomes across all age groups. Furthermore, pre-transplant frailty is a strong predictor of post-transplant prognosis, with frail patients exhibiting higher post-transplant mortality, prolonged hospital stays, and increased rates of non-home discharge (Lai et al., 2022). In light of this evidence, the American Society of Transplantation advocates for the integration of frailty assessment into standard pre-transplant evaluations to provide a more comprehensive assessment of transplant candidates (Romero-Ortuno, 2013). However, the current literature on the impact of frailty in older patients undergoing or being considered for liver transplantation remains highly heterogeneous, largely due to the inconsistent use of frailty assessment tools (Vogliotti et al., 2023).

Building on existing evidence, this study aims to investigate the effects of both age and frailty on clinical outcomes and mortality among old patients evaluated for liver transplantation. Specifically, we will examine the onset of decompensation symptoms, hospitalization rates, listing and delisting processes, waitlist survival, and post-transplant mortality in cirrhotic patients. This research seeks to provide a comprehensive understanding of how frailty, as a measure of overall physiological reserve, interacts with age to influence outcomes, ultimately informing improved patient selection and management strategies in liver transplantation.

Patients and methods

Study population

This observational study was conducted on patients attending the outpatient clinics of the Regional Center for Liver Diseases within the Clinical Medicine 5 Department, in collaboration with the Multivisceral Transplant and Hepatobiliary Surgery Units of the University Hospital of Padua. The study was carried out by a highly specialized team in liver diseases and transplantation. As part of this multidisciplinary approach, our comprehensive geriatric assessment was integrated into the care pathway established by internists and surgeons. All patients, recruited between December 2018 and November 2022, were followed for at least 2 years, during which data on disease complications, hospitalizations, and mortality were collected. Additionally, all included patients were aged ≥65 years. The inclusion criteria were as follows: diagnosis of advanced liver cirrhosis and listing for liver transplantation; ability to provide informed consent for the use of data in clinical research; capability to undergo physical performance tests.

The study protocol adhered to good clinical practice guidelines and the ethical standards outlined in the 1964 Declaration of Helsinki, revised in 2000, and was approved by the local Ethics Committee (Comitato Etico per la Sperimentazione Clinica della Provincia di Padova, protocol number 0014675). Participants received a comprehensive explanation of the potential risks and benefits of participation and provided both oral and written informed consent for data publication.

Data collected

The following information was collected from each participant by trained physicians.

Patients's characteristics

Physiological, clinical, and pharmacological data were collected from each participant during a medical interview with a skilled physician. Smoking and alcohol consumption habits, social and environmental conditions, and Model for End stage Liver Disease (MELD), and Child-Turcotte-Pugh score (CTP) scores were reported. Moreover, information related to liver disease such as etiology, prognostic scores, presence of clinical signs of decompensation (including refractory ascites, spontaneous bacterial peritonitis, overt episodes of hepatic encephalopathy, gastrointestinal bleeding, and development of hepatorenal syndrome) any related hospitalizations until the time of transplantation or death, and recent hospitalizations, were collected. Dates of listing for transplantation and removal from the list, as well as dates of transplantation or death, were also recorded.

Multidimensional evaluation

The geriatric multidimensional assessment has been previously described (Vogliotti et al., 2023). In summary, it included evaluating comorbidities using the Cumulative Illness Rating Scale (CIRS), nutritional status with the Mini Nutritional Assessment (MNA), functional status through Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL), and cognitive status with the Mini-Mental State Examination (MMSE). Body weight and height were measured with participants wearing light indoor clothing and no shoes, and the body mass index (BMI) was calculated as weight divided by height squared (kg/m^2).

Frailty assessment

To assess frailty, we calculated the Liver Frailty Index [LFI- (Lai et al., 2019)] and the Survey of Health, Ageing and Retirement in Europe Frailty Index [SHARE-FI- (Romero-Ortuno, 2013)] using dedicated tools. In the Liver Frailty Index, patients were categorized into three groups: robust with a score below 3.2, pre-frail with a score between 3.2 and 4.4, and frail with a score of 4.5 or higher. Regarding the SHARE-FI, frailty was evaluated through a specific algorithm, differentiated by gender. For women: non-frail with a score below 0.32, pre-frail with a score between 0.32 and 2.13, and frail with scores above 2.13; for men: non-frail with a score below 1.21, pre-frail with a score between 1.21 and 3.01, and frail with scores above 3.01.

Statistical analysis

For the study purposes, patients were divided into two groups based on their age at baseline (the first group comprised patients aged 70 years or younger, while the second group included patients older than 70 years) and according to SHARE-FI scores (robust, pre-frail and frail groups). The characteristics of the sample compared by age groups and frailty status are expressed as means ± standard deviation for the continuous quantitative variables with a normal distribution, and as medians (interquartile range-IQR) for those with a non-normal distribution. The normality of the distributions of the continuous quantitative variables was verified by the Shapiro–Wilk test. Categorical variables are expressed in numbers (percentages). The characteristics of the study participants were compared according to their degree of frailty using the Student's t-test or Chi-square test depending on the type of variable. We conducted Kaplan-Meier analyses to evaluate 24-month survival and hospitalization risk, stratifying the results by age groups and SHARE-FI scores. Additionally, with a sensivity analyses, Kaplan-Meier curves were performed both in patients with only Hepatocellular Carcinoma (HCC) and considering patients MMSE scores, categorized as low or high according to the median value. The abilities of MELD, CTP, SHARE-FI and LFI to predict mortality were compared by receiver operating characteristic (ROC) curve analysis, and measurement of the area under the curve (AUC). We analyzed the predictors of overall survival in the entire sample using Cox regression, focusing on MELD, CTP, and frailty indicators. Five models were tested: Model 1 was adjusted for sex, age, and liver disease etiology; Model 2 included these variables along with MELD and SHARE-FI; Model 3 was adjusted for MELD and LFI. Model 4 accounted for sex, age, liver disease etiology, CTP, and SHARE-FI, while Model 5 included CTP and LFI as additional predictors. A sensitivity analysis was performed only in patients with HCC. The statistical tests were considered significant at $p < 0.05$. All analyses were performed with IBM SPSS Statistics 29.0 (Armonk, NY: IBM Corp).

Results

Characteristics of the sample

Table 1 presents the baseline characteristics of the sample, stratified by age groups. Among the total participants, 40 were aged 70 years or younger, while 60 were over 70 years old. The proportion of males was comparable between the two groups. Regarding etiology, 23% of patients had HCV, 14% had HBV, 31% had alcohol-related liver disease, and 15% had NASH. Alcohol-related liver disease was significantly more prevalent in the younger group compared to the older group (44.5% vs. 21.6%, p = 0.002). Conversely, HCC was more frequently observed in older patients, whereas ascites was more common among younger individuals. In the multidimensional assessment, the CIRS comorbidity index and functional scores did not differ significantly between the two groups (p = 0.34 and p = 0.55, respectively). However, MNA and MMSE scores were significantly lower in the younger group compared to the older group [MNA: 22.0 (20.0–23.6) vs 24.5 (21.0–26.5), p = 0.002; MMSE: 26.2 ± 3.4 vs 28.1 ± 1.5, p = 0.01]. Additionally, the SHARE-FI score was significantly higher in the younger group.

Frailty assessment identified 25 frail patients, 28 pre-frail patients, and 47 robust patients. Frail individuals were

TABLE 1 Characteristics of the sample at baseline, all sample and by age groups.

Variable	All (n = 100)	Age ≤70 (n = 40)	Age>70 (n = 60)	p-value
Male sex	67 (67%)	27 (67.5%)	39 (65%)	0.14
Weight (kg)	76.7 ± 14.4	83.4 ± 17.1	72.5 ± 10.6	**0.001**
BMI (kg/m^2)	25.5 ± 4.5	24.8 ± 3.4	26.3 ± 5.9	0.21
Etiology				
HCV	23 (23%)	9 (22.5%)	14 (23.3%)	0.65
HBV	14 (14%)	4 (11.2%)	10 (16.6%)	0.78
Alcool	31 (31%)	18 (44.5%)	13 (21.6%)	0.002
NASH	15 (15%)	4 (11.2%)	11 (18.3%)	0.24
Altro	17 (17%)	5 (12.5%)	12 (20.0%)	0.30
HCC	54 (54%)	13 (32.5%)	41 (68.3%)	**0.001**
MELD at baseline	14 (10–19)	14 (11–17)	13 (9–19)	0.78
CTP at baseline	7 (6–10)	8 (6.5–10)	7 (6–9.3)	0.14
Hospitalizations in the preceding 3 months	41 (41%)	14 (35%)	27 (45%)	0.35
Ascites	46 (46%)	24 (60%)	22 (36.6%)	**0.02**
Esophageal varices	55 (55%)	25 (62.5%)	30 (50%)	0.45
Hepatic encephalopathy	24 (24%)	12 (30%)	12 (20%)	0.24
Multidimensional evaluation				
CIRS-CI	2 (2; 4)	2 (1; 3)	3 (2; 4)	0.34
ADL	6 (5; 6)	6 (6; 8)	6 (5; 6)	0.55
IADL	7 (6; 8)	6 (5; 6)	7 (6; 8)	0.76
MNA	23.0 (21.0; 25.5)	22.0 (20.0; 23.6)	24.5 (21.0; 26.5)	**0.002**
MMSE	26.7 ± 3.2	26.2 ± 3.4	28.1 ± 1.5	**0.01**
SHARE-FI	1.45 (−0.71; 2.82)	2.25 (−0.29; 4.15)	0.82 (−0.74; 2.53)	**0.028**
Liver Frailty Index	4.04 (3.69; 4.57)	4.14 (3.69; 5.21)	3.96 (3.69; 4.32)	0.21

Notes: Numbers are expressed as number (percentages), median (IQR) or mean ± standard deviation. Significant p-values are reported in bold.
Abbreviations: HCV, Hepatitis C Virus; HBV, Hepatitis B Virus; NASH, Non-Alcoholic SteatoHepatitis; HCC, hepatocellular carcinoma; MELD, model for end stage liver disease; CTP, Child-Turcotte-Pugh score; BMI, body mass index; ADL, activity of daily living; IADL, instrumental activity of daily living; MNA, mini nutritional assessment; MPI, multidimensional prognostic index; SPMSQ, short portable mental status questionnaire; MMSE, mini mental state examination; SHARE-FI, frailty instrument of the survey of health, Ageing and Retirement in Europe.

significantly younger than the other two groups [67.0 (56.5–71.0) vs 71.0 (60.3–72.0) vs 72.0 (69.3–73.0), p = 0.011]. They also exhibited more severe liver disease, with higher MELD scores [21 (14–25) vs 18 (12–21) vs 12 (8–15), p = 0.003], but a lower prevalence of HCC. Clinically, frail patients had higher rates of ascites (72% vs. 50.0% vs 29.9%, p = 0.002), esophageal varices, and hepatic encephalopathy. Furthermore, they demonstrated lower scores in MNA, ADL, and IADL (p < 0.001 for all). (Refer to Supplementary Table S1 for additional details.).

Evaluation of clinical outcomes by age group before liver transplantation

Clinical outcomes were analyzed across the two age groups, focusing on the onset of disease decompensation symptoms, hospitalizations, listing and delisting, and transplant-free survival. No significant differences were observed in the prevalence of clinical complications—including spontaneous bacterial peritonitis, hepatic encephalopathy, hepatorenal syndrome, or acute-on-chronic liver failure—between older and younger patients (data not shown). Younger patients had a higher probability of being listed for liver transplantation (57.5% vs 35.0%, p = 0.04) and were more likely to undergo transplantation (69.5% vs 38.0%, p = 0.001). However, their hospital stays were significantly longer than those of older patients [21 (14–40) days vs 12 (7–15) days, p = 0.02; data not shown]. Younger patients also had a higher number of hospitalizations during follow-up (p = 0.03) and a greater probability of hospitalization at 24 months (p = 0.002) (Figure 1). No significant differences were found in transplant-free survival between the two groups (Figure 1). Regarding frailty assessment, the incidence of clinical complications did not significantly differ among frailty groups. Similarly, the proportion of patients listed for liver transplantation was comparable across groups (data not

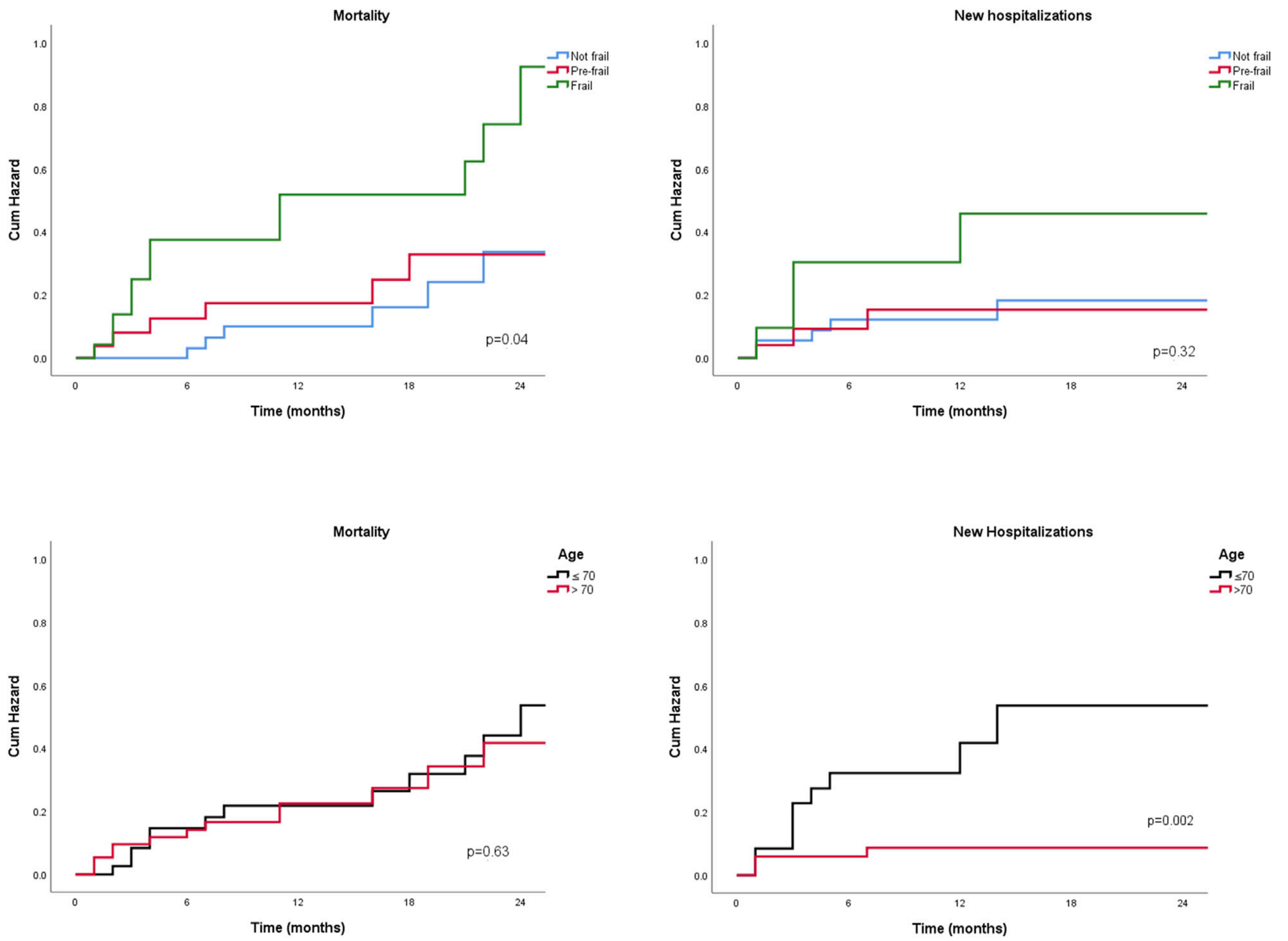

FIGURE 1
Two-years probability for new hospitalization and mortality, by age groups and by frailty degree.

shown). However, the rate of actual transplantation varied: 41.4% of robust patients, 50.0% of pre-frail patients, and 77.8% of frail patients underwent transplantation, though this difference was not statistically significant. Hospitalization rates were significantly higher among frail patients, with 48.0% of frail individuals requiring admission, compared to 17.0% of robust patients and 28.5% of pre-frail patients. However, the overall probability of hospitalization did not reach statistical significance (Figure 1). Survival rates differed significantly based on frailty status, with survival probabilities of 80.4% for robust patients, 81.5% for pre-frail patients, and 52.0% for frail patients ($p = 0.026$). The probability of death also varied significantly among frailty groups ($p = 0.04$) (Figure 1). When stratifying patients by MMSE median values, frailty was associated with a significantly higher probability of mortality ($p = 0.04$) and new hospitalizations ($p = 0.03$) among those with lower MMSE scores. In this low-MMSE subgroup, older patients also had a significantly higher likelihood of hospitalization ($p < 0.001$; data not shown). Additionally, in a sensitivity analysis conducted exclusively on patients with HCC, frail individuals exhibited a significantly higher probability of death ($p = 0.008$), while older patients demonstrated an increased likelihood of hospitalization ($p = 0.007$; data not shown).

Predictors of overall survival

A total of 24 patients underwent liver transplantation. During the observation period, 26 patients died, including six post-transplant deaths. The predictive accuracy of variables such as MELD and CTP scores for transplant listing, as well as frailty scores (SHARE-FI and LFI), was assessed using ROC curves. MELD and CTP scores demonstrated strong predictive accuracy for mortality risk [AUC = 0.71 (0.60–0.83), $p = 0.002$ and AUC = 0.73 (0.61–0.85), $p = 0.001$, respectively]. Among frailty scores, only SHARE-FI showed significant predictive power [AUC = 0.71 (0.58–0.83), $p = 0.003$], whereas LFI did not reach statistical significance [AUC = 0.63 (0.48–0.78), $p = 0.21$] (Figure 2).

The multivariate Cox models for mortality prediction (Table 2) highlight the associations between clinical and frailty indicators and overall mortality risk, including among liver transplant recipients. MELD remained significantly associated with mortality across all models [HR = 1.17, 95% CI: 1.07–1.29, $p = 0.001$ and HR = 1.11, 95% CI: 1.02–1.21, $p = 0.002$]. Among frailty indicators, only LFI demonstrated a significant association with mortality (HR = 1.69, 95% CI: 1.03–2.77, $p = 0.04$). Similarly, CTP was significantly associated with mortality in both models in which it was included [HR = 1.43, 95% CI: 1.35–1.81, $p = 0.003$ and HR =

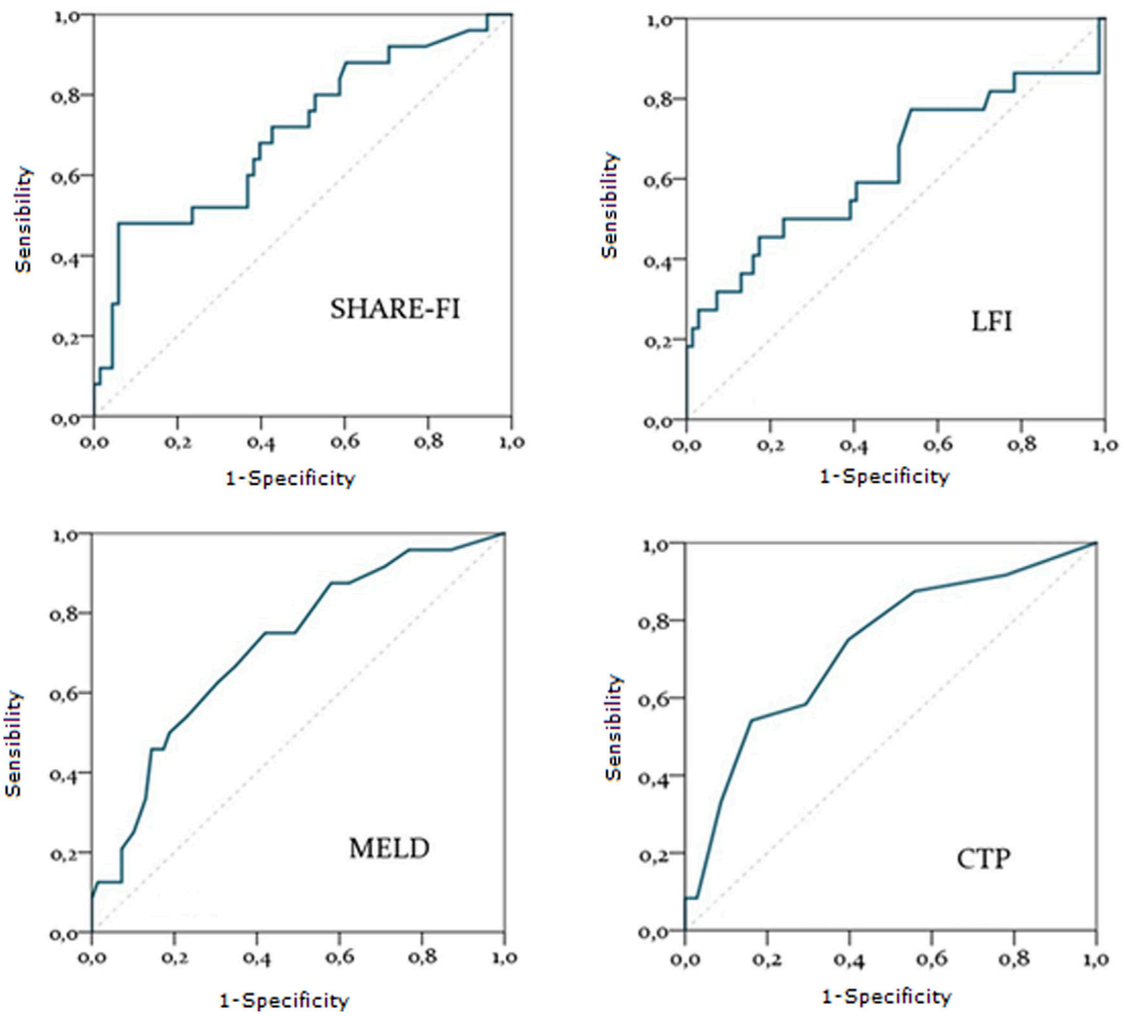

FIGURE 2
Diagnostic accuracy of SHARE-FI, LFI, MELD and CTP in predicting mortality. Abbreviations: SHARE-FI, Frailty Instrument of the Survey of Health, Ageing and Retirement in Europe; LFI, Liver frailty Index; MELD, Model for End stage Liver Disease; CTP, Child-Turcotte-Pugh score.

1.41, 95% CI: 1.10–1.79, p = 0.006]. Conversely, neither SHARE-FI nor LFI showed significant associations in other models [HR = 1.08, 95% CI: 0.83–1.40, p = 0.60 and HR = 1.30, 95% CI: 0.75–2.26, p = 0.35, respectively]. In the sensitivity analysis conducted on patients with HCC (Table 3), MELD remained the only significant predictor of mortality [HR = 1.18, 95% CI: 1.02–1.36, p = 0.03], while no significant associations were observed for frailty indicators or CTP. All models retained statistical significance even after adjusting for MMSE (data not shown).

Discussion

Our study highlights frailty and its severity as key predictors of post-transplant survival in older cirrhotic patients, whereas chronological age alone was not associated with mortality in this population.

In recent years, advancements in antiviral therapies and treatments for decompensated liver disease, alongside improvements in surgical techniques, have significantly reshaped the epidemiology of liver disease. Consequently, the proportion of cirrhotic patients within the geriatric population has risen, prompting critical discussions in hepatology, particularly regarding liver transplantation (Su et al., 2016). The increasing number of transplant-eligible patients, coupled with the rising age of recipients, underscores the need to refine criteria for both patient selection and organ allocation (Su et al., 2016).

Our study focused on frailty, a geriatric syndrome associated with increased vulnerability to stressors (Terziotti et al., 2023), examining its role both as a potential criterion for liver transplant selection and as a predictor of mortality. While interest in the impact of frailty in surgical and transplant settings has grown in recent years, our study stands out as one of the most relevant in this field. Our findings highlight that preoperative assessment should not rely solely on chronological age but should instead incorporate a thorough frailty evaluation, which appears to be a key determinant of post-transplant outcomes. Our data confirm that frail patients had significantly lower survival rates and a higher risk of mortality. These findings align with existing geriatric literature, which consistently demonstrates

TABLE 2 Multivariate cox models for mortality prediction.

Variables	Model 1	Model 2	Model 3	Model 4	Model 5
	HR (CI95%), p-value	HR (CI95%), p-value	HR (CI95%), p-value	HR (CI95%), p-value	HR (CI95%), p-value
AGE	0.97 (0.93; 1.01), p = 0.18	0.95 (0.91; 1.03), p = 0.19	0.97 (0.93; 1.02), p = 0.16	0.97 (0.93; 1.03), p = 0.24	0.97 (0.93; 1.01), p = 0.26
MELD	1.62 (1.08; 1.25), p < 0.001	1.17 (1.07; 1.29), p = 0.001	1.11 (1.02; 1.21), p = 0.002	—	—
CTP	1.49 (1.21; 1.85), p < 0.001	—	—	1.43 (1.35; 1.81), p = 0.003	1.41 (1.10; 1.79), p = 0.006
LFI	1.91 (1.18; 3.11), p = 0.009	—	1.69 (1.03; 2.77), p = 0.04	—	1.30 (0.75; 2.26), p = 0.35
SHARE-FI	1.28 (1.03; 1.60), p = 0.003	1.07 (0.83; 1.39), p = 0.59	—	1.08 (0.83; 1.40), p = 0.60	—

Notes: Model 1 was adjusted for sex, age, and liver disease etiology. Model 2 included these factors along with MELD, and SHARE-FI, while Model 3 was adjusted for MELD, and LFI., Model 4 incorporated sex, age, liver disease etiology; CTP, and SHARE-FI, and finally, Model 5 included CTP, and LFI, as additional predictors.
Abbreviations: MELD, model for end stage liver disease; CTP, Child-Turcotte-Pugh score; MPI, multidimensional prognostic index; MMSE, mini mental state examination; SHARE-FI, frailty instrument of the survey of health, Ageing and Retirement in Europe; LFI, liver frailty index.

TABLE 3 Multivariate Cox Models for Mortality Prediction in patients with HCC.

Variables	Model 1	Model 2	Model 3	Model 4	Model 5
	HR (CI 95%), p-value	HR (CI 95%), p-value	HR (CI 95%), p-value	HR (CI 95%), p-value	HR (CI 95%), p-value
AGE	0.96 (0.88; 1.05), p = 0.37	0.98 (0.88; 1.09), p = 0.65	0.93 (0.83; 1.04), p = 0.20	1.02 (0.89; 1.16), p = 0.81	0.97 (0.85; 1.10), p = 0.61
MELD	1.22 (1.08; 1.37), p = 0.001	1.18 (1.02; 1.36), p = 0.03	1.09 (0.90; 1.31), p = 0.37	—	—
CTP	1.52 (1.07; 2.16), p = 0.02	—	—	1.50 (0.83; 2.38), p = 0.14	1.31 (0.85; 2.04), p = 0.22
LFI	2.92 (1.16; 7.35), p = 0.02	—	2.01 (0.58; 7.02), p = 0.27	—	1.97 (0.55; 7.02), p = 0.30
SHARE-FI	1.52 (1.01; 2.29), p = 0.04	1.34 (0.81; 2.21), p = 0.25	—	1.37 (0.91; 2.05), p = 0.13	—

Notes: Model 1 was adjusted for sex, age, and liver disease etiology. Model 2 included these factors along with MELD, and SHARE-FI, while Model 3 was adjusted for MELD, and LFI., Model 4 incorporated sex, age, liver disease etiology; CTP, and SHARE-FI, and finally, Model 5 included CTP, and LFI, as additional predictors.
Abbreviations: MELD, model for end stage liver disease; CTP, Child-Turcotte-Pugh score; MPI, multidimensional prognostic index; MMSE, mini mental state examination; SHARE-FI, frailty instrument of the survey of health, Ageing and Retirement in Europe; LFI, liver frailty index.

that frailty is associated with worse mortality outcomes, regardless of the assessment tool used (Ekram et al., 2021), with effects extending up to 10–18 years (Salminen et al., 2020). Within this framework, frailty is undoubtedly influenced by factors such as sarcopenia, a well-known risk factor that, in a vicious cycle, further exacerbates its progression and associated adverse outcomes. In the context of cirrhosis, sarcopenia has been linked to reduced survival, although some degree of recovery after liver transplantation has been reported. Notably, it affects approximately 40% of patients on the liver transplant waiting list and has been shown to double the risk of death while awaiting transplantation. Importantly, this increased mortality risk has been found to be independent of MELD scores, suggesting that sarcopenia could serve as a crucial determinant of frailty and a key prognostic factor in this patient population (Soldera, 2018). Moreover, the risk of mortality in frail patients was higher than in pre-frail individuals. Notably, clinical outcomes were worse in frail patients with lower MMSE scores. This finding is not surprising, given that the prevalence and severity of frailty increase as MMSE scores decline. Supporting this evidence, a study conducted on outpatients attending CCDDs centers in Lombardy, Italy, reported that the prevalence of severe frailty ranged from 7.2% among individuals with an MMSE score of 24 or higher to 24.2% among those with an MMSE score below 10 (Bellelli et al., 2023). These findings suggest that implementing structured interventions aimed at improving physical and nutritional status before transplantation could be beneficial in optimizing clinical outcomes. A particularly intriguing aspect of our study is the lack of significant differences in transplant rates among frail, pre-frail, and robust patients. Although frailty is recognized as a negative prognostic factor, no official criteria currently exclude frail patients from transplant eligibility. Instead, transplant selection teams primarily consider disease severity, organ functional reserve, and comorbidities rather than frailty alone. It is plausible that frail patients, who exhibited higher MELD scores, were prioritized for transplantation regardless of their frailty status. This could explain the absence of significant differences in transplant rates across the groups.

Regarding predictors of mortality in liver transplantation, both the MELD score and the CTP score have demonstrated strong prognostic value (Ekram et al., 2021). The MELD score is a crucial tool for assessing mortality risk in patients awaiting transplantation, with higher scores directly correlating with increased mortality. Patients with elevated MELD scores face greater risks of death both while on the waitlist and post-transplant (Kim et al., 2023). Similarly, the CTP score has been linked to post-transplant mortality, with patients scoring below 10 exhibiting significantly better survival rates than those with scores of 10 or higher (Yao et al., 2004). This finding aligns with our ROC curve analysis and regression models for estimating 24-month mortality risk across the entire sample, in which both MELD and CTP consistently emerged as significant predictors of survival. In our analysis of frailty as a potential predictor of mortality in this population, we found that frailty was a significant determinant of overall mortality, but only when assessed using the LFI. This finding may seem paradoxical, given that our ROC curve analysis indicated that the SHARE-FI demonstrated promising predictive ability, whereas the LFI did not. The LFI and SHARE-FI are among the most widely used tools for assessing frailty in liver transplant recipients (Haugen et al., 2020; Salminen et al., 2020; Soldera, 2018; Kim et al., 2023). Notably, the LFI, developed by Lai et al., in 2019, has been validated as a reliable predictor of mortality risk in cirrhotic patients on the transplant waiting list (Lai et al., 2019). The discrepancy observed in our study may stem from fundamental differences between these two indices. The LFI incorporates factors particularly relevant to mortality risk, such as functional limitations and malnutrition risk, which directly impact survival and are specifically tailored to patients with liver disease. It aligns with Linda Fried's frailty criteria, which define frailty as the presence of at least three of the following: involuntary weight loss, reduced muscle strength (handgrip), slow walking speed, low levels of physical activity, and increased fatigability (Fried et al., 2001). In contrast, SHARE-FI focuses on broader health status indicators that may not correlate as strongly with mortality risk in this specific patient population (Romero-Ortuno et al., 2011). Our findings suggest that the LFI may be the most clinically useful index for estimating mortality risk in older patients undergoing liver transplantation. In our analysis, the LFI and SHARE-FI showed a significant association with mortality in certain models, suggesting an independent prognostic value. However, when included in more comprehensive models (e.g., Model 5 for LFI and Model 2 for SHARE-FI), this effect was no longer significant, which may indicate that frailty shares part of its predictive capacity with liver disease severity. These findings suggest that frailty may not only be an independent risk factor but also a marker of clinical deterioration in patients with advanced cirrhosis. However, its specific contribution relative to traditional disease severity scores warrants further investigation in larger cohorts with longitudinal assessments. Among patients with HCC, only MELD remained a significant predictor of mortality, while no meaningful associations were observed between CTP, frailty indicators, and mortality. Notably, patients with HCC in our cohort were older than those without HCC but were also more frequently classified as robust. This may partly explain why frailty did not emerge as a predictor of mortality in this subgroup. In contrast, traditional liver function metrics may provide more reliable mortality predictions in this population. The MELD score specifically evaluates liver function and its associated complications, offering a direct assessment of the physiological factors influencing mortality risk. Frailty, on the other hand, does not necessarily correlate with liver function severity, meaning that patients with high frailty scores may still exhibit relatively preserved liver function.

Previous studies have largely focused on the role of age in geriatric patients undergoing liver transplantation. Although recent updates to transplant guidelines no longer consider age a strict limiting factor (Huang et al., 2023; Su et al., 2016), older patients are often burdened with increased comorbidities and functional decline, which can render them ineligible for transplantation. For instance, Leibovici-Weissman et al. identified age as a key predictor of long-term post-transplant survival, independent of MELD score (Leibovici-Weissman et al., 2017). Similarly, Sharpton et al. demonstrated that both high MELD scores (≥28) and advanced age (≥70 years) independently increase the risk of graft loss, with a synergistic effect that significantly worsens outcomes when both factors are present (Sharpton et al., 2014). In our study, age did not significantly influence mortality among older cirrhotic patients. This finding underscores two important considerations. First, age alone may not fully account for the impact of other critical factors, such as comorbidities, which can strongly affect patient prognosis (Radonjić et al., 2022). Second, assessing mortality risk in liver disease is inherently complex, requiring a multifactorial approach. Interestingly, younger patients exhibited a higher probability of new hospitalizations. This may, in part, be attributed to the fact that, in our sample, younger patients had a higher prevalence of alcohol-related liver disease, which is known to be associated with a more aggressive disease course, higher rates of decompensation, and increased healthcare utilization (Matovic Zaric et al., 2024). Alcohol-related liver disease often presents with acute exacerbations, including episodes of alcoholic hepatitis, infections, and gastrointestinal bleeding, which frequently require hospitalization (Osna et al., 2024). Furthermore, clinically, younger individuals are more likely to present with acute conditions that necessitate frequent hospital visits for management and stabilization. In contrast, older patients often follow a more chronic disease trajectory, managing their established comorbidities more effectively and consequently requiring fewer hospitalizations (Mohan et al., 2022). Healthcare access and utilization patterns may also contribute to this trend. Younger patients might be more inclined to seek emergency care rather than engage in regular follow-ups, potentially due to a lack of awareness regarding the importance of ongoing disease management. Additionally, barriers such as insurance coverage and limited access to specialized care can delay necessary treatments, exacerbating conditions and leading to increased hospitalizations. Although not explicitly assessed in our study, psychosocial factors likely play a significant role in these differences. Younger individuals often struggle with adherence to medical regimens, a key component in managing chronic liver disease. Poor adherence can lead to worsening symptoms and an increased need for hospitalization (Leibovici-Weissman et al., 2017; Sharpton et al., 2014; Radonjić et al., 2022). Frailty, however, did not appear to influence hospitalization rates, except in patients with low MMSE scores, where frailty was associated with a higher probability of readmission within 24 months. Cognitive impairment may interact with frailty in a way that amplifies health risks. It can impair a patient's ability to manage their condition, adhere to treatments, and recognize early signs of deterioration, ultimately increasing the likelihood of hospitalization and readmission (Rezaei-Shahsavarloo et al., 2020).

Our findings prompt a broader reflection on the concept of frailty in the context of liver transplantation. While traditionally considered an independent prognostic factor, frailty may also serve as a marker of disease severity, reflecting the cumulative impact of end-stage liver disease (ESLD) progression rather than being solely an age-related condition. This raises the question of whether frailty should be regarded not only as a modifiable risk factor but also as a marker of disease severity itself. From this perspective, frailty could reflect the cumulative burden of systemic inflammation, sarcopenia, and multi-organ dysfunction that accompany ESLD progression, rather than being merely an age-related syndrome. Recognizing frailty as an intrinsic component of ESLD progression rather than an isolated variable could have important implications for patient management. Instead of viewing frailty purely as a separate entity requiring independent intervention, a more comprehensive approach might involve addressing both frailty and liver disease severity simultaneously. This could entail optimizing nutritional and physical rehabilitation strategies alongside standard hepatologic care to mitigate the impact of frailty on clinical outcomes. Future studies should further investigate the dynamic interplay between frailty and disease progression, exploring whether targeted interventions aimed at improving frailty could also influence the natural history of ESLD and transplant outcomes. These considerations highlight the need for future longitudinal research to better delineate the interplay between frailty and liver disease progression.

Limitations and strengths

Several limitations of this study should be acknowledged, particularly the small sample size, which restricts the generalizability of our findings. However, the study's distinct focus on geriatric patients makes it one of the few to specifically address this critical population in the context of liver transplantation. Additionally, further investigation into the interplay between cognitive function and frailty in this cohort would be valuable, as a deeper understanding of this relationship could offer important insights into the multifaceted nature of frailty in older liver transplant candidates.

Conclusion

Our study highlights that frailty—rather than age—may serve as a reliable predictor of overall mortality in liver transplant recipients. Future research is needed to validate these findings and further refine the assessment of frailty, with the goal of optimizing patient selection for transplantation.

Key summary points

Aim: This study aims to evaluate the impact of age and frailty on clinical outcomes, including hospitalizations, waitlist survival, and post-transplant mortality, in cirrhotic older patients undergoing evaluation for liver transplantation.

Findings: Younger patients had a higher risk of hospitalization during follow-up ($p = 0.03$) and a greater 24-month hospitalization probability ($p = 0.002$). MELD, CTP, and LFI scores were significant predictors of mortality, with SHARE-FI showing additional predictive power among frailty indices.

Message: Frailty, rather than age, appears predictive of mortality in older liver transplant candidates.

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 humans were approved by Comitato Etico per la Sperimentazione Clinica della Provincia di Padova, protocol number 0014675. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MV: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft. CCe: Writing – original draft. MR: Writing – original draft. CCu: Visualization, Writing – review and editing. MDe: Visualization, Writing – review and editing. MT: Visualization, Writing – review and editing. CCa: Visualization, Writing – review and editing. JV: Conceptualization, Data curation, Investigation, Writing – review and editing. MG: Visualization, Writing – review and editing. UC: Visualization, Writing – review and editing. PB: Visualization, Writing – review and editing. PA: Visualization, Writing – review and editing. GS: Supervision, Visualization, Writing – review and editing. MDR: Project administration, Supervision, Visualization, Writing – review and editing.

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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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fragi.2025.1539688/full#supplementary-material

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Association between care complexity individual factors and older inpatients with COVID-19: a cross-sectional study

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Background: Many elderly people required hospitalization during the pandemic period, but broader care complexity factors have not been studied in this population. This study aimed to identify the care complexity factors according to age in older people hospitalized with COVID-19.

Methods: A multicenter cross-sectional study was conducted from 1 March 2020 to 31 March 2022 at eight public hospitals in Spain. All older patients hospitalized with COVID-19 were classified in the following groups: young-old (65–74 years), middle-old (75–84 years), and oldest-old (≥85 years). The main variable was care complexity individual factors (CCIFs), which included 27 CCIFs classified in four domains: comorbidity/complications, psycho-emotional, mental-cognitive, and sociocultural. Multinomial logistic regressions were performed to identify the association of each CCIFs with age group.

Results: A total of 5,658 admissions were included. Of these, 46.3% were young-old (65–74 years), 34.8% middle-old (75–84 years) and 18.8% oldest-old (≥85 years). The analysis shows that middle-old (75–84 years) patients were associated with chronic disease, position impairment, urinary or fecal incontinence, anatomical and functional disorders, vascular fragility, involuntary movements, fear or anxiety and mental status impairments. Extreme weight, communication disorders, aggressive behavior, agitation and perception reality disorders were additional factors associated with the oldest-old (≥85 years) inpatients with COVID-19. The median number of CCIFs was higher in the oldest-old than in the other age groups (four in young-old [65–74 years]; six in middle-old [75–84 years]; seven in oldest-old [≥85 years] [OR:2.9; 95%CI:2.8–3.1; $p < 0.001$]).

Conclusion: The oldest groups of patients (≥75 years) admitted with COVID-19 had more CCIFs than the young-old group. CCIFs should be included in patient assessment in order to identify care needs in older hospitalized patients.

KEYWORDS

care complexity, patient assessment, older adults, hospitalization, COVID-19

Highlights

Many older adults required hospitalization during the pandemic period, however CCIFs have not been studied in this population.

We found that the oldest groups of patients (≥75 years) admitted with COVID-19 had more CCIFs than the young-old group.

This study strengthens the argument for considering broader patient assessment to identify care complexity needs.

Introduction

The COVID-19 pandemic disproportionately affected individuals over 65 years old. According to data from Spain, more than 60% of COVID-19 patients hospitalized during the first months of the pandemic were aged over 65 years, and this demographic group accounted for approximately 85% of deaths from the disease (Instituto Nacional de Estadística. Instituto Nacional de Estadística INE, 2024).

Prior studies focusing on older people hospitalized with COVID-19 focused on identified risk factors and frailty indicators associated with unfavorable outcomes (Wiemers et al., 2024; Wei et al., 2020; Szklarzewska et al., 2023; Alsahab et al., 2021; Smits et al., 2022) however, broader care complexity factors have not been studied in this population. Understanding care complexity individual factors (CCIFs) is crucial for developing more effective and personalized management strategies for older adults with COVID-19. CCIFs are a set of patient characteristics related to different health dimensions that may complicate care delivery and contribute to adverse events (Juvé-Udina et al., 2010). Previous studies have shown the association of CCIFs with unfavorable outcomes in hospitalized patients in general and in those admitted for COVID-19 (Jiménez-Martínez et al., 2024; Adamuz et al., 2018; Adamuz et al., 2021). Therefore, prior identification of CCIFs could help to identify patients with a higher risk of complications (Adamuz et al., 2020). The use of assessment tools considering these factors could improve care planning accuracy and optimize resource allocation. This approach could inform public health policies aimed at strengthening the health system's capacity to respond to future health emergencies and the needs of the aging population (De Foo et al., 2023). However, few studies have provided data about CCIFs in the vulnerable elderly population hospitalized with COVID-19.

The aim of this study was to identify CCIFs according to the age of older adults hospitalized with COVID-19.

Methods

Study population

A multicenter cross-sectional study was conducted from 1 March 2020 to 31 March 2022 at eight public health hospitals in Spain: three high-tech hospital (tertiary metropolitan facilities), three urban university centers and two community hospitals. All patients with a medical diagnosis of COVID-19 infection admitted to a ward or step-down unit from 1 March 2020 to 31 March 2022 with a completed hospital minimum data set report were included. Patients directly admitted and discharged from intensive care units (ICU) were excluded.

This study was evaluated and approved by the institutional review board. Ethical and data protection protocols related to anonymity and data confidentiality (access to records, data encryption and archiving of information) were complied with throughout the study.

Data source

All data were collected from the electronic health record system, the hospital minimum data set and the clinical data warehouse. A unique identification number was used to link the data sets from these sources.

Variables

Consistent with the literature, older adults were categorized as young-old (65–74 years), middle-old (75–84 years), and oldest-old (≥85 years) (Neugarten, 1974; Johfre and Saperstein, 2023). The main variable was care complexity individual factors (CCIFs) (Juvé-Udina et al., 2010). CCIFs are a group of patient characteristics related to different health dimensions that may complicate care delivery and contribute to adverse outcomes. They are classified into four domains: (i) comorbidity/complications, (ii) psycho-emotional, (iii) mental-cognitive sociocultural, and iv) sociocultural. Patients were considered to have CCIFs if they presented at least one related defined characteristic according to previous inquiries. CCIFs were collected from the nursing assessment e-charts as structured data based on the Architecture, Terminology, Interface, Knowledge (ATIC) terminology (Juvé-Udina and Adamuz, 2023; Juvé-Udina, 2013). In this study we included the following CCIFs. The comorbidity/complications domain contained: (i) major chronic disease, (ii) hemodynamic instability (intensive control of vital signs or state of shock), (iii) high risk of haemorrhage (coagulation disorders, thrombocytopenia, anticoagulant therapy), (iv) communication disorders (aphasia, dysphasia, dysarthria, laryngectomy, tracheostomy), (v) urinary or faecal incontinence, (vi) vascular fragility (capillary fragility, tortuous veins), (vii) position impairment, (viii) involuntary movements (continuous involuntary movements), (ix) extreme weight (low weight, obesity), (x) dehydration (skin turgor), (xi) oedema, (xii) uncontrolled pain (verbal numerical rating scale above three

TABLE 1 Baseline characteristics among patients hospitalized with COVID-19 according to the age category of older adults.

Characteristics	Study population n = 5,658		Young old (65–74) n = 2,622		Middle-old (75–84) n = 1,971		Oldest-old (≥85) n = 1,065		*p-value*
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	
Demographic characteristics									
Age (years)_mean (SD)	76.5	(7.9)	69.5	(2.9)	79.0	(2.9)	88.9	(3.3)	**<0.001**
Female sex	2,414	(42.7)	1,042	(39.7)	809	(41.0)	563	(52.9)	**<0.001**
Clinical characteristics									
Length of stay_median (IQR)	9	(5–15)	9	(6–17)	9	(9–15)	8	(5–13)	**<0.001**
Continuity of care (discharged to another facility)	1,068	(18.9)	418	(15.9)	388	(19.7)	262	(24.6)	**<0.001**
High-tech hospital	3,785	(66.9)	1,756	(67.0)	1,313	(66.6)	716	(67.2)	0.937
Step-down unit	558	(9.9)	330	(12.6)	195	(9.9)	33	(3.1)	**<0.001**
ICU	1,371	(24.2)	907	(34.6)	397	(20.1)	67	(6.3)	**<0.001**
Underlying disease									
Arterial hypertension or chronic heart failure	3,074	(54.3)	1,356	(51.7)	1,117	(56.7)	601	(56.4)	**0.001**
Diabetes or chronic kidney disease	2,175	(38.4)	822	(31.4)	843	(42.8)	510	(47.9)	**<0.001**
Chronic respiratory disease	1,035	(18.3)	430	(16.4)	401	(20.3)	204	(19.2)	**0.002**
Cancer	542	(9.6)	237	(9.0)	224	(11.4)	81	(7.6)	**0.002**
Neurodegenerative disease	115	(2.0)	22	(0.8)	50	(2.5)	43	(4.0)	**<0.001**
Chronic liver disease	73	(1.3)	37	(1.4)	25	(1.3)	11	(1.0)	0.650
Immunosuppression	42	(0.7)	27	(1.0)	15	(0.8)	0	(0.0)	**0.004**
Dementia	70	(1.2)	6	(0.2)	20	(1.0)	44	(4.1)	**<0.001**

Abbreviations: SD, standard deviation; IQR, interquartile range; ICU, intensive care unit. Bold values indicate statistical significance (p<0.05).

points), (xiii) transmissible infections (isolation measures), (xiv) immunosuppression and (xv) anatomical and functional disorders (amputation, deformities, joint stiffness). The psycho-emotional domain comprised: (i) aggressive behaviour, (ii) fear/anxiety and (iii) impaired adaptation (disruptive behaviour, hopelessness or surrender). The mental-cognitive domain included: (i) agitation, (ii) mental status impairments (confusion, disorientation, stupor, transient loss of consciousness), (iii) impaired cognitive functions (intellectual disability, amnesia) and (iv) perception of reality disorders (delirium, hallucinations, disconnection from reality). Finally, the sociocultural domain included: (i) language barriers, (ii) social exclusion (extreme poverty), (iii) belief conflict (spiritual distress), and (iv) lack of caregiver support.

We also collected information regarding the demographic and clinical characteristics of the patients, sex, underlying disease, continuity of care (discharged to another facility), length of hospital stay, and admission to ICU during hospitalization. Facilities were classified into two categories: high-tech hospitals or other. High-tech hospitals were defined as referral university centres that provide tertiary care for either open-heart surgery or major organ transplants.

Statistical analysis

Descriptive analysis of data was performed to describe the patients' demographic and clinical characteristics. For categorical variables, a comparative analysis for detecting significant differences between each age group was carried out using the Fisher's exact test. For continuous variables the Mann-Whitney U test was used. Univariate multinomial logistic regressions of each CCIFs were performed to detect which ones were potentially associated with the different age groups (Table 2). The young-old (65–74) group was used as the reference category. The findings obtained were corroborated after adjusting for potential confounders: sex and hospital type (high-tech hospital) (Supplementary Material). The median-based CCIF categories shown in Table 2 were included solely for descriptive purposes and were not used in any regression models. The results of the logistic-regressions analyses were reported as odds ratios (OR) and 95% confidence intervals (CI). P values less than 0.05 were considered statistically significant. All reported p values are two-tailed. Statistical analysis was performed using the SPSS software package version 25.0 (SPSS, Chicago, IL).

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TABLE 2 Association of CCIFs among patients hospitalized with COVID-19 according to the age category of older adults.

Characteristics	Study population n = 5,658		Young-old (65–74) n = 2,622		Middle-old (75–84) n = 1,971					Oldest-old (≥85) n = 1,065				
	No.	(%)	No.	(%)	No.	(%)	OR	95% CI	*p-value*	No.	(%)	OR	95% CI	*p-value*
Care complexity individual factors (CCIFs)														
Comorbidity/complications														
Hemodynamic instability	5,074	(89.7)	2,328	(88.8)	1,779	(90.3)	1.17	0.97–1.42	0.109	967	(90.8)	1.25	0.98–1.58	0.073
Transmissible infection	4,023	(71.1)	1,850	(70.6)	1,412	(71.6)	1.05	0.93–1.20	0.424	761	(71.5)	1.04	0.89–1.22	0.586
Chronic disease	4,621	(81.7)	1,974	(75.3)	**1,679**	**(85.2)**	**1.89**	**1.62–2.20**	**<0.001**	**968**	**(90.9)**	**3.28**	**2.61–4.11**	**<0.001**
Uncontrolled pain	1,165	(20.6)	528	(20.1)	412	(20.9)	1.05	0.91–1.21	0.52	225	(21.1)	1.06	0.89–1.27	0.499
Extreme weight	526	(9.3)	228	(8.7)	172	(8.7)	1.00	0.82–1.23	0.97	**126**	**(11.8)**	**1.41**	**1.12–1.77**	**0.004**
Position impairment	807	(14.3)	200	(7.6)	**294**	**(14.9)**	**2.12**	**1.75–2.57**	**<0.001**	**313**	**(29.4)**	**5.04**	**4.15–6.13**	**<0.001**
Urinary or faecal incontinence	906	(16.0)	189	(7.2)	**348**	**(17.7)**	**2.76**	**2.29–3.33**	**<0.001**	**369**	**(34.6)**	**6.82**	**5.62–8.29**	**<0.001**
Anatomical and functional disorders	409	(7.2)	115	(4.4)	**162**	**(8.2)**	**1.95**	**1.53–2.50**	**<0.001**	**132**	**(12.4)**	**3.08**	**2.38–4.00**	**<0.001**
Communication disorders	185	(3.3)	61	(2.3)	56	(2.8)	1.23	0.85–1.77	0.274	**68**	**(6.4)**	**2.86**	**2.01–4.08**	**<0.001**
Vascular fragility	159	(2.8)	36	(1.4)	**64**	**(3.2)**	**2.41**	**1.60–3.64**	**<0.001**	**59**	**(5.5)**	**4.21**	**2.77–6.42**	**<0.001**
Immunosuppression	42	(0.7)	27	(1.0)	15	(0.8)	0.37	0.39–1.39	0.345	0	(0.0)			
Involuntary movements	46	(0.8)	12	(0.5)	**19**	**(1.0)**	**2.12**	**1.02–4.37**	**0.043**	**15**	**(1.4)**	**3.11**	**1.45–6.60**	**0.004**
High risk of haemorrhage	30	(0.5)	11	(0.4)	14	(0.7)	1.70	0.77–3.75	0.190	5	(0.5)	1.12	0.39–3.23	0.834
Oedema	17	(0.3)	7	(0.3)	5	(0.3)	0.95	0.30–3.00	0.930	5	(0.5)	1.76	0.56–5.56	0.334
Dehydration	6	(0.1)	0	(0.0)	3	(0.2)	-	-	-	3	(0.3)	-	-	-
Psycho-emotional														
Fear/anxiety	441	(7.8)	169	(6.4)	**169**	**(8.6)**	**1.36**	**1.09–1.70**	**0.006**	**103**	**(9.7)**	**1.55**	**1.20–2.01**	**0.001**
Impaired adaptation	385	(6.8)	192	(7.3)	139	(7.1)	0.96	0.77–1.20	0.73	**54**	**(5.1)**	**0.68**	**0.49–0.92**	**0.014**
Aggressive behaviour	28	(0.5)	6	(0.2)	10	(0.5)	2.22	0.81–6.13	0.122	**12**	**(1.1)**	**4.97**	**1.86–13.27**	**0.001**
Mental-cognitive														
Mental status impairments	1,985	(35.1)	491	(18.7)	**765**	**(38.8)**	**2.75**	**2.41–3.15**	**<0.001**	**729**	**(68.5)**	**9.42**	**8.01–11.07**	**<0.001**
Agitation	104	(1.8)	25	(1.0)	30	(1.5)	1.61	0.94–2.74	0.082	**49**	**(4.6)**	**5.01**	**3.01–8.15**	**<0.001**
Impaired cognitive functions	8	(0.1)	5	(0.2)	3	(0.2)	0.80	0.19–3.34	0.757	0	(0.0)	-	-	-

(Continued on following page)

TABLE 2 (*Continued*) Association of CCIFs among patients hospitalized with COVID-19 according to the age category of older adults.

Characteristics	Study population n = 5,658		Young-old (65–74) n = 2,622		Middle-old (75–84) n = 1,971					Oldest-old (≥85) n = 1,065				
	No.	(%)	No.	(%)	No.	(%)	OR	95% CI	*p-value*	No.	(%)	OR	95% CI	*p-value*
Perception of reality disorders	19	(0.3)	3	(0.1)	8	(0.4)	3.56	0.94–13.43	0.061	**8**	**(0.8)**	**6.61**	**1.75–24.95**	**0.005**
Sociocultural														
Lack of caregiver support	5,658	(100)	2,622	(100)	1,971	(100)	-	-	-	1,065	(100)	-	-	-
Belief conflict	4	(0.1)	4	(0.2)	0	(0.0)	-	-	-	0	(0.0)	-	-	-
Language barriers	79	(1.4)	58	(2.2)	**18**	**(0.9)**	**0.41**	**0.24–0.69**	**0.001**	**3**	**(0.3)**	**0.12**	**0.04–040**	**<0.001**
Illiterate	6	(0.1)	0	(0.0)	4	(0.2)	-	-	-	2	(0.2)	-	-	-
Social exclusion	1	(0.0)	1	(0.0)	0	(0.0)	-	-	-	0	(0.0)	-	-	-
CCIFs count, median (IQR)	5	(4–6)	4	(3–5)	**6**	**(5–7)**	**2.24**	**2.12–2.36**	**<0.001**	**7**	**(5–8)**	**2.96**	**2.79–3.15**	**<0.001**

Abbreviations: CCIFs, care complexity individual factors; IQR, interquartile range; OR, odds ratio; CI, confidence interval. The dependent variable of the multinomial logistic regression is the group that each individual belongs to. The young-old (65–74) group was used as the reference category. Bold values indicate statistical significance (p<0.05).

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Results

A total of 5,658 older adult admissions were included. Of these, 46.3% (n = 2,622) were young-old (65–74 years), 34.8% (n = 1,971) middle-old (75–84 years) and 18.8% (n = 1,065) oldest-old (≥85 years) inpatients with COVID-19.

The baseline characteristics among patients hospitalized with COVID-19 according to the age category of older adults are presented in Table 1. Female sex and being discharged to another facility were more common in the oldest-old (≥85 years) than the other groups. Almost 91% of patients in the oldest-old group (≥85 years) presented underlying disease, mainly arterial hypertension or chronic heart failure (56.4%), diabetes or chronic kidney disease (47.9%) and chronic respiratory disease (19.2%) ($p < 0.05$). Conversely, length of stay (8 vs 9 days), admission to step-down unit (3.1% vs 12.6%) and transfer to ICU (6.3% vs 34.6%) were less common in the oldest-old (≥85 years) than in the young-old group (65–74 years) ($p < 0.001$).

Regarding CCIFs, we observed that lack of caregiver support, hemodynamic instability, chronic disease, transmissible infection, mental status impairments, and fear or anxiety were the most common CCIFs presented. The multinomial analysis showed that middle-old (75–84 years) patients were associated with chronic disease, position impairment, urinary or fecal incontinence, anatomical and functional disorders, vascular fragility, involuntary movements, fear or anxiety and mental status impairments. Extreme weight, communication disorders, aggressive behavior, agitation and perception reality disorders were additional factors associated with the oldest-old (≥85 years) inpatients with COVID-19. The median number of CCIFs was higher in the oldest-old than in the other age groups (four in young-old [65–74 years]; six in middle-old [75–84 years]; seven in oldest-old [≥85 years] [OR:2.9; 95%CI:2.8–3.1; $p < 0.001$]) (Table 2). Similar results we obtained after adjusting for potential confounders (Supplementary Material).

Discussion

This study shows that the oldest groups of patients (≥75 years) admitted with COVID-19 had more CCIFs than the young-old group (65–74 years). Moreover, several CCIFs related to comorbidity/complications, psycho-emotional, mental-cognitive, and sociocultural domains were associated with the older patient groups.

The proportions of the subgroups of older adults described in this study are very similar to those found in the overall Spanish population (Instituto Nacional de Estadística. Instituto Nacional de Estadística INE, 2024). Furthermore, the number of CCIFs was higher in the study population compared with previous studies of admitted COVID-patients, being highest among the oldest-old patients (Seven CCIFs in patients ≥85 years old vs Four CCIFs in patients ≥18 years old) (Adamuz et al., 2021). Chronic disease, position impairment, urinary or fecal incontinence, anatomical and functional disorders, involuntary movements, vascular fragility, extreme weight, communication disorders, fear or anxiety, aggressive behavior, mental status impairments, agitation and perception reality disorders were the CCIFs associated with the middle (75–84 years), and oldest-old groups (≥85 years). As described in other studies, older and very old hospitalized individuals exhibit a higher prevalence of comorbidities and physical deterioration (Szklarzewska et al., 2023; Casas-Rojo et al., 2020) such as incontinence or position impairments. Moreover, the presence of cognitive impairment or dementia has been associated with an increase in care management complexity, due to difficulties in communication and adapting to the hospital environment (Veronese et al., 2022; Covino et al., 2020; Tondo et al., 2021). Additionally, social isolation and emotional stress, which were exacerbated during the pandemic, negatively affected the wellbeing of older patients, potentially complicating the recovery process and increasing the demand for psychosocial support (McNabney et al., 2022; Hwang et al., 2020). Finally, ICUs were often overwhelmed, and prioritization decisions for admission to these units generated ethical controversies (Hostiuc et al., 2021). In our study, the oldest-old group (≥85 years) was the least admitted to the ICU. Mortality, readmission and post-discharge functional status were not collected in this study, but we considered that this should be one of the future lines of research.

This research included a large sample size hospitalized with COVID-19 with the aim of identifying CCIFs associated with older adults. Notwithstanding, this study excluded patients directly admitted to and discharged from the ICU because CCIFs were not included in their electronic health records, and we relied on compliance in completing the healthcare history. The CCIFs included in this study, like other tools such as the Comprehensive Geriatric Assessment (CGA), provide a holistic patient assessment that involves biological, functional, psycho-affective, and social domains (Veronese et al., 2022). The CCIFs and CGA provide tools that allow healthcare staff to identify patients with a high risk of complications, and therefore prior identification of complexity factors can help to implement strategies to improve health outcomes and quality of life for older adults (Zurlo and Zuliani, 2018). The broader health assessment should be implemented in care models (McNabney et al., 2022) in order to help quantify the care burden and to estimate safe staffing for older patients. This would help establish age-friendly health systems and encourage geroscience (Inouye, 2021). Future studies should evaluate the incremental value of CCIFs relative to established tools—such as frailty indices and the CGA—since our analysis did not compare their respective discriminative performance; moreover, because CCIFs can be automatically extracted from routine nursing electronic health records, whereas frailty scales and CGA usually require times-consuming bedside assessments, they could therefore facilitate wider use and implementation compared with other tools.

Limitation

It is important to point out certain limitations of this research:

- Data quality is supported by standard nursing documentation protocols; nevertheless, certain elements—particularly sociocultural factors—may have under-recorded, and no specific data-quality audits were conducted for this study, which we acknowledge as a limitation. Missingness for the four sociocultural CCIFs ranged from 0.1% to 3%, indicating possible under-recording, consistent with findings from previous studies in non-COVID populations (Adamuz et al., 2020).

- This analysis did not adjust for other potential confounders—including vaccination status, pandemic wave, baseline disease severity, and received treatments—which may have influenced the observed associations.
- Future longitudinal research should capture post-discharge functional end-points—such as objective mobility or activities-of-daily-living measures—to determine whether a high CCIF burden, particularly in patients with chronic conditions like arterial hypertension or ischemic heart disease, translates into poorer functional recovery after COVID-19 hospitalization (Borchev et al., 2024).

Conclusion

The oldest groups of patients (≥75 years) admitted with COVID-19 had more CCIFs than the young-old group. Moreover, several CCIFs related to comorbidity/complications, psycho-emotional, mental-cognitive, and sociocultural domains were associated with the older patient groups. CCIFs should be included in patient assessment in order to identify care complexity individual needs in older hospitalized patients.

Data availability statement

The datasets presented in this article are not readily available because Datasets are property of the Catalan Institute of Health; therefore, any data sharing will require that institution's prior approval. Data may be available from the corresponding author upon reasonable request and with permission from the Catalan Institute of Health. Requests to access the datasets should be directed to jadamuz@bellvitgehospital.cat.

Ethics statement

The studies involving humans were approved by this study was approved by the Clinical Research Ethics Committee of Bellvitge University Hospital (reference 293/20). The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because Informed consent was waived due to the study's retrospective design. Ethical and data protection protocols related to anonymity and data confidentiality (access to records, data encryption and archiving of information) were complied with throughout the study. The manuscript presents research on animals that do not require ethical approval for their study.

Author contributions

JA: Conceptualization, Formal Analysis, Funding acquisition, Investigation, Methodology, Resources, Validation, Writing – original draft. JG-V: Conceptualization, Formal Analysis, Methodology, Writing – original draft. MG-S: Data curation, Formal Analysis, Writing – original draft. M-ML-J: Data curation, Writing – original draft. AU: Data curation, Writing – review and editing. OP-M: Formal Analysis, Software, Writing – original draft. SA-F: Data curation, Resources, Writing – original draft. SE-S: Writing – review and editing. SB-T: Conceptualization, Data curation, Writing – review and editing. M-EJ-U: Conceptualization, Project administration, Supervision, Writing – review and editing.

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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 author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

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Health outcomes and health-seeking behaviour following traumatic brain injury among older people: a prospective cohort study in Bangladesh

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Background: Older adults are at high risk for traumatic brain injury (TBI), yet there is limited evidence on their vulnerability to mortality, morbidity, and associated risk factors in low-and-middle-income countries. This study assessed the burden, health outcomes, and health-seeking behavior of TBI in older adults at the largest teaching hospital in Bangladesh.

Methods: The study analyzed data from individuals aged 60+ years who were part of a prospective observational cohort of TBI patients admitted to a teaching hospital in Dhaka, Bangladesh, from May to June 2017. Data were collected at admission and during discharge or a 30-day follow-up (whichever came earlier) using a pre-tested semi-structured questionnaire, including the Glasgow Coma Scale (GCS), Glasgow Outcome Scale (GOS), and EuroQol-5D-3L. Descriptive analyses assessed the burden, characteristics, and health-seeking behavior for TBI, while relative risks were calculated to evaluate the risk of mortality by socio-demographic characteristics and clinical status.

Results: During the study period, 117 older TBI patients were admitted, with 78.6% being male. Road traffic injuries (RTI) accounted for 71.3% of cases, followed by falls (16%). Half of the patients did not receive treatment at the primary and secondary facilities they initially visited, and 16% experienced over 24 h' delay in treatment initiation. On admission, 25% presented with severe injury (GCS ≤8), and all had a history of loss of consciousness. The mortality rate was 5.2 per 1,000 person-days. Severe mobility issues and anxiety/depression were reported by 11% during follow-up. Bivariate analysis indicated higher mortality risk in patients with low socio-economic status, GCS ≤8, and over 1-h duration of both loss of consciousness and post-traumatic amnesia.

Conclusion: RTI and falls are major causes of TBI, disproportionately affecting older adults of lower socio-economic status. Treatment accessibility gaps exist, and clinical status at admission is critical for predicting mortality. Findings can inform policies for preventive and rehabilitative strategies, including priority management protocols for older TBI patients in Bangladesh.

KEYWORDS

traumatic brain injury (TBI), Road Traffic Injuries (RTI), older People, Bangladesh, LMIC

1 Introduction

Traumatic Brain Injury (TBI) among all injury types is considered to be the most severe in terms of clinical management and often has life-altering consequences, which makes it a major public health problem globally (Puvanachandra and Hyder, 2009). The incidence rate of TBI has increased by about 10% over the last 3 decades (Guan et al., 2023). In 2019, an estimated 49 million people endured TBI of all causes worldwide (Guan et al., 2023). TBI also results in high rates of mortality, morbidity, and it often leads to lifelong permanent disability (Gardner et al., 2018). It accounts for seven million YLD's (Year loss in disability) annually, estimated in 2019 (Guan et al., 2023). Furthermore, injuries to the brain create substantial economic difficulties and compromise the quality of life for the affected individual and family members and burden the healthcare system for a nation at large. The direct and indirect costs associated with TBI related deaths were estimated to be around 1.1 billion in the USA (Humphreys and Wood, 2013). In addition to creating high personal and social burdens, TBI consumes a high volume of healthcare resources both at the acute and rehabilitation stages (Humphreys and Wood, 2013). The treatment and recovery process for TBI can be very difficult and lengthy. Often a multi-system approach that targets both the physical and psychological damages incurred in such an incident is needed for a meaningful and sustainable recovery.

The burden of TBI is particularly predominant in low- and middle-income countries (LMIC's) which deal with a large number of these cases and have inadequate and under-resourced healthcare infrastructures to provide acute care for these individuals and manage the long-term health consequences (Hyder et al., 2007). LMICs have a higher incidence rate of TBI compared to an estimated global incidence rate (Bryan-Hancock and Harrison, 2010) and a review article by Puvanachandra and Hyder reports that the Southeast Asian and Western Pacific countries face the highest overall burden of TBI (Puvanachandra and Hyder, 2009). Yet, there is a lack of evidence from these regions that identify the risk factors and consequences of TBI (Bryan-Hancock and Harrison, 2010). LMIC's generally have a weaker social safety net and almost non-existent supportive systems to look after the TBI patients after they survive and try to integrate back to society. Further, the economies of the LMICs are primarily based on manufacturing, transportation, construction and agriculture which make the risk of sustaining TBI high at the same time make it very difficult for the TBI victims to reintegrate into the labour force. This calls for epidemiological and preventive research on TBI specific to LMICs as the evidence from the high-income countries may not be applicable there. Since TBI incidents are mostly preventable, data on epidemiological profile and pattern of TBI in LMICs are vital for the development and implementation of region and context specific prevention programs (Puvanachandra and Hyder, 2009).

The old age population has been identified previously as the second most vulnerable group for TBI, preceded by younger adults (Goodman and Englander, 1992). Studies reveal a bimodal trend where young adults and older adults have the highest rate of TBI in all levels of severities (Bruns and Hauser, 2003). With the fast growing worldwide aging population, the incidence of TBI is rising in this population group, which has increased by two-fold in the past 18 years according to one study (Mak et al., 2012). In many Western countries, the epidemiology of TBI is evolving with a growing proportion of critically ill older TBI patients admitted to Intensive Care Units (Stocchetti et al., 2012). The risk factors and consequences of TBI among older patients are likely different from younger patients. Age alone contributes to the increased risks of hospital admission following TBI (Peschman et al., 2011). For older patients, even mild TBI poses a significant mortality risk (Cheng et al., 2014). Further, older adults also have a greater need for long-term care and rehabilitation services in comparison to young and middle-aged patients (LeBlanc et al., 2006). Moreover, the financial burden for TBI treatment of older patients is also higher than in other age groups (Chan et al., 2009). For this group of the population, prompt admission and comprehensive management are even more important to have a better treatment outcome along with the quality of life (Papa et al., 2012).

Although older adults are a particularly vulnerable group, evidence on TBI among them remains scarce (Mak et al., 2012), especially in LMICs. The few research studies that have been conducted on TBI in the LMICs such as India, Sub-Saharan Africa, including Bangladesh, did not provide much information on older population-who are the most vulnerable (Agrawal et al., 2016; Tran et al., 2015; Hossain et al., 2018). A study in India's Level-1 trauma centre reports higher mortality rates among >50 aged patients due to head injury, but no further substantial information has been provided on this group (Agrawal et al., 2016). Another study on a tertiary healthcare centre of Uganda which tried to explore the distribution and characteristics of TBI had very few old-age patients and therefore their vulnerability picture could not be depicted in the study (Tran et al., 2015). Similarly, In Bangladesh, there is a lack of age-specific TBI research. Since the lifestyle and health status are different in older adults than young people (Rahman et al., 2021a; Tasnim et al., 2024), risk factors and characteristics of the victims should be explored in-depth to develop and implement age-specific prevention programs and offer a better and may be a different clinical management plan for them. The current study was conducted to provide a comprehensive picture of TBI among older patients by investigating the causes, clinical characteristics, outcomes, and health-seeking behaviors of this population. Additionally, it investigated the association of clinical characteristics and sociodemographic profiles with health outcomes among this population.

2 Methods and materials

2.1 Study design, site, and population

A prospective observational cohort study was conducted at Dhaka Medical College and Hospital (DMCH), the largest government teaching hospital in Bangladesh, located in Dhaka (Rahman et al., 2025). All patients admitted to the emergency department of DMCH with a primary diagnosis of Traumatic Brain Injury from May 1 to 30 June 2017, were included in the study. The primary diagnosis was based on the initial attending doctor's assessment using patient history and clinical findings. This study analyzed the data of patients aged 60 years and above.

2.2 Data collection and instruments

Data were collected through face-to-face interviews with patients or their attendants if the patient was unable to respond. Data were collected at two time points: upon admission and at discharge, or 30 days after admission, whichever occurred first. At admission, detailed socio-demographic information (age, sex, education, occupation, family structure, monthly income) and clinical characteristics (Glasgow Coma Scale [GCS], duration of loss of consciousness, duration of post-traumatic amnesia) were recorded. Additionally, information on the causes of TBI and initial health-seeking behaviors was collected. At discharge, outcome variables were assessed using the Glasgow Outcome Scale (GOS) and the EuroQol-5D-3L (EQ-5D-3L) questionnaire.

The GCS was used at admission to evaluate the patient's initial clinical status. The GCS score is derived from eye, verbal, and motor response assessments, and categorized into three levels: 3-8 represents a severe head injury (coma), 9–12 indicates a moderate injury, and 13–15 reflects a mild injury. The GOS, utilized at follow-up, helped to determine the patient's recovery outcome which ranged from death to good recovery. It assesses the functional outcome following a brain injury with five levels: one indicates death, two means a persistent vegetative state, three represents severe disability (conscious but dependent on others), four indicates moderate disability (independent but with some deficits), and five signifies good recovery (resumption of normal life with minor deficits). The GCS and GOS both are widely used instruments to clinically assess the condition of patients with TBI. Among the alive patients, EuroQol five domains three levels questionnaire (EQ-5D-3L) was also used during follow-up to gather information on health outcomes. EQ-5D-3L is a well-known, patient- or respondent-informed standardized indicator of health status (Instruments, 2020). For this study, the descriptive system of EQ-5D-3L was used which measures health condition in five domains (Mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each of which has three stages of responses (no problem, some problem, extreme problem). The study involved registered medical practitioners to conduct the data collection, including administration of GCS, GOS, and EQ-5D-3L.

2.3 Case definition

Traumatic Brain Injury was defined in alignment with the International Classification of Diseases, 10th Revision (ICD-10). The diagnosis by the first attending clinician determined eligible cases. TBI was treated as a nature-of-injury, with data collected on the causes and outcomes of the injury. The patient's clinical condition, including clinical death, was recorded based on both the attending clinician's declaration in the medical record of the hospital, and evaluation by GOS and EQ-5D-3L during follow-up.

2.4 Data analysis

Descriptive analysis was conducted with STATA to explore socio-demographic characteristics, causes and pattern of injury, and health-seeking behaviour of older TBI patients. Relative risk was calculated to explore the associations between socio-demographic factors and clinical presentations with TBI outcomes, with outcome variables including the patient's status (dead or alive) at follow-up. Additional analysis included the chi-square test to examine the vulnerability of older TBI patients by exploring their susceptibility to poor outcomes compared to other age groups.

3 Results

The original cohort consisted of 659 TBI patients recruited over a 3-month study period, of whom 117 (17.8%) were aged 60 years and above and were included in this analysis. The following sections present the data for TBI patients aged 60 years and above from this cohort.

3.1 Sociodemographic profile of the patients

The mean age of the patients was 67.8 years, and majority (78.6%) of them were male. More than half of them had no formal education (54.7%) and had a living arrangement with their children's family (60.7%). Majority of them (73.5%) were not working at the time of data collection, where most males were retired and most of the females were housewives. About half (49.6%) of the respondents had family income within 10–20 thousand BDT (Bangladesh Taka) per month (equivalent to 118–235 USD). (Table 1).

3.2 Causes and characteristics of the traumatic brain injury

Almost all (91%) of the injuries occurred accidentally/by unintentional means. Road Traffic Injuries (RTI) was found to be the leading cause of TBI among old age patients (74%, n = 87), followed by fall (16%, n = 19) from any level. Other causes of TBI in this group includes physical assault and self-harm (Figure 1).

The majority (63.2%, n = 55) of the patients who experienced RTI were pedestrians. One-fourth other were passengers (n = 23),

TABLE 1 Sociodemographic profile of the older TBI patients at a tertiary care teaching hospital in Bangladesh.

Variables	Male N (%)	Female N (%)	Total N (%)
Age			
Up to 70 years	58 (80.6%)	14 (19.4%)	72 (61.5%)
70+ years	34 (75.6%)	11 (24.4%)	45 (38.5%)
Education			
No formal education	51 (79.7%)	13 (20.3%)	64 (54.7%)
Primary	18 (72%)	7 (28%)	25 (21.4%)
Secondary and above	23 (82.1%)	5 (17.9%)	28 (23.9%)
Occupation			
Currently not working/Retired/Housewives	72 (83.7%)	14 (16.3%)	86 (73.5%)
Farmer	11 (57.9%)	8 (42.1%)	19 (16.2%)
Business/Service/other skilled work	9 (75%)	3 (25%)	12 (10.3%)
Family Structure			
Single family	32 (84.2%)	6 (15.8%)	38 (32.5%)
Joint family	60 (84.5%)	11 (15.5%)	71 (60.7%)
Family Income per month (in BDT)			
10 thousand and less	37 (82.2%)	8 (17.8%)	45 (38.5%)
10 to 20 thousand	46 (79.3%)	12 (20.7%)	58 (49.6%)
More than 20 thousand	9 (56.3%)	7 (43.8%)	16 (13.7%)

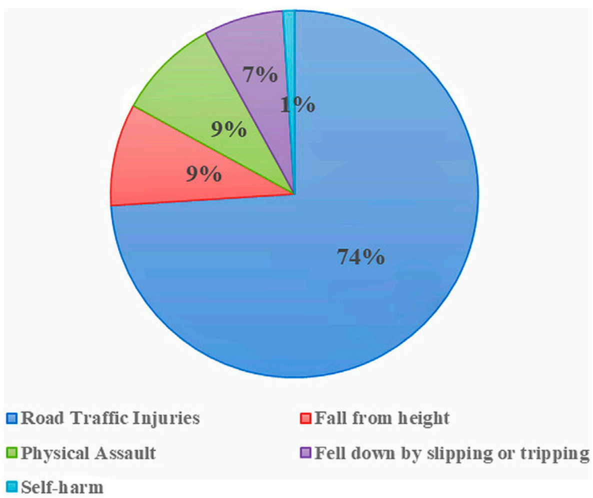

FIGURE 1
Events that led to TBI among older people in a tertiary care teaching hospital in Bangladesh.

and only few (10.5%, n = 9) were in the driving role. Nearly all (98.5%) of older TBI patients reported not using any safety measures during the incident. This included neglecting to use footpaths, foot over bridges, or safe crosswalks as pedestrians, as well as failing to wear seatbelts or helmets when they were passengers or drivers. Of the patients who got injured from falling (n = 19), more than half of them fell from height. Of the respondents who fell from height, most (60%, n = 7) got injured by falling from trees. Main road was predominant among the places where TBI among older patients occurred, followed by home environment. In home, incidents of TBI occurred mostly (63.6%) in bathroom.

3.3 Clinical presentation of TBI patients at admission

On admission, about one-third (31.6%, n = 37) of the TBI patients presented with severe injury with GCS score 8 or less, and half of the respondents presented with mild injury with GCS score 13 or more. All respondents reported experiencing loss of consciousness at some point after the injury, ranging from a few seconds to over 24 h; approximately 15% (n = 17) remained unconscious for more than 24 h. Further, a large proportion of patients (60.6%, n = 71) complained of suffering from post-traumatic amnesia (PTA) during admission. Although, in most of them, the PTA persists from few seconds to few minutes, 14.1% (n = 10) had PTA of more than 24 h' duration. Also, about 30% (n = 34) patients had associated injuries with TBI, majority of which were limb injuries (Table 2).

3.4 Health outcome of the older patients following TBI

Following admission, 15.4% (n = 18) of the older TBI patients needed surgical intervention and the rest were treated with

TABLE 2 Clinical presentation of older TBI patients during admission at a tertiary-care teaching hospital in Bangladesh.

Variables	Number (n)	Percentage (%)
Glasgow Coma Scale (GCS)		
Mild (≥13)	42	35.9
Moderate (9–12)	38	32.5
Severe (≤8)	37	31.6
Loss of Consciousness		
Few minutes to 1-h	80	68.4
>1–24 h	20	17.1
More than 24 h	17	14.5
Post-Traumatic Amnesia (PTA) [N = 71]		
Few seconds to few minutes	49	69.0
1–24 h	12	16.9
More than 24 h	10	14.1
Associated Injury [N = 34]		
Spinal	3	8.8
Thoracic	6	17.6
Limb	17	50.0
Others	8	23.5

conservative methods, i.e., medicine. Half of the surgical interventions involved debridement procedures and others included decompression, elevation of depressed fracture and burr hole.

Mortality rate (within 30-days) for TBI among the older patients was 5.2 per 1,000 person-days (CI: 2.7–7.6) [n = 17]. According to GOS, almost half of the older patients had good recovery and one-fourth were able to carry on activities independently. (Figure 2). Furthermore, reported levels of EQ-5D-3L by older TBI patients (n = 100) during follow-up revealed that more than half respondents did not have any problem in maintaining self-care or did not suffer from any pain or anxiety. However, a considerable number (about 40%) reported to have some problem in all the five dimensions. Severe problem in mobility and severe anxiety/depression were reported by 11% of the respondents. (Figure 3). Moreover, at the time of discharge 21.5% of them registered some form of residual complications. PTA (35.7%) and communication and behavioural problem (42.8%) were predominant among the residual complications during discharge.

3.4.1 Association between sociodemographic and clinical factors and mortality risk among older TBI patients

Table 3 presents the risk of mortality following TBI among older adults, categorized by sociodemographic and clinical factors. A significant association was observed between income level and mortality; individuals earning less than 10,000 BDT monthly had nearly three times higher mortality (24%) compared to those with higher incomes (8%), with a relative risk (RR) of 2.9 (95% CI: 1.2–7.3). Similarly, the severity of TBI, as indicated by the GCS score, showed a significant association, with patients experiencing severe TBI facing a mortality rate that was three times greater (27%) than those with mild to moderate injuries (9%), corresponding to an RR of 3.1 (95% CI: 1.3–7.5). Duration of loss of consciousness was also a significant factor, where those unconscious for over an hour had a 29% mortality rate, which was more than three times higher than the 9% observed in patients with shorter unconscious periods (RR: 3.3, 95% CI: 1.4–8.1).

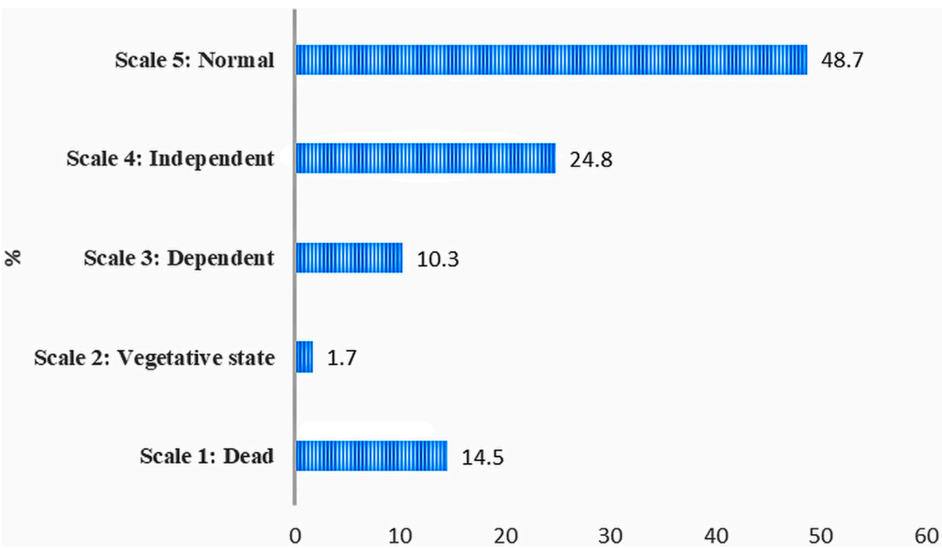

FIGURE 2
Distribution of glasgow outcome scale (GOS) outcomes among older TBI patients in a tertiary care teaching hospital in Bangladesh.

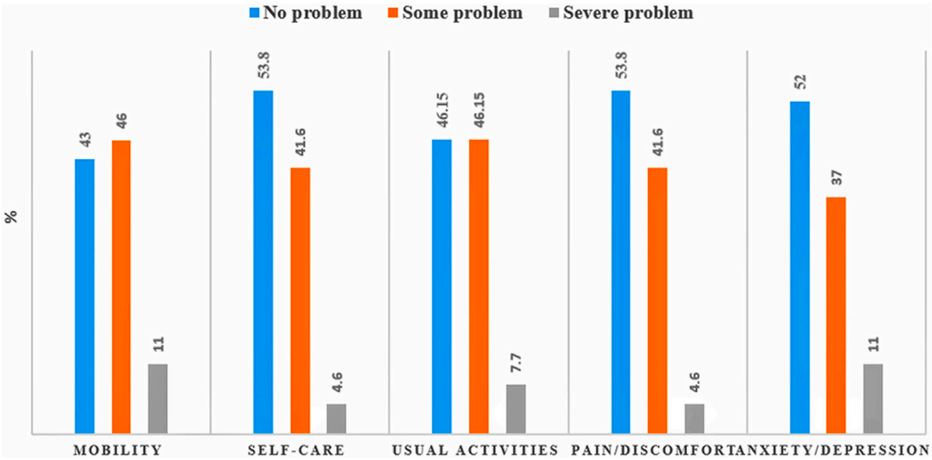

FIGURE 3
Reported levels of EQ-5D-dimensions of Older TBI Patients at a Tertiary-care Teaching-hospital in Bangladesh.

TABLE 3 Risk of mortality following TBI among older people in Bangladesh by sociodemographic and clinical status.

Variable	Outcome		RR	95% CI
	Alive, N (%)	Dead, (%)		
Gender				
Male	81 (88)	11 (12)	2	0.8–4.8
Female	19 (76)	6 (24)		
Education				
No formal education	55 (86)	9 (14)	0.9	0.3–2.2
Literate	45 (85)	8 (15)		
Income (monthly)				
Less than 10 thousand BDT	34 (76)	11 (24)	2.9*	1.2–7.3
10 thousand and more	66 (92)	6 (8)		
Glasgow Coma Scale				
Severe	27 (73)	10 (27)	3.1*	1.3–7.5
Mild to Moderate	73 (91)	7 (9)		
Duration of loss of consciousness				
More than 1 h	25 (71)	10 (29)	3.3*	1.4–8.1
Less than 1 h	75 (91)	7 (9)		
Duration of Post Traumatic Amnesia				
More than 1 h	15 (68)	7 (32)	3.1*	1.1–8.7
Less than 1 h	44 (90)	5 (10)		

*Statistically significant at $p < 0.05$.

Additionally, extended post-traumatic amnesia was linked with increased mortality; individuals with amnesia lasting more than an hour had a rate of 32%, compared to 10% in those with shorter amnesia duration, with an RR of 3.1 (95% CI: 1.1–8.7). Conversely, no significant associations were found between mortality and factors such as gender or education level.

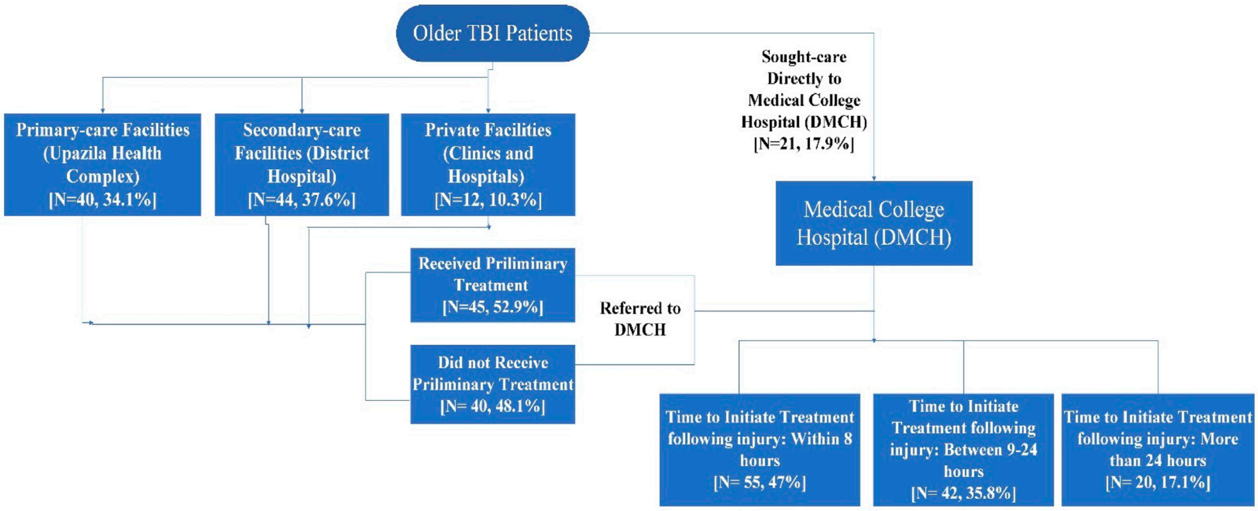

FIGURE 4
Health-seeking behaviour of older patients following traumatic brain injury (TBI) in Bangladesh.

3.5 Health-seeking behaviour of TBI patients

Figure 4 presents the health-seeking behaviour of older patients after TBI. Following injuries, a substantial number (71.5%) of older patients sought care from local semi-urban primary to secondary level health facilities that are district hospitals (37.7%) and upazila health complexes (34.1%); from these facilities they were referred to Medical College Hospital (DMCH). Only 17.9% of the patients went directly to the DMCH for treatment. The remainder of the patients went to private facilities, and were referred to DMCH from there. Furthermore, of all patients who were referred from other hospitals, half of them reported receiving no treatment for their injury prior to referral. Majority (68.4%) of the older patients suggested their preference of first place of care was focused on the near distance from the location of the injury. Almost all (94.7%) older TBI patients reported that they did not receive any first aid treatment after the injury. Even though few received first aid services, none of their caregivers were trained in first aid emergency response. About 17% patients had more than 24 h' delay in initiation of treatment from the time of injury. Further, more than one-third (35.8%) of the patients had a time gap between 9–24 h from occurrence of the injury to initiation of treatment. Those who got discharged within the 30-days follow-up, none of them received any rehabilitative management including psychosocial counselling.

4 Discussion

Although TBI research has expanded over the years, older adults remain underrepresented despite being a highly vulnerable group (Gardner et al., 2018). In Bangladesh, where injury rates are high, understanding TBI is particularly important as it is among the most severe forms of injury. This study is the first in Bangladesh to focus on older adults with TBI and one of the few from LMICs. It offers a comprehensive overview of the burden, key characteristics, associated risk factors, and health-seeking behaviors in this population.

Analyzing data from patients aged 60 and above within a larger cohort, the study found that approximately two out of every 10 TBI cases involved older adults. Likewise, studies in US found that older patients consist about 20% of the total TBI patients, and accounts for about 40% of the deaths due to TBI (Peschman et al., 2011; Waltzman et al., 2022). This implies a significant burden for older population group in Bangladesh which makes up 7.5% of its' total population (Barikdar et al., 2016). Males are identified as predominant sufferer from TBI in general as culturally men are more exposed to outer world and responsible for wage earning in the family. The Bangladesh Health and Injury Survey (BHIS), 2016 also found that males, across all age groups, experienced head injuries more frequently than females. (Hossain et al., 2018).

The study also shows income to be significantly associated with the mortality outcome in older TBI patients. Similar findings are shared by several previous studies which tried to explore the impact of socio-economic status on the outcome of TBI patients (Haines et al., 2019; McQuistion et al., 2020). Even having treated with uniform treatment protocols in a public healthcare facility, older adults of low economic status experience poorer outcome; this may be explained by the presence of co-morbidities, poor nutritional status, inadequate hygiene and weak immunity in this group of people (Dhandapani et al., 2012). Beyond healthcare access and comorbidities, emerging research also suggests a biological underpinning linking low SES with worse neurocognitive and recovery outcomes after brain injury. Chronic psychosocial stress, often embedded in poverty, is associated with elevated levels of glucocorticoids and neuroinflammatory markers such as IL-6 and TNF-α, which are known to exacerbate neural injury and impede recovery after TBI (Muscatell et al., 2020). The concept of "psychosocial defeat", common among individuals in structurally disadvantaged contexts, is implicated in chronic microglial activation and prolonged neuroinflammation, potentially worsening outcomes following neurotrauma (Kraynak et al., 2018).

Road traffic injuries were the predominant cause of TBI among older adults which is not a surprise for a country where road accidents claim on average about 12,000 lives annually (Alam, 2018; Rahman and Rahman, 2019). Another hospital-based survey in DMCH and a national survey on injury also found RTI to be responsible for majority of TBI among all ages in Bangladesh (Hossain et al., 2018; Mondol et al., 2013). The study also examined the role of older adults in RTIs, finding that most were pedestrians who lacked access to safe options such as footpaths, footbridges, or designated crosswalks. Similar findings have been reported in a North American rehabilitation clinic study, which identified pedestrian accidents as a common cause of TBI among older individuals (Goodman and Englander, 1992).

Falls were the second most common cause of TBI among older people in Bangladesh, accounting for about one-fourth of cases. In contrast, most studies from high-income countries identify falls as the leading cause of geriatric TBI (Goodman and Englander, 1992; Mak et al., 2012), highlighting a distinct pattern in LMICs. In an agricultural country like Bangladesh, falling from tree during fruit harvesting season is a big concern, and the study depicts similar picture as majority of the falls from height occurred by falling from the trees. Additionally, the study shows about 10% of the incidents occurred in home environment. This is important as older adults spend a considerable amount of time in home and it is generally considered to be a safe space for them. The incidents in home mostly occurred by falling or tripping on the ground and primarily took place in the bathroom. This suggests a lack of understanding and information about protective measures, which is also supported by the fact that none of the older adults used any safety measures such as gripping aid or anti-slip mat during those incidents. The mechanism of fall in older TBI patients in Bangladesh differ considerably from developed country scenario where most of the fall related injury results from sports or physical exercise related activities such as falls while skiing or bi-cycle riding (Gardner et al., 2018; Chehuen Neto et al., 2018). Although different in mechanism, the causes and nature of fall incidents in Bangladesh suggest that they are also largely preventable with proper awareness and prevention strategies (Rahman et al., 2021b). To prevent the fall incidents among older group, awareness regarding household risk factors such as low lighting, slippery floors, obstacles, long clothes, etc., and the practice of using safety tools such as anti-slip mat, safety bars, safety shoes and walking aid sticks can be beneficial (Chehuen Neto et al., 2018).

Older patients were found to have substantial adverse outcome both in terms of mortality and morbidity following TBI. CRASH (Corticosteroid Randomization after Significant Head Injury) data on global incidents also identified old age group as most vulnerable but evidence for Bangladesh was unavailable till date (Biswas et al., 2017). Several other studies also confer that outcome in old age group following TBI is worse than that of other age groups (LeBlanc et al., 2006; Papa et al., 2012). Advanced age is a recognized predictor of poor TBI outcomes, and our findings align with this evidence. Biological factors such as reduced neuroplasticity, diminished neurogenesis, and impaired cortical remapping limit recovery in older adults (Orr et al., 2015). Aging brains are also more susceptible to secondary injury mechanisms, including oxidative stress and mitochondrial dysfunction, which worsen prognosis even in mild TBI (Shively et al., 2012). These factors, combined with the lack of age-specific rehabilitation services in LMICs such as Bangladesh, underscore the urgent need for tailored geriatric TBI care and long-term management strategies.

About half of the older patients had moderate problem in all the five domains of EQ-5D-3L during discharge. Further, although more than half of the older respondents had moderate to severe difficulty in mobility at the time of discharge, no rehabilitative management or physiotherapy was given to them. Difficulty in movement and the need for intensive rehabilitative management for older TBI patients is also suggested by several other studies focusing outcome in geriatric patients (Goodman and Englander, 1992; LeBlanc et al., 2006; Alam, 2018). No psychosocial counselling was provided to any of the patients either despite about half of them had some to severe form of anxiety or depression. Similarly, a research report on geriatric TBI showed that depression is prevalent in around 50% of older TBI patients and often has a major effect on their quality of life (Papa et al., 2012). This also supports the fact that rehabilitation and psychosocial supports are generally unavailable for patients in most healthcare facilities of Bangladesh, even in a tertiary care centre, despite having a substantial demand (Mamin and Hayes, 2018; Islam, 2015).

This study also showed that health condition of older TBI patients at admission assessed by GCS ranking, length of lack of consciousness and PTA have independent influence on mortality. Further statistical analysis could not be performed due to the study's small sample size. Comparable findings have been shared by other studies which also identified GCS score, length of coma and severity of injury as predictors of outcome in older TBI patients (Goodman and Englander, 1992; Stocchetti et al., 2012; Chan et al., 2009).

Moreover, older patients were primarily referred from their nearest secondary or primary healthcare facilities without receiving any prior treatment. The transportation and referral process eventually cause a long delay between injury and initiation of treatment. Waiting time in an overloaded public healthcare facility further delayed the initiation of treatment to more than 24 h in about one-fifth of older patients which have serious implications as prompt treatment in initial hours is vital after a head injury (Ashadullah et al., 2017). Nearly none of them received any first aid care either. All of these point towards an inadequate emergency care and a lack of trained first aid response team at root level or rural level where two-thirds of the country's total population reside. Since there is a dearth of information regarding TBI among old age population in resource poor settings, these findings could not be compared with similar research.

4.1 Strengths and limitations

The study was conducted at the largest public teaching hospital in the country and usually only people from lower socioeconomic background attend this hospital. While this poses the limitation for single-institution based study, it is also one of the very few institutions which has functioning neurosurgical facility for patients in Bangladesh. It does draw and is attended by patients from all over the country, and the study results indicate that patients were referred from various primary or secondary health facilities across the whole country, thus enhancing the generalizability of the results. Another drawback of this study is that it has not reported the co-morbidities and behavioural risk factors that could have an effect on risk factors and outcome. There are, however, few research studies that indicated outcome of TBI on older group does not depend on comorbid conditions or behavioural factors (Stocchetti et al., 2012; Cheng et al., 2014). While mobility, anxiety or depression were assessed at discharge using EQ-5D-3L, the study did not capture baseline information on these conditions prior to injury. This limits our ability to distinguish pre-existing issues from injury-related outcomes. However, data collectors were trained to clarify whether these complaints emerged or persisted after the injury during EQ-5D-3L assessment, partly addressing this limitation. Moreover, although patients were followed up for 30 days, a longer follow-up period could have provided more comprehensive insights into the long-term disability, mortality, and other consequences associated with TBI, offering a deeper understanding of its outcomes. Additionally, since the data were analyzed from a larger cohort that did not exclusively focus on geriatric TBI, the study had to contend with a limited sample size, which constrained the scope for advanced and robust statistical analysis. Stratified analysis by injury severity to assess independent effects of factors like PTA and loss of consciousness could have provided deeper insights, but was not feasible due to the small sample size.

Despite the aforementioned limitations, this study is likely the first to explore geriatric TBI cases in Bangladesh using a prospective follow-up approach to examine outcomes and associated factors in this population. It provides a comprehensive view not only by highlighting the burden and associated factors but also by offering insights into the health-seeking behavior of older TBI patients treated at the country's largest tertiary care center. This research establishes a valuable evidence base for further investigation and intervention studies on geriatric TBI in Bangladesh. Future research could benefit from larger sample sizes and extended follow-up periods to assess long-term disability and mortality. Additionally, exploring other outcomes, such as social and economic impacts alongside health outcomes, and considering the influence of comorbidities on these outcomes, could provide a more holistic understanding of geriatric TBI.

5 Conclusion

Road Traffic Injuries (RTIs) and falls are the leading causes of TBI in Bangladesh, disproportionately affecting older males from low socio-economic backgrounds. Including general road safety measures, specific safety programs such as educating the older group on safe pedestrian's strategies and local collision hotspots, and make them aware on their functional limitations and physical vulnerability that needs to be considered while using road, is critical to prevent RTI in this group. Preventive measures in home regarding fall of older adults can be largely beneficial as well. The association of poor socio-economic condition with mortality among older TBI patients demands further in-depth research and actions such as increase awareness building in this group. In a resource-poor setting like Bangladesh where healthcare system is mostly overburdened, the value of predictive clinical status for outcome at admission needs to be further explored for proper triage and prompt case management. Aggressive treatment needs to be ensured in this older population group with separate geriatric ward, tailored treatment protocol, dedicated institution and management facility which is currently minimal to missing in Bangladesh. Mostly, primary and secondary healthcare facilities of rural Bangladesh need to be upgraded with appropriate emergency services to address TBI and a timely referral system should be in place. Comprehensive multi-system approach targeted to the old age group is essential to reduce this preventable burden of traumatic brain injury in Bangladesh.

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.

Ethics statement

The study involved human participants and obtained ethical approval from the Institutional Ethical Review Committee (ERC) of Centre for Injury Prevention and Research Bangladesh (CIPRB) (Project Number: PS/02/2017). Informed written consent was obtained from all respondents, including consent for dissemination of study findings. Patient anonymity and confidentiality were strictly maintained. Patients were provided with a contact address for further inquiries about the study process and findings. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

FR: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review and editing. SD: Conceptualization, Investigation, Methodology, Project administration, Resources, Validation, Writing – original draft, Writing – review and editing. MC: Data curation, Formal Analysis, Resources, Visualization, Writing – original draft, Writing – review and editing. MK: Writing – original draft, Writing – review and editing. SM: Conceptualization, Data curation, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review and editing.

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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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fragi.2025.1513137/full#supplementary-material

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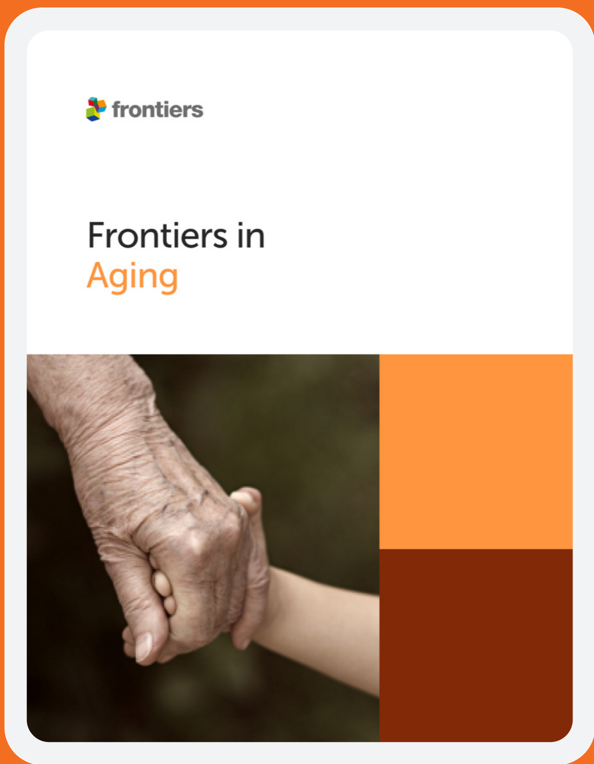

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