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Epidemiological characteristics and related risk factors of older population aged over 75 years

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Epidemiological characteristics and related risk factors of older population aged over 75 years

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Predictors of Emergency Room Access and Not Urgent Emergency Room Access by the Frail Older Adults

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Background: Emergency rooms (ERs) overcrowded by older adults have been the focus of public health policies during the recent COVID-19 outbreak too. This phenomenon needed a change in the nursing care of older frail people. Health policies have tried to mitigate the frequent use of ER by implementing community care to meet the care demands of older adults. The present study aimed to investigate the predictors of emergency room access (ERA) and not-urgent emergency room access (NUERA) of community-dwelling frail older adults in order to provide an indication for out-of-hospital care services.

Method: Secondary analysis of an observational longitudinal cohort study was carried out. The cohort consisted of 1,246 community-dwelling frail older adults (over 65 years) in the Latium region in Italy. The ER admission rate was assessed over 3 years from the administration of the functional geriatric evaluation (FGE) questionnaire. The ordinal regression model was used to identify the predictors of ERA and NUERA. Moreover, the ERA and NUERA rate per 100 observations/year was analyzed.

Results: The mean age was 73.6 (SD $\pm$ 7.1) years, and 53.4% were women. NUERAs were the 39.2% of the ERAs; robust and pre-frail individuals (79.3% of the sample) generated more than two-third of ERAs (68.17%), even if frails and very frails showed the higher ER rates per observation/year. The ordinal logistic regression model highlighted a predictive role on ERAs of comorbidity ($OR = 1.13$, $p < 0.001$) and frailty level ($OR = 1.29$; $p < 0.001$). Concerning NUERAs, social network (OR 0.54, $P = 0.015$) and a medium score of pulmo-cardio-vascular function (OR 1.50, $P = 0.006$) were the predictors.

Conclusion: Comorbidity, lack of social support, and functional limitations increase both ERA and NUERA rates generated by the older adult population. Overall, bio-psycho-social frailty represents an indicator of the frequency of ERAs. However, to reduce the number of ERAs, intervention should focus mainly on the robust and pre-frail needs for prevention and care.

Keywords: frail older adults, emergency department, functional geriatric evaluation, emergency room utilization, social determinants, health determinants

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INTRODUCTION

During the twenty-first century, public health policies have constantly focused on overcrowding of the Emergency Departments (EDs) by older adults (1–3). However, some authors have shown how public policy needs to reduce overcrowding to guarantee satisfactory care quality and safety (4, 5). The Australasian College for Emergency Medicine had defined Emergency Room (ER) overcrowding as "the percentage of patients who were admitted or planned for admission but discharged from the ED without reaching an inpatient bed, transferred to another hospital for admission, or died in the ED whose total ED time exceeded 8 h" (6, 7).

Several studies have focused on the significant characteristics of an ER user to define the "frequent user" (2, 8–11). However, there was no unique definition of the frequent use that could include patients who access the ED from 2 to 12 times per year (2, 8). Despite the complexity of the phenomenon, Wang et al. (12) have identified the shortage of ED beds available compared to the high number of patients accessing the ER daily as the leading cause of overcrowding. Moreover, Erenler et al. (13), have analyzed the impact on the overcrowding of the frequent users, highlighting the need to manage the repetitive admissions. Given the multidimensional nature of the overcrowding phenomenon, a single cause has not been highlighted. The most significant reasons seem to be the inappropriate use of EDs (14, 15) and the lack of "long-term care" (2, 16), specifically those which are aimed at frail older people. Other authors have focused on the significant consequences of overcrowding (12, 17, 18). The big factors associated with overcrowding seem to increase adverse outcomes for the patient and worsen the quality of care (12, 17, 18).

The consequences of this phenomenon gain even more relevance as a result of the recent COVID-19 outbreak. This pandemic demanded a rapid health system reorganization (19–21) because of the crucial role of EDs (21). A systematic review by Aminzadeh et al. (22) drew attention to the inappropriate use of EDs by older adults and the complex clinical characteristics of this population due to the high presence of comorbidities. Other studies emphasized the complexity of the frail elderly care needs, increasing the risk of readmissions after discharge (2, 23, 24).

Moreover, some authors have investigated the importance of social support on Emergency Room Access (ERA) of older adults, even if in a systematic review by Valtorta et al. (25), there was no significant association between the ERA of older adults and the social support. Nevertheless, lack of social support and disability seems to be the strongest independent determinants for increasing the occurrence of adverse outcomes among older adults (26) and the use of hospital services, such as ERA, hospital admissions, and Day Hospital services. However, the analysis of the determinants of ED accesses has not dedicated sufficient consideration to the aspect of multidimensional frailty, defined as a dynamic state determined by the loss of one or more functional areas (clinical physical, cognitive, psychological, functional, social, and economic) which causes a higher increase in the risk of adverse outcomes as mortality and hospitalization (27).

The purpose of this study is to investigate the predictors of ERA and Non-Urgent Emergency Room Access (NUERA) by community-dwelling frail older adults.

METHODS

Study Design

This is a secondary analysis of an observational longitudinal cohort study whose main aim is to assess frailty in community-dwelling older people. Recruitments started in January 2014 and finished in December 2017. A detailed description of the survey (28) and follow-up (29, 30) has been published elsewhere.

Participants

The sample was enrolled in 2014 from a population aged over 64 years resident in the Lazio region (Italy). After the recruitment and the assessment of frailty, the sample was followed up for 3 years. Eligibility criteria for baseline recruitment were: (a) age of 65 years or higher; (b) residence in the Lazio region, except for those living in an institution; (c) people with cognitive impairments were included in the study thanks to the support of caregivers. According to the inclusion criteria, 1,331 individuals aged more than 64 years participated in the study. During the 3-year follow-up, 84 people were lost mainly because of residence change, so the sample involved in this study consists of 1,247 individuals.

Data Collection

At baseline, block randomization was performed to represent the Lazio region resident population aged over 64 years. Initially, a randomization list was drawn from the local health authorities (LHA) archives in order to select a group of general practitioners (GPs) to be involved in the study. Subsequently, randomization was performed by sampling from the GPs list to place a maximum of 25 patients over 64 years. The aims of the study were explained to GPs and patients, and then, all the participants signed the informed consent form.

After 3 years, follow-up data collection was conducted upon administrative data of admissions recorded by the regional health database. The regional health database collects all health services provided by the regional hospitals.

Outcome

The primary outcome of the study was to explore the association between the level of frailty, disability, and comorbidity, and ERA and NUERA.

The outcome variables analyzed in this study were:

- ERA: the absolute frequency of ERA for each participant, along with the assessment of the level of frailty during the 3-years of follow-up. Moreover, the ERA rate per 100 observations/year has been analyzed.
- NUERA: the frequencies of NUERA, defined as all the ERAs classified as "non-critical state of health; immediate care is not required" by the triage personnel.

Measurement

The functional geriatric evaluation (FGE) questionnaire (31) was administered to assess the multidimensional bio-psycho-social frailty. FGE stems from the Grauer functional rating scale (32), modified and validated for the Italian population by Palombi et al. (31, 33, 34). This questionnaire stratifies the population according to the level of frailty (robust, pre-frail, frail, and very frail) associated with a growing risk of mortality, hospitalization, and institutionalization (28, 30, 35). FGE collects sociodemographic data and information on five domains: physical health, mental health, functional state, social resources, and economic resources. These domains contributed to the final score (FS), ranging from −108 to 101. According to FS, the final synthetic score (FSS) identified the level of frailty as: very frail (score ≤10), frail (score >10 but <50), pre-frail (score ≥50 but ≤70), robust (score >70). With the support of the GPs, the presence or absence of the disease was ascertained for each participant.

To define disability, Activities of Daily Life (ADL) and Instrumental Activities of Daily Life (IADL) were assessed (36, 37). Moderate disability corresponded to any dependence in performing IADL and severe disability to any dependence in performing ADL. The absolute number of ERAs as well as the urgency code to identify NUERA has been retrieved from the Regional Health Database. The frequent ERA users were defined as elderly with two or more access per year.

Ethical Consideration

All the data collection was performed in line with the ethical standards of the 1965 Declaration of Helsinki and subsequent amendments. The Independent Ethical Committee of the University of Rome "Tor Vergata" approved the study (registration number: 95/15). Written consent was obtained by all the participants before data collection.

Statistical Analysis

The statistical analyses were carried out with IBM SPSS Statistics version 25.0. The absolute number of ERA and NUERA rates have been calculated for each person, and the NUERA and ERA rate per 100 observations/year is stratified for frailty level. The one-way ANOVA analysis was accomplished to compare the mean rates. Descriptive statistics, such as means, SD, frequencies, and percentages, were used to describe the sociodemographic characteristics of the sample. Univariate and bivariate analyses (Spearman's correlations or chi-square) have been performed to select the variables (the ones analyzed by the FGE questionnaire plus ADL and IADL, **Table 1** and **Supplementary Tables 2–4**) associated with the dichotomized ERA and NUERA (no access vs. any access). Moreover, the descriptive statistics and univariate analyses were performed to address the 84 individuals lost during the follow-up compared to the total sample (**Supplementary Table 1**). A chi-square on contingency tables was carried out to select the variables included in the multivariate model, and statistical significance was determined by a value of $p < 0.05$. Finally, the variables that showed a statistically significant association with the ERA and NUERA were included as covariates in a final multivariable generalized linear (GENLIN) ordinal regression model (38). The ordinal regression analysis was appropriate because the dependent variables (NUERA and ERA) were included as ordinal variables (no access, 1, 2, 3, and >3 accesses). The use of the SPSS GENLIN model aimed to explore which covariate was independently associated with NUERA and ERA. The fit model was assessed with Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) measures.

TABLE 1 | Sociodemographic characteristics of the sample (*N* = 1,247).

		No-ERA *N* (%)	ERA *N* (%)	tot. *N* (%)	χ^2 *p*-value
Age	<74	384 (47.5)	159 (36.3)	543 (43.5)	0.001
	75–85	339 (41.9)	221 (50.5)	560 (44.9)	
	>86	86 (10.6)	58 (13.2)	144 (11.6)	
Gender	Female	450 (55.6)	215 (49.1)	665 (53.4)	0.027
Education	No education	57 (7.1)	39 (8.9)	96 (7.7)	NS
	Primary school	379 (46.8)	211 (48.2)	590 (47.4)	
	Middle school	203 (25.1)	107 (24.4)	310 (24.8)	
	High school	129 (16.0)	60 (13.7)	189 (15.2)	
	Degree	40 (5.0)	21 (4.8)	61 (4.9)	
Cohabitants	Alone	162 (19.8)	98 (22.4)	260 (20.7)	NS
	Spouse	422 (52.2)	223 (50.9)	645 (51.7)	
	Child	180 (22.2)	91 (20.8)	271 (21.7)	
	Others	28 (3.5)	14 (3.2)	59 (3.4)	
	Home worker	19 (2.3)	12 (2.7)	31 (2.5)	
Frailty	Robust	382 (47.2)	160 (36.6)	542 (43.5)	
	Pre-frail	282 (34.9)	157 (35.8)	439 (35.2)	<0.001
	Frail	99 (12.2)	75 (17.1)	174 (14.0)	
	Very frail	46 (7.9)	46 (10.5)	92 (7.3)	
Comorbidity	Yes	768 (94.9)	425 (97.0)	1,193 (95.7)	<0.001
Disability	No	599 (74.0)	267 (61.0)	866 (69.5)	<0.001
	Moderate	170 (21.1)	126 (28.7)	296 (23.7)	
	Severe	40 (4.9)	45 (10.3)	85 (6.8)	

No-ERA, no emergency room access; ERA, emergency room access, χ^2, chi-square of the cross table; NS, not statistically significant. No-ERA was for the sample which did not access the ER during the 3 years of follow-up; ERA was for those who had one or more access to the ER during the follow-up.

RESULTS

Of the 1,331 eligible patients at baseline, 1,247 (93.68%) were included in 2017 during follow-up. The sociodemographic and clinical characteristics of the final sample are shown in **Tables 1**, **2**.

Patients are mostly women (53.4%) and, the sample average age is 73.64 (SD ±7.16). Patients belong mainly to two age groups, <74 years and between 74 and 85 years old, 43.5% and 44.9%, respectively. The education achievement level is more represented by those who have left at primary school (47.4%) than those who have a higher educational level (middle school 24.8% and high school 15.2%), and most of them live with their spouse (51.7%), their children (21.7%), or alone (20.7%).

TABLE 2 | Prevalence of ERA (*N* = 823) and NUERA (*N* = 323), and one-way ANOVA of ERA and NUERA rate (per 100 observations/year), stratifies for frailty levels.

	ERA**		NUERA**	
	***N* (%)**	**Rate (per 100 observation/ year)**	***N* (%)**	**Rate (per 100 observation/ year)**
Robust	263 (31.96)	20.89	115 (35.60)	8.16
Pre-frail	298 (36.21)	32.70	109 (33.75)	11.15
Frail	171 (20.77)	68.33	76 (23.53)	22.43
Very frail	91 (11.06)	64.55	23 (7.12)	23.01

*ERA, emergency room access; NUERA, non-urgent emergency room access; ** p-value of one-way ANOVA < 0.001.*

Based on the FSS, the sample was 43.5% robust, 35.2% pre-frail, 14.0% frail, and 7.3% very frail.

The cumulative percentage of individuals with comorbidities (two or more active diseases) was 95.7%. **Figure 1** shows the prevalence of the disease in the sample. The most frequent pathologies are cardiovascular (hypertension, cardiopathy, vascular diseases, and vascular or pressure ulcers, 63.99, 34.32, 29.35, and 9.62%, respectively), arthrosis or arthritis (59.34%), dental diseases (35.28%), and urinary tract diseases (26.62%).

Sociodemographic variables of the 84 individuals who were lost during follow-up (see **Supplementary Table 1**) did not differ from the total sample except for gender.

The specific characteristics of the population significantly associated ($P < 0.05$) with more access to the ER (**Table 1**) are: being men (50.9%), age between 75 and 85 years (50.5%), and comorbidity (97.0%) but with moderate disability condition (28.7%). Overall, to be frail or pre-frail was associated with higher number of ERA (35.8 and 36.6, respectively).

During 3 years of the study, 35.1% of the sample (438 individuals) accessed the ER department at least once and generated 823 accesses, of which 39.24% were NUERA (**Table 2**). The frequent ERA users were 6.1% (elderly with two or more access per year). The ERA and NUERA rates were 34.89 per 100 observations/year [95% *CI* 29.06; 40.71] and 12.30 [95% *CI* 9.84; 14.76], respectively. The one-way ANOVA shows (**Table 2**) a significant difference according to the level of frailty, both for ERA rate $F_{(3,1243)} = 11.94$, $p < 0.001$, and for NUERA rate $F_{(3,1243)} = 6.61, p < 0.001$.

The percentage of ERA and NUERA stratified by level of frailty is shown in **Table 2**. The total number of ERAs carried out by the sample was 823, of which 31.96% were made by robust, 36.2% by pre-frail, 20.8% by frail, and 11.1% by very frail. For NUERA, the total accesses were 323 of which 35.60, 33.75, 23.53, and 7.12% were carried out by robust, pre-frail, frail, and very frail, respectively.

A univariate analysis was conducted before choosing the variable to insert in the predicting model (as shown in **Supplementary Tables 1–3**). In the Supplementary Tables, the single items of the FGE (as shown in **Supplementary Table 2**), the prevalence of disease (as shown in **Supplementary Table 3**), and ADL/IADL (as shown in **Supplementary Table 4**) were analyzed to evaluate the level of correlation with the outcome variable, ERA, and NUERA. Although some variables were significant on univariate analysis, they did not explain the dependent variable when introduced in the multivariate model.

The ordinal logistic regression (GENLIN) model was carried out to identify the predictors of ERA and NUERA (**Table 3**). Patients had significantly more ERAs if they were men (*OR* 1.54, $P < 0.001$, 95% *CI*: 1.22; 1.95). The risk of high number of ERAs increased with increased frailty levels (*OR* 1.29, $P<0.001$, 95% *CI* [1.13; 1.47]). Finally, the person with comorbidities had a significantly increased risk of ERA than their counterparts (*OR* 1.13, $P < 0.001$, 95% *CI* [1.06; 1.20]).

Community-dwelling older people had significantly more NUERA if they had no social network than if they had (*OR* 0.54, $P = 0.015$, 95% *CI* [0.33; 0.89]). Moreover, a medium score of pulmo-cardio-vascular function ("able to climb a flight of stairs or walking for one city block" compared with "no restriction") increase the number of NUERA (*OR* 1.50, $p = 0.006$, 95% *CI* [1.12; 2.01]) that was not the case for people with more severe limitation compared with "no restriction."

DISCUSSION

Frequent access to the ERs has increasingly become a worldwide public health issue with significant consequences (i.e., overcrowding) on the management of EDs (4). This framework is crucial to understand the factors associated with routine access to the ER generated by older adults in order to optimize the resources. This paper aimed to analyze the predictors of ERA and NUERA for community-dwelling older people; moreover, the study addressed to investigate how older adults access the EDs. The main difference between the two models seems to be linked to the level of urgency of the accesses. Accesses associated with a high level of urgency were significantly associated with physical issues, while non-urgent accesses were generated also by social issues. These results can explain predictors involved in the ERAs.

Although there was no clear definition of frequent ED access (10, 39), we used the percentage of frequent users to compare with other international studies on ERA and NUERA rates. Our results show that the frequent ERA users were 6.1% (elderly with two or more access per year). This result agreed with data reported in other studies (8, 9, 40, 41).

Some studies (42–45), both in the United States and Europe, investigated the prevalence of frailty in the ER patient that ranged from 7 to 80%, according to the frailty definition used by the authors. Our study defined frail 21.3% of the population, using a bio-psycho-social description (27). The higher level of frailty has been associated with a higher ED access rate per observation year in the present study as well as in others (43). However, the highest portion of ERA and NUERA is generated by robust and pre-frail patients because of the prevalence of robust and pre-frail older people in the sample (about 80%) and in agreement with other authors (2, 43). Moreover, NUERA represents about

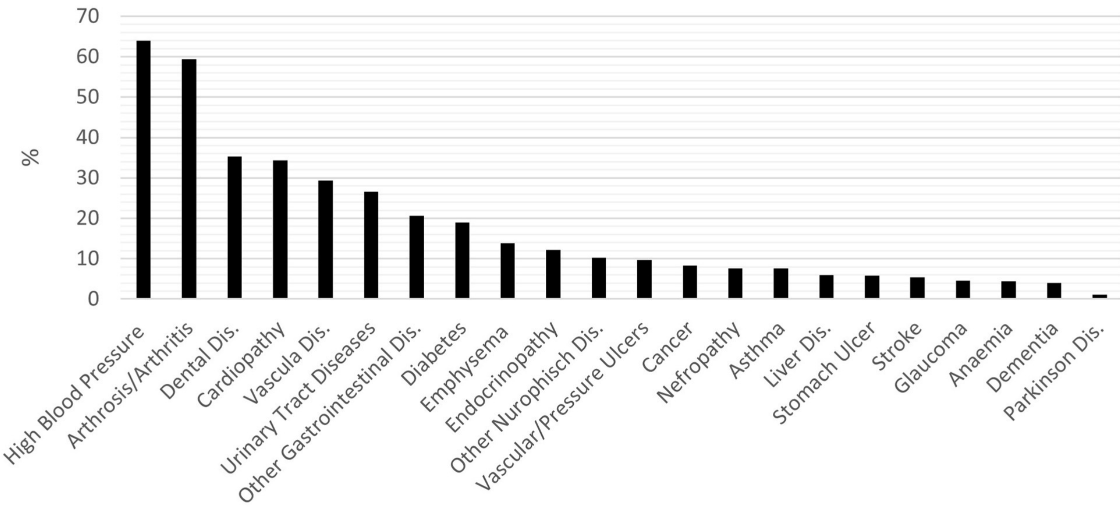

FIGURE 1 | Prevalence of disease among the sample.

TABLE 3 | Ordinal logistic (GENLIN) models were predicting determinants of ERA and NUERA.

			Hypothesis test				95% confidence interval	
Predictors of ERA	β	Std. Er.	Wald χ^2	*df*	*p*-value	OR	Lower	Upper
Gender (male)	0.434	0.1198	13.126	1	<0.001	1.544	1.221	1.952
Frailty	0.256	0.0663	14.844	1	<0.001	1.291	1.134	1.47
Comorbidity	0.123	0.0313	15.356	1	<0.001	1.131	1.063	1.202
Predictors of NUERA								
Social network	−0.607	0.2498	5.901	1	0.015	0.545	0.334	0.889
Pulmo-Cardio-Vascular Function (Medium score)	−.410	0.1484	7.620	1	0.006	1.506	1.126	2.015
Pulmo-Cardio-Vascular Function (Bad score)	−0.053	0.3479	0.023	1	0.880	0.949	0.480	1.876

ERA, emergency room access. Dependent variables: absolute number of ERA and NUERA. Covariate's variable = Comorbidity and frailty. Test omnibus $\chi^2_{(3)}$ =51.73, P < 0.001; ERA AIC = 662.89 and BIC = 698.77. NUERA, not-urgent emergency room access. Dichotomic variable = Social network. NUERA test omnibus $\chi^2_{(3)}$ = 14.049, P = 0.003; NUERA Akaike information criteria (AIC) = 93.75 and Bayesian information criteria (BIC) = 124.52.

40% of the ERAs independently from frailty, showing that reasons for accessing the ER should be further investigated since only clinical emergencies seem not to explain all the ERAs.

As reported by other authors and confirmed in the current study results, the ER frequent user profile was male (50.9%, $P = 0.027$) (9), aged between 75 and 85 years (44.9%, $P = 0.001$) (46), with comorbidities, namely, with a high prevalence of cardiovascular and urinary tract disease (47).

There is a general agreement to the significant role played by comorbidity on healthcare needs, especially on the ERA for the older adults (48). The findings of the current study demonstrated that a high level of comorbidity was a predictor of a high ERA rate. The management of comorbidities and clinical problems seems to be the primary cause that oriented the EDs to the medical model (48). However, this model did not take into consideration the complexity of this type of patient.

All world countries are dealing with the increase of inappropriate use of ER by the elderly, which results in the EDs overcrowding. We have observed that the pre-frail and robust represented the groups generating the majority of ERA and NUERA. Few studies focused on the NUERA (15, 46). There was confusion on the definition of not critical ERA because it was often associated with the medical point of view (49, 50). The increase of older adults admitted in the ERs with not urgent triage (50) reflects a social need or an inadequate social network to match the needs of individuals for care (51–53). In agreement with these studies, the current study results show that enough social networks decrease the risk of NUERA (*OR* 0.54). Moreover, an important fact has emerged from the current research: 39.24% of the total ERA was NUERA, confirming the international trends (50, 52, 54). Faulkner et al. argue that a directly proportional link between the increase in the elderly population and the inappropriate use of EDs could influence ER overcrowding (50). A 2013 mixed-method study revealed that a critical cause of increasing the number of non-urgent accesses was represented by a long waiting list that prevents access to primary care for the elderly, mainly due to the lack of a well-established primary care system (55). Other authors confirm that these barriers involve a "rational choice" of the patient in accessing the ER rather than primary care (53, 56). The second factor associated with the increase of NUERA is a moderate impairment of cardiovascular and respiratory function related to a generic initial imbalance of physical performance, a sign of not-stabilized clinical issues.

We observed the primary role of robust and pre-frail community-dwelling people in using the ER. Moreover, this study highlighted the need to change the management of older adults at the community level to reduce ER overcrowding, according to the definition of Australasian College for Emergency Medicine (6). The change should address precisely the robust and pre-frail older adults, which account for about 78% of both ERA and NUERA, through community health and social care that stabilize the clinical situation and support socially isolated individuals. Frequently a not-stabilized clinical condition is associated with the lack of social network (i.e., difficulties in following complicated drug schedule that results in reduced adherence to medication prescription or respecting follow-up appointments because of problems in moving alone out of the house).

The present study has some points of strength. First, to our knowledge, this is the only study that examines the association between frail older adults and access to the ER, focusing on not urgent ERA. Moreover, this research is original because the people involved in the study represent the regional population stratified for frailty. According to the bio-psycho-social model, the evaluation of frailty can help an early identification of robust, pre-frail, frail, and very frail people to address an adequate response to prevent an adverse outcome (mortality, hospitalization, and institutionalization or access to EDs).

Finally, the main limitations identified in this study are represented by two key points. The first one is related to the questionnaire of FGE. While this questionnaire is validated and has a higher predictive power of the adverse outcome, it is not widely used. The second is represented by the health service characteristics of the Lazio region; it is characterized by low community services, especially for robust and pre-frail older people. Another limitation linked to the current results showed that a different distribution by gender in the 84 individuals lost during the follow-up compared with the total sample. However, the higher prevalence of men among the lost to follow-up could only strengthen the result that the male gender represents a risk factor for the occurrence of ERA. These features can reduce the international generalizability and reproducibility of the results of the study. Moreover, further studies should address the differences between urgent and not-urgent ERA, focusing on the association with the mix of clinical instability and lack of social network.

CONCLUSION

In conclusion, this study has some important implications for public health policy and clinical practice. A paradigm shift is required to lessen the impact of the growing increase in not urgent or inappropriate access by the elderly to the ER. The change should go beyond the clinical model toward a biopsychosocial model by implementing primary care to identify the needs of robust and pre-frail elderly. Early identification can decrease the overcrowding of ERs and improving care for moderate to severe acute cases. Furthermore, primary care should focus on the social support required by these patients. In the future, it will be crucial to conduct more multicenter studies to assess non-urgent access for the frail community-dwelling older population.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Independent Ethical Committee of the University of Rome Tor Vergata. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GL, PS, and SG: conceptualization. SG, PS, GL, and FR: methodology and writing, reviewing, and editing. SG and LE: data analysis. GL and PS: investigation. PS, GL, and FR: resources. SG, GL, and LE: data curation and visualization. SG, GL, and FR: writing—original draft preparation. PS, GL, and FR: supervision. GL: project administration. All authors have read and agreed to the published version of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.721634/full#supplementary-material

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Prevalence of Dementia in China in 2015: A Nationwide Community-Based Study

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Objective: This study aims to estimate the prevalence of dementia and Alzheimer's disease (AD) and associated risk factors among the general Chinese population.

Methods: We carried out a nationwide study including 24,117 participants aged 60 years and older in China using a multistage clustered sampling. Dementia and AD were diagnosed according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders and the criteria issued by the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association. Face-to-face interviews were administered by the trained interviewers to obtain information on demographics, lifestyle factors, and previous diseases.

Results: The overall weighted prevalence of dementia was 4.22% (95%CI 2.27–6.17%) for people aged 60 years and older, was higher in women than in men and increased with age. Daily tea drinking and daily exercises were the protective factors for both dementia and AD. Engaging in social and intellectual activities was significantly associated with a lower risk of dementia and AD.

Conclusions: A large number of population with dementia posed a significant challenge to China where the population is rapidly aging. The increase of public awareness, building more care facilities, and training dementia specialists and professional caregivers are all urgently needed and should be the future priorities of dementia care in China.

Keywords: dementia, prevalence, risk factors, Alzheimer's disease, cross-sectional study

INTRODUCTION

China is aging much faster than other low- and middle-income countries. WHO estimated that the proportion of the population aged 60 years and over will increase from 12.4% in 2010 to 28% in 2040 (1). Accompanying the aging of the society is an increase in age-associated diseases, with dementia playing an important role. The World Alzheimer Report 2015 estimated that there were over 9.9 million new cases of dementia each year worldwide, implying one new case every 3.2 s (2). The Global Burden of Disease Study 2016 reported that the number of patients with dementia in China accounted for ∼25% of the entire population with dementia worldwide (3). A few studies have reported the prevalence of dementia in China, and the estimates remain inconsistent, ranging from 5.0 to 7.7% for people aged 60 years and older and from 2.0 to 13.0% for people aged 65 years and older (4). Most of the previous studies were carried out in single cities or a few localities with small sample sizes, and the significant variations might be mainly due to the different diagnostic criteria, instruments used to assess dementia, the time of the study, and a different sampling scheme, and the characteristics of the study participants. A multicity cross-sectional study reported that the prevalence was 5.60% (3.50–7.60%) for people aged 65 years and above in 2013, based on 5,326 study participants (5). A recent meta-analysis summarized 96 studies and reported an overall prevalence of dementia of 5.30% (4.30–6.30%) for Chinese population aged 60 years and above (6), which was lower than the estimate for China (6.19%) and southeast Asia (7.64%) by the World Alzheimer Report 2015 (2).

In an aging society such as China, an understanding of the current prevalence of dementia and its risk factors is important for policymakers to prioritize patient care and allocate limited health resources. In this article, we reported the prevalence of dementia and Alzheimer's disease (AD) and associated risk factors among the general population aged 60 years and older, based on a large nationwide study carried out in China in 2015.

METHODS

Study Population

The Prevention and Intervention on Neurodegenerative Disease for Elderly in China (PINDEC) study was initiated in 2015 aiming to understand the epidemiology of neurodegenerative diseases and associated risk factors among the population aged 60 years and above in China. We used multistage clustered sampling to select the study population. According to the geographic location, population size, and level of economic development, we first selected Beijing, Shanghai, Hubei, Sichuan, Guangxi, and Yunnan as study provinces, representing 20.7% of the total Chinese population and 22.2% of the population aged 60 years and above in 2015 (**Appendix 1**). Within each province, one urban district and one rural county were randomly selected as the study sites (counties or districts). Within each site, one subdistrict in urban areas or one township in rural areas was selected with probability proportional to its size. Within each subdistrict or township, four to eight neighborhood communities or administrative villages were selected with probability proportional to their size. Within each neighborhood community or administrative village, 100–200 households with people aged 60 years and above were randomly selected as the study households. In the final stage, study participants were selected based on the inclusion and exclusion criteria. The inclusion criteria are as follows: (1) aged 60 years and above (2) have registered Hukou, and (3) lived in the household for more than 1 year. The Hukou system is a family registration program that serves as a domestic passport in China, regulating population distribution and rural-to-urban migration. All individuals register their Hukou in Public Security Department as a legal document, and the Hukou statistics are normally used as a reliable and stable source to reflect the local demography as it is not biased by a rapidly growing number of the migrant population. Subjects who refused to participate, had a life-threatening illness, were living in hospitals, or were institutionalized were excluded. **Figure 1** shows the flow chart of this study. A total of 26,164 people were selected, and 24,117 participated in the survey. The overall response rate was 92.2%. The main reasons for refusal included participants who were too busy, temporarily visited families living in other cities, or they think the survey is not important to themselves.

Data Collection

Data collection was conducted either in examination centers at local health stations in the residential area of participants or in the household of participants by the trained staff according to a standard protocol, from June to December 2015. A comprehensive questionnaire, including information on demographic characteristics, medical history, and lifestyle factors, was administered by the trained interviewers. Bodyweight, height, and waist circumference were measured according to a standard protocol, and body mass index (BMI) was calculated as the weight in kilograms divided by the height in square meter. Based on the Chinese criteria of the China Obesity Working Group (7), normal weight was defined as $18.5 \leq \text{BMI} < 24.0$, low weight was defined as BMI < 18.5, overweight was defined as $24.0 \leq \text{BMI} < 28.0$, and obesity was defined as $\text{BMI} \geq 28.0$. Blood pressure was measured at the non-dominant arm three times consecutively with a 1-min interval between the measurements in a seating position after 5 min of rest using an automated device. Blood samples were collected in all participants after overnight fasting of at least 10 h. Fasting blood glucose (FBG) and serum total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were measured. Diabetes was defined as (1) a self-reported previous diagnosis by healthcare professionals, and (2) the FBG level of 126 mg/dl (7.0 mmol/L) or higher (8). The 2016 Chinese Guideline for the Management of Dyslipidemia in Adults (Chinese guideline) (9) was used to classify the serum TC, LDL-C, HDL-C, and TG levels. High TC was defined as TC ≥ 6.22 mmol/L. High LDL-C was defined as LDL-C ≥ 4.14 mmol/L. Low HDL-C was defined as LDL-C < 1.04 mmol/L and high TG was defined as TG ≥ 2.26 mmol/L. The presence of other diseases was a self-reported previous diagnosis by healthcare professionals.

To ensure the validity and reliability of the data, a stringent quality control protocol was implemented throughout the data collection process. All investigators, interviewers, and laboratory staff underwent intensive training sessions with written and practical exams after the training. Only certified staff were approved to participate in this study and to carry out data collection in the field sites. All questionnaires were administered using a portable PAD with automatic skip pattern and logic checking. All interviews were recorded, and 5% of the total

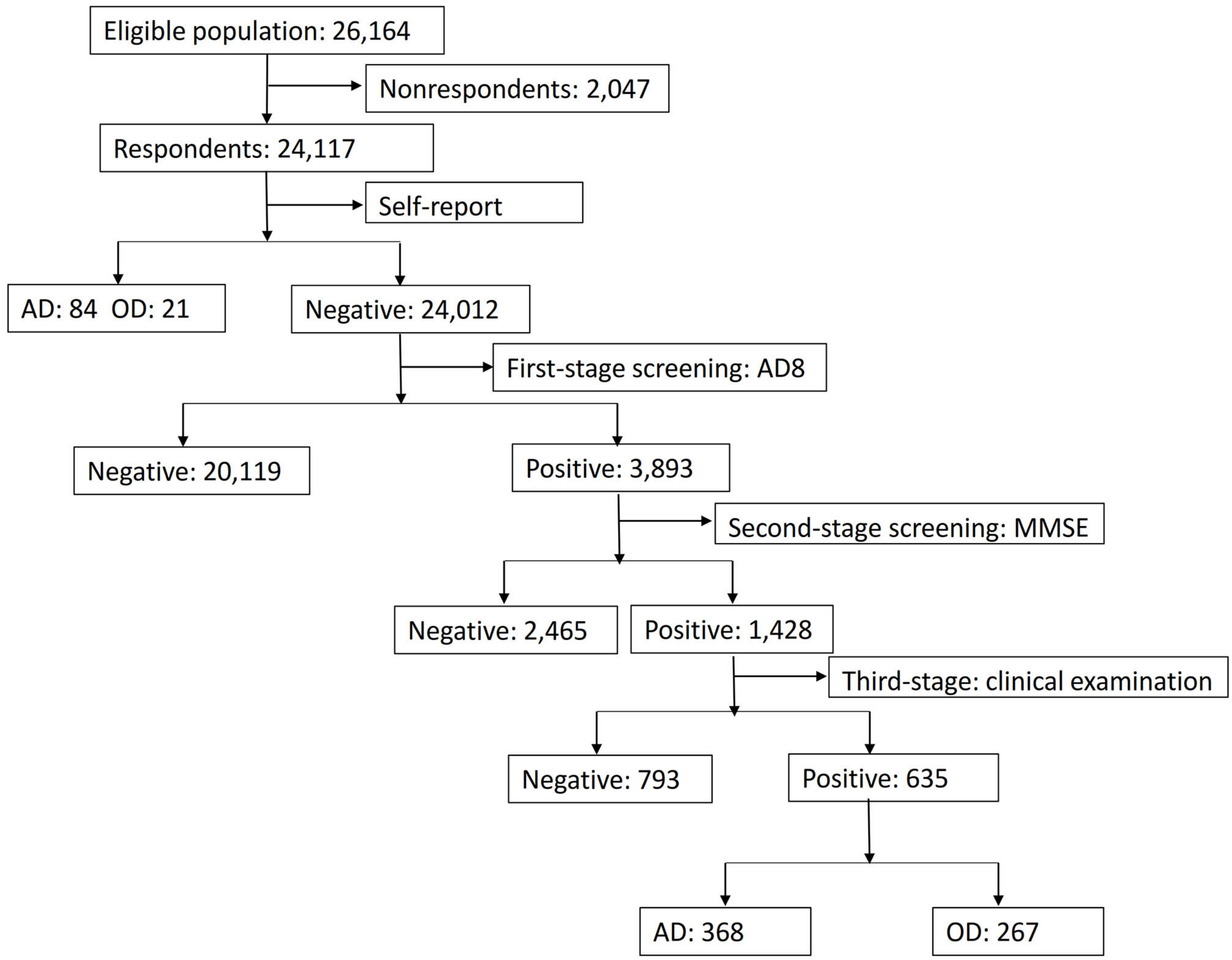

FIGURE 1 | Study flow chart. AD, Alzheimer's disease; OD, other types of dementia; AD8, Ascertain Dementia 8; MMSE, Mini-Mental State Examination.

recordings were randomly selected to check consistency and data coding quality.

Dementia and AD Assessment

When the study participant was selected in the final sampling stage, all participants were asked whether they have been previously diagnosed with dementia by health professionals. Medical records were obtained for those with an affirmative answer, and a self-reported diagnosis was made if the diagnosis was made with clinical examinations in hospitals confirmed by the interviewers. The rest of the participants underwent a three-stage approach for dementia assessment. They were first screened with a Chinese version of the Ascertain Dementia 8 (AD8), which has been proven to be a useful and simple screening tool with good validity in the Chinese population (93.9% sensitivity and 76.0% specificity) (10). Participants with an AD8 score of $\geq$2 were then assessed with Mini-Mental State Examination (MMSE), and cognitive impairment was defined as MMSE $\leq$ 17 for illiterate, $\leq$ 20 for primary school, and $\leq$ 24 for junior high school and above (11, 12). In the final stage, all participants with a cognitive impairment underwent a thorough clinical examination by neurologists. Dementia was diagnosed based on the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (13). The diagnosis of AD was made based on the criteria issued by the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (14). A regional expert committee comprised of neurologists at each of the six provinces was available to review all the diagnoses, and a national working committee gathered together to discuss difficult cases until a consensus was reached.

Statistical Analysis

There were very few missing data in the questionnaires, and they were imputed with median or mean values for the same gender and age group in the dataset. Demographic characteristics of study participants and associated factors were described in means (95% CIs) for continuous variables and percentages (95% CIs) for categorical variables in the overall population and in the subgroups of sex, location (urban/rural), age, and educational level. The prevalence of dementia and AD was estimated separately for the overall population and for subgroups. All estimates were weighted to represent the overall Chinese population aged 60 years or older. We calculated sampling weighting, non-response weighting, and post-stratification weighting to derive a final weighing for each study participant. The detailed weighting procedure and the results were shown in **Appendix 2**. To compare with the prevalence from previous studies, we also estimated the prevalence of dementia for people aged 65 years and over. Multivariable logistic regression was used to examine the association of demographic, lifestyle, and metabolic factors with the odds of dementia and AD. We presented the results for both the crude and fully adjusted models. All P p-values were two-tailed, and the p-value of < 0.05 was considered statistically significant. All statistical analyses were conducted using the SAS system, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

The characteristics of study participants are presented in **Table 1**. Among the 24,117 people aged 60 years and above included in the analysis, 44.5% were men, 53.7% were in urban areas, and 21.1% were widowed. We found no statistically significant difference between men and women with respect to living in urban/rural areas and living alone or with family. The mean age was 70.5 years (SD 7.0), and the median age was 69.0 years. The current smoking rate was 40.3% for men and 2.1% for women. The mean BMI was 23.5 kg/m^2, and 80.1% had regular exercise. About 70.7% socialized with neighbors on daily basis, and 92.9% almost never used the internet. The prevalence of diabetes was 19.0%, and the prevalence of high TC, high LDL-C, low HDL-C, and high TG was 10.2, 7.0, 12.1, and 15.8%, respectively.

The overall weighted prevalence of dementia was 4.22% (95%CI 2.27–6.17%), 2.04% (95%CI 1.54–2.55%) in men and 6.32% (95%CI 2.77–9.86%) in women, 2.90% (95%CI 1.61–4.19%) in urban areas, and 5.26% (95%CI 2.91–7.60%) in rural areas. The prevalence increased with age from 1.95% (95%CI 0.97–2.92%) in 60–64 years to 9.46% (95%CI 7.11–11.81%) in the age group 80 years and above. The prevalence of dementia was the highest in the illiterate group, decreased with more years of education but increased again in people with the highest educational level (more than 8 years). The weighted prevalence of AD was 2.32% (95%CI 1.60–3.05%), and the pattern in different subgroups was similar to dementia (**Table 2**). The weighted prevalence of dementia and AD for people aged 65 years and over was 5.34%, 95%CI 3.08–7.61% and 2.94%, 95%CI 2.10–3.78%, respectively (**Appendix 3**). There were substantial geographic variations in the weighted prevalence of dementia with the highest in Sichuan province (6.25%, 95%CI 5.50–7.00%) and the lowest in Guangxi province (1.05%, 95%CI 0.73–1.37%) (**Appendix 4**).

Figure 2 shows the estimated prevalence rate of dementia by different behavioral and metabolic risk factors. The prevalence of dementia was lower in daily tea drinkers than those who did not drink tea on daily basis and was lower in people with daily exercises than those who did not have regular exercise for both men and women. The prevalence of dementia was the highest in low BMI and the lowest in those with the obesity group for women, and the highest in normal BMI, and the lowest in the overweight group for men. The differences were not statistically significant in terms of smoking status and alcohol drinking. We tested the interaction for different risk factors with gender, and the results showed that there were interactions for occupation ($p = 0.006$), BMI ($p = 0.011$), and regular exercises ($p < 0.0001$) with gender, but not for the others.

Table 3 shows the odds ratios (OR) of different risk factors for dementia and AD. Age was a strong risk factor for dementia and AD. The educational level at primary school (6 years) was associated with a lower prevalence rate compared with illiterate people. However, when the educational level is increasing to junior high school or above, the association was no longer significant. Regular tea drinking, daily exercises, daily socializing with neighbors, reading newspapers or books on a daily basis, and daily use of the internet were the protective factors for both dementia and AD. Engaging in intellectual activities was significantly associated with a lower risk of dementia and AD. Smoking was associated with a higher prevalence of AD (adjusted OR 1.51, 95%CI 1.12–2.04) but not with dementia. Alcohol drinking, the presence of diabetes, and the presence of stroke were associated with a higher prevalence of dementia but not with AD. The presence of chronic obstructive pulmonary disease (COPD) and arthritis was both associated with a higher prevalence of dementia and AD.

Appendix 5 shows the estimated prevalence of dementia using the different forms of dyslipidemia. The prevalence of dementia was higher in men with high TC, high LDL-C, and low HDL-C than those without these diseases. The dementia rate was higher in women with high TG than those without a high TG level. However, when controlling the confounding factors in the logistic regression analysis, the association between dementia and the different forms of dyslipidemia was no longer significant.

DISCUSSION

In this large-scale community-based survey recently carried out in China, we found that the prevalence of dementia and AD was 4.22% (95%CI 2.27–6.17%) and 2.32% (95%CI 1.60–3.05%) in individuals aged 60 years and above in 2015. The prevalence increased with age and was higher in women than in men. Regular tea drinking, daily exercises, and frequent participation in social and intellectual activities were significantly associated with a lower prevalence of dementia and AD.

Systematic review articles all reported the pooled rates of dementia/AD among older adults aged 60 or above, and our estimates (4.22%) fall within the range of 3.0–5.3% reported in these studies (6, 15, 16). In comparison with the latest study from Jia et al. (4), our estimates on the prevalence of dementia for individuals aged 60 years and above were in the lower range of previous estimates. This might be explained by our study sample.

TABLE 1 | General characteristics of the study population in 2015, *n* (%).

	Total	Men	Women	*P*-value
Overall	24,117 (100.0)	10,722 (100.0)	13,395 (100.0)	
Age groups, years				0.008
60–64	5,346 (22.2)	2,232 (20.8)	3,114 (23.2)	
65–69	7,033 (29.2)	3,142 (29.3)	3,891 (29.0)	
70–74	5,076 (21.0)	2,353 (21.9)	2,723 (20.3)	
75–79	3,639 (15.1)	1,647 (15.4)	1,992 (14.9)	
≥80	3,023 (12.5)	1,348 (12.6)	1,675 (12.5)	
Location				0.816
Urban	12,950 (53.7)	5,553 (51.8)	7,397 (55.2)	
Rural	11,167 (46.3)	5,169 (48.2)	5,998 (44.8)	
Marital status				<0.001
Married	18,613 (77.2)	9,194 (85.7)	9,419 (70.3)	
Single/divorced/separated	418 (1.7)	303 (2.8)	115 (0.9)	
Widowed	5,086 (21.1)	1,225 (11.4)	3,861 (28.8)	
Educational level				<0.001
Illiterate	9,376 (38.9)	2,676 (25.0)	6,700 (50.0)	
Primary school	7,652 (31.7)	4,077 (38.0)	3,575 (26.7)	
Junior high school	4,546 (18.8)	2,504 (23.4)	2,042 (15.2)	
Junior high school and above	2,543 (10.5)	1,465 (13.7)	1,078 (8.0)	
Occupation				0.002
Farmer	14,049 (58.2)	5,580 (52.1)	8,469 (63.2)	
Worker	5,760 (23.9)	2,932 (27.3)	2,828 (21.1)	
Non-manual worker*	4,308 (17.9)	2,210 (20.6)	2,098 (15.7)	
Current smoker	4,601 (19.1)	4,325 (40.3)	276 (2.1)	<0.001
Regular exercise	19,323 (80.1)	8,762 (81.7)	10,561 (78.8)	0.005
Daily tea drinking				<0.001
Green tea	4,935 (20.5)	3,500 (32.6)	1,435 (10.7)	
Black tea	1,488 (6.2)	951 (8.9)	537 (4.0)	
Alcohol drinking	5,344 (22.2)	4345 (40.5)	999 (7.5)	<0.001
BMI (kg/m^2)_	23.5 ± 0.02	23.2 ± 0.03	23.7 ± 0.03	<0.001[#]
Living status				0.056
Alone	2,824 (11.7)	1,057 (9.9)	1,767 (13.2)	
With family	21,293 (88.3)	9,665 (90.1)	11,628 (86.8)	
Socializing with neighbors				0.002
Almost never	3,567 (14.8)	1,802 (16.8)	1,765 (13.2)	
Occasional	3,506 (14.5)	1,666 (15.5)	1,840 (13.7)	
Daily	17,044 (70.7)	7,254 (67.7)	9,790 (73.1)	
Reading newspapers				<0.001
Almost never	17,329 (71.9)	6,716 (62.6)	10,613 (79.2)	
Occasional	3,493 (14.5)	1,993 (18.6)	1,500 (11.2)	
Daily	3,295 (13.7)	2,013 (18.8)	1,282 (9.6)	
Use of internet				0.001
Almost never	22,393 (92.9)	9,792 (91.3)	12,601 (94.1)	
Occasional	783 (3.2)	405 (3.8)	378 (2.8)	
Daily	941 (3.9)	525 (4.9)	416 (3.1)	
Diabetes	19.0	17.9	19.9	0.050
Dyslipidemia				
High TC	2,457 (10.2)	781 (7.3)	1,676 (12.5)	0.001
High LDL-C	1,697 (7.0)	569 (5.3)	1,128 (8.4)	<0.001
Low HDL-C	2,923 (12.1)	1,521 (14.2)	1,402 (10.5)	0.014
High TG	3,802 (15.8)	1,404 (13.1)	2,398 (17.9)	<0.001

Non-manual worker includes teacher, researcher, doctors, office workers, and other occupations apart from farmer and worker.
[#]*ANOVA was used to compare the difference of body mass index (BMI) between men and women.*

TABLE 2 | The estimated prevalence of dementia and Alzheimer's disease (AD) in the Chinese population.

	Dementia		AD	
	No.	**Weighted prevalence % (95%CI)**	**No.**	**Weighted prevalence % (95%CI)**
Overall	740	4.22 (2.27–6.17)	452	2.32 (1.60–3.05)
Sex				
Men	220	2.04 (1.54–2.55)	147	1.41 (1.03–1.78)
Women	520	6.32 (2.77–9.86)	305	3.20 (2.00–4.40)
Age groups, years				
60–64	73	1.95 (0.97–2.92)	46	1.07 (0.71–1.43)
65–69	129	2.76 (1.21–4.31)	65	1.14 (0.71–1.57)
70–74	130	3.80 (1.88–5.72)	70	1.93 (1.03–2.84)
75–79	188	8.31 (3.85–12.77)	110	3.93 (2.78–5.08)
≥80	220	9.46 (7.11–11.81)	161	6.91 (4.60–9.22)
Location				
Urban	356	2.90 (1.61–4.19)	214	1.78 (0.96–2.59)
Rural	384	5.26 (2.91–7.60)	238	2.75 (2.04–3.45)
Marital status				
Married	485	3.36 (1.85–4.88)	291	1.80 (1.27–2.33)
Single/divorced/separated	16	3.19 (2.12–4.26)	12	2.54 (1.32–3.75)
Widowed	239	7.37 (4.01–10.73)	149	4.16 (2.58–5.74)
Education, years				
Illiterate	454	7.26 (3.02–11.5)	268	3.92 (2.35–5.50)
Primary school	157	2.19 (1.36–3.03)	102	1.22 (0.75–1.68)
Junior high school	80	1.96 (1.18–2.75)	47	1.02 (0.42–1.62)
Junior high school and above	49	2.32 (1.73–2.91)	35	1.67 (1.17–2.16)

We randomly selected the study participants from communities across the urban and rural areas in China and represented the general Chinese population. In comparison with other studies, our estimate on Chinese population aged over 60 years was higher than a meta-analysis in 2007 and 2012 (15, 16) and our estimates on Chinese population aged over 65 years (5.35%) were in keeping with a five-city study (17) (5.14%) in 2008–2009 and the multicity study (5) in 2012 (5.6%). When we further compared the prevalence rate among different 5-year age groups, we found our estimates for the 65–69, 70–74, and 75–79 age groups were all comparable with the estimates from Jia et al. (17) for both urban and rural areas. However, our estimates for the age group 80 years and above were remarkably lower, resulting in our overall estimates in the lower range of the previous estimates. This can be mainly explained that the elderly participants in our study were relatively healthy because our sample was selected from the general population and excluded those in hospitals or institutionalized.

In consistent with previous studies, we observed a significantly higher prevalence in rural areas than in urban areas, in women than in men, for both dementia and AD. The prevalence of dementia in women was particularly higher than the prevalence of dementia in men, compared with a recent large-scale cross-sectional study (18). The magnitude of the differences might be due to different study populations and settings, and further studies are needed to fully address the discrepancy. The prevalence of dementia and AD among the widowed participants was more than 2-fold of the non-widowed participants, which is also in line with previous reports from both developed countries and China (19–21). Educational level has been identified as an important factor associated with dementia, and illiterate individuals had the highest prevalence rate of dementia and different types of dementia, as indicated in many previous studies (22, 23). Jia et al. reported that the prevalence of AD decreased with more years of education in urban areas in China, while in rural areas, the prevalence was the lowest for those with 7–9 years of education and slightly higher in those with more than 9 years of education (17).

Accumulated evidence from prospective cohort studies proved an increased risk of dementia in smokers. Our study found that smoking was associated with a higher prevalence of AD but not for dementia. Another multicity study in China found no association between tobacco smoking and the prevalence of AD and vascular dementia in urban and rural Chinese populations (17). The reason remains unclear, and further studies with biomarker assessment for smoking are needed to illustrate the true association between smoking and dementia in the Chinese population. Previous studies indicated that the association between alcohol consumption and the risk of dementia is dependent on the amount of alcohol (24, 25). Although the information on the quantity of alcohol was not obtained in the current study, an analysis on frequency showed that daily alcohol drinking was significantly associated with a higher risk of dementia. For tea-drinking, our result showed

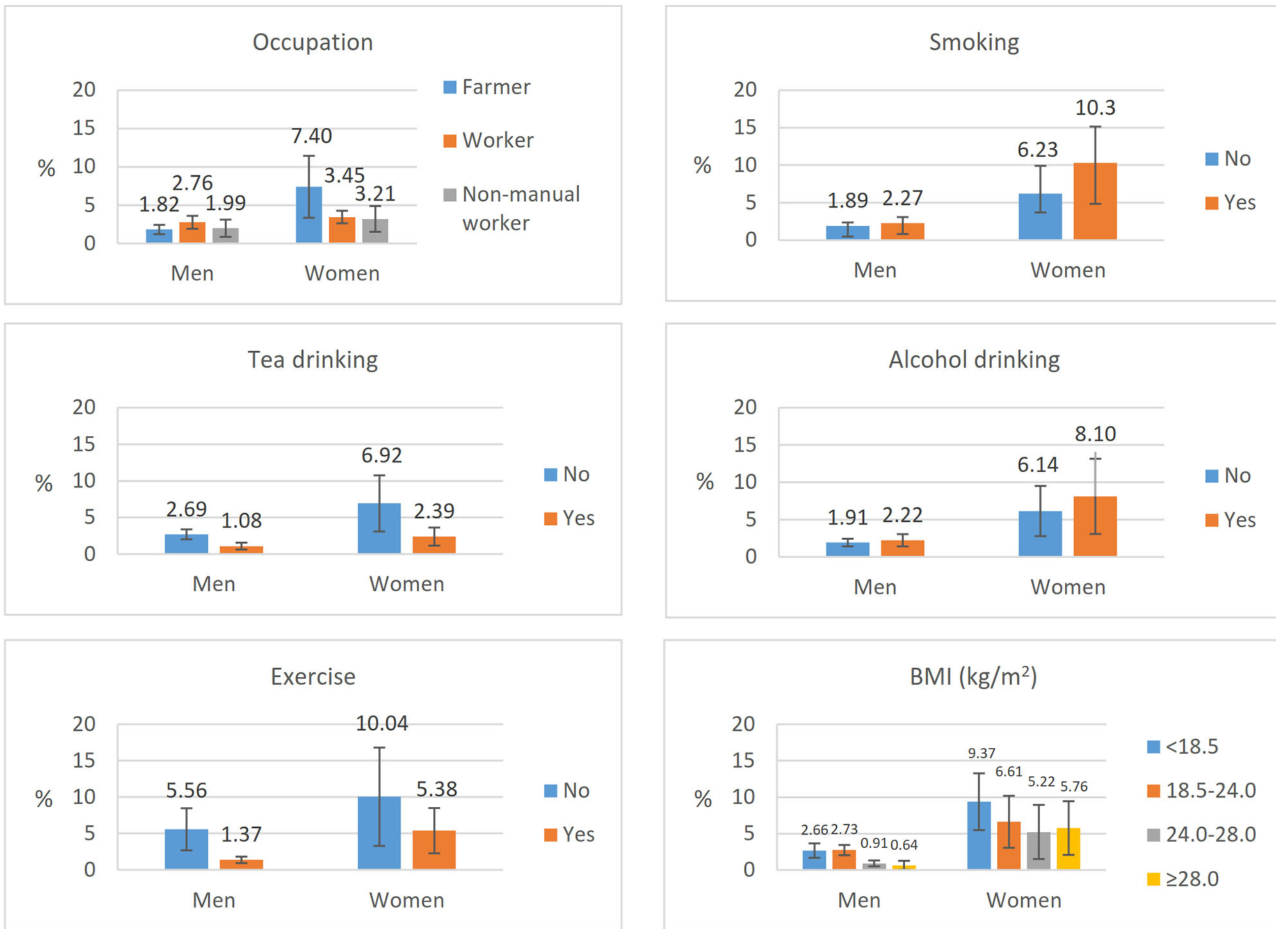

FIGURE 2 | The estimated prevalence of dementia stratified by behavioral and metabolic risk factors.

that both green tea and black tea were the protective factors for dementia and AD. A few studies have reported the hypothesis that green tea intake might reduce the risk for dementia, AD (26). However, whether black tea intake was associated with dementia and AD needs further research.

Previous studies found that rheumatoid arthritis (RA) increased the risk of dementia, and also reported that a decreased risk of new-onset dementia was seen in patients with RA and was greater among older men, which may be due to the use of the antirheumatic drug (27, 28). In our study, the measurement for arthritis only used self-report, and we did not collect the information about arthritis type and medical history. Potential reasons can be further explored in future studies. Consistent with many studies, a higher prevalence of dementia and AD was seen in patients with COPD (29–31).

The most recent World Alzheimer Report 2019 indicated that 80% of the general public are concerned about developing dementia at some point, and one in four people think that there is nothing we can do to prevent dementia, and almost 62% of the healthcare providers worldwide think that dementia is part of normal aging (32). According to a recent national WeChat-based (a popular instant messaging app) survey on public knowledge about dementia in China, the overall correct rate of total dementia knowledge was 63% and only half of the participants could identify risk factors accurately (33). Their findings indicated that Chinese people have a low level of knowledge about dementia, especially those aged more than 60 years, with low education and living in rural areas, which are exactly the group of the population at the highest risk of dementia. Urgent actions need to be taken to increase public awareness of dementia in China, especially among the vulnerable groups.

Our study confirmed that people with chronic conditions, especially those with diabetes, stroke, COPD, and arthritis, tended to have a higher prevalence of dementia, posing the importance of the prevention and treatment of these chronic diseases. Due to economic difficulties and low awareness of the disease among patients with dementia and their families, ∼70–80% of them have not received treatment in China (34). The major challenge associated with the treatment of patients with

TABLE 3 | Logistic regression analysis of potential risk factors for dementia and AD (odds ratios (OR), 95%CI).

	Dementia		AD	
	Model 1	**Model 2**	**Model 1**	**Model 2**
Sex				
Men (ref)	1.00	1.00	1.00	1.00
Women	**3.06 (1.70–5.51)**	**2.79 (2.05–3.80)**	**2.15 (1.51–3.07)**	**1.83 (1.24–2.69)**
Age groups, years				
60–64 (ref)	1.00	1.00	1.00	1.00
65–69	**1.43 (1.13–1.82)**	**1.40 (1.14–1.72)**	1.07 (0.74–1.54)	1.04 (0.73–1.49)
70–74	**1.99 (1.63–2.43)**	**1.86 (1.55–2.21)**	**1.82 (1.27–2.61)**	**1.67 (1.18–2.36)**
75–79	**4.57 (3.66–5.71)**	**3.53 (2.96–4.21)**	**3.79 (3.32–4.32)**	**2.85 (2.22–3.66)**
≥80	**5.27 (3.76–7.38)**	**3.17 (2.21–4.55)**	**6.87 (5.40–8.73)**	**4.42 (3.51–5.55)**
Education, years				
Illiterate (ref)	1.00	1.00	1.00	1.00
Primary school	**0.35 (0.22–0.56)**	**0.53 (0.42–0.67)**	**0.39 (0.23–0.66)**	**0.52 (0.34–0.79)**
Junior high school	**0.32 (0.17–0.63)**	0.82 (0.62–1.08)	**0.34 (0.15–0.78)**	0.76 (0.43–1.33)
Junior high school and above	**0.33 (0.15–0.72)**	1.05 (0.66–1.66)	**0.46 (0.27–0.78)**	1.43 (0.84–2.43)
Residing status				
Alone (ref)	1.00	1.00	1.00	1.00
Living with family	0.81 (0.67–1.00)	0.96 (0. 82–1.13)	0.72 (0.54–1.00)	**0.78 (0.64–0.96)**
Smoking				
Never (ref)	1.00	1.00	1.00	1.00
Ever	0.67 (0.33–1.36)	1.24 (0.93–1.66)	0.95 (0.62–1.46)	**1.51 (1.12–2.04)**
Alcohol drinking				
No (ref)	1.00	1.00	1.00	1.00
Yes	0.83 (0.68–1.02)	**1.51 (1.25–1.83)**	0.81 (0.60–1.09)	1.19 (0.91–1.56)
Daily tea drinking				
No (ref)	1.00	1.00	1.00	1.00
Green tea	**0.28 (0.21–0.37)**	**0.54 (0.43–0.68)**	**0.27 (0.19–0.37)**	**0.48 (0.36–0.62)**
Black tea	**0.20 (0.08–0.50)**	**0.33 (0.15–0.72)**	**0.25 (0.12–0.50)**	**0.37 (0.19–0.74**
Regular exercise				
No (ref)	1.00	1.00	1.00	1.00
Yes	**0.47 (0.33–0.68)**	**0.63 (0.42–0.95)**	**0.52 (0.36–0.77)**	**0.72 (0.49–0.97)**
Socializing with neighbors				
Almost never (ref)	1.00	1.00	1.00	1.00
Occasional	0.74 (0.40–1.40)	0.73 (0.45–1.19)	0.65 (0.39–1.07)	0.69 (0.46–1.04)
Daily	**0.41 (0.24–0.70)**	**0.44 (0.27–0.73)**	**0.47 (0.26–0.82)**	**0.54 (0.33–0.88)**
Reading newspapers				
Almost never (ref)	1.00	1.00	1.00	1.00
Occasional	**0.22 (0.06–0.78)**	0.44 (0.16–1.20)	0.36 (0.13–1.02)	0.62 (0.27–1.44)
Daily	**0.14 (0.05–0.38)**	**0.31 (0.13–0.73)**	**0.11 (0.04–0.30)**	**0.19 (0.07–0.48)**
Use internet				
Almost never (ref)	1.00	1.00	1.00	1.00
Occasional	**0.15 (0.05–0.46)**	**0.40 (0.18–0.91)**	**0.12 (0.02–0.98)**	0.29 (0.03–2.95)
Daily	**0.14 (0.05–0.41)**	**0.33 (0.17–0.64)**	**0.21 (0.08–0.55)**	**0.42 (0.20–0.90)**
Diabetes				
No (ref)	1.00	1.00	1.00	1.00
Yes	**1.43 (1.15–1.79)**	**1.22 (1.01–1.48)**	1.24 (0.95–1.60)	1.00 (0.81–1.23)
High TC				
No (ref)	1.00	1.00	1.00	1.00
Yes	1.19 (0.70–2.01)	0.71 (0.46–1.10)	1.67 (0.92–3.01)	1.02 (0.56–1.84)

(Continued)

TABLE 3 | Continued

	Dementia		AD	
	Model 1	**Model 2**	**Model 1**	**Model 2**
High LDL-C				
No (ref)	1.00	1.00	1.00	1.00
Yes	**1.82 (1.10–3.00)**	1.56 (0.98–2.49)	**2.39 (1.39–4.11)**	1.72 (0.96–3.06)
Low HDL-C				
No (ref)	1.00	1.00	1.00	1.00
Yes	1.23 (0.77–1.95)	1.17 (0.91–1.49)	1.17 (0.82–1.66)	0.99 (0.74–1.33)
High TG				
No (ref)	1.00	1.00	1.00	1.00
Yes	0.92 (0.60–1.40)	0.81 (0.54–1.21)	0.95 (0.65–1.40)	0.84 (0.50–1.41)
CHD				
No (ref)	1.00	1.00	1.00	1.00
Yes	**1.89 (1.19–3.00)**	1.24 (0.94–1.65)	**2.07 (1.45–2.95)**	1.31 (0.99–1.72)
Stroke				
No (ref)	1.00	1.00	1.00	1.00
Yes	**2.91 (1.86–4.57)**	**2.21 (1.62–3.01)**	**2.23 (1.27–3.92)**	1.35 (0.78–2.32)
Cataract				
No (ref)	1.00	1.00	1.00	1.00
Yes	1.52 (0.94–2.43)	1.07 (0.75–1.52)	**1.86 (1.14–3.04)**	1.27 (0.82–1.98)
COPD				
No (ref)	1.00	1.00	1.00	1.00
Yes	**2.06 (1.38–3.08)**	**1.94 (1.48–2.54)**	**2.19 (1.54–3.12)**	**1.84 (1.46–2.32)**
Arthritis				
No (ref)	1.00	1.00	1.00	1.00
Yes	**1.83 (1.41–2.36)**	**1.44 (1.23–1.69)**	**2.01 (1.54–2.61)**	**1.60 (1.21–2.11)**

Model 1: Unadjusted crude analysis.
Model 2: Adjusted for age, sex, marital status, region, educational level, occupation, smoking status, alcohol drinking, tea drinking, BMI, exercise, residing status, socializing with neighbors, reading newspapers, use of the internet, and the presence of some diseases.
Bold values: P-value < 0.05.

dementia in China is the lack of a well-functioned dementia care system, which is further affected by the high cost of care and low levels of public awareness, and poor education among caregivers (35).

We found that daily green tea drinking, regular physical activity, reading books or newspapers, daily use of the internet, and frequent social activities were the protective factors for dementia, which are also reported in studies in China and other countries (36, 37). Our findings supported the importance of an active, intellectual, and socially integrated lifestyle among the elderly. In the most recent Healthy China 2030 action plan (38), promoting geriatric health is an important component, and specific actions included encouragement and support of the University for the Elderly, Activity Center for the elderly and Elderly Associations to organize healthy activities across the country.

One important strength of our study is the large sample size and stringent quality control. The study was carried out in 12 counties in 6 provinces across China. A total of 150 interviewers were involved, all of whom attended intensive training sessions and passed exams. A regional expert committee comprised of five provincial-level neurologists confirmed the clinical diagnosis of all cases in each province, and a central expert panel comprised of eight neurologists from the top hospitals in China worked together on difficult cases until a consensus was reached. With strong support from the central and local government of project sites, all the local project activities were well-organized, such as assigning the experienced interviewers to work early morning or night to coordinate with the schedule of participants, offering transportations to the study participants, and the provision of a green channel for all the clinical examinations by local hospitals. All these efforts contributed to the good data quality in this study. The structure of the weighted population was similar to the China Census 2010, proving the representativeness of our study population.

This study has some important limitations. First, temporal associations cannot be inferred due to the cross-sectional nature of the analysis, and recall and response biases might affect the prevalence estimates. Second, despite the weighting use and a high response rate, a limited number of provinces (only six) were selected to represent the national estimates. Older adults from remote rural areas and ethnic minority groups may have been left out. Third, our study participants were selected from the general community residents, with the exclusion of hospital and institutional communities, therefore the prevalence might be underestimated due to the institutionalization of some of the elderly individuals. Fourth, we were not able to identify the other subtypes of dementia, such as vascular disease, and cannot depict the whole picture of dementia prevalence. Finally, although we included many potentially associated factors in the logistic regression models, some of the variable categories were still crude. For example, we only asked the frequency of alcohol drinking, and information on the type and units of alcohol was not recorded.

Our study represents the most up-to-date study with large sample size and standard diagnosis in China to estimate the prevalence of dementia and AD in the general Chinese population. Based on the China National Statistics Bureau, there were 212.42 million Chinese population aged 60 years and over in 2015. If our prevalence estimates are correct, the number of people with dementia would be 8.96 million in China, posing a heavy burden to the family, society, and economy. This finding has serious implications for geriatric health and health services in the rapidly aging society in China. Our study lends further support to increase the awareness of dementia in the general public and to implement effective prevention and control measures on dementia in the Chinese population.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by National Center for Chronic and Noncommunicable Disease Control and Prevention of Chinese Center for Disease Control and Prevention. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZW and DP contributed to conception and design of the study. QZ, YX, YD, ZD, YS, and JM contributed to the project execution. HZ organized the database. SQ performed the statistical analysis and wrote sections of the manuscript. PY wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.733314/full#supplementary-material

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The Multi-Modal Risk Analysis and Medical Prevention of Lumbar Degeneration, Fatigue, and Injury Based on FEM/BMD for Elderly Chinese Women Who Act as Stay-Home Grandchildren Sitters

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Background: An increasing number of Chinese elderly women stay at home and act as grandchildren sitters. In consequence of the frequent load-bearing, chronic lumbar fatigue probably caused a higher risk of lumbar degeneration, fatigue, and injury which has become one of the most important aging and health problems in China. In this study, a multi-mode lumbar finite element model (FEM) with specific bone mineral density (BMD) were developed and validated for further spine injury prevention and control.

Methods: The material properties of lumbar vertebra were modified according to degenerated bone mineral density, and geometry was adjusted based on intervertebral disc height. The motion of lifting children was simulated by a 76 year-old Chinese women's FEM, and the stress distribution was calculated and predicted.

Results: The pressure of L5-S intervertebral disc in the bending 3-year-old dummy lifting posture was significantly higher than the same posture without lifting, the maximum effective stress of endplate cartilage in the upright child lifting posture was 1.6 times that of the bending without lifting posture. And the fatigue risk limitation frequency of the upright with dummy posture was predicted with the functional equation of fatigue and stress which was deduced by genetic algorithm, which combined with the effective stress of lumbar vertebrae spongy bone calculated from FEM.

Conclusions: The child-lifting motion could increase the risk of lumbar degeneration, fatigue, and injury in elderly women, and they should keep below the frequency limit of the motion of lifting children in their daily life. This study could put forward scientific injury prevention guidance to Chinese elderly women who lift children in daily life frequently.

Keywords: reverse engineering, injury prevention, aging and health problems, spine fatigue limitation frequency, lumbar degenerative disease, public health, left-behind elderly

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INTRODUCTION

Grandparent-raising refers to the situation where children are raised up by grandparents alone, or mainly by grandparents while parental rearing only plays a minor role. This phenomenon has attracted more and more investigators' attention (1–5). Grandparent-raising is influenced by cultural differences and mainly exists in East-Asian countries, especially in China. Because traditional culture in these countries emphasizes family harmony and collective happiness in the whole family, it is a common phenomenon that children are taken care of by their grandparents instead of their parents (1, 5, 6). Moreover, in these families, it is usually the responsibility of women to take care of children (5). During the course of babysitting, the action of lifting children, which involves bending, flexing, and the upright motion of the lumbar region, is inevitable and repeated frequently. In the view of biomechanics, those movements increased load-bearing on the lumbar vertebra and soft tissues. Because of the characteristics of the lumbar vertebra in elderly women, such daily lifting behavior is likely to increase the risk of lumbar fatigue (7, 8). With severe population aging and baby booming caused by the implementation of the second-child policy in China, more and more elderly women are at the risk of lumbar fatigue due to such daily behavior.

Different from injury of other parts of the human body (e.g., intervertebral disc protrusion) (9), lumbar fatigue, also called the silent epidemic, is usually asymptomatic and is easily neglected by the public (10). Most lumbar vertebral fractures are caused by common actions in daily life (8), movements like bending and lifting light objects are likely to increase the risk of lumbar vertebral fractures (7). Osteoporotic vertebral fracture is common in the elderly, representing a serious event, causing reduced activity or bedridden status with high mortality and morbidity rates, imposing a heavy burden on public health and social development (11). Due to the high misdiagnosis rate of this silent epidemic in clinical imaging examination (12–15), most elderly women with minor lumbar problems fail to get the doctors' warning and still frequently perform movements of bending, flexing, and lifting motions in raising their grandchildren, which leaves a latent danger of further serious damage. Therefore, it is crucial to predict and quantitatively evaluate the risk of such daily movements before serious lumbar injury occurs.

Some research efforts have been focused on applying the finite element model (FEM) to predict the degenerative disorder of lumbar/cervical spine and detect lumbar stress during operations (16–18). In addition, the use of the genetic algorithms in the quantitative evaluation of the body's tolerability to injury has made significant progress (19, 20). Based on these improvements, our study first developed a FEM based on two main characteristics of lumbar spine in elderly women, i.e., the decreased bone mineral density (BMD) and the reduced intervertebral space. Secondly, based on the measured result of the lumbar activity range of volunteering experiment subjects when they are lifting a dummy representative of a 3-year-old, we used FEM to set the range of motion and then calculated and predicted the muscle force and effective stress response of the intravertebrae disc, endplate cartilage in bending without lifting, bending with lifting a 3-year-old child, and upright with lifting 3-year-old child respectively. Thirdly, according to the fatigue-frequency curve of the lumbar spongy bone (21), we used the genetic algorithm to predict the frequency limitation of bending and upright posture with lifting corresponding to the effective stress of vertebrae spongy bone, then proposed a frequency limitation of such daily lifting movement and provided a quantitative reference for lumbar protection in elderly women who get involved with daily grandparent raising.

METHODS

Description of the Finite Element Model

The FE model includes: vertebral body, intervertebral discs, main ligaments, and muscles (as shown in **Figure 1A**). Most anatomical geometry of the model comes from the CT scanning of 75-year-old women without clinical symptoms of lumbar degeneration. Lamellar thickness is 0.5 mm and resolution is 512 × 512. Then MIMICS software (Version 12.0, Materialize Inc., Leuven, Belgium) was used for the three-dimensional reconstruction. The intervertebral disc, endplate cartilage, and ligament were reconstructed according to anatomical position and reference from the radiologist. In order to make the FE model more consistent with the morphological characteristics of the target population, we adjusted the intervertebral space according to Shao's study (22). Elastic modulus of cancellous bone was adjusted according to the BMD of Chinese women population in Wu's report (23). The BMD was calculated based on equation (1)

$$BMD(age) = 0.317 + 0.486 \bullet age - 0.0011 \bullet age^2 + 0.0000066 \bullet age^3 \quad (1)$$

Herein age was 60, and young's modulus was calculated by equation (2)

$$E = 24 \bullet BMD - 3.73 \quad (2)$$

Young's modulus of vertebrae spongy bone for Chinese elderly women was obtained, as shown in Appendix Data 1.

Validation of the Lumbar FE Model Without Muscle

Since there is not available cadaver experimental data of the muscle for validation, in order to ensure the biofidelity of our model, we removed the muscle, then the lumbar FE model was validated by comparing its predictions with range of motion (ROM) observed *in vitro* under the flexion (8 Nm), extension (6 Nm) loading condition without preloading (24). The same as the description of the experiment *in vitro*, the boundary condition of the lumbar FE model without muscle was set identically with experiments *in vitro*, as shown in **Figure 1B**.

Muscle Model Setting (Muscle Function Description)

In order to simulate the movement of an elderly woman in the process of lifting a child, the main muscles that

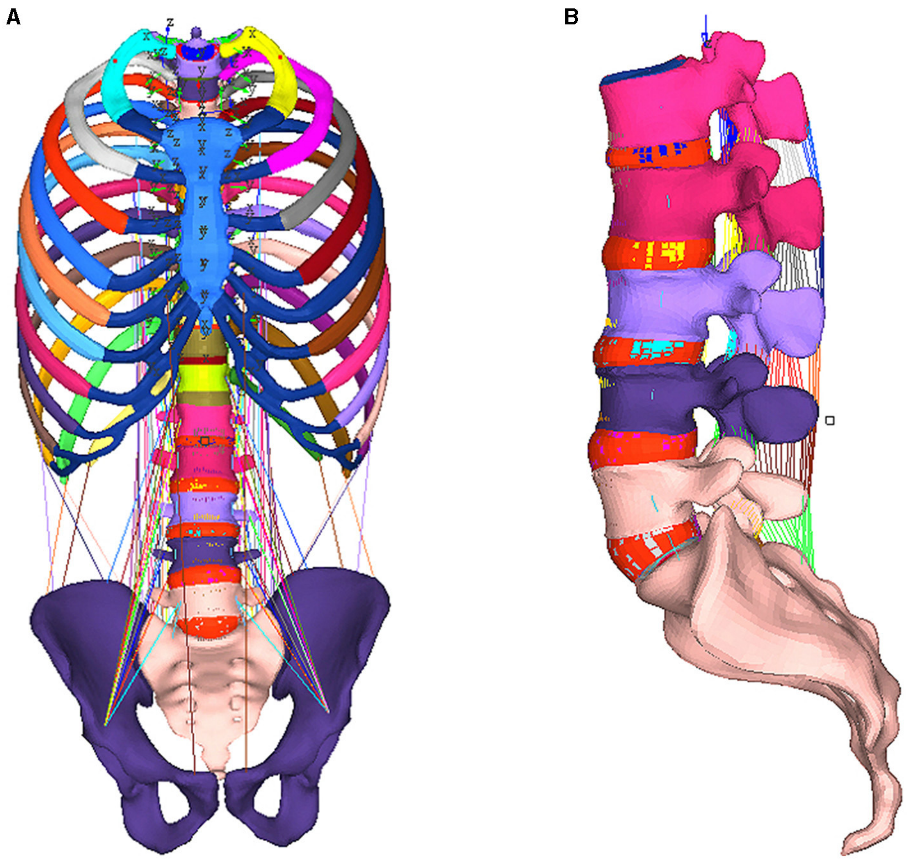

FIGURE 1 | Integral map of lumbar spine model **(A)** and the lumbar spine FE model [**(B)** excluding muscle].

maintain the stability of the trunk and waist when load-bearing were added into the model: Erector spinae, rectus abdominis, internal oblique muscle, external oblique muscle, lumbar major muscle, quadratus lumborum and multifidus. The psoas, multifidus, and quadratus lumborum muscle groups are reported to act as stabilizers of the lumbar spine. The erector spinae and the abdominal muscles are the primary locomotors of the spine. The parameters of the material properties are in the attachment (I–II), referring to the findings of Christophy (25). We referred to spine surgeons in Xiangya 3rd hospital when deciding the muscle starting and stopping points. The material parameters were converted according to PCSA (physiological cross-sectional area) and maximal force with equation (3), herein σ was the maximum engineering stress, $F_{\max}$ was the maximum force, the PCSA was the physiological cross-sectional area.

$$\sigma = \frac{F_{\max}}{PCSA} \quad (3)$$

These variables were utilized as parameters of the fiber element parameter in LS-DYNA (LS-DYNA3D 971, LSTC, Livermore, CA, USA), as shown in Appendix II, and calculated in finite element model simulations. Similar settings were used to simulate the neck muscle response in the front impact study by Matthew's group (26).

Volunteer Experiment and the Simulation of an Elderly Woman Lifting a Child

In order to simulate the motion trajectory of an elderly woman lifting a child, a high-speed camera imaging system (Redlake MotionXtra HG-LE, DEL Imaging Systems, LLC. Chesshire. CT, US) was used to obtain the lumbar spine track in the process of volunteers lifting a dummy representative of a 3-year-old, as shown in **Figures 2A,C**. A standard 3-year-old child model (weight 16 kg, height 115 cm, P3 child dummy, Hunan SAF Automobile technology Co. Ltd, China) was used in this experiment. After labeling on the lumbar spine of the volunteers (Labeling spot was located on Spinous), video with a speed of 200 frames per second was recorded. (The characteristics of the volunteers: Age 76, 159.3 cm, 60.4kg, which is near the approximate the median of Chinese elderly women). The posture of the FE model was adjusted, as shown in **Figures 2B,D**, the range of motion of lumbar FE model was set identically to

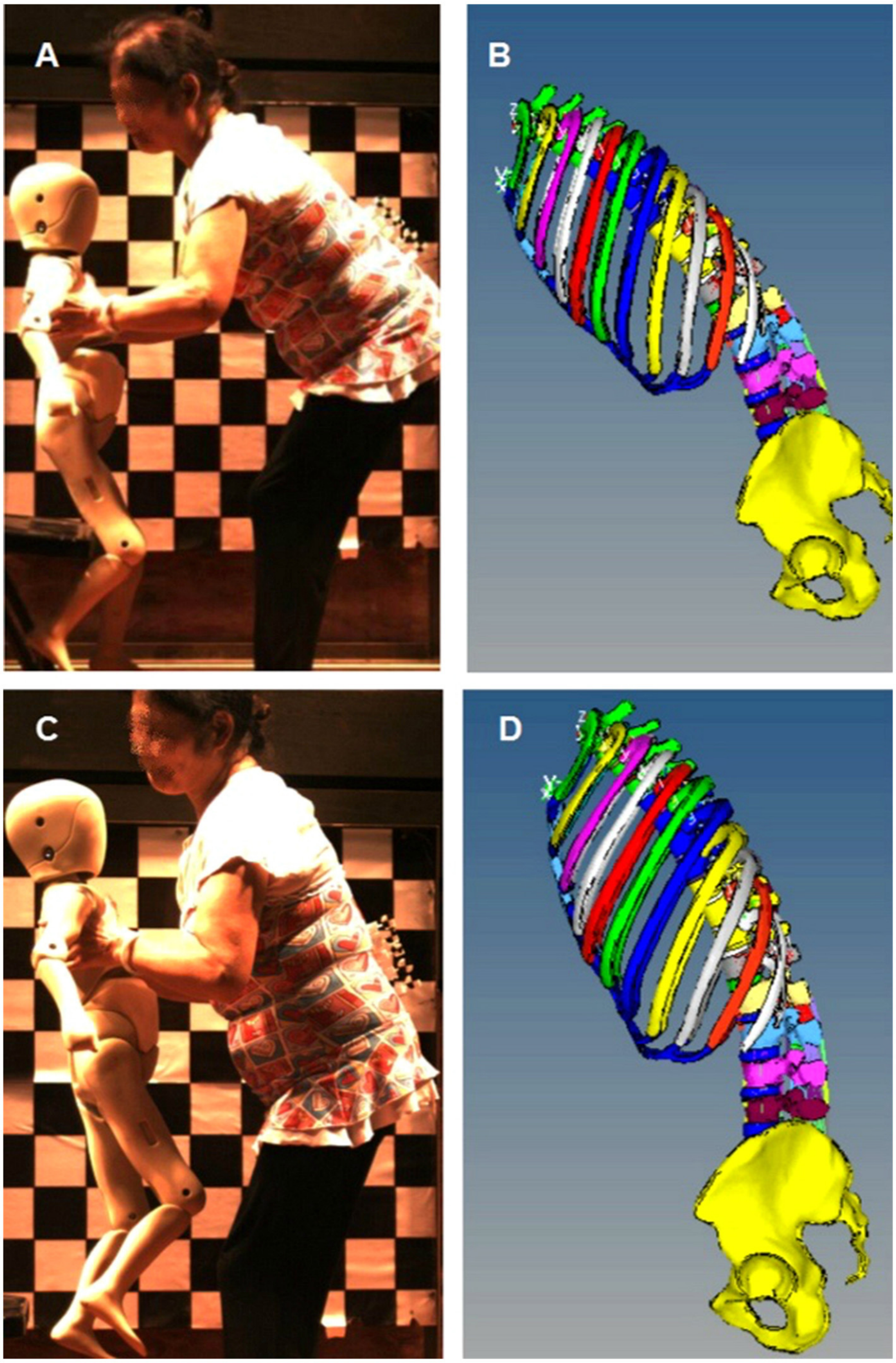

FIGURE 2 | FEM mechanical simulation of volunteers lifting dummy. **(A)** Bending posture with lifting 3-year-old dummy, **(B)** Lumbar FEM adjusted posture according **(A,C)** Upright posture with lifting 3-year-old dummy, **(D)** Lumbar FEM adjusted posture according **(C)**.

the volunteer's experiments. Three postures were simulated, the stress of the lumbar spine was calculated and predicted under bending without lifting posture, bending with lifting 3-year-old child posture, and upright with lifting 3-year-old child posture, respectively.

Fatigue Curve

Repetitive loading lower than ultimate loads may cause failure (21), which presents a certain functional relationship between the action frequency and maximum stress. In this study, an equation was deduced from low cycle and high cycle fatigue studies with

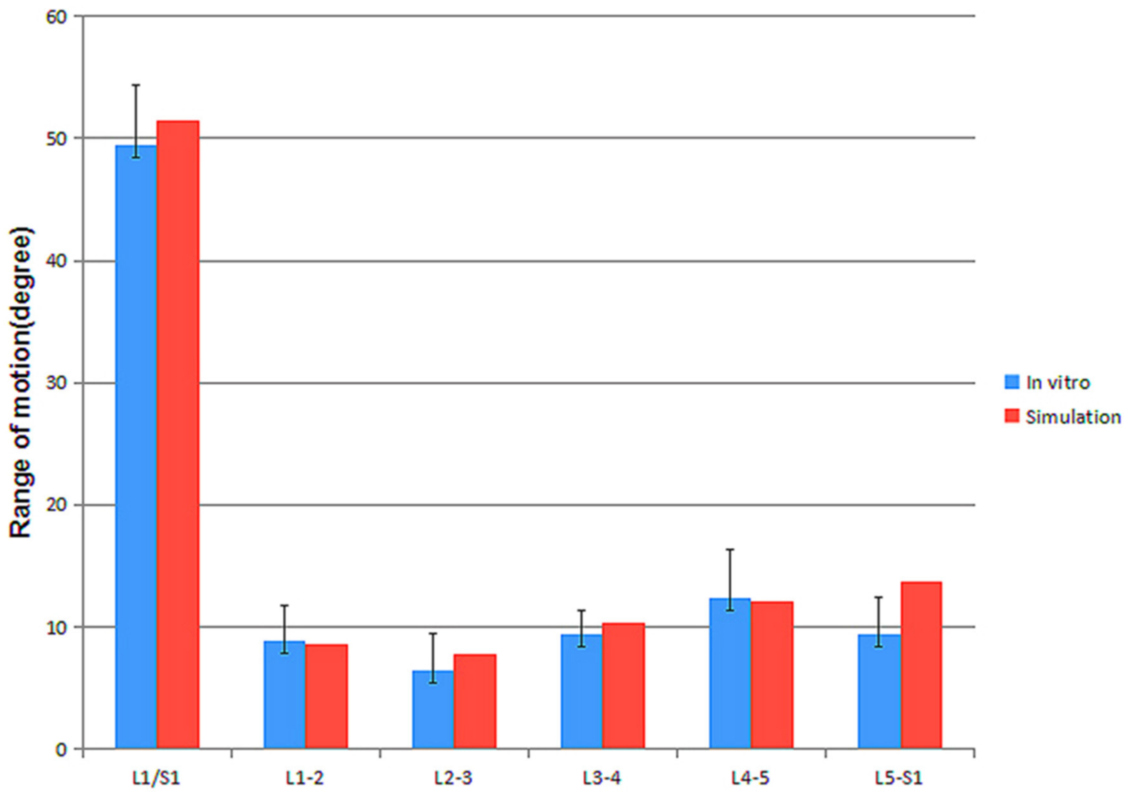

FIGURE 3 | FEM simulation compared to the *in vitro* experiments data.

a genetic algorithm, as shown in equation (4). Herein σ_{eff} was effective stress, the unit was kPa, N was the number of cycles to failure.

$$N = 1525 - 3.38 \bullet \sigma_{eff}^{0.56} \tag{4}$$

Based on the effective stress of vertebral spongy bone calculated from the 2.4 section, the combined genetic algorithm and the equation (4), our study quantitatively predicted the limited frequency of the lumbar vertebral spongy bone during the movement of elderly women lifting children.

RESULTS

ROM Results Compared to *in vitro* Experiments

As shown in **Figure 3**, the ROM predicted by the lumbar FEM were in good agreement with the *in vitro* results at all segmental levels (24), except the L5-S1 ROM predicted was 13.7°, which was slightly above the *in vitro* result 9.43 ± .5°.

FE Model Prediction of the Soft Tissue in Bending, Bending With 3-Year-Old Baby, and Upright With 3-Year-Old Child Posture

The experimental result showed that the maximum erector spinae tension was 4.32 kN, 4.9 kN, and 3.7 kN, in the bending without lifting weight, the bending with lifting 3-year-old child, and upright with 3-year-old child posture respectively, as shown in **Figure 4**. The calculated maximum intradiscal pressure was located in L5-S, which were 3.56 Mpa, 5.38 Mpa, and 1.47 Mpa, in the bending without lifting weight, the bending with lifting 3-year-old child, and upright with 3-year-old child posture respectively, as shown in **Figure 5**. The maximum effective stress contribution of endplate cartilage was located in posterior edge of L5 up and down endplate cartilage, which were 16.55 Mpa, 23.58 Mpa, and 26.55 Mpa in the bending without lifting weight, the bending with lifting 3-year-old child, and upright with 3-year-old child posture respectively, as shown in **Figure 6**.

The detailed sagittal views of the effective stress in lumbar vertebrae spongy bone were shown in **Figure 7**, as the vertebrae spongy bone was the primary compression-bearing structure. In the bending without lifting posture, the maximum effective stress of vertebrae spongy bone was located in the lateral posterior part and the vertebral pedicle of L5, which was 26.3 Mpa. When the 3-year-old child was lifted, the maximum effective stress contribution of the vertebrae spongy bone was moved into the middle posterior part and vertebral pedicle of L5, which was 38.5 Mpa, an increase of 46.3% compared to the bending without lifting weight posture. More increments occurred in the upright with 3-year-old child posture, the maximum effective stress contribution of the vertebrae spongy bone was moved into the bottom part and vertebral pedicle of L5, which was

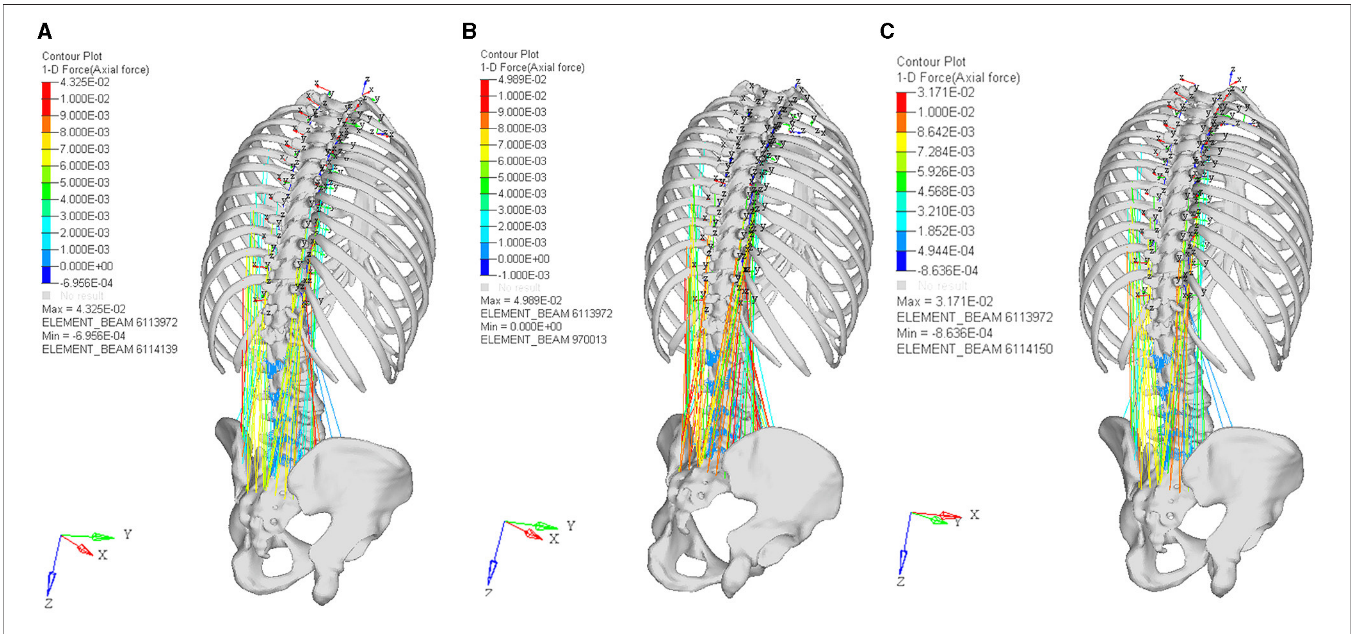

FIGURE 4 | The muscle force contribution of bending without lifting weight posture **(A)**, the bending with lifting 3-year-old child posture **(B)**, and upright with 3-year-old child posture **(C)**.

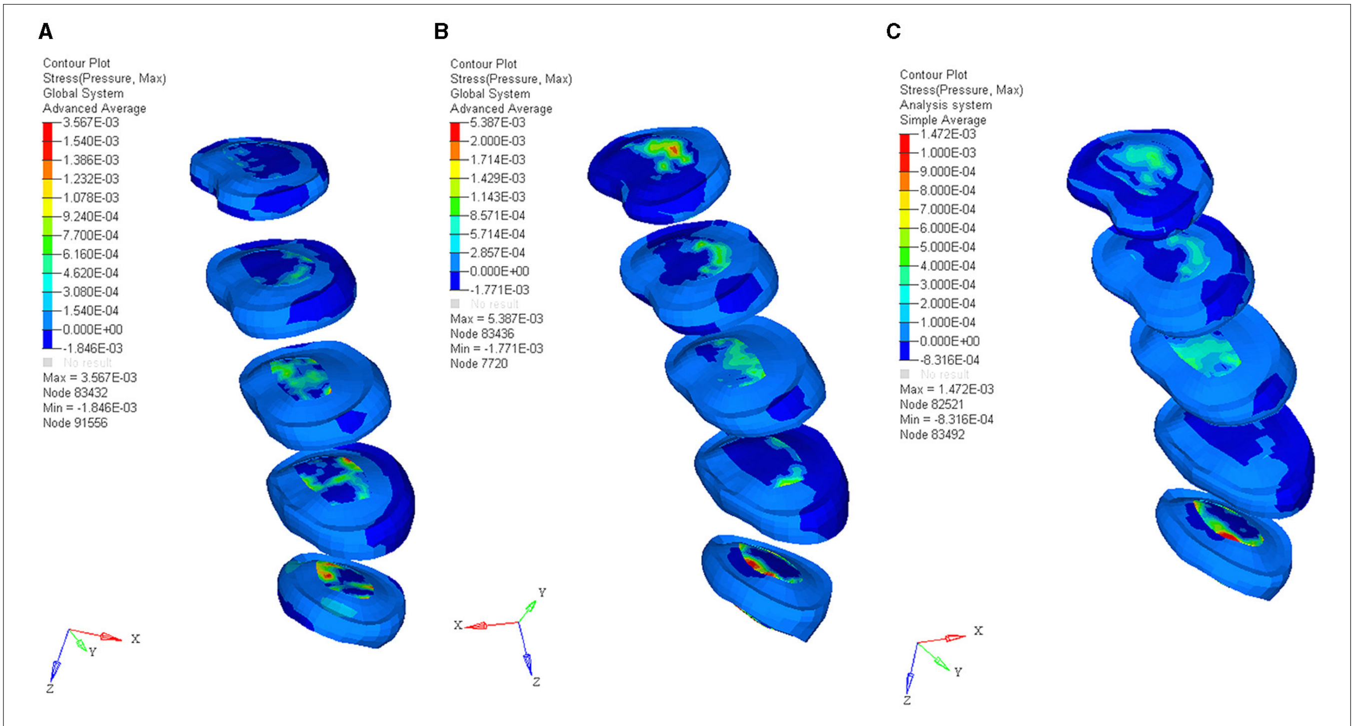

FIGURE 5 | The maximum intradiscal pressure of bending without lifting weight posture **(A)**, the bending with lifting 3-year-old child posture **(B)**, and upright with 3-year-old child posture **(C)**.

53.8 Mpa, an increase of 39.7% compared to the bending with lifting posture. In spongy bone, the cycle to failure was intimately correlated to the effective stress, according to the cycle of failure vs. and the stress curve, the cycle to failure of lumbar vertebrae spongy bone in three different postures were shown in **Table 1**.

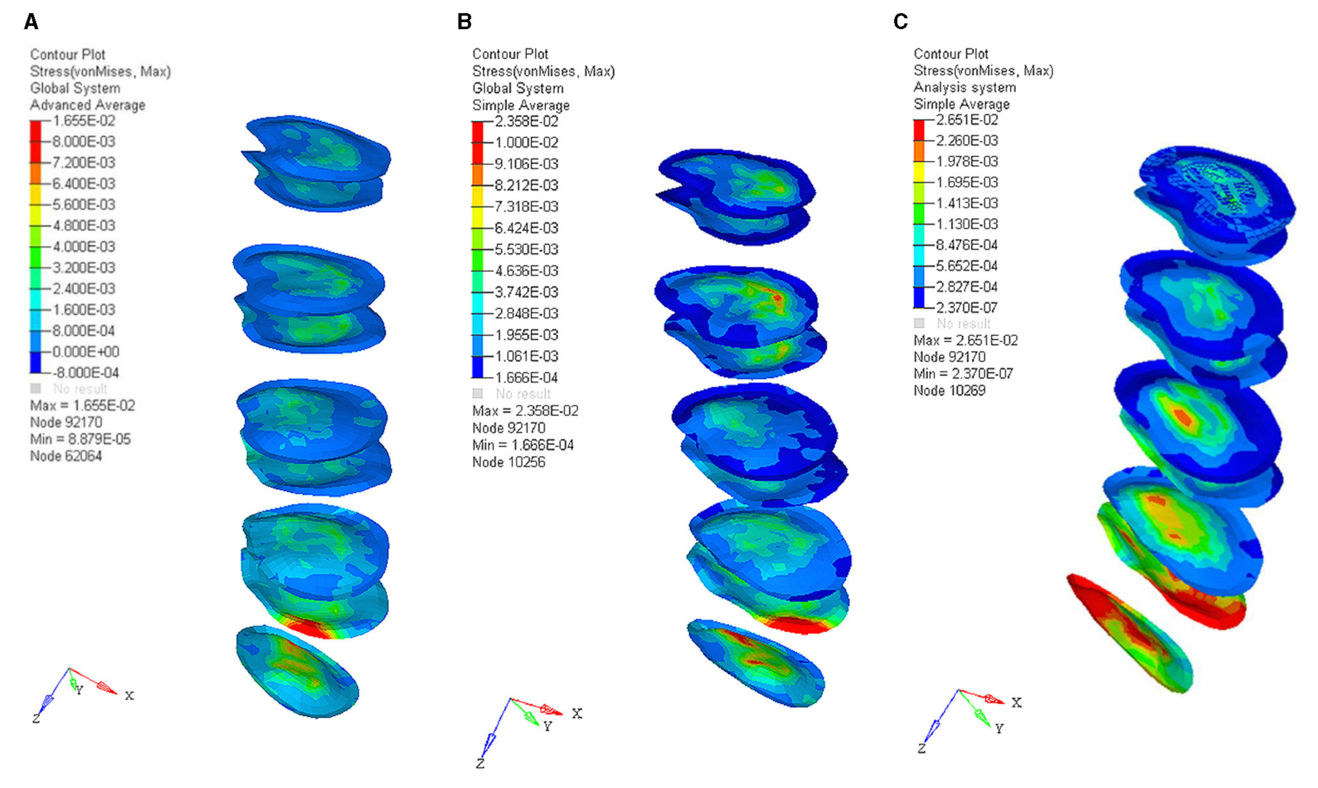

FIGURE 6 | The effective stress of endplate cartilage in bending without lifting weight posture **(A)**, the bending with lifting 3-year-old child posture **(B)**, and upright with 3-year-old child posture **(C)**.

DISCUSSION

Computer simulation could be used to better understand the mechanical and biology change *in vivo* by the prediction of the three-dimensional finite element method recently (27). To analyze the mechanical effect of the daily baby lifting motion on the Chinese elderly women, a lumbar finite element model with the unique geometry of Chinese elderly women was developed in this study. The muscle force, intradiscal pressure, and effective stress of endplate cartilage and vertebrae in three critical motion postures were calculated. In this section, we will assess mechanical change on the lumbar soft tissue degeneration and the risk of vertebrae spongy fatigue in the daily baby-lifting motion of Chinese elderly women, based on our predicted results and the previous reports.

The Mechanical Change on Soft Tissue and Relevant Lumbar Degenerations

Before and after lifting, the maximum muscle force in bending posture has no significant change, the primary tense muscles were erector spinae, psoas major, quadratus lumborum, obliquus internus abdominis, obliqus externus abdominis, and rectus abdominis. After upright with lifting of 3-year-old baby, the muscular tension of erector spinae was relaxed, the maximum muscle force was decreased 24.5%. Ekholm measured that the erector spinae tension was 3.9 kN in lifting 12.8 kg with straight knees, and decreased 20.4% compared to lifting 12.8 kg with bending posture (28). Our muscle analysis result was in good agreement with the previous lumbar loading kinematic study, which will improve the biofidelity of this FE modeling and provide a more accurate prediction to muscle kinematic response analysis.

After lifting a 3-year-old child, the calculated intradiscal pressure was 1.51 times that of the bending without lifting posture, compared to after upright with 3-year-old child posture, the calculated intradiscal pressure in bending posture with the same loading was 2.38 times that of upright posture. As Sato measured the *in vivo* volunteer introdiscal pressure in different body postures, the different postures had a significant influence on intradiscal pressure, the intradiscal pressure in bending posture was reported to be 2.45 times that of the upright posture in the same loading (29). As the increased intradiscal pressure was considered as the primary impact factor of intervertebral disc degeneration in old age population (30). Collectively, the bending posture will cause the intradiscal pressure to increase, the increased intradiscal pressure will increase the risk of lumbar degeneration, typically the elderly women who frequently lift babies in a bending posture, this bending loading-bear posture might expedite the intravertebrae disc degeneration of the elder women.

In three different postures, the maximum effective stress of endplate cartilage is both located on the upper and lower

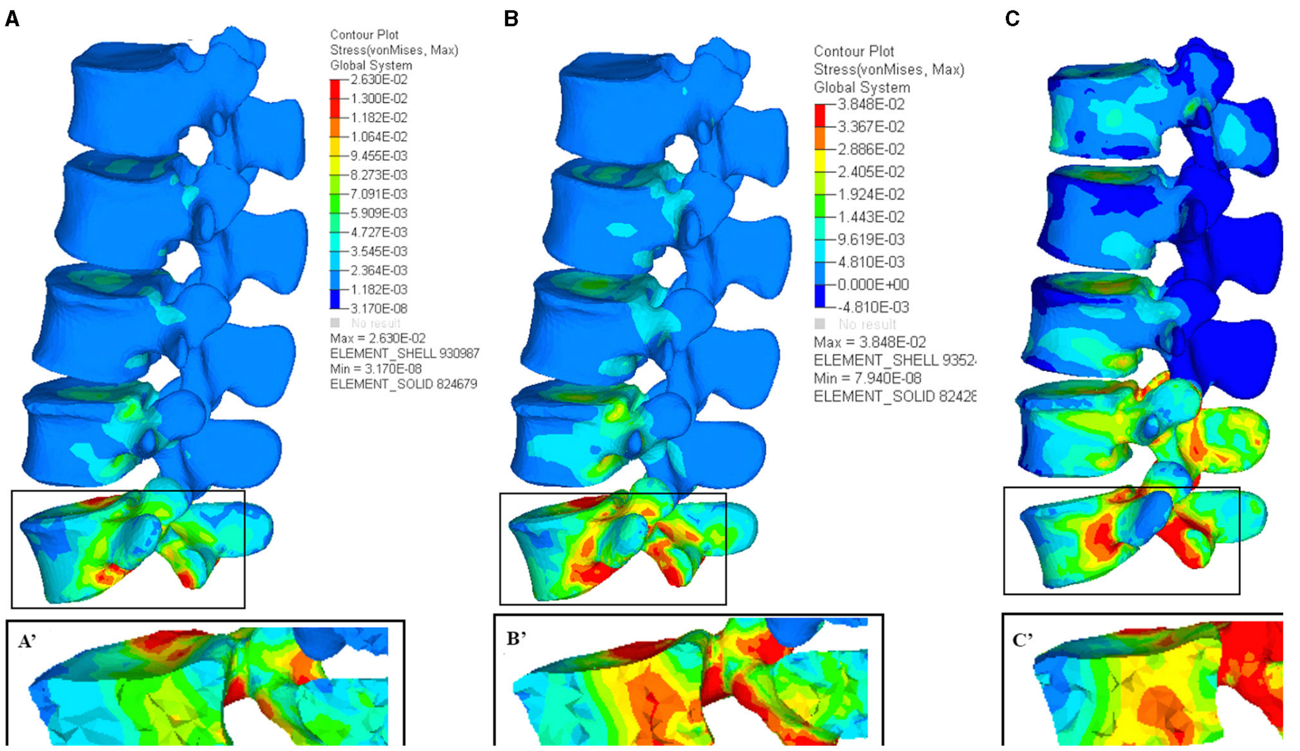

FIGURE 7 | The vertebrae effective stress contribution in bending without lifting weight posture **(A)**, the bending with lifting 3-year-old child posture **(B)**, and upright with 3-year-old child posture **(C)**, the A', B', and C' were the detailed sagittal view of spongy bone of **(A–C)** respectively.

TABLE 1 | The corresponding cycle to failure of three postures were deduced from the effective stress according to the cycle number to failure vs. the stress curve.

Posture	Maximum effective stress (Mpa)	Corresponding cycle to failure
Bending without lifting weight posture	26.3	515
Bending with lifting 3-year-old child posture	38.5	275
Upright with 3-year-old child posture	53.8	18

endplates of L5. After lifting a 3-year-old child in a bending posture, the maximum effective stress of endplate cartilage is increased to 1.42 times that of the bending without lifting posture. More incrementally, upright with lifting 3-year-old child posture, was 1.6 times that of in the bending without lifting posture. As Adams reported, the repeated increase of endplate cartilage compression will cause the change of stress contribution in adjacent intravertebrae disc, and the annulus fibrosus cell appeared metabolically abnormal (31). Taken all together, these results suggested that the cyclic lifting motion of a 3-year-old child in daily life will aggravate the degeneration of intravertebrae disc.

Fatigue Risk Caused by Mechanical Loading of Spongy Bone

Equivalent stress distribution of lumbar spongy bone: When the old woman is not lifting children, posterior vertebral pedicle of L4–L5 bears the largest force, which is 26.3 Mpa. When the old woman was bending and lifting a child, the effective stress on this part significantly increased by 44.3%. A larger increment occurred when the subject is standing upright after lifting a child and the effective stress reaches 53.8 Mpa. This is consistent with Pollintine's finding (32, 33). This change in stress suggests that when elderly women lift a child and finally reach the state of being upright, the pressure on posterior vertebral pedicle reaches its peak. After conferring to fatigue data (21), we found that in the case of bending without lifting, the fatigue limit is rather high, which is 515 times, so no obvious fatigue risk exists in this situation. The fatigue limitation frequency of the bending with lifting 3-year-old child posture is 275 times. Basically, a few risks of fatigue exist in this situation as well. In the case of upright with lifting a child, the corresponding fatigue limitation frequency of maximum load-bearing in the posterior vertebral body is low to 18 times. The result suggests that if the movements of upright and lifting a three-year-old child is done over 18 times continuously, the posterior vertebral body and pedicle spongy bone of L4–L5 will face the risk of fatigue failure.

However, it should be noted that the fatigue curves we referred to are based on *in vitro* experiments of cadaverous spongy bone. Nevertheless, the material properties of *in vivo* and *in vitro* spongy bone are different. Taylor's study found that spongy bone *in vivo* can self-repair the injury caused by stress fatigue (21). Thus it can be speculated that *in vivo* spongy bone has a higher fatigue tolerance than *in vitro* spongy bone. However, since there is no reference data about the relationship between the load-bearing of *in vivo* spongy bone and its fatigue, our calculation is based on the *in vitro* data. Therefore, the risk frequency (18 times) in this study can only be considered as a conservative reference value for the limiting frequency of the lifting child movement in elder women.

Actually, the lifting movement which our study focused on is called Knee Straight Lifting (KSL), the fracture risk of which is the highest among all common kinds of lifting movements (7). For Chinese women over 55 years old, lumbar loading is a high-risk factor for lumbar degeneration (11). Mechanical and biological factors, which were interconnected and amplified each other (34, 35), were considered the primary roles of lumbar degeneration. In this study, the lifting baby motion will accelerate the lumbar degeneration and increase the risk of fracture in the following ways: increasing intervertebral disc pressure, increasing endplate cartilage pressure, and fatigue failure of vertebral spongy bone due to the repeated loading-bear. Increasing bone strength and avoiding high-risk action are two approaches to prevent such risk. This study provides a reference for elderly women in China and East Asia, which is trying to avoid continuous straight-standing action in the daily movement of lifting children. In a word, the frequency of KSL movement especially with burden should not be too much. The experimental model and stress analysis fully considered several closely related factors: BMD degeneration (23), muscle movement (25), ligament material parameters, and patient-specific skeletal geometry of asymptomatic elderly women. The article aims to simulate the biomechanical characteristics of Chinese elderly women as accurately as possible and quantitatively analyzes the movement of lifting children, which happens frequently in Chinese elderly women. The study possesses following characteristics. First, we added the main muscles and ligaments of the waist into the model, which helps to simulate the dynamic process of lifting a child with higher biofidelity. Second, in the motion simulation, the model simulated the process of lifting a child according to the result of high-speed photography in volunteers' experiments. Thirdly, the fatigue property of vertebral spongy bone was taken into consideration. We combined the research result with fatigue curve and get the fatigue limit frequency of vertebral part bearing the most pressure and quantified the effect of such pressure on the vertebral body's fatigue failure.

CONCLUSIONS

Although China started its transformation earlier than other socialist countries, it is still undergoing social changes. Especially after the three-child policy change, more children would be left with their grandparents who have to provide support for their 8-to-6-working son or daughter, which commonly happens in China. Moreover, it is usually the responsibility of women to take care of children. And now, China is facing new ramifications from the three-child policy. More and more elderly Chinese women who act as stay-home grandchildren sitters are difficult to bear for the increasing expenditure of medical costs. The reform of medical insurance system and the process of medical privatization in China have resulted in medical treatment prices which have increased the difficulties of plenty of elderly women's capability to access healthcare. This study obtained the frequency limit of lifting child movement in the case of lumbar degeneration and put forward scientific guidance to elderly Chinese women especially for those aged over 75 years. With the deterioration of the aging problem in China and the increasing number of newborns, our study has practical significance to protect the lumbar health of elderly women.

Risk factors and mechanisms of injury-related health problems are of the most stubborn but most easily neglected issues in older Chinese people. We do hope that the multi-modal risk analysis of lumbar degeneration, fatigue, and injury based on FEM/BMD could put forward scientific injury prevention guidance to elderly Chinese women who are lifting lift children in daily life frequently, not only providing evidence for improving the health status of elderly women but also raising the women's health standard and improve the ability to prevent injury, as well as further explore the factors affecting the injury-related health problems of the elderly in China, which will also make a positive contribution to healthy aging globally.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

JS and NL contributed to the conceptualization of the study, formal analysis, and supervision. KX and XD contributed to the data curation and conceptualization. MC contributed the write-up and editing of the article. JS contributed to the supervision, conceptualization, data curation, and final version write-up. All authors have read and agreed to the published version of the manuscript.

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REVIEW
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Aging Immune System and Its Correlation With Liability to Severe Lung Complications

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Aging is considered to be a decline in physical and physiological events that extensively affect the body's immunity, and is linked with deterioration in both innate and adaptive immune responses. The immune system exhibits profound age-associated variations, known as immunosenescence, comprising a significantly low production of B and T lymphocytes in bone marrow and thymus, a decreased function of mature lymphocytes in secondary lymphoid tissues, a decrease in the synthesis of fresh naïve T cells, and reduced activation of T cells. Elderly individuals face a greater risk for many diseases particularly respiratory diseases due to their poor response to immune challenges as vigorously as the young. The current review explored the aging immune system, highlight the mortality rates of severe lung complications, such as pneumonia, COVID-19, asthma, COPD, lung cancer, IPF, and acute lung injury, and their correlation with aging immunity. This study can be helpful in better understanding the pathophysiology of aging, immune responses, and developing new approaches to improve the average age of the elderly population.

Keywords: aging immunity, immunosenescence, mortality, lung complications, lymphocytes

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INTRODUCTION

Health systems around the world are facing major challenges due to global demographic fluctuations. In both the developed and developing worlds, a reduced mortality rate has enhanced life expectancy (1). The resulting shift in age demographics necessitates innovative ways to ensure that longer life spans do not come at the cost of aging populations' life quality. The worsening impact of aging on organ and system activity, as well as the intrinsic and extrinsic elements of the environment that influence the progression of this deterioration, must all be considered in new approaches (2). Aging is marked by a decline in physical as well as physiological events that considerably affect the body's defense system. The immune system undergoes a variety of changes with advancing age, eventually losing the ability to mount an effective cellular defense against infection (3). Immunosenescence is a multifactorial phenomenon that affects both arms of the immune system and can be greatly affected by genetic factors as well as extrinsic factors like food, physical activities, co-morbidities, physical and mental stress, prior exposure to microorganisms, toxins, and prescribed medications (4–7).

Research continues to discover approaches to overcoming age-related declines in immunity. Novel approaches to specifically target the immune system as well as geroscience-directed approaches, which target the underlying causes of aging, should provide us with exciting new therapies to extend the healthspan of older adults. Several approaches are already in use or are undergoing testing. First, vaccines specifically formulated for older adults are now available and have been shown to provide greater protection from viral infections such as influenza (8). These vaccines have higher concentrations of antigen or are formulated with adjuvants to boost aging immune responses (8). Second, approaches that alter metabolic activities such as treatment with metformin (9) or mTOR inhibitors (10) could help improve immunity and resistance to infectious diseases in older adults. Last, senolytics, which are a novel class of drugs that target the destruction of senescent cells, have been shown to alleviate age-related diseases in animal models and could also improve aged immune function (11).

AGING AND ADAPTIVE IMMUNITY

The adaptive immune system deteriorates rapidly with age and is the most common problem among the elderly. Immunity relies on T and B cells producing a vast repertoire of antigen receptors, followed by activation and clonal proliferation (12). The stimulation of adaptive immunity is dependent not only on the identification of a specific antigen receptor but also on key signals provided by the innate immune system. The decrease of *de-novo* production of T and B cells is a well-known age-associated immune system modification (13).

B lymphocytes' principal purpose is to produce specific antibodies against a specific pathogen's infection. The B cell arm of the adaptive immune system undergoes considerable changes with aging (14). Delayed B cell responses and ineffective antibodies generation are common in aging individuals, resulting in a diminished capacity to efficiently respond to viral and bacterial pathogens (15). According to the reported studies, the formation of antibodies in response to vaccination against hepatitis B virus infection was considerably lower in 61-year-old donors compared to 33-year-old donors (16). The population of memory B lymphocytes IgG^+ IgD^- $CD27^-$, double negative, DN increases in the aged people with a characteristic inflammatory microenvironment. IgG^+ IgD^- $CD27^-$ DN B cells, particularly, have a tissue trafficking phenotype and can be induced to generate granzyme-B. DN cells are believed to be exhausted B cells that produce high levels of inflammatory cytokines, such as TNF-α, IL-1, and IL-6. Increased systemic levels of pro-inflammatory cytokines are associated with aging. Multiple studies have found a chronic mild inflammation in aging, described as "inflame-aging," which may enhance age-related complications (17).

T cells are considered to be one of the main constituents of the adaptive immune system. T cells play a crucial role in devastating infected host cells, triggering other immune cells, generating cytokines, and regulating immune reactions. In the context of major histocompatibility complex (MHC), these cells can be separated into CD4 and CD8 detecting antigens (15). Regression of the thymus (age-associated) has been linked with the decreased production of naïve T cells. The underlined phenomenon may results in the decreased T cell diversity in aged people that lead to the higher susceptibility to autoimmune diseases and infectious disorders (18). With increasing age, chronic antigenic load and oxidative stress lower the vulnerability of lymphocytes to damage-induced cell death and raise proinflammatory state, resulting in greater activation of induced-cell death (19). The lymphocyte composition and function in secondary lymphoid tissues can be influenced by a variety of age-associated alterations. $CD4^+$ Th cells show greater conversion into Th17 cells. Furthermore, older $CD4^+$ Th cells have been observed with several activation abnormalities. In humans, $CD8^+$ T cells expand oligoclonally and lose CD28, resulting in poor function. Antibody avidity in response to carbohydrate antigens is lowered, and the number of B cells that act against influenza is reduced. Inflammatory cytokines, which may be produced by stroma, dendritic cells (DCs), or aged B and T lymphocytes are also present in higher concentrations in the tissue microenvironment (20). The elevated number of memory cells occupying tissue niches, as well as the inflammatory site, may make it more difficult to migrate naive B and T cells from the thymus and bone marrow to settle in the tissue. Hence, an increase in memory T cells that have lost CD28 expression is associated with a decrease in immunity which is thought to be a key feature of senescent T cells. *In vitro* experiments have shown that loss of telomerase activity occurs concurrently with loss of CD28 expression in T cells, indicating that CD28 signaling is required for optimal telomerase up-regulation. Senescent cells frequently change their gene expression, making them less prone to apoptosis, and many secrete molecular factors like cytokines, which influence their microenvironment (21). The immune function of aged individuals is weakened as a result of the underlined alterations as represented in **Figure 1**.

Furthermore, **Figure 2** revealed that primary lymphoid organ degeneration reduces the production of naive B and T cells, resulting in decreased migration to antigen encounter regions and secondary lymphoid organs. In addition, proinflammatory mediators can accumulate in the lungs and extrapulmonary organs (22).

AGING AND INNATE IMMUNITY

The host's initial line of defense against infectious diseases is the innate immune system (24). Neutrophils, natural killer (NK) and natural killer T (NKT) cells, monocytes/macrophages, and DCs are all part of the innate immune system, which mediates the first interactions with pathogens. These types of cells have age-related defects in their activation, which are associated with compromised signal transduction cascades, such as the Toll-like Receptors (TLRs) (25). Multiple studies suggested that aging has a deleterious impact on the functions of innate immunity (26). Moreover, in non-healthy aged individuals, innate immunity is considerably weakened, and this impairment makes a significant contribution to a decline in overall immune responses as well as increased morbidity and mortality in the elderly due to infections (27). According to several studies in human and animal models, TLR expression and function decrease with age. In aged DCs, mitochondrial membrane potential, ATP turnover and coupling

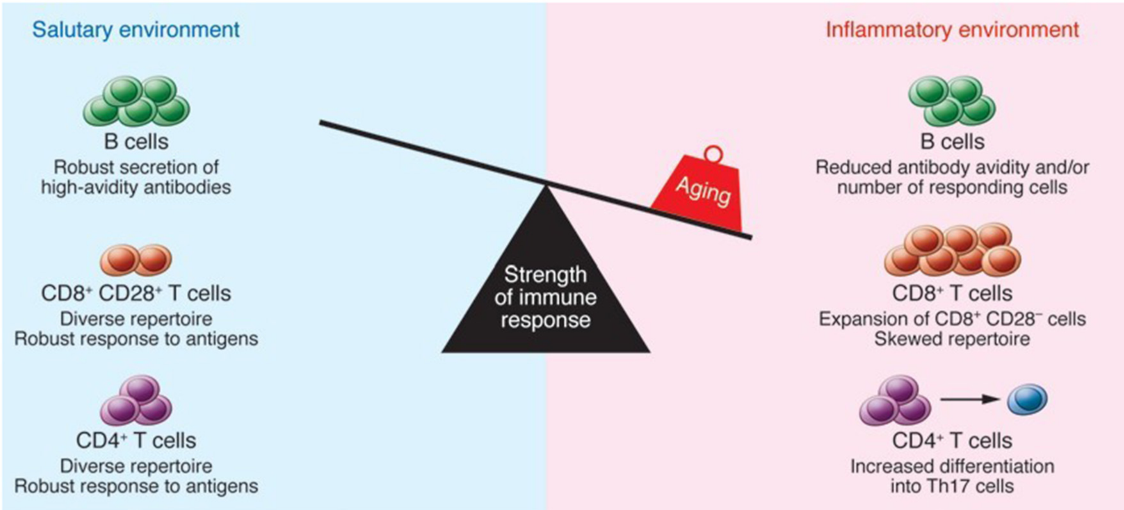

FIGURE 1 | The impact of aging on immune function. Reproduced with permission from Montecino-Rodriguez et al. (22).

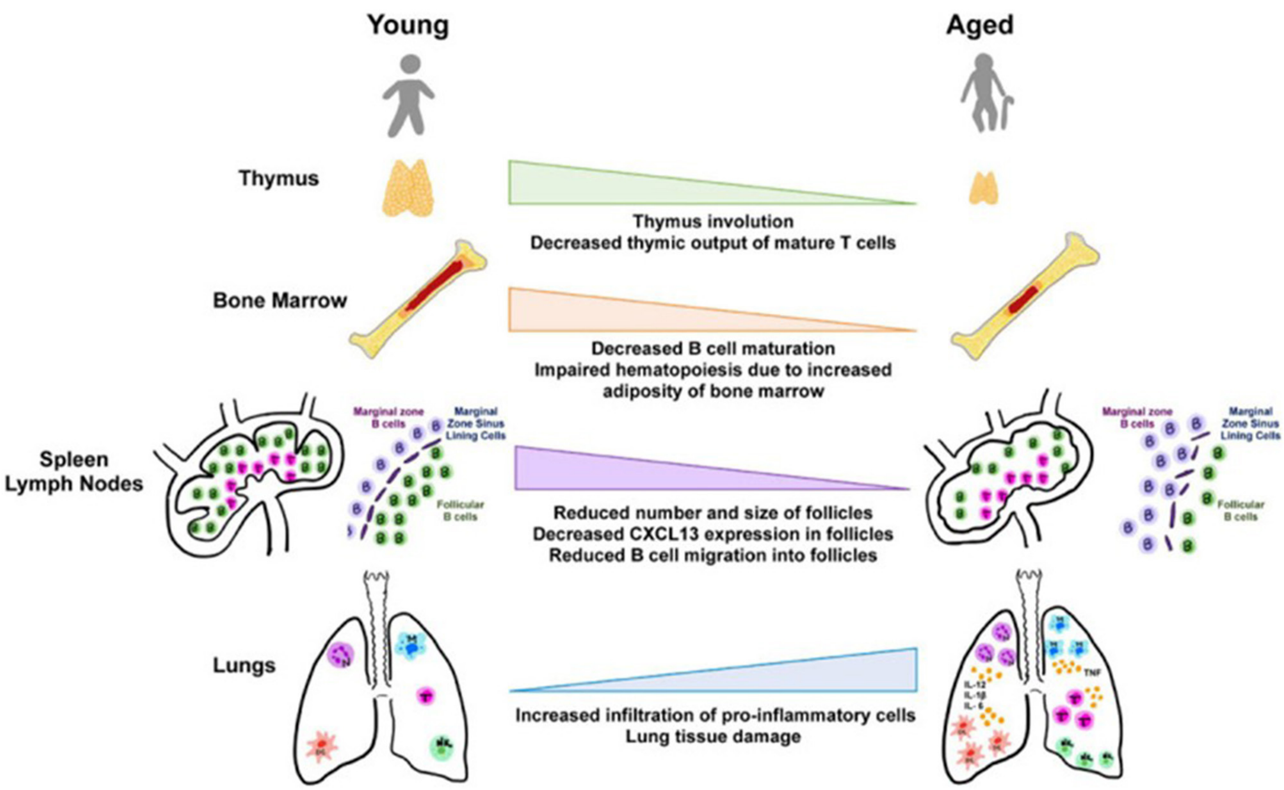

FIGURE 2 | Aging and tissues in immunity (23).

efficiency, and baseline oxidative phosphorylation were found to be decreased. Moreover, an increase in proton leak and reactive oxygen species (ROS) production were observed in aged DCs (16). Hence, DC appears to be functionally impaired in aging when it comes to antigen uptake, and phagocytosis of apoptotic cells. Other DC elements that change with age are associated with TLR function (inappropriate persistence of TLR activation in specific systems), antigen processing, and cell migration, which is linked to a change in the phosphoinositide 3 kinase pathway (28). Interleukin (IL)-15 interferon-alpha (INF-α) and tumor necrosis factor alpha (TNF-α) levels have also been found to be lowered in aged people. Furthermore, a study demonstrated that older mice's DCs have an inadequate ability to stimulate $CD8^{+}$ T cells (29). Reduced TNF- production and lower DC maturation have been linked to impaired influenza-specific $CD8^{+}$ T cell response in elderly people. While neutrophils and macrophages are phagocytic cells of first-line defense, their phagocytic functions diminish with advanced aging which contributes to chronic low-grade inflammation and dysregulation of macrophage-mediated immunosuppression. Because of the constant activation of the PI3K cascade in older people, neutrophils migrate incorrectly and spread further in response to stimuli, have lower phagocytosis, and have lower intracellular killing activity. Impaired anti-apoptotic responses to GM-CSF facilitated by JAK-STAT tyrosine kinase and PI3K-AKT cascades are the primary causes of age-related defects in neutrophils (30). The aged non-hematopoietic environment plays a key role in NK cell maturation and function. Increased reactivation rates of latent Mycobacterium tuberculosis, decreased inflammatory responses, and an increase in bacterial and fungal infections are all linked to changes in NK cell biology that occur with human aging (16).

In view of these facts, studies of the innate immune system in aged individuals who are not influenced by systemic diseases that could affect the immune system, as well as studies that use medications that could interfere with immunological parameters, could provide information primarily on the intrinsic impact of aging on immune responses (31). In contrast, studies on unhealthy elderly people with extrinsic factors like chronic infections, cancer, malnutrition, inflammatory diseases, and neurological conditions are biased. However, studies on innate immunity should be encouraged not only in healthy elderly but also in unhealthy and frail elderly people, as these people are at a higher risk of infection and related complications (32). Since innate immunity is the first line of defense against pathogens, increasing innate immunity in the elderly could be a viable option for fighting infection and improving the quality of life, providing that inflammatory diseases are not exacerbated (33).

LUNG COMPLICATIONS AND THEIR MORTALITY RATES WITH RESPECT TO AGE

Pneumonia

Pneumonia is an infection that causes inflammation of one or both lungs. The lungs are comprised of small sacs known as alveoli which are the primary site of gaseous exchange. When a healthy person breathes, their alveoli are filled with air, but in individuals suffering from pneumonia, the alveoli are filled with fluid and pus which results in breathing difficulty due to a limited amount of oxygen (22, 34). TLR4 expression, which is important for the response to *Streptococcus pneumoniae*, is lower in the elderly and during infection. In mice, aging has been shown to decrease CD8 T-cell diversity as well as the immune response to influenza virus infection. The number of naive and memory T-cells decreases as people age (35).

More than 2,000 patients (aged $\geq$ 65 years) were analyzed by Conte et al., which revealed that age $\geq$ 85 years was considerably linked with an increased mortality rate (2, 36). In Europe, death rates for pneumonia were considerably elevated in children (up to the age of four) and adults (aged 75 and over) relative to other age groups. Pneumonia mortality rates were greater among the elderly in Western Europe (279 deaths per 100,000 people) (3). A study reported in 2017 revealed an elevated mortality rate among aged people (70 and older) suffering from pneumonia and in this age group, around 261 patients (out of 100,000 people) were died due to pneumonia, as indicated in **Figure 3**.

Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a deadly lung disease with unknown reasons. IPF is an irreversible disease that is considerably associated with aging. The mechanism regarding IPF pathogenesis is not clearly understood and up to date, there is no specific treatment for this disease (37).

Among the elderly population, the quality of life was decreased in patients suffering from IPF. Moreover, the reported studies have also been indicated that in aged people, the majority of IPF patients suffer from comorbidities (38). IPF is characterized by abnormal activation of alveolar epithelial cells, fibroblasts and myofibroblasts accumulation, and excessive extracellular matrix (ECM) formation (39). Furthermore, telomeres in lung epithelia and peripheral blood cells are shortened in patients with IPF. Programmed cell arrest (senescence) and apoptosis occur when telomeres reach a critical length. Patients with IPF have abnormal cellular senescence, particularly in bone marrow-derived stem cells including fibrocytes (40).

Reported studies have been revealed that aging immunity considerably contributes in the progression of fibrosis. Macrophages, both alveolar and interstitial can develop fibrosis-modifying features in response to exposure with pathogen-associated molecular patterns or danger-associated molecular patterns, or activation with different mediators and results in the production of TGFβ1and soluble mediators that cause accumulation and activation of fibroblasts, generation of TIMPS, and MMPS which involved in the remodeling of ECM, formation of angiogenic factors, secretion of lipid mediators, and regulation of stem cell renewal and structural cell injury. Neutrophils produce NE, TIMPS, and MMPs, which determine whether ECM aggregates or degrades. Neutrophils also play a role in the creation of neutrophil extracellular traps, which may induce fibrosis by releasing TGF1 and activating myofibroblasts. Circulating fibrocytes are mesenchymal cells generated from bone marrow that enter the lungs through the bloodstream. They perform a variety of functions in the lung, including differentiation into myofibroblasts and fibroblasts, ECM formation, wound contraction, antigen presentation, production of cytokines and chemokines, and production of soluble mediators regulate the angiogenesis-related pathways. Immunosuppressive cells known as myeloid-derived suppressor cells (MDSC, blue) have been linked to ECM remodeling and pulmonary hypertension. Innate lymphoid cells secrete cytokines that may play a role in the regulation of fibroblast accumulation

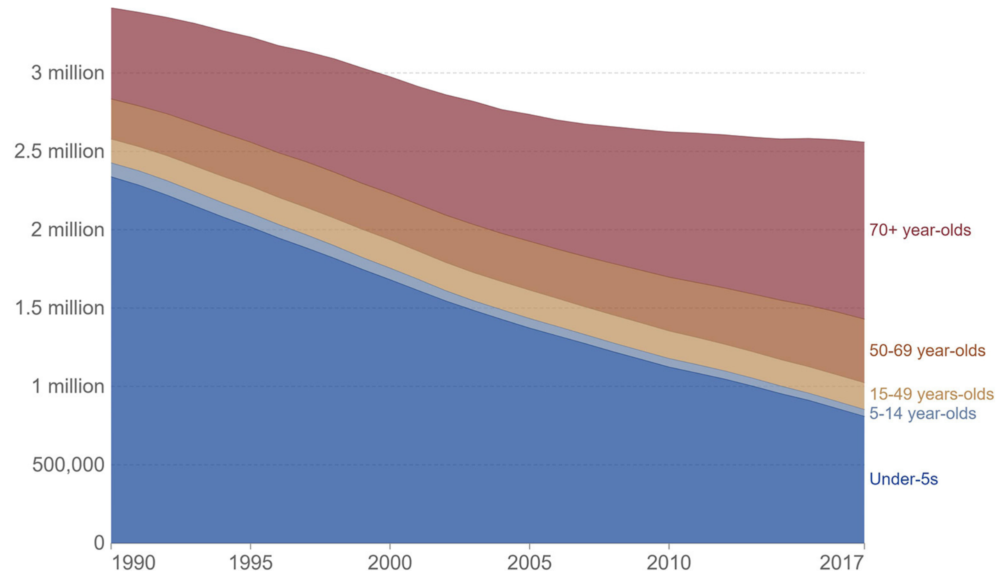

FIGURE 3 | IHME, global burden of disease study (GBD), OurWorldInData.org/pneumonia.

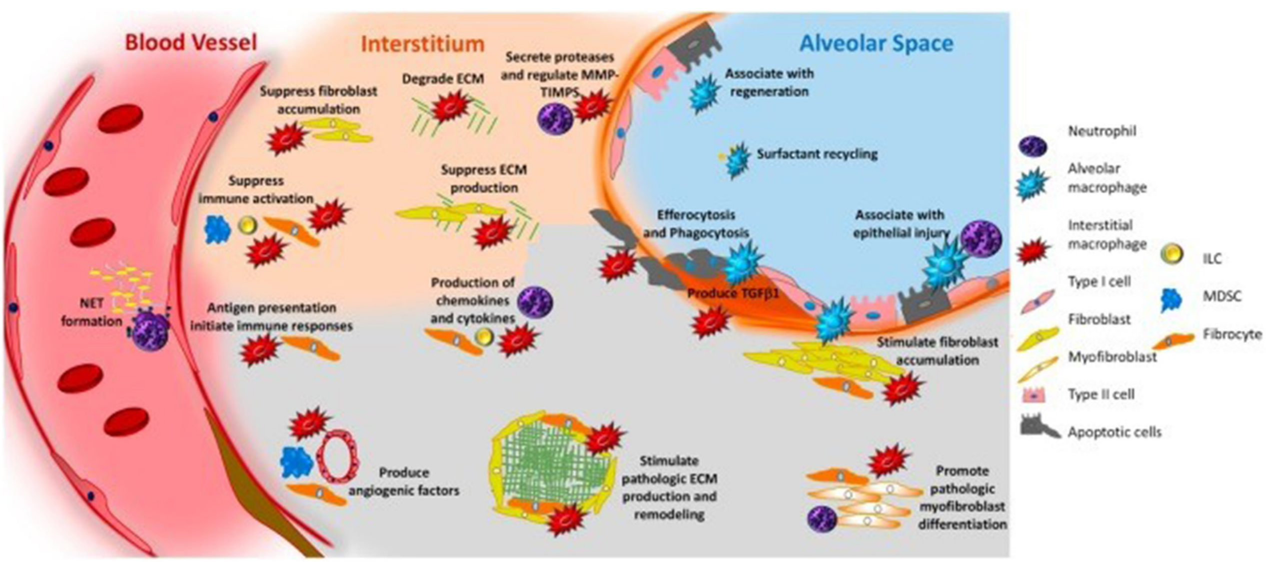

FIGURE 4 | Immune system and pulmonary fibrosis (41).

and ECM formation. In **Figure 4**, the roles of each cell are displayed in a typeface that matches the cell's color.

Furthermore, IPF is linked to a poor prognosis, while the mortality rates of patients associated with IPF rise with aging and are substantially greater in males than in women (42). According to the reported survey, the estimated mean survival rate for IPF was determined to be 2–5 years from the time of diagnosis (43). Men died at a rate of 64.3 deaths per million, while women died at a rate of 58.4 deaths per million (44).

Coronavirus Disease-2019 (COVID-19)

The COVID-19 pandemic, caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARSCoV2), had wreaked havoc on the world as of early December 2020, with more than 72 million morbidities and 1.6 million deaths. The aged group has a disproportionately high number of illnesses and deaths. Several cases of pneumonia with unclear etiology were reported in Hubei, China in December 2019, and were later identified as COVID-19 caused by SARS-CoV-2. The virus uses angiotensin-converting enzyme 2 (ACE2) receptors to enter the body. ACE2 is a part of the renin-angiotensin-aldosterone system and is expressed in the lower respiratory tract along the alveolar epithelium. The reported studies have revealed that aging has been linked to a decrease in ACE2 expression. A reduction in ACE2 receptor expression, in combination with aging-related immune inflammation and comorbidities, may compromise the anti-inflammatory response and predispose older people to enhance inflammatory responses, which is one of COVID-19's hallmarks (45). Aging impairs immune cell migration and signaling downstream of pattern recognition receptors (PRR) activation, resulting in increased cytokine secretion and dysregulation. In innate immune cells, age-related changes in TLR protein expression can trigger the production of cytokines. An elevated level of cytokines reflects high basal TLR activation, which cannot be further activated in response to a pathogen, resulting in innate immune response failure (46). Because IFN production is impaired in COVID-19 patients, there is an imbalance between pro-inflammatory and pro-repair airway macrophages. Antigen-presenting cells become functionally impaired as a result of age-related reductions in IL-12 production by DCs and changes in the microenvironment caused by changes in the splenic marginal zones (47). Changes in the pulmonary microenvironment affect DC maturation and migration to lymphoid organs, affecting T cell activation in COVID-19 patients (45).

There were no noticeable variations in viral load between symptomatic and asymptomatic individuals (7), resulting in global dissemination and an underestimated death ratio (4). Furthermore, the virus affects people of all ages, but those with co-morbidities or who are older have a significantly higher rate of morbidity and mortality (5, 6). Patients with co-morbidities of Ischemic Heart Disease, hypertension, and diabetes had increased odds of fatal cases in China, according to an analysis of fatal cases. However, no evidence of a greater risk among pregnant women has been found (12). According to the literature, the death rate among hospitalized patients was 15%, with an average time from onset of symptoms to death of 14 days (13). Based on the data collected from Italy and China, Corona patients have a mortality rate of 2.3%, with more than half of the mortality reported in patients with age 50 years or older (14). Case mortality was 36% in patients at an age of 64 years or older in the largest published series from Northern Italy (15). The global mortality rate from COVID-19 approaches 15% at age 80 (48), as represented in **Figure 5**. In the given figure, the rat**e** of mortality was calculated by the following formula;

$$\text{Mortality rate} = (\text{number of deaths/number of cases}) = \text{probability of dying if infected by the virus} (\%).$$

Asthma

Asthma is the most common disease which affects around 300 million people (all age groups) across the globe. However, the diagnosis, as well as management of asthma is very difficult in aged people because of physiological and immunological variations associated with age (17). In spite of recent considerable enhancements in the treatment of asthma, there is still a need for further improvement in care and patient outcomes, especially in elderly patients suffering from asthma. Elderly individuals in their middle years have the highest incidence, yet, the mortality ratio is higher in the elderly. The underlying pathophysiology of asthma in older individuals, as well as the best ways to treat it, have long been disregarded. Aged asthma patients have the highest rates of morbidity and mortality, as described in **Figure 6**. The etiology of asthma in older adults is complicated since it is influenced by decline immune functions associated with aging as well as changes in inflammation (18).

In 2015, 3,615 people (10 people/day) were died because of asthma in the united states. The death rate has been elevated in the elderly, as depicted in **Figure 7** and as people get older, their chances of dying from asthma rises because they are probably misdiagnosed, undertreated, and are managing several health complications with a weak immunity (52).

The mechanism underlying asthma is unknown. However, it has been suggested that it may occur as a result of viral infection that promotes persistent inflammatory change when coupled with the effects of immunosenescence. Antibody production may be decreased in the aged, resulting in elevated antigen persistence and specificity. T-cell population shifts, varied B-cell antigen processing, and eosinophil function coupled with a decrease in phagocytic potentials are all caused by thymic involution and all these events contribute to a distinct immunological environment in older asthmatic patients (53). Furthermore, T-cells activation has been elevated in the elderly, with overexpression of human leukocyte antigen (HLA-) DR and CD69. An elevation in airway neutrophils has also been seen in older asthma patients, implying that asthmatic phenotypes varied as people age. These findings suggest a possible link between immunosenescence and asthma. However, this relationship has not yet been fully established (54).

Chronic Obstructive Pulmonary Disease (COPD)

COPD is a chronic respiratory condition marked by persistent respiratory symptoms and restricted airflow. COPD has a significant influence on public health, owing to its rising prevalence, morbidity, and mortality rates (55). COPD's prevalence and burden are likely to rise in the next decades as a result of ongoing exposure to risk factors and the global population's aging, and it is expected to become the world's third leading cause of death by 2020 (56, 57). COPD morbidity and mortality rates are higher as people get older. The morphological and functional resistance of the respiratory system deteriorates with age, resulting to a rise in morbidity. Individuals aged 60–79 years have a higher rate of respiratory morbidity and a lower FEV1/FVC ratio, according to the European Lung White Book (58).

The lung function of approximately 10,000 participants was examined in the Burden of Obstructive Lung Disease (BOLD) study (59). Spirometry testing, as well as questionnaires regarding respiratory symptoms, health status, and exposure to COPD risk factors, were used in the BOLD project to assess the prevalence of COPD. BOLD estimated that 10% of adults aged 40 and over in 12 nations (including Australia, China, Turkey, Iceland, Germany, the United States, and Canada) have COPD. As shown

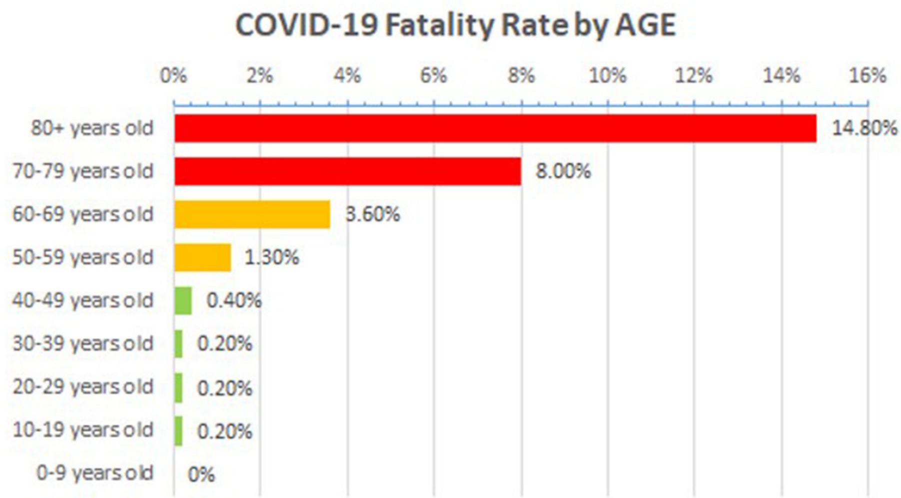

FIGURE 5 | Age-associated mortality rate in COVID-19 patients across the globe, Source data: https://www.worldometers.info/coronavirus/coronavirus-age-sex-demographics/ (accessed March 13, 2020).

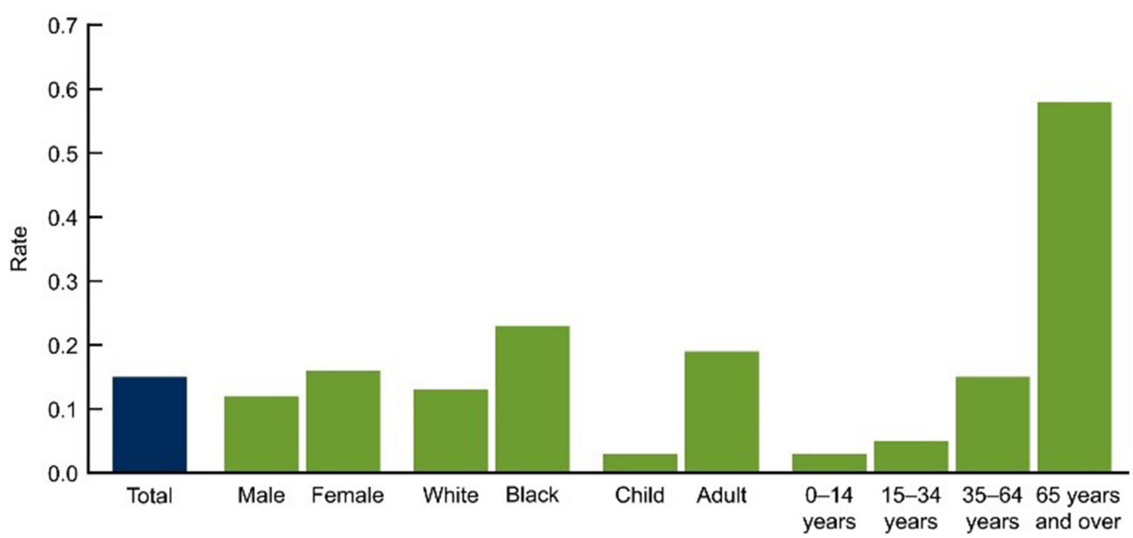

FIGURE 6 | Asthma deaths per 1,000 by demographic (2007–2009) (49). CDC/NCHS, National Vital Statistics System, and National Health Interview Survey Data for table available online at: http://www.cdc.gov/nchs/products/databriefs/db94.htm.

in **Figure 8**, the COPD prevalence was found to be 7.5% for those aged 40 and over and 30 percent for people aged 75 and over in later research conducted in Australia using a technique that closely resembled that employed in the worldwide BOLD study (60).

There is evidence that aging and COPD have multiple pathways and processes in common. Individuals with COPD have a suppressed innate immune system, making them more susceptible to infections and malignancies (61). Aging is linked to diminished epithelial barrier function (62), cilia structure and function defects (63), and reduced generation of antimicrobial and anti-inflammatory peptides by epithelial cells, such as SLPI (64). Elevated numbers of phagocytes, such as macrophages, monocytes, and neutrophils, are linked to both COPD and aging. There is also a decrease in host defensive mechanisms such as macrophage phagocytosis, inefficient chemotaxis, diminished neutrophil bactericidal function, and altered dendritic and natural killer cell capabilities. Inflamm-aging is commonly linked to immunosuppression and low-grade inflammation (65). Subsequent inflammation develops when secondary lung infection occurs as a result of a weakened host response (66). Immunosenescence promotes telomere shortening in COPD

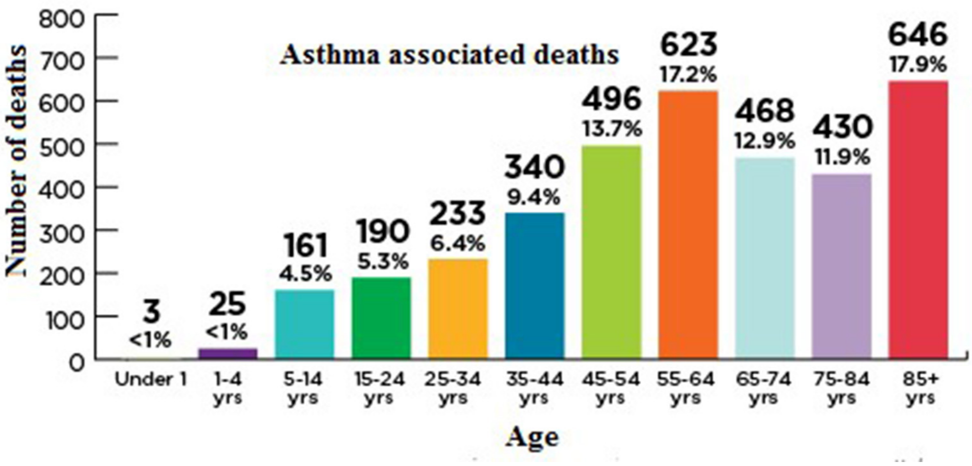

FIGURE 7 | Age-associated mortality rate in asthma patients. Asthma and Allergy Foundation of America asthmacapitals.com.

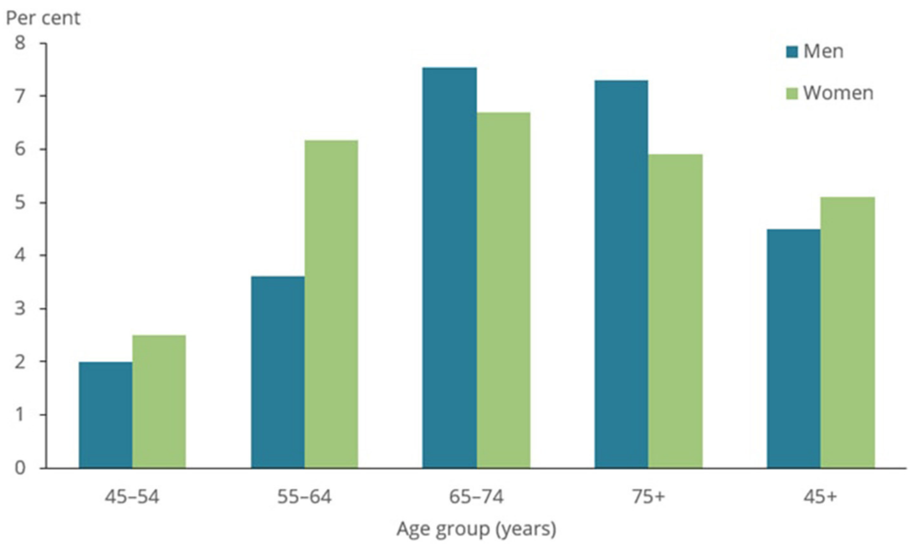

FIGURE 8 | Prevalence of COPD among people aged 45 and over, by sex and age group, 2017–18 (50).

patients' leukocytes regardless of smoking status, as well as an increase in inflammatory markers, suggesting that disease-specific variables may contribute to immune cells' premature aging (67).

Lung Cancer

Lung cancer is a deadly respiratory disease that mostly affects older people. Around 50% of lung cancer has been diagnosed in patients aged ≥70 years while around 14% has been observed in patients older than 80. Physiological as well as medical features of elderly patients (suffering from cancer) make the choice of their better treatment more challenging. As discussed in the above respiratory complications, the increasing incidence of lung cancer is also significantly linked with the age-associated decline in immune functions. NSCLC (Non–small cell lung cancer) is the most common form of lung cancer, accounting for around 85% of cases (68). Lung cancer incidence and prevalence have increased in the elderly population, demonstrating a link between aging and the development of cancer. Oncogenes become more active and tumor suppressor genes become inactive when cells are damaged by either free radicals or viruses (69). Age-related immune adaptations play a role in the development of cancer. The immune stimulation of T-cells by DCs, for example, is critical for their activation under normal circumstances, but this is altered as people age. The link between T-cell immunosenescence and terminal differentiation, as well as the decrease in circulating naive $CD8^+$ lymphocytes in senescent patients, suggests that the immune system's ability to respond to tumor antigenic diversity and emerging neoantigens may be impaired in T-cell immunosenescence (69). TLR signaling becomes less effective as

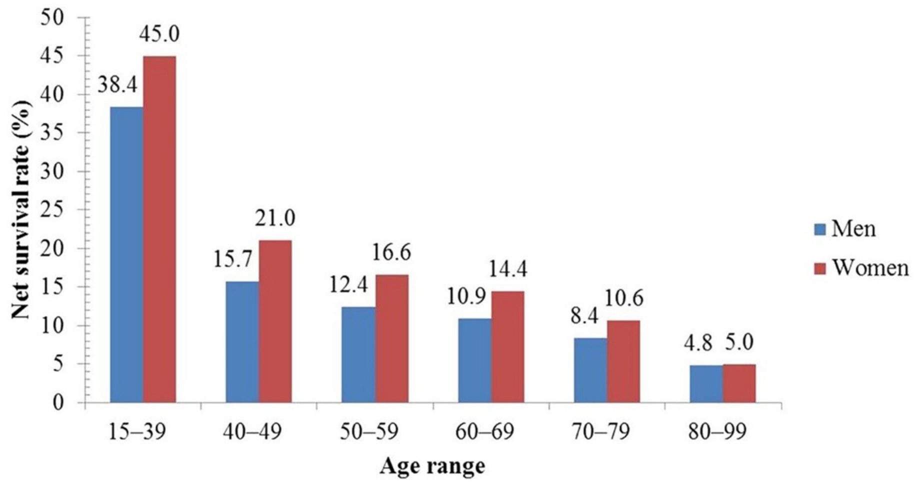

FIGURE 9 | Five-year net survival rate of lung cancer patients by age in the UK (51).

people get older, resulting in a variety of abnormal responses and phagocytic dysfunction. Ineffective neutrophil and macrophage function in the elderly also contributes to the development and progression of tumors (70).

Reported studies revealed that < 0.5% of deaths (associated with lung cancer) occur at an age < 40 years (71) while an elevated rate of incidence has been reported elderly population. In the UK (United Kingdom), each year around 6 in 10 cases (61%) of lung cancer are diagnosed in people aged ≥70 years (72). Up to the age of 39, both men and women have a 0.03% chance of having lung cancer (71). The incidence rates begin to rise sharply at the age of 45–49, peaking in the male and female age groups of 85–89 and 80–84, accordingly. In the US, the median age of diagnosis is 70 years, and 68% of patients are diagnosed after the age of 65 (71) and 14% of lung cancers are detected in individuals over the age of 80 (71). Another study from the UK found that between 2007 and 2011, the 5-year age-standardized net survival rates for males with lung cancer lowered from 38.4 to 4.8%, and for women from 45.0 to 5.0%, as shown in **Figure 9**. This study revealed that 5-year survival (in lung cancer) is elevated in the youngest men and women and diminishes with increasing age (51, 73).

CONCLUSIONS

The findings we summed up in the current review revealed that aging hallmarks are the key variables associated with the high mortality rates of severe respiratory diseases, such as pneumonia, coronavirus infection, asthma, COPD, lung cancer, IPF, and acute lung injury. These accumulating evidences also suggest that age is a cause of many diseases. Our study will help the future research of physiological variations that occur with age and, more importantly, their impact on respiratory illnesses that are the major cause of morbidity and mortality in the elderly.

AUTHOR CONTRIBUTIONS

MP: review design. YL: data collection. CW: draft manuscript preparation. All authors reviewed and approved the final version of the manuscript.

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Determinants of Urinary Incontinence and Subtypes Among the Elderly in Nursing Homes

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Urinary incontinence (UI) is a common problem among older adults. This study investigated the prevalence of UI in nursing home residents aged ≥75 years in China and examined potential risk factors associated with UI and its subtypes. Data were collected during face-to-face interviews using a general questionnaire, the International Consultation Incontinence Questionnaire Short-Form, and the Barthel Index. A total of 551 participants aged ≥75 years residing in Changsha city were enrolled from June to December 2018. The UI prevalence rate among nursing home residents aged ≥75 years was 24.3%. The most frequent subtype was mixed (M) UI (38.1%), followed by urge (U) UI (35.1%), stress (S) UI (11.9%), and other types (14.9%). In terms of severity, 57.5% had moderate UI, while 35.1% had mild and 7.5% had severe UI. Constipation, immobility, wheelchair use, cardiovascular disease (CVD), and pelvic or spinal surgery were significant risk factors for UI. Participants with a history of surgery had higher risks of SUI (odds ratio [OR] = 4.87, 95% confidence interval [CI]: 1.55–15.30) and UUI (OR = 1.97, 95% CI: 1.05–3.71), those who were immobile or used a wheelchair had higher rates of MUI (OR = 11.07, 95% CI: 4.19–29.28; OR = 3.36, 95% CI: 1.16–9.78) and other UI types (OR = 7.89, 95% CI: 1.99–31.30; OR = 14.90, 95% CI: 4.88–45.50), those with CVD had a higher rate of UUI (OR = 2.25, 95% CI: 1.17–4.34), and those with diabetes had a higher risk of UUI (OR = 2.250, 95% CI: 1.14–4.44). Use of oral antithrombotic agents increased UUI risk (OR = 4.98, 95% CI: 2.10–11.85) whereas sedative hypnotic drug use was associated with a higher risk of MUI (OR = 3.62, 95% CI: 1.25–10.45). Each UI subtype has distinct risk factors, and elderly residents of nursing homes with a history of CVD and pelvic or spinal surgery who experience constipation should be closely monitored. Reducing time spent in bed and engaging in active rehabilitation including walking and muscle strengthening may aid in UI prevention and treatment.

Keywords: urinary incontinence, geriatric, older adult, elderly population, prevalence, risk factor, nursing home, subtype

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INTRODUCTION

Urinary incontinence (UI) is defined by International Continence Society (ICS) as complaint of involuntary loss of urine (1). It's common in elderly patients and usually play a major role in independent person in the community or dependent person in the nursing home (2, 3). UI affects nearly 40% of women aged 80 years and older, 10–35% of older men, and up to 80% of long-term care residents and can severely impair an individual's quality of life (QoL) (4, 5) because of the associated hygiene and social problems (6). Therefore, healthcare providers need to demonstrate sensitivity in evaluating and discussing UI, particularly with older adults.

There are three major subtypes of UI—urge (U), stress (S), and mixed (M)—which have different risk factors and etiologies (7). UUI and SUI are the most common subtypes in older persons, while MUI is the combination of both types (8). UI is a risk factor for mortality in the elderly (9–11) and is closely related to declines in cognitive function and performance of activities of daily living (ADL) as well as age, obesity, diabetes, loss of independence, depression and anxiety levels, and agitation (8, 11–14). It is important to clarify the association between UI and cardiovascular risk factors through screening (14) to prevent the development of cardiovascular disease (CVD). However, there is little known about the prevalence of UI in the elderly population of China.

There are many factors that affect urinary incontinence in older adults, such as age, frailty, depression, neurologic conditions, cognitive impairment, mobility impairment, lower urinary tract symptoms (15–18), race, education, hypertension, smoking, diabetes, increased parity, higher body mass index, and oral hormone therapy, and radical prostatectomy for prostate cancer in men (15, 16, 19–21). However, in the very old population, whether there are more special factors of UI or not for this high-risk population, these are worthy of our consideration.

The aims of this study was to determine the prevalence of UI in the very old population (aged $\geq$ 75 years old) in nursing homes, examine potential risk factors associated with UI and its subtypes, which may provide evidence for further development of UI strategies for this high-risk populations.

MATERIALS AND METHODS

Study Design

This nursing institution-based cross-sectional study was carried out with face-to-face surveys conducted between June and December 2018 among older adults residing in Changsha city, the capital of Hunan province, China. Changsha is located in the east of Hunan, with an area of 11,819.5 km^2. Changsha comprises Furong, Tianxin, Yuelu, Kaifu, Yuhua, and Wangcheng districts; Changsha and Ningxiang counties; and Liuyang city. The study involved 20 of the 83 nursing homes in Changsha, with over 551 nursing home residents enrolled.

Study Population

Older adults $\geq$75 years old who had resided for a minimum of 1 year in the study area with normal cognition and communication ability were eligible to participate. Mentally unstable nursing home residents with life-threatening diseases were excluded. The study was approved by the Medical Ethics Committee of Central South University. Written informed consent to participate in the study was provided by the participants or their legal guardian/next of kin.

Study Size

The sample size was calculated using the formula $n = \mu\alpha^2\pi(1-\pi)/\delta^2$, where α is 0.05; π is the prevalence rate of UI, which was taken to be 25.0% from a previous study (22); and δ is 0.15 π. Based on this calculation, the minimum sample size for this study was determined as 512.

Survey Instrument

A questionnaire for collecting data on general characteristics was used in the face-to-face interview. The data included age, nationality, marital status, occupation, source of income, education level, and medical history, among other characteristics. Height and weight were measured with the same ruler and electronic scales for each participant.

UI was assessed using the International Consultation Incontinence Questionnaire—Short Form (ICIQ-SF), which continues to be the most internationally used questionnaire and has been translated into over 60 languages (23). It comprises three scored items and an unscored self-diagnosis item to determine the prevalence, frequency, and severity of urinary leakage and its impact on QoL (24). The sum of scores for the three items ranging from 0 to 21, and higher scores indicating increased UI severity and greater impact on QoL. The scale has demonstrated high internal reliability in British patients at a urology clinic and in a community-based study (Cronbach's $\alpha = 0.95$) (24, 25). Mild UI was defined as $<$7 points; moderate UI as 7–14 points; and severe UI as $>$14 points.

ADL performance was significantly associated with UI (12), the Barthel Index (BI) was used to assess each individual's ADL performance (Cronbach's $\alpha = 0.93$) (12). This 100-point clinical rating index includes 10 items related to self-care ability (i.e., bowels, bladder, grooming, toilet use, feeding, dressing, and bathing) and mobility (i.e., transfer, mobility, and stairs), with a higher score indicating a lower level of physical dependence. The Barthel index scores are classified as follows: 0–20 points: total dependency; 21–60 points: high-level dependency; 61–90 points: mid-level dependency; 91–99 points: low-level dependency; 100 points: total independence (26).

Data Analysis

EpiData v3.1 (https://www.epidata.dk/index.htm) and SPSS v25.0 (IBM Corp., Armonk, NY, USA) were used for data management and analysis, respectively. Numerical variables are expressed as the mean $\pm$ standard deviation (SD) and categorical variables as frequency and percentage. Differences in frequency distributions between groups were assessed with Pearson χ^2 tests, and determinants of UI and its subtypes were assessed using binary logistic regression (LR) models. For all tests, 2-tailed $p < 0.05$ were considered statistically significant.

RESULTS

General Characteristics of Older Adults in Nursing Homes

Of the 551 study participants, 67.0% were female; 55.7% were 70–79 years old, 44.3% were $>$80 years old, and the mean age ($\pm$SD) was 84.16 ($\pm$4.84) years. In terms of education level, 37.2% of

TABLE 1 | General characteristics of older adults in nursing homes.

Characteristics	Category	*N* (%)
Gender	Male	182 (33.0)
	Female	369 (67.0)
Age	<80 years old	307 (55.7)
	≥80 years old	244 (44.3)
Occupation	Institution	208 (37.7)
	Enterprise/individual household	196 (35.6)
	Others	147 (26.7)
Education level	Primary school	168 (30.5)
	Middle and high school	205 (37.2)
	At least bachelor	178 (32.3)
Marriage	Single and divorce	10 (1.8)
	Couples	167 (30.3)
	Widowed	374 (67.9)
Economic source	Retirement pension	493 (89.5)
	Others	58 (10.5)
Month income	<2,000 yuan	80 (14.5)
	2,000–2,999 yuan	180 (32.7)
	3,000–3,999 yuan	121 (21.9)
	≥4,000 yuan	170 (30.9)
ADL score	≤40	25 (4.5)
	41–60	35 (6.4)
	61–99	149 (27.0)
	100	342 (62.1)
Body index mass (kg/m^2)	<18.5	50 (9.1)
	18.5–23.9	347 (63.0)
	24–27.9	126 (22.9)
	≥28	28 (5.0)

TABLE 2 | The constituent ratio of different UI among 134 UI patients.

Characteristics	*N*	ratio (%)
Type		
SUI	16	11.9
UUI	47	35.1
MUI	51	38.1
Other UI	20	14.9
Severity		
Mild UI	47	35.1
Moderate UI	77	57.5
Severe UI	10	7.5
Total UI	134	100.0

participants had completed middle or high school and almost 40% had >40 years of work experience. Most participants had been married; 30.5% were still married and 67.9% were widowed. In most cases, the source of income was retirement pension (89.5%), and only 14.5% of participants had a monthly income <2,000 yuan. In terms of functional status, 62.1% of participants were fully independent in ADL as measured by BI; 6.4% were impaired, and 4.5% were disabled. Based on body mass index (BMI), 22.9% of participants were overweight and 5.1% were obese (BMI $\geq$ 28 kg/m^2) (**Table 1**).

UI Prevalence in the Geriatric Population of Nursing Homes

We found 134 UI in all 551 participants, with a UI prevalence rate of 24.3%. Of which MUI accounted to 38.1%; UUI 35.1%; SUI 11.9%; and other types 14.9%; 57.5% of UI was moderate UI, 35.1 % was mild UI, and 7.5% had severe UI (**Table 2**).

General Characteristics of UI in the Geriatric Population

There was no difference in UI prevalence between males (22.5%) and females (25.2%) or between obese (23.5%) and non-obese (39.3%) participants. Anxiety and depression were associated with higher rates of UI (32.3%, $\chi^2 = 7.39$, $p = 0.007$) and other types of UI (6.5%, $\chi^2 = 4.91$, $p = 0.027$). In terms of functional status, immobile participants had a higher frequency of UI and MUI (75.0%, 45.0%), whereas those who could walk independently had a low rate of UI (19.9%) ($\chi^2 = 51.82$, $p < 0.001$). Mobility was a strong predictor of MUI and other UI types ($\chi^2 = 36.68$, $p < 0.001$, $\chi^2 = 41.82$, $p < 0.001$). Participants with a history of hypertension or urinary tract infection (UTI) had a higher rates of UI than those without this medical history (hypertension: 27.8% vs. 19.4%, $\chi^2 = 5.11$, $p = 0.024$; UTI: 53.8% vs. 23.6%, $\chi^2 = 6.31$, $p = 0.012$). Participants with constipation had higher rates of UI and MUI than those without constipation (UI: 32.7% vs. 20.7%, $\chi^2 = 6.31$, $p = 0.012$; MUI: 13.9% vs. 7.3%, $\chi^2 = 6.15$, $p = 0.013$). Participants with a history of CVD had a higher rate of UI and UUI (UI: 32.9% vs. 21.3%, $\chi^2 = 7.67$, $p = 0.006$; UUI: 16.1% vs. 5.9%, $\chi^2 = 14.12$, $p < 0.001$) and those with a history of surgery had a higher rate of UI (30.6% vs. 20.3%, $\chi^2 = 7.51$, $p = 0.006$), SUI (5.6% vs. 1.2%, $\chi^2 = 8.86$, $p = 0.003$), and UUI (11.6%, $\chi^2 = 4.22$, $p = 0.040$) than those without these in their medical history. Finally, participants who were taking oral antilipidemic and antithrombotic medications had higher rates of UI than those who were not taking these drugs (antilipidemics: 44.0%, $\chi^2 = 5.51$, $p = 0.019$; antithrombotics: 44.1%, $\chi^2 = 5.60$, $p = 0.018$) (**Table 3**).

Factors Associated With UI and Its Subtypes

Binary LR was carried out to evaluate the association between UI, SUI, and other types of UI (dependent variable, dichotomized into UI vs. no UI, SUI vs. no SUI, and other UI vs. no other UI) and general characteristics of UI (covariates: anxiety/depression, constipation, mobility, CVD, hypertension, history of surgery, UTI, antilipidemic and antithrombotic medications). UI-related characteristics that were significant on Pearson χ^2 tests were entered into the LR model by backward stepwise regression, with mobility as the last categorical covariate (independent walking; α In = 0.05, α Out = 0.10).

TABLE 3 | Prevalence rate of UI in different character of nursing homes ($n = 551$).

Characteristics	Category	*N*/total (%)	χ^2 (*P*)
UI			
Gender	Male	41/182 (22.5)	0.474 (0.491)
	Female	93/369 (25.2)	
Obesity	No	123/523 (23.5)	3.590 (0.058)
	Yes	11/28 (39.3)	
Anxiety/depression	No	84/369 (21.2)	7.385 (0.007)
	Yes	50/155 (32.3)	
Constipation	No	80/386 (20.7)	9.047 (0.003)
	Yes	54/165 (32.7)	
Mobility	Immobility	15/20 (75.0)	51.819 (<0.001)
	Wheelchair use	15/24 (62.5)	
	Assisted walking	13/50 (26.0)	
	Independent walking	91/457 (19.9)	
Cardiovascular disease	No	87/408 (21.3)	7.666 (0.006)
	Yes	47/143 (32.9)	
Hypertension	No	44/227 (19.4)	5.111 (0.024)
	Yes	90/324 (27.8)	
Surgical history	No	68/335 (20.3)	7.507 (0.006)
	Yes	66/216 (30.6)	
Urinary tract infection	No	127/538 (23.6)	6.307 (0.012)
	Yes	7/13 (53.8)	
Antilipidemic medications	No	123/526 (23.4)	5.511 (0.019)
	Yes	11/25 (44.0)	
Antithrombotic medications	No	120/517 (23.2)	5.595 (0.018)
	Yes	14/34 (41.2)	
SUI			
Surgical history	No	4/335 (1.2)	8.860 (0.003)
	Yes	12/216 (5.6)	
UUI			
Cardiovascular disease	No	24/408 (5.9)	14.124 (<0.001)
	Yes	23/143 (16.1)	
Surgical history	No	22/335 (6.6)	4.220 (0.040)
	Yes	25/216 (11.6)	
Antilipidemic medications	No	40/526 (7.6)	12.724 (<0.001)
	Yes	7/25 (28.0)	
Antithrombotic medications	No	36/517 (7.0)	26.358 (<0.001)
	Yes	11/34 (32.4)	
Alcohol consumption	No	41/520 (7.9)	4.933 (0.026)
	Yes	6/31 (19.4)	
Diabetes	No	16/122 (13.1)	4.222 (0.040)
	Yes	31/429 (7.20)	
MUI			
Constipation	No	28/386 (7.3)	6.151 (0.013)
	Yes	23/165 (13.9)	
Mobility	Immobility	9/20 (45.0)	36.679 (<0.001)
	Wheelchair use	5/24 (20.8)	
	Assisted walking	3/50 (6.0)	
	Independent walking	34/457 (7.4)	
Age	<85 years old	36/307 (11.7)	5.038 (0.025)
	≥85 years old	15/244 (6.1)	
Sedative hypnotic drug	No	46/527 (8.7)	4.004 (0.045)
	Yes	5/24 (20.8)	
Other UI			
Anxiety/depression	No	10/396 (2.5)	4.909 (0.027)
	Yes	10/155 (6.5)	
Mobility	Immobility	3/20 (15.0)	41.820 (<0.001)
	Wheelchair use	6/24 (25.0)	
	Assisted walking	1/50 (2.0)	
	Independent walking	10/457 (2.2)	

Binary LR was used to assess the independent association between UUI (dependent variable, dichotomized into UUI vs. no UUI) and general characteristics of UI and MUI (covariates: anxiety/depression, constipation, mobility, CVD, hypertension, history of surgery, UTI, antilipidemic and antithrombotic medicines, alcohol consumption, and diabetes). All UI- and UUI-related characteristics that were significant in Pearson χ^2 tests were entered into model by backward stepwise regression, with mobility as the last categorical covariate (independent walk; probability for stepwise entry = 0.05, removal = 0.10). The binary LR model was used to assess the independent association between MUI (dependent variable, dichotomized into MUI vs. no MUI) and general characteristics of MUI (covariates: anxiety/depression, constipation, mobility, CVD, hypertension, surgical history, UTI, antilipidemic and antithrombotic medicines, age, and sedative/hypnotic drugs). All UI- and MUI-related characteristics that were significant in Pearson χ^2 tests were entered into the model by backward stepwise regression, with mobility as the last categorical covariate (independent walking; probability for stepwise entry = 0.05, removal = 0.10). The multivariate-adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) and *p*-values were calculated. All analyses met the goodness-of-fit criterion as determined with the Hosmer–Lemeshow tests.

The results showed that constipation, immobility, wheelchair use, CVD, and history of surgery were significant risk factors for UI (**Table 3**). Participants with a history of surgery had a higher risk of SUI (OR = 4.87, 95% CI: 1.55–15.30) and UUI (OR = 1.97, 95% CI: 1.05–3.71), and immobile and wheelchair-assisted older adults had a higher frequency of MUI (OR = 11.07, 95% CI: 4.19–29.28; OR = 3.36, 95% CI: 1.16–9.78) and other types of UI (OR = 7.89, 95% CI: 1.99–31.30; OR = 14.90, 95% CI: 4.88–45.50). Compared to participants with no history of CVD, those with CVD history reported a higher frequency of UUI (OR = 2.25, 95% CI: 1.17–4.34). Participants with diabetes were more likely to experience UUI than those without diabetes (OR = 2.250, 95% CI: 1.14–4.44). Use of oral antithrombotic drugs was associated with a higher risk for UUI (OR = 4.98, 95% CI: 2.10–11.85), and a history of sedative hypnotic drug use was associated with a higher risk of MUI (OR = 3.62, 95% CI: 1.25–10.45) (**Table 4**).

TABLE 4 | Multivariate logistic regression model with UI and subtypes in the geriatric population of nursing homes.

Variables	UI *OR (95%CI)/P*	SUI *OR (95%CI)/P*	UUI *OR (95%CI)/P*	MUI *OR (95%CI)/P*	OTHER *OR (95%CI)/P*
Constipation (reference = No)	1.62 (1.03,2.55)/0.038				
Immobility (reference = Independent walk)	13.13 (4.44, 38.80)/<0.001			11.07 (4.19, 29.28)/<0.001	7.89 (1.99, 31.30)/0.003
Wheelchair Independent (reference = walk)	6.58 (2.70, 16.03)/<0.001			3.36 (1.16, 9.78)/0.026	14.90 (4.88, 45.50)/<0.001
Cardiovascular disease (reference = No)	2.15 (1.34, 3.43)/0.001		2.25 (1.17, 4.34)/0.015		
Surgical history (reference = No)	2.02 (1.31, 3.12)/0.001	4.87 (1.55, 15.30)/0.007	1.97 (1.05, 3.71)/0.035		
Antithrombotic drugs (reference = No)			4.98 (2.10, 11.86)/<0.001		
Diabetes (reference = No)			2.25 (1.14, 4.44)/0.019		
Sedative hypnotic drug (reference = No)				3.62 (1.25, 10.45)/0.018	
Constant	0.035	0.002	0.017	0.187	0.022

DISCUSSION

In this study, the UI prevalence of nursing home residents aged ≥75 years was 24.3%, which is lower than that reported in other studies of individuals aged ≥65 years (4, 22). General good health, consciousness, and good cognitive ability may explain the lower rate in our cohort. Our results showed that CVD was a risk factor for UI and UUI, which was in line with previous findings that UI had a high prevalence among heart failure patients (27, 28). As bladder function is affected by many cardiovascular risk factors, UI is a possible consequence of metabolic syndrome (14). Water–sodium retention and impaired bladder function are associated with CVD, while diuretics used in CVD treatment may lead to nocturia and increase the occurrence of UI (29). Despite patients' perception that diuretics are unpleasant and make it difficult for them to leave their home, patients in one study were generally compliant with their medication regime; nonetheless, nearly half experienced urine leakage, and most found urgency and incontinence bothersome (28). The assessment and management of UI or UUI in patients with CVD warrant further exploration.

The relationship between mobility in ADL and UI and its subtypes was evaluated based on immobility, wheelchair dependence, and assisted and independent walking. Immobility and wheelchair dependence were found to be risk factors for UI, MUI, and other UI types in the study participants, which is in accordance with earlier observations (29, 30). The use of walking aids and activity training may reduce or prevent the occurrence of UI in the elderly (30, 31); thus, promoting walking ability may be effective in preventing UI in nursing home residents.

Constipation has been shown to increase the risk of UI in the elderly (29, 32), which is consistent with our findings. The anatomy and angle of the urethra may be altered with chronic constipation, leading to problems such as overactive bladder (OAB), urinary retention, and UI (32, 33); conversely, treatment of constipation may prevent UI.

In contrast to a previous study (34), we found no relationship between diabetes and UI in older adults; however, diabetes can lead to glycosuria and has been shown to be associated with UUI risk in multiple models. In one study, diabetes was associated with increased urination frequency and urine volume and thereby exacerbated UI and OAB by osmotic diuresis (35). Thus, stabilizing blood glucose level is a potential strategy for preventing UUI.

A history of pelvic or spinal surgery was an independent risk factor for UI and two subtypes (SUI and UUI). Damage to nerves or connective tissues near or in the bladder can occur during surgery (29), and radical pelvic dissection can result in direct and indirect injury to the pelvic plexuses, resulting in SUI and UUI (36). UI prevalence was reported to be higher among patients who had undergone spinal surgery (37).

Sedative hypnotic and antithrombotic drug use was identified as a determinant of MUI risk in our cohort. Insomnia is among the most common sleep disorders in the geriatric population (38), and the use of nighttime sedatives in this group may lead to nocturnal enuresis by inducing a deep sleep from which an individual fails to awaken in order to void (36). Antithrombotic drugs that inhibit platelet or coagulation factors are commonly prescribed drugs for preventing and treating cardiovascular disorder (39). Repeated low doses of aspirin can block arachidonic acid receptors and inhibit thromboxane A2 production by acetylating a serine residue near the narrow catalytic site of the cyclooxygenase (COX)-1 channel (40); and high doses of aspirin inhibit both COX-1 and COX-2, which have anti-inflammatory and analgesic effects (41). Oral aspirin potentially inhibits COX and decreases prostaglandin (PGE)2, a regulator of inflammation and metabolism (42) that acts through the G protein-coupled PGE2 receptors (EP) 1, EP2, EP3, and EP4. EP1 and EP3 activation in the detrusor muscle of the bladder induces muscle contraction, whereas EP4 activation causes muscle relaxation (43). Aspirin may target EP1, EP2, EP3, and EP4 to reduce bladder sphincter contraction and detrusor relaxation, leading to involuntary urine leakage, although the precise underlying mechanism remains to be determined.

Obesity was not a significant risk factor for UI in our cohort in the binary LR model, which is inconsistent with previous findings (14, 44). Obesity was previously reported as a risk factor for UI, although the observed trends are contradictory, with decreased SUI and increased MUI rates found to be associated with higher BMI (44). Older males with a reduction in strength but not increases in body or fat mass were linked to an increased frequency of UI (45). Changes in body composition including an increase and redistribution of fat mass occur in old age, and current BMI classification may not accurately reflect the associated physical risks in the elderly, who may require age-specific BMI cut-off points (46). Thus, BMI in itself should not be considered as an independent predictor of UI in the geriatric population but should be considered in the context of fat mass, muscle strength, or other indicators.

CONCLUSION

In this study, we found that distinct factors contribute to the risk of different UI subtypes. Our results indicate that care providers in nursing homes should pay particular attention to residents with a history of CVD and pelvic or spinal surgery who are at risk of UI and may benefit from the treatment of constipation, less time spent in bed, and active training in walking and muscle strengthening. Further study is needed into the relationship between the use of antithrombotic drugs and UI, and age-specific BMI cut-off points in the elderly population must be established to determine how these factors influence UI risk.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

HTan and HTai designed the study. SL and HW performed the experiments. HTai wrote the manuscript and analyzed the data. All authors contributed to the article and approved the submitted version.

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Prevalence of Fear of Falling and Its Association With Physical Function and Fall History Among Senior Citizens Living in Rural Areas of China

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Background: Fear of falling (FOF) is as significant as a fall, leading to limited physical activity and poor quality of life among senior citizens. This study aimed to investigate the prevalence of FOF and its association with physical function and fall history among the senior citizens (≥75 years old) living in rural areas of China.

Methods: This was a cross-sectional study conducted in eastern China from June to October 2019. All elderly participants were recruited during their attendance for the free health examinations in villages and towns organized by the local healthcare authorities. Data on sociodemographics, fall history, FOF conditions, self-reported comorbidity and regular medications were collected by face-to-face interview, and the physical function status was evaluated through a field test. Univariate and multivariate analyses were performed to compare the differences in physical function and fall history of senior citizens with/without FOF.

Results: A total of 753 senior citizens (mean age = 79.04) participated in this study. Of these, 63.5% were aged 75–80. FOF was reported in 22.8% of the participants, while 18.5% had a fall in the past year. Among the senior citizens with and without a fall history, the prevalences of FOF were 38.8 and 19.2%, respectively. On multivariate analyses, FOF was independently associated with the Time Up and Go Test (TUG) duration (OR = 1.080; 95% CI: 1.034–1.128), 4-Stage Balance Test score (OR = 0.746; 95% CI: 0.597–0.931), fall history (OR = 2.633; 95% CI: 1.742–3.980), cerebral apoplexy (OR = 2.478; 95% CI: 1.276–4.813) and comorbidities (≥2) (OR = 1.637; 95% CI: 1.066–2.514), while the correlation between FOF and the 30-s chair stand test was only statistically significant in univariate analysis ($Z = -3.528$, $p < 0.001$).

Conclusion: High prevalence of FOF is observed among the senior citizens living in rural areas of China. FOF is strongly correlated with physical function performance and fall history. Therefore, the implementation of targeted FOF prevention measures is key to improve the physical activity of the senior citizens, which would ultimately lead to fall prevention and improved quality of life.

Keywords: fear of falling (FOF), accidental fall, senior citizens, physical functional performance, rural

INTRODUCTION

Fall is a global public health concern given the aging population worldwide (1). It may negatively impact individual physical and mental health, potentially leading to functional decline, disability, and premature death (2, 3). Fall-related psychological disorders mainly include fear of falling (FOF), loss of self-efficacy, and avoidance of certain activities, which threaten the overall health of senior citizens (4, 5). In particular, FOF is considered equally as important as falls in the elderly and demands effective management (6). Investigations on the FOF shed light on further understanding of falls in the elderly. Compared with falls that occur only at a time point, FOF as an outcome variable provides superior consistency of research. As a psychological phenomenon and without intervention, FOF is unlikely to decrease but persist and progress over time (7). With differences in the definitions and methods of FOF measurement used in various studies and the population objects, the prevalence of FOF of senior citizens has been reported to range widely from 3 to 85% (8, 9).

FOF is defined as ongoing concern about falls, which may result in an individual avoiding daily living tasks (one or more) that he/she is otherwise capable of due to continuous attention to fall issues (10). Activities restricted by such concerns are usually closely related to fall risk, a common and serious complication among the elderly (11). FOF is attributed to many factors. It has been initially described as a post-fall syndrome, suggesting its association with previous fall experience (12). However, studies have found that senior citizens with a fall history have a FOF prevalence of 40–73%, while half of those without a fall history have also reported FOF (13). Hence, senior citizens may be exposed to FOF regardless of their fall histories (8). In addition, some scholars have acknowledged the need to assess the physical function (such as balance, gait, muscle strength, etc.) along with the psychological support in older individuals, given that FOF is expected to decrease with improvements in physical performance (6, 14). Besides fall history and physical function, factors including gender, age, medication history, comorbidity, etc., may also contribute to FOF in the elderly (15, 16). The falls efficacy scale or a single question "Are you afraid of falling?" is a generally accepted tool used by researchers to measure FOF (17, 18).

Previous studies have mainly focused on the impact of a single physical function performance on FOF, and involved participants who are primarily elderly over 60 years old in urban communities or those suffering from a specific disease. To date, data on FOF and the physical function of the elderly living in rural areas of China are scarce. Given that the living facilities and medical security in rural areas are more deficient when compared with those in urban areas, the elderly in rural areas may have a higher risk of falling and the incidence of FOF, which deserves our attention. Our study aimed to evaluate the prevalence of FOF and its association with physical function and fall history among senior citizens (>75 years old) living in rural areas of China, which would provide a valuable reference for the future screening, prevention, and treatment of FOF and its associated adverse outcomes.

MATERIALS AND METHODS

Study Design and Participants

This cross-sectional study was conducted on the basis of an annual free physical examination for the elderly in the township organized by the Kunshan Health Commission of Jiangsu Province and undertaken by the Physical examination Center of Jinxi People's Hospital. All the elderly who participated in physical examination came from the Jinxi town and its 20 administrative villages. Senior citizens undergoing physical examination from June to October 2019 were recruited. The inclusion criteria were aged 75 years or older, living in the local area for more than 10 years, able to communicate verbally, and able to walk independently (with the walking aids was allowed). Senior citizens diagnosed with dementia or with Mini-Mental State Examination (MMSE) score $\leq$24 (19) and who had attended the emergency room or been hospitalization within 3 months were excluded. A total of 753 senior citizens were recruited in the study, with the mean MMSE score of participants of 28.61 (1.01). Written informed consent was obtained from all the participants. This study was approved by the medical ethics committee of Chinese PLA General Hospital (Approval No.: S2018-048-01).

Data Collection

Data on socio-demographics and comorbidity of participants, including age, gender, residence status, body mass index (BMI), self-reported medical illness (hypertension, diabetes, cerebral apoplexy, osteoporosis, arthritis and urinary incontinence) and types of medication, FOF and falls were obtained by face-to-face interviews. Data on physical function (balance, gait and muscle strength) was evaluated through a field test. Surveys were conducted by experienced medical personnel who regularly engaged in geriatric care and had received formal training before the survey. All investigators were divided into two groups, those responsible for collecting physical function data or other data. Investigators who collected the physical function data were blinded to the FOF results.

Fear of Falling

All participants were asked a single question, "Are you afraid of falling"? When the participant answered "yes," we would consider he or she had FOF. This single-item question had a simple structure and was easy to implement and manage, even in individuals with cognitive impairment. Therefore, it has been widely used and considered a gold standard evaluation (7). Previous studies have revealed that the evaluation outcomes of the single question were equivalent to that of the Fall Efficacy Scale and Fall Efficacy Scale–International (FES-I) (18, 20). For identifying FOF in the population, the re-test result of using the single question within 2 weeks was reliable ($kappa = 0.72$) (21).

Physical Function

The Time Up and Go (TUG) test was used to evaluate the dynamic balance of the body, the activity of lower limbs and gait characteristics (22). Studies have shown that the TUG test has good sensitivity ($Sen = 91\%$) and specificity ($Spe = 82\%$), which is a reliable tool to identify fall risk in senior citizens (23, 24). During the test, participants were required to wear comfortable shoes. To begin, the participant was required to sit on a standard seat with a seat height of 43 cm and an arm height of 21 cm. When the participant heard the "start" command, he/she got up and walked 3 meters away with normal steps, turned back to the seat and sat down. The time (seconds) of the whole process and any abnormal gaits during walking were recorded, including slow tentative pace, loss of balance, short strides, little or no arm swing, steadying self on walls, shuffling, and bloc turning (25). Upon standing up or sitting down, participants were allowed to be supported by their arms. During walking, participants were also allowed to use walking aids if required. If walking aids were used, the appropriate and correct use of the equipment was recorded. Each participant was required to complete three repeats of the TUG test.

The 4-stage balance test was performed to evaluate the static balance, which required the participant to complete four standing postures with a gradual increase in difficulty, including (a) standing with feet close together and side by side; (b) standing with feet close together and half in series; (c) standing with feet in series (heel-toe); (d) standing on one foot (26). Each posture was considered complete and awarded 1 point if the participant successfully maintained the posture for 10 s without support or help. Otherwise, 0 points were awarded. The total score ranged from 0 to 4 points. A high score indicated a good balance (27). Several authors have reported that the test has excellent test-retest ($r = 0.97$) and inter-evaluator reliabilities (kappa $= 0.92$) (17).

The 30-s chair stand test was performed to measure the lower limb muscle endurance, which has been verified to have a high test-retest correlation and good criterion-related validity in both males and females ($r = 0.78$ in men and $r = 0.71$ in women) (28). To begin, the participant was required to sit on a chair with a seat height of 43 cm and no arms, holding his/her arms across the chest and the feet were shoulder-width apart. When the "start" command was heard, the participant quickly stood up from the chair, stood completely straight, and then quickly sit down (25). Participants were requested to complete the "stand up-sit down" action as swiftly as possible, and the number of complete actions within 30 s was recorded.

Falls

The unified question: "Have you ever fallen in the past 12 months?" was asked to the participants to determine any incidence of fall in the past year. A "yes" to the question indicated a positive fall history or otherwise. A fall was defined as an unintentional fall to the ground, floor, or lower level (29).

Statistical Analysis

Statistical analyses were performed by using the SPSS 24.0 statistical software. Categorical variables were described by frequency and percentage. Continuous variables with normal distribution were described by mean and standard deviation, while non-normal distribution data were expressed by median and quartile. Bivariate analyses were performed using the Chi-square test for categorical variables and the Mann-Whitney U-test for continuous variables. Finally, taking the FOF as the dependent variable, variables with a statistically significant difference in the univariate analysis were determined as the independent variables and included in the binary Logistic regression model to explore the correlations of FOF with physical activity and fall history in senior citizens. A P-value of <0.05 was considered statistically significant.

RESULTS

A total of 753 senior citizens were recruited in the study. The mean age of participants was 79.04 (3.66) years, and most belonged to the group aged from 75 to 80 (63.5%). Of all participants, 45.4% were female, 17.5% lived alone, 55.2% had BMI within the normal range (18.5–23.9), 58.4% suffered from hypertension, 7.3% suffered from diabetes, 6.9% had cerebral apoplexy, 9.8% were diagnosed to have osteoporosis, 18.2% had arthritis, 1.6% reported to have urinary incontinence, 24.2% had 2 or more chronic diseases, and 3.3% took $\geq$5 regular medications. There were 172 (22.8%) participants who reported having FOF, and 139 (18.5%) had at least one fall in the past year.

The proportions of individuals with FOF in the 80–85-year-old (29.1%) and over 85-year-old groups (26.1%) were higher than that in the 75–80-year-old group (19.7%) (**Table 1**). Meanwhile, the prevalence of FOF in females was higher than that of males (26.3 vs. 20.0%). When compared with healthy senior citizens, those with hypertension, cerebral apoplexy, or urinary incontinence had a higher prevalence of FOF, and senior citizens with FOF were more likely to have two or more comorbidities. Furthermore, senior citizens taking$\geq$5 regular medications had a higher proportion of individuals with FOF than those taking less than five.

The TUG tests revealed that senior citizens with FOF generally took a significantly longer time to complete the test than those without FOF ($Z = -4.473$, $p < 0.001$), showed more apparent gait abnormalities and required walking aids (**Table 2**). Moreover, senior citizens with FOF scored significantly lower in the 4-Stage Balance Test than those without FOF ($Z = -3.882$, $p < 0.001$). Furthermore, senior citizens with FOF completed a significantly lower number of the "stand up-sit down" actions in the 30-s chair stand test ($Z = -3.528$, $p < 0.001$). Additionally,

TABLE 1 | Comparisons of socio-demographic characteristics and comorbidities between participants with and without FOF.

Variables	Total samples ($n = 753$)	With FOF ($n = 172$)	Without FOF ($n = 581$)	p-value
Age (years), n (%)				0.021*
75–80	478 (63.5)	94 (19.7)	384 (80.3)	
80–85	206 (27.3)	60 (29.1)	146 (70.9)	
≥85	69 (9.2)	18 (26.1)	51 (73.9)	
Gender, n (%)				0.038*
Female	342 (45.4)	90 (26.3)	252 (73.7)	
Male	411 (54.6)	82 (20.0)	329 (80.0)	
Living alone, n (%)	132 (17.5)	33 (25.0)	99 (75.0)	0.515
BMI (kg/m^2), n (%)				0.307
<18.5	66 (8.8)	13 (19.7)	53 (80.3)	
18.5–23.9	416 (55.2)	87 (20.9)	329 (79.1)	
24–27.9	223 (29.6)	58 (26.0)	165 (74.0)	
≥28	48 (6.4)	14 (29.2)	34 (70.8)	
Hypertension, n (%)	440 (58.4)	112 (25.5)	328 (74.5)	0.043*
Diabetes, n (%)	55 (7.3)	17 (30.9)	38 (69.1)	0.139
Cerebral apoplexy, n (%)	52 (6.9)	25 (48.1)	27 (51.9)	<0.001**
Osteoporosis, n (%)	74 (9.8)	22 (29.7)	52 (70.3)	0.137
Arthritis, n (%)	137 (18.2)	40 (29.2)	97 (70.8)	0.050
Urinary incontinence, n (%)	12 (1.6)	6 (50.0)	6 (50.0)	0.024*
Comorbidities (≥2), n (%)	182 (24.2)	62 (34.1)	120 (65.9)	<0.001**
Types of medication (≥5), n (%)	25 (3.3)	11 (44.0)	14 (56.0)	0.010*

*Comorbidities (≥2): Two or more medical illnesses (hypertension, diabetes, cerebral apoplexy, osteoporosis, arthritis and urinary incontinence). FOF, fear of falling; BMI, body mass index. *p-value < 0.05, **p-value < 0.01.*

TABLE 2 | Correlation of FOF of senior citizens with physical function and fall history.

Variables	Total samples ($n = 753$)	With FOF ($n = 172$)	Without FOF ($n = 581$)	p-value
TUG score, [Md(P_{25},P_{75})]	11.0 (9.0, 13.8)	12.0 (9.7, 15.8)	10.8 (8.8, 13.4)	<0.001**†
Abnormal gait, n (%)	485 (64.4)	134 (27.6)	351 (72.4)	<0.001**
Use walking aids, n (%)	24 (3.2)	12 (50.0)	12 (50.0)	0.001*
4-Stage Balance Test score, [Md(P_{25},P_{75})]	3.0 (2.0, 3.0)	3.0 (2.0, 3.0)	3.0 (2.0, 3.5)	<0.001**†
30-s chair stand test score [Md(P_{25},P_{75})]	11.0 (9.0, 14.0)	10.0 (9.0, 12.0)	12.0 (9.0, 14.0)	<0.001**†
Fall history, n (%)	139 (18.5)	54 (38.8)	85 (61.2)	<0.001**

FOF, fear of falling; TUG, time up and go.
†Mann-Whitney U-test.
**p-value < 0.05, **p-value < 0.01.*

FOF was more prevalent among senior citizens who had fallen in the past year (38.8%) than those with no fall history (19.2%).

Correlation of FOF With Physical Function and Fall History

The multivariate regression analysis revealed that FOF was associated with times to complete the TUG test (OR = 1.080; 95% CI: 1.034–1.128), 4-Stage Balance Test scores (OR = 0.746; 95% CI: 0.597–0.931), fall history (OR = 2.633; 95% CI: 1.742–3.980), cerebral apoplexy (OR = 2.478; 95% CI: 1.276–4.813) and two or more comorbidities (OR = 1.637; 95% CI: 1.066–2.514) (**Table 3**).

DISCUSSION

To date, few studies have investigated FOF in senior citizens, especially those over 75 years old living in rural areas of China. As a result of significant disparity between health policies implemented in the urban and rural areas by the central and local governments, health-related concerns among senior citizens living in rural areas have somewhat been overlooked (30). Notably, the rural residents account for nearly 50% of the total population (∼605,990,000) in China. Therefore, it is essential to evaluate FOF in senior citizens living in rural areas of China, whereby our findings provided an intuitive understanding of FOF and its relationship with physical functions in geriatrics,

TABLE 3 | Multivariate regression analysis of variables associated with FOF among senior citizens.

Independent variables	B	S.E.	Wald	*p*-value	OR (95% CI)
TUG score	0.077	0.022	12.119	<0.001**	1.080 (1.034–1.128)
4–Stage Balance Test score	−0.293	0.113	6.699	0.010*	0.746 (0.597–0.931)
Fall history	0.968	0.211	21.104	<0.001**	2.633 (1.742–3.980)
Cerebral apoplexy	0.908	0.339	7.182	0.007*	2.478 (1.276–4.813)
Comorbidities (≥2)	0.493	0.219	5.062	0.024*	1.637 (1.066–2.514)
Constants	−1.785	0.486	13.482	<0.001**	0.168

*Comorbidities (≥2): two or more medical illnesses (hypertension, diabetes, cerebral apoplexy, osteoporosis, arthritis and urinary incontinence). FOF, fear of falling; TUG, time up and go. *p-value < 0.05, **p-value < 0.01.*

which may be helpful for fall risk management of the elderly in the rural communities.

The prevalence of FOF in senior citizens varies by population. A cross-sectional study on FOF among senior citizens aged over 65 in Hong Kong, China has shown that 64.7% of the participants had FOF, while 65.6% of the participants had no fall history (31). Another study from China has found the FOF prevalence of 81.0% in senior citizens of urban communities (32). In our study, the overall FOF prevalence was 22.8%, while the FOF prevalences among senior citizens with and without fall history were 38.8 and 19.2%, respectively, which was far lower than those reported in previous studies. The low FOF prevalence in our study might be attributed to our participants mainly consisted of farmers who work all year round demanding intense ability in physical activity and reasonable confidence that they will not fall. Consistent with our study, a Thai study on the FOF among the elderly in suburban and semi-rural areas has also reported a relatively low incidence of FOF, 25.2%, with most participants of the study being farmers, who were adapted to life working in paddy fields and wetlands (33). Moreover, our participants were senior citizens undergoing physical health checks in the hospital, who were relatively active and healthy, and thus had a higher fall efficacy (34). Nevertheless, further studies would be conducted to explore the difference in FOF among senior citizens from rural and urban communities.

The association between decreased physical function and FOF is multifaceted and multidirectional (35). Reduced physical performance may lead to a degree of fear of falling (36), while individuals with FOF may avoid physical activities, resulting in a decline in physical function (37). Our findings revealed that senior citizens with FOF not only scored significantly lower in the 4-Stage Balance Test but also required significantly longer time to complete the TUG test, accountable for a higher proportion of individuals with abnormal gait and using walking aids. These findings were consistent with the study by Hoang et al. (38) and Kalinowski et al. (39), indicating that senior citizens with FOF are more inclined to have a relatively poor balance and walking ability. Although our multivariate analysis did not demonstrate an independent association of FOF with gait abnormalities and walking aids usage, other variables including the time taken to complete the TUG test and 4-Stage Balance Test score were independent predictors of FOF. These suggest that regardless of fall history, a decreased physical performance may lead to reduced ability to respond to physical challenges (such as adaptability to challenges in physical balance), which might increase the fear of falls, and vice versa. Conversely, FOF may also directly affect physical function performance (40, 41). Previous studies have demonstrated the association of FOF with lower limb muscle strength (42). Senior citizens may reduce their daily activities due to FOF, resulting in a further decrease in muscle strength. Perpetually, as a result of muscle weakness, they may be unable to perform a routine daily activity that further weakens their muscle strength, leading to the loss of confidence in completing daily tasks without falling (43). However, although our univariate analyses demonstrated a significant correlation between lower limb muscle strength and FOF, this correlation was not evident in the multivariate analysis, which is consistent with the study by Khalil et al. (44). These disparities in findings from different studies are likely attributed to variability in population characteristics or living environments. Despite the cross-sectional nature of our study and the relative time of decreased physical function and FOF being elusive, their interaction remains undebatable.

It has been observed that community-based tai chi, home-based exercises, and multifactorial physical intervention toward minimizing falls at home have reduced FOF rates (45). Perhaps, a well-planned exercise and rehabilitation program applied with the cohort in rural areas may lessen FOF and fall rates, consequently increasing their quality of life, which will be conducive to the realization of active aging.

Our study showed that fall history was the key influencing factor of FOF in senior citizens (>75 years old) living in rural areas of China. Moreover, senior citizens with a fall history had 2.6 folds higher prevalence of FOF than those with no fall history, which was consistent with the findings of previous studies. Earlier studies on the association between fall history and FOF have focused on older individuals in healthy communities or with specific diseases, with little research on rural senior citizens (14, 46). Thus, our study has contributed to the completeness of this data. Moreover, it also reminds us of the obligation to investigate the fall history during the health examination. However, more recent studies have reported that senior citizens with no fall history are also exposed to severe FOF (13). An 11-year longitudinal study of incident events in older individuals has found that the history of falls at baseline did not predict acquiring a FOF, nor did FOF predict a fall later (47). Despite inconsistencies regarding the correlation between FOF and fall history, most studies have provided supporting evidence on the universality of FOF in senior citizens. Our study has highlighted that the preventative intervention for FOF should be instituted on senior citizens with a fall history in the past year. Meanwhile, those with no history of falls but have deteriorating physical function may also benefit from such intervention. Additionally, consistent with findings of previous studies (41, 48), our analyses also revealed that factors including cerebral apoplexy and two or more comorbidities were independently associated with FOF. Expectantly, senior citizens with cerebral apoplexy or multiple comorbidities would likely be in poor health and lacking in physical ability, leading to FOF.

There were limitations to our study. Firstly, our cross-sectional study did not allow for analyses of causality, which should be explored in future longitudinal studies of older populations living in rural areas. Secondly, significant selection bias might have occurred in our study. Given that all participants in our study came from one physical examination center and did not show substantial cognitive impairment, our results might not be generalisable to all rural senior citizens. Thirdly, recall bias might have been introduced in our data collection, and the daily physical activities of the elderly and some other potential confounders (such as types of medication, visual acuity, hearing ability, etc.) were not collected. Thus, future research should expand the included factors to further clarify the relationship between FOF and physical function.

CONCLUSIONS

FOF among senior citizens living in rural areas of China has a robust independent relationship with physical function and fall history. Early identification and management of FOF are vital to prevent further deterioration in physical function. On the other hand, improving the adaptability of senior citizens to challenges in physical balance, enhancing autonomy in physical activity, and fall prevention are effective strategies to curb FOF, which ultimately leads to improvements in the quality of life of senior citizens.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Chinese PLA General Hospital Medical Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

QS conceived the idea with HP, collected the data and did the data analysis. HP supervised the project. QS drafted the manuscript. All authors contributed to data analysis and manuscript revising.

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Effect of Charlson Comorbidity Index and Treatment Strategy on Survival of Elderly Patients After Endoscopic Submucosal Dissection for Gastric Adenocarcinoma: A Multicenter Retrospective Study

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Background: The optimal treatment strategy for elderly patients with early gastric adenocarcinoma (EGAC) after non-curative endoscopic submucosal dissection (ESD) remains unclear. The purpose of this research was to explore the effectiveness of additional treatments after ESD and the factors affecting survival in elderly patients (≥60 years of age) with EGAC.

Methods: A total of 639 elderly patients (≥60 years) treated with ESD for EGAC from 2006 to 2018 were retrospectively reviewed. Positive lymphatic infiltration, submucosal infiltration, and positive/indeterminate vertical resection margins are considered high risk factors in histology. According to the risk of lymph node metastasis in patients with EAGC and the treatment strategies adopted after ESD, patients were divided into three groups: there were 484 patients in group A with low risk, 121 patients in group B with high risk, without additional treatment, and 36 patients in group C with high risk, with additional treatment. The 5- and 8-year survival rate, as well as the prognostic factors of survival rate after ESD was studied.

Results: The median follow-up time was 38, 40, and 49 months, respectively. There were 3, 4, and 3 deaths related to gastric adenocarcinoma in groups A, B, and C, while deaths from other diseases were 20, 5, and 3, respectively. There were significant differences in overall survival rates between groups (94.3; 86.4; 81.2%, $p = 0.110$), but there was no significant difference in disease-specific survival rates (98.4; 92.7; 92.4%, $p = 0.016$). In the multivariate analysis, the Charlson Comorbidity Index (CCI) ≥ 2 was an independent risk factor for death after ESD (hazard ratio 2.39; 95% confidence interval 1.20–4.77; $p = 0.014$).

Conclusions: The strategy of ESD with no subsequent additional treatment for EGAC may be a suitable option for elderly patients at high risk, especially for CCI ≥ 2.

Keywords: endoscopic submucosal dissection, gastric adenocarcinoma, charlson comorbidity index, overall survival, comorbidity

INTRODUCTION

There were an estimated 16,910 new cases of early gastric adenocarcinoma and 12,720 deaths related to gastric adenocarcinoma in China in 2020 (1). The 5-year survival rate for gastric cancer is 30% (2), and its prognosis is closely related to early detection and treatment (3, 4). With the development of flexible endoscopic diagnosis and treatment tools, ESD is currently recommended as the standard surgical method for the endoscopic treatment of early gastric adenocarcinoma.

ESD has the following advantages: (1) it is less affected by the size of the lesion, and it can almost always provide adequate En bloc specimens for histological examination, so it has the greatest diagnostic and therapeutic benefits; (2) compared with traditional endoscopic mucosal resection (EMR), ESD has better oncologic outcomes.

Previous studies have showed that compared with gastrectomy, endoscopic treatment provides better surgical safety and acceptable oncology results in early gastric cancer (5–8). However, the study of comparing ESD in treating early gastric adenocarcinoma (EGAC) was lacking. Furtherly, for elderly patients with early gastric adenocarcinoma (EGAC), the best treatment strategy after ESD is still unclear, which still needs more detailed clinical research data support. Some studies proved that ESD treatment of early gastric cancer in elderly patients is even safe and feasible (9–12). However, the post-ESD treatment is currently not standardized, especially elderly patients tend to have more complications, limited life expectancy, poorer general conditions, and poor tolerance to post-ESD additional treatment. In addition, Elderly patients are at higher risk of all-cause death, which has caused people to worry and pay attention to the safety and effectiveness of additional treatments after ESD. Moreover, China's aging problem is getting more and more serious, and it is expected that many countries will face similar situations in the future. The purpose of this study was to explore the effectiveness of additional treatments after ESD and survival predictors of elderly patients ($\geq$60 years of age) in the hospital-based EGAC cohort. It typically occurs in elderly cancer patients with multiple comorbidities and CCI is a reliable tool that can estimate prognosis of cancer based on type and number of comorbidities. Therefore, in this study, CCI was used as the survival predictor of elderly patients with EGAC.

METHODS

Patients and Study Design

The patient population in this study came from a multicenter retrospective cohort study of five tertiary referral hospitals in China. We retrospectively reviewed the treatment and follow-up data of all elderly EGAC patients who received ESD from January 1, 2006, to December 31, 2018. The last follow-up time was December 2019.

A total of 639 consecutive elderly EGAC patients who met the following criteria were included: (i) age $\geq$ 60 years; (ii) treatment-naïve EGAC; (iii) pathologically confirmed adenocarcinoma of excised gastric specimen; and (iv) no metastasis. The exclusion criteria were: (i) patients with a history of surgical gastrectomy because a remnant stomach could affect survival outcomes; (ii) patients with premalignant lesions (high-grade intraepithelial neoplasia) and intraepithelial adenocarcinoma; The indication criteria for ESD in gastric cancer were: (i) no lymph node or distant metastasis was detected by computer imaging; (ii) tumor staging based on endoscopy indicating superficial invasion; and (iii) Written informed consent is required. According to the confirmed pathological results of the excised specimens, the risk of Post-ESD is classified and evaluated (low risk and high risk).

According to the resection effect and pathology, we considered the following cases to be at high risk: non-curative ESD, including positive lymphatic or/and venous infiltration, positive or indeterminate vertical margins, submucosal infiltration, and at low risk: curative resection (tumor depth does not exceed lamina propria mucosae, negative horizontal/vertical margin, and negative lymphatic and vascular invasion) or non-curative resection with tumor invasion up to MM or/and horizontal margins as positive/indeterminate. We divided patients into three groups based on post-ESD treatment strategies and the level of lymph node metastasis (LNM) risk: group A, low-risk patients; group B, high-risk patients without any post-ESD additional treatment; and group C, high-risk patients with additional treatment after ESD. Charlson Comorbidity Index (CCI) was used to assess the risk of death from comorbidities. CCI comprises 19 weighted comorbidities (such as cardiovascular disease, chronic kidney disease, uncomplicated diabetes, and liver disease, etc.) according to the original definition (13, 14). CCI quantified disease burden and comorbidity burdens, with high burden defined as a score of $\geq$2 (15), so the best CCI cut-off value was 2. This study was approved by the Institutional Ethics Review Committee of PLA General Hospital.

Histological Assessment

Hematoxylin and eosin and immune-histochemical staining were performed after the specimen is cut into slices of ~2 mm, and the slices were evaluated by pathologists in each institution according to the standards for diagnosis and treatment of gastric cancer in china in 2018. We evaluated the tumor invasion depth, horizontal and vertical margin status, lymphovascular invasion, and histological characteristics based on the above standards. The depth of submucosal invasion is classified as SM1 (<500 μm) or SM2 (≥500 μm). Hematoxylin and eosin staining was used to evaluate lymphatic and venous invasions. Elastica van Gieson staining was used for the assessment of vascular invasion, and D2-40 is used for the assessment of lymphatic invasion.

Post-ESD Management and Outcome Assessment

During the treatment of this study, doctors judged the appropriate indications for post-ESD additional treatment based on the patient's treatment, his/her own condition and personal preference for treatment strategies. The additional treatment post-ESD in our study specifically refers to gastrectomy.

The main outcome was the all-cause mortality at the end of follow-up (at least 6 months) in patients with EGAC. Secondary outcomes included the following indicators (2) the incidence of severe nonfatal adverse events and perioperative mortality; (3) additional treatment; (4) cumulative disease-specific mortality and tumor recurrence or metastasis at the end of follow-up period.

Follow-Up

The patients were followed up at the 3rd and 6th months, and then every 6 months until the third year, and yearly afterward. Outpatient visits, blood tests, endoscopy, and computed tomography were the main follow-up methods. We defined loss of follow-up as a follow-up of fewer than 6 months with no known recurrence, metastasis, or death. The decision of post ESD additional treatment was made case by case. In general, additional treatment was recommended for all patients with positive margin cancer and ESD patients with T1b lesions, especially those with deeper, or wider invasion, lymphatic involvement, or poor differentiation. However, the decision for additional treatment also took into account age, physical condition, comorbidity, life expectancy, and, most importantly, patient preferences.

Statistical Analysis

Statistical analyses were performed using IBM SPSS (version 26.0). Categorical statistics were represented as a number and percentage, while continuous statistics were represented as a mean average and standard deviation. Statistical methods used in this study include the Student's *t*-test (or Mann-Whitney U test), Fisher's exact test (or Pearson's chi-square test), the Kaplan-Meier method for survival analysis, and Cox hazards regression analysis. The adjustment covariates in multivariate cox regression analyses were demographic characteristics (age, sex), Post-ESD treatment strategy. As shown in **Table 3**, the category variables of sex and Post-ESD treatment strategy were used as covariates and the continuous variable of age was used as covariate. The schoenfeld test was used to evaluate the proportional hazards (PH) assumption when conducting cox regression analysis. In a sensitivity analysis, we extended the follow-up of the primary and secondary outcome to 6 months after ESD. The start of the follow-up period was defined as the initial date of the ESD treatment, while the end date of follow-up was the date of final contact or the date of death until December 2019. Cumulative survival analysis was performed with the use of Kaplan-Meier methods and curves were compared with the log-rank test. After excluding patients with follow-up <6 months, we then performed a Kaplan-Meier survival analysis. Kaplan-Meier, Cox hazards regression, sensitivity analysis were performed by R version 4.1.1. A $p < 0.05$ indicated the difference is statistically significant.

TABLE 1 | Patient demographics and lesion cancer.

Patient demographics	CCI ≤ 1 *n* = 527	CCI ≥ 2 *n* = 112	*P* value
Age, years	67.0 (63.0–72.0)	69.0 (64.0–74.0)	0.003
Men	410 (77.8)	92 (82.1)	0.373
Post-ESD treatment strategy			0.247
Group A	401 (76.1)	81 (72.3)	
Group B	100 (19.0)	21 (18.8)	
Group C	26 (4.9)	10 (8.9)	
Smoking	155 (29.4)	41 (36.6)	0.165
Drinking	140 (26.6)	38 (33.9)	0.144
BMI, kg/m2	23.8 ± 3.1	24.4 ± 3.5	0.087
Lesion location			0.672
Upper third	210 (39.8)	41 (36.6)	
Middle third	124 (23.	5) 25 (22.3)	
Lower third	193 (36.6)	46 (41.1)	
Tumor morphology			0.979
Elevated	307 (58.3)	66 (58.9)	
Flat or depressed	220 (41.7)	46 (41.1)	

Values are mean ± SD, n (%), or median (interquartile range).
CCI, Charlson Comorbidity Index.

RESULTS

Patients

A total of 639 elderly patients were included and analyzed, of which 527 (82.5%, 527/639) were assessed as CCI ≤ 1 group, while the other 112 (17.5%, 112/639) were assessed as CCI ≥ 2 group. Of the 527 CCI ≤ 1 patients, 100(19.0%, 100/527; group B) received ESD without additional treatment, whereas 26 (4.9%, 26/527; group C) underwent ESD with additional treatment. And, the patient details are summarized in **Table 1**. There were no significant differences in Post-ESD treatment strategy, sex, smoking, drinking, BMI, lesion location, tumor morphology between CCI ≤ 1 group and CCI ≥ 2 group. However, the age of CCI ≥ 2 group was higher than CCI ≤ 1 group, and there was a significant difference.

The pathological result of ESD for elderly patients with gastric cancers was summarized in **Table 2**. In group B, the lesion diameter tended to be larger when compared to group C. The proportion of undifferentiated histologic appearance tended to be higher in group B than in group C (31.4 vs. 19.4%, $p < 0.001$). The ratio of positive vertical margin to positive vertical margin in group C is often higher than that in group B (33.3 vs. 9.1%, $p <$

TABLE 2 | Pathological result and outcomes of endoscopic submucosal dissection for the 639 elderly patients with gastric cancers.

Patient demographics	Group A $n = 482$	Group B $n = 121$	Group C $n = 36$	*P*
Lesion diameter, cm[a]	1.2 (0.8–2.0)	2.0 (1.2–3.0)	1.6 (1.0–2.0)	<0.001
Histologic appearance				<0.001
Differentiated	462 (95.9)	83 (68.6)	29 (80.6)	
Undifferentiated	20 (4.1)	38 (31.4)	7 (19.4)	
Depth of invasion[b]				<0.001
M	465 (96.5)	74 (61.2)	15 (41.7)	
SM1	17 (3.5)	19 (15.7)	5 (13.9)	
SM2	0	28 (23.1)	16 (44.4)	
Positive horizontal margin	0	16 (13.2)	9 (25.0)	<0.001
Positive vertical margin	0	11 (9.1)	12 (33.3)	<0.001
Lymphovascular invasion[c]	0	18 (14.9)	3 (8.3)	<0.001
Short-term clinical outcomes				
En bloc resection	480 (100.0)	84 (70.0)	25 (69.4)	<0.001
R0 resection[d]	480 (100.0)	64 (53.3)	9 (25.0)	<0.001
Hospital stay, days	13 (11–17)	13 (11–17)	17 (13–32)	<0.001
Postoperative hospital stay, days	6 (5–7)	7 (5–8)	6 (5–12)	<0.001
Hospital cost, USD	26973.6 (22301.1–32277.4)	32000.9 (25132.8–35025.8)	9389.2 (6040.5–11856.7)	<0.001
Nonfatal adverse events	15 (3.1%)	2 (1.7%)	1 (2.8%)	0.686
Postoperative bleeding	13 (2.7)	2 (1.7%)	1 (2.8%)	0.812
Delayed perforation	1 (0.2)	0	0	1.000
Pneumonia	1 (0.2)	0	0	1.000
Anastomosis stenosis	2 (0.4)	0	0	1.000
Postoperative intestinal obstruction	0	1 (0.8)	0	0.246
Adjuvant therapy				<0.001
Repeat endoscopy	0	0	5 (13.9%)	
Repeat surgery	0	0	30 (83.3%)	
Chemotherapy	0	0	1 (2.8%)	
Oncologic outcomes, follow-up[e]				
All-cause mortality	24 (5.0)	8 (6.6)	6 (16.7)	0.016
Disease-specific mortality	4 (0.8)	3 (2.5)	3 (8.3)	0.001
Recurrence/metastasis	40 (8.3)	9 (7.4)	8 (22.2)	0.015

Values are mean ± SD, n (%), or median (interquartile range).
[a]Naked-eye measurement of the largest-diameter lesion on stretched and nonfixed pathology specimens.
[b]Tumoral infiltration of the submucosa was subclassified as SM1 (<500 um from the muscularis mucosae) or SM2 (≥500 um from the muscularis mucosae).
[c]Lymphovascular invasion for endoscopic submucosal dissection specimens.
[d]Horizontal and vertical margins free from cancerous and precancerous tissues (high-grade intraepithelial neoplasia).
[e]Median 27 (range, 6–143) months.

0.001; 25.0 vs. 13.2%, $p < 0.001$; respectively). The proportion of lymphovascular invasion in group B is similarly higher than that in group C.

Survival Analysis

The median follow-up time of group A, group B, and group C were 38, 40, and 49 months, respectively. A total of 38 gastric adenocarcinoma patients died during the follow-up study. The 5-year overall survival rates in group A, group B, and group C were 94.3% (95% CI 94.8–98.7%), 86.4% (95% CI 75.4–99.0%), and 81.2% (95% CI 67.6–97.6%), respectively, whereas the 8-year overall survival were 84.3% (95% CI 77.6–91.5%), 71.1% (95% CI 51.7–97.8%), and 73.8% (95% CI 56.8–95.9%), respectively (**Figure 1A**). There was no significant difference in overall survival between the three groups ($p = 0.11$). The 5-year disease-specific survival were 98.4% (95% CI 96.4–100%), 92.7% (95% CI 84.5–100%), and 92.4% (95% CI 82.7–100%) in group A, group B, and group C, respectively (**Figure 1B**). The disease-specific survival between the three groups showed a significant difference ($p = 0.016$).

Prognostic Factors for Survival

We summarized the risk factors for overall survival in **Table 3**. In the univariate analysis results, elder age, increased CCI, the greater risk for LNM, diabetes were significantly associated with poor overall survival. On multivariate analysis, CCI ≥ 2 (hazard ratio, 2.39; 95% CI 1.20–4.77, $p = 0.014$) was associated with impaired overall survival. We also found that age is an

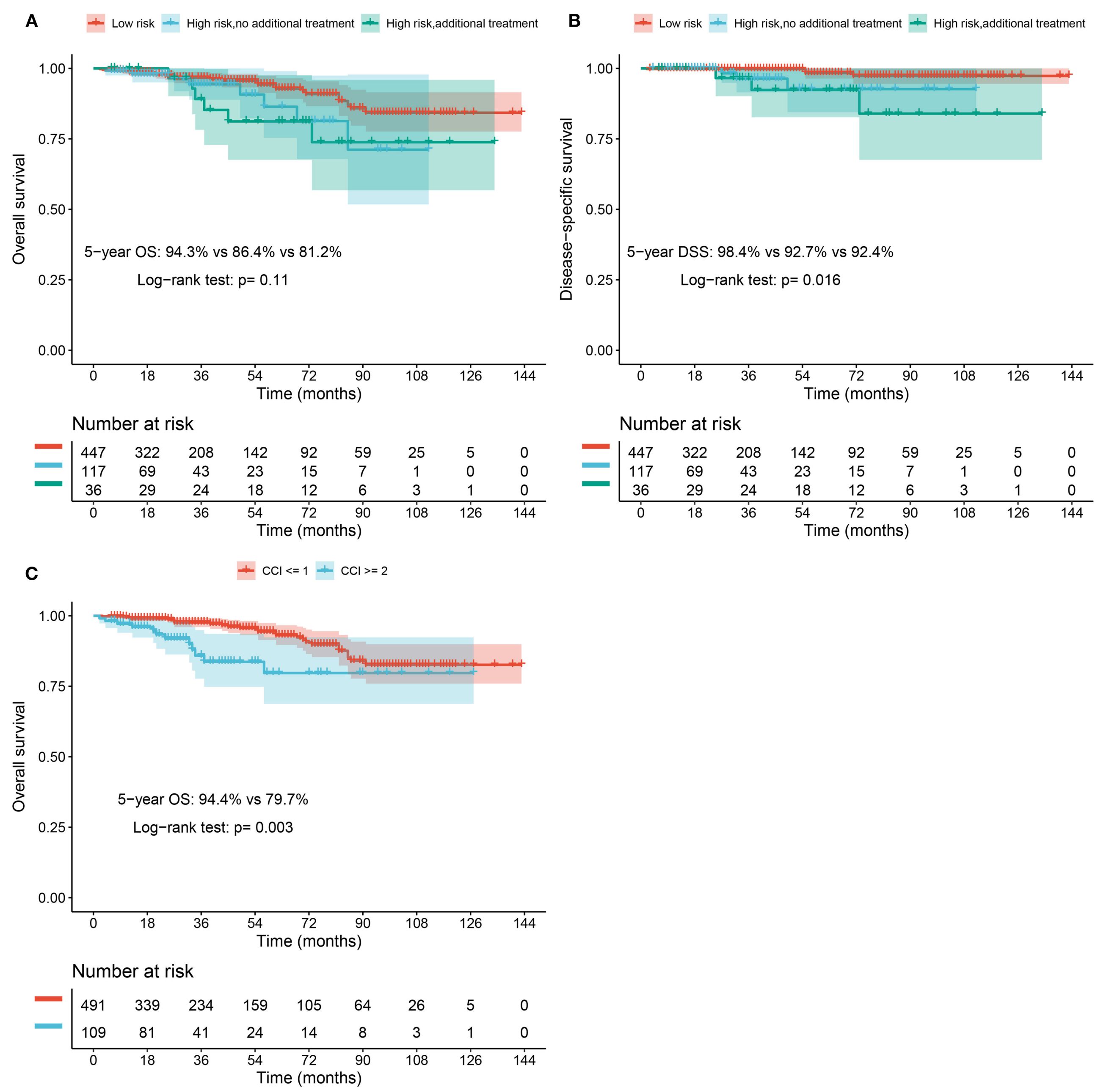

FIGURE 1 | (A) Overall survival rate of elderly patients with EGAC after ESD stratified based on the risk of LNM. **(B)** Disease-specific survival rate of elderly patients with EGAC after ESD stratified based on the risk of LNM. **(C)** Overall survival rate of elderly patients with EGAC after ESD in CCI $\geq$ 2 and CCI $\leq$ 1 groups.

important independent risk factor for impaired overall survival in elderly patients ($\geq$60 years of age) with EGAC. The 5-year overall survival rates of patients with CCI $\geq$ 2 were significantly lower than that of patients with a CCI $\leq$ 1 (79.7 and 94.4%, respectively, $p = 0.003$) (**Figure 1C**). According to the analysis results of **Supplementary Table 1**, CCI had no significant effect on overall survival (hazard ratio, 1.41; 95% CI 0.53–3.80) or disease-specific survival (hazard ratio, 2.05; 95% CI 0.21–20.10) in the low-risk group, but had a significant effect on recurrence or metastasis (hazard ratio, 2.17; 95% CI 1.10–4.28). Different cox models yielded robust results regarding significant and non-significant outcomes.

The survival rate of high-risk patients was further analyzed according to post-ESD treatment strategy and CCI classification. We re-stratified post-ESD high-risk patients (group B and group C) according to CCI classification (CCI $\leq$ 1 and CCI $\geq$ 2),

TABLE 3 | Risk factors associated with poor overall survival.

Variables	No. of patients	No. of deaths	Univariate		Multivariate	
			HR (95% CI)	*p*	HR (95% CI)	*p*
Post-ESD treatment strategy						
Group A	482	24	Reference		Reference	
Group B	121	8	1.78 (0.79–3.97)	0.162	2.16 (0.69–3.49)	0.290
Group C	36	6	2.26 (0.92–5.54)	0.075	2.16 (0.89–5.30)	0.094
Risk for LNM						
Low risk	482	24	Reference			
High risk	157	14	1.96 (1.01–3.79)	0.046		
Age, years						
Continuous variable	639	38	1.08 (1.03–1.14)	<0.001	1.08 (1.03–1.13)	0.002
CCI						
0–1	527	26	Reference		Reference	
≥2	112	12	2.74 (1.38–5.45)	0.004	2.39 (1.20–4.77)	0.014
History of cancer						
Present	37	4	1.05 (0.56–1.99)	0.379		
Absent	602	34	Reference			
Cardiovascular disease						
Present	285	18	1.05 (0.56–1.99)	0.871		
Absent	354	20	Reference			
Respiratory disease						
Present	38	3	1.36 (0.42–4.43)	0.609		
Absent	601	35	Reference			
Liver disease						
Present	40	1	0.47 (0.06–3.42)	0.456		
Absent	599	37	Reference			
Renal disease						
Present	31	4	2.13 (0.76–6.00)	0.153		
Absent	608	34	Reference			
Diabetes						
Present	102	13	2.78 (1.42–5.43)	0.003		
Absent	537	25	Reference			

The p value was calculated by Cox hazards regression analysis.
CCI, Charlson Comorbidity Index.

and compared the overall survival as follows: each CCI scoring range was compared with and without additional treatment: CCI ≤ 1 and CCI ≥ 2 for each ESD post-processing intervention (**Figures 2A,B**).

Analysis of high-risk patients with CCI ≤ 1, the 5- and 8-year overall survival rates of patients who did not receive additional treatment were 93.7 and 75.3%, respectively, while those who received additional treatment were 90.3 and 81.3%, and there was no significant difference ($p = 0.836$) between the two groups receiving additional treatment and not receiving additional treatment (**Figure 2C**). Analysis of high-risk patients with CCI ≥ 2, the 5- and 8-year overall survival rates of the patient who did not receive other interventions were 39.1 and 39.1%, respectively, while those who received additional treatment were 50 and 50%, and those who did not receive additional treatment there was no significant difference between high-risk patients and high-risk patients receiving additional treatment ($p = 0.948$) (**Figure 2D**).

In high-risk cases that did not involve other interventions after ESD, patients with CCI ≥ 2 had significantly lower overall survival than those with CCI ≤ 1 ($p = 0.002$). Among the high-risk patients receiving other interventions after ESD, the overall survival rate of patients with CCI ≥ 2 was lower than that of patients with CCI ≤ 1, and the difference was significant ($p = 0.034$).

Sensitivity Analysis

We performed a sensitivity analysis to examine the degree of bias introduced by the patients who were follow-up for <6 months. No difference was found in the distribution of treatment strategy, age, gender, comorbidities, CCI, smoking, drinking, BMI, lesion characteristics/pathology in **Table 4**. In view of the similar characteristics of patients, surgery, and perioperative parameters, there is no significant impact on the result analysis, despite the follow-up time being <6 months in part patients.

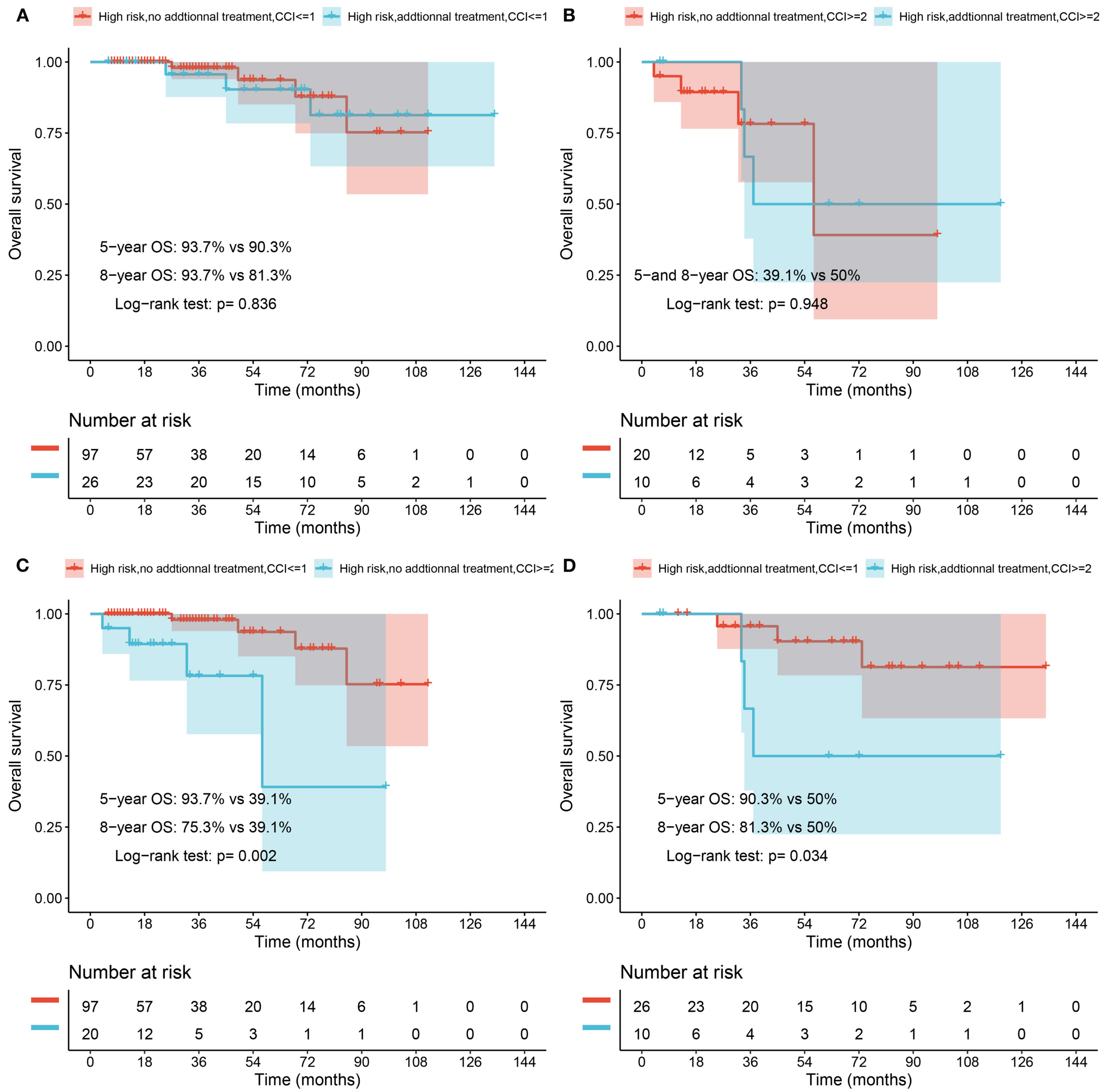

FIGURE 2 | (A) Overall survival rate of elderly EGAC patients with high risk and CCI $\leq$ 1 after ESD in no additional treatment and additional treatment groups. **(B)** Overall survival rate of elderly EGAC patients with high risk and CCI $\geq$ 2 after ESD in the follow-up and additional treatment groups. **(C)** Overall survival rate of elderly EGAC patients with high risk and no additional treatment after ESD in CCI $\leq$ 1 and CCI $\geq$ 2 groups. **(D)** Overall survival rate of elderly EGAC patients with high risk and receiving additional treatment after ESD in CCI $\leq$ 1 and CCI $\geq$ 2 groups.

DISCUSSION

In this hospital-based cohort study for elderly patients with EGAC treated using ESD, we clarify the significance of CCI as a prognostic factor. After analyzing 639 consecutive patients, our findings demonstrate the triage value of CCI regarding mortality, appropriate treatment, and survival gain after additional treatment. For patients at high-risk LNM after EGAC ESD, we suggest that for elderly patients over 60 years old with CCI $\leq$ 1, close observation and follow-up without additional treatment after ESD treatment may be a feasible option. For patients, the risk of LNM is very high. Additional treatment afterward is a reasonable choice.

The CCI is a reliable co-morbidity index to be used in research, especially for surgical patients. However, few previous studies aimed to explore the necessity of an additional treatment

TABLE 4 | Sensitivity analysis.

Variable	Follow-Up ≥6 Months or Death Before 6 Months		*P*
	Yes (*n* = 600)	No (*n* = 39)	
Post-ESD treatment strategy			0.077
Group A	447 (74.5)	35 (89.7)	
Group B	117 (19.5)	4 (10.3)	
Group C	36 (6.0)	0	
Age, years	68.3 ± 6.3	69.6 ± 6.9	0.202
Men	476 (79.3)	26 (66.7)	0.062
Comorbidities			
Cardiovascular disease	273 (45.5)	12 (30.8)	0.073
Respiratory disease	38 (6.3)	0	0.105
Liver disease	39 (6.5)	1 (2.6)	0.325
Renal disease	30 (5.0)	1 (2.6)	0.493
Diabetes	97 (16.2)	5 (12.8)	0.580
Charlson comorbidity index, *n* (%)			0.095
0–1	491 (81.8)	36 (92.3)	
≥2	109 (18.2)	3 (7.7)	
Smoking	189 (31.5)	7 (17.9)	0.075
Drinking	171 (28.5)	7 (17.9)	0.154
BMI, kg/m2	23.9 ± 3.2	23.3 ± 2.5	0.213
Lesion location			0.069
Upper third	239 (39.8)	12 (30.8)	
Middle third	134 (22.3)	15 (38.5)	
Lower third	227 (37.8)	12 (30.8)	
Tumor morphology			0.354
Elevated	353 (58.8)	20 (51.3)	
Flat or depressed	247 (41.2)	19 (48.7)	
Depth of invasion			0.112
M	516 (86.0)	38 (97.4)	
SM1	40 (6.7)	1 (2.6)	
SM2	44 (7.3)	0	
Lymphovascular invasion	19 (3.2)	2 (5.1)	0.506

Values are n (%), mean ± SD, or median (interquartile range).
ESD, endoscopic submucosal dissection.

strategies for elderly patients with EGAC after ESD. In the current study, we found that there was no significant difference in overall survival rate and disease-specific survival rate between patients who received additional treatment and patients without any post-ESD treatment (16–18). Because of the shorter life expectancy of these elderly patients with high recurrence risk after surgery, the necessity of additional treatment after ESD is difficult to determine clearly, and extra treatment may not effectively prolong the life expectancy. Therefore, our research results demonstrated that CCI ≤ 1 can be regarded as a meaningful indicator for judging whether post-ESD high-risk patients aged ≥60 need adjuvant therapy after treatment. A meaningful result showed that there was a significant difference in disease-specific survival rate between patients who performed additional treatment and patients without any post-ESD treatment. Usually, compared with follow-up observations, patients with LNM identified as high-risk target population after ESD are more inclined to receive further treatment. These results indicated that some post-ESD elderly patients can benefit from additional treatment.

Several studies have clarified the relationship between CCI and complications of elderly gastric patients after ESD, which showed CCI can serve as an independent prognostic factor (12, 19–21), and the significance of CCI in patients with non-curative EGAC after ESD remained unclear. Our study demonstrated that age and higher CCI score (≥2) were independent prognostic factors in elderly patients with EGAC treated using ESD, similar to the findings reported in previous studies. Moreover, we established 2 as the optimal CCI threshold upon ROC curve analysis. According to the CCI grade and the treatment strategy after ESD, According to the CCI classification and treatment strategy after ESD, we mainly focus on the survival results of high-risk patients with EGAC after ESD, and have not explored the risk of all-cause death and primary cancer death in low-risk LNM patients with EGAC after ESD. Moreover, among elderly patients underwent ESD with high risk, we found special factors affecting high mortality, with diabetes was emphasized as a prognostic factor in univariate analysis. CCI remained an independent factor affecting survival after we eliminated the factor from multivariate analysis as it already reflected in CCI. Therefore, CCI can be used as a valuable indicator to evaluate the survival of elderly EGAC patients after ESD.

In recent studies, CCI was reported that it performed well in predicting the prognosis of various diseases, such as ischemic stroke, end-stage renal disease, cirrhosis, and lung cancer (22–24). Our findings show that among high-risk group of EGAC patients with CCI ≤ 1 or CCI ≥ 2, there was no significant difference in 5- and 8-year overall survival rates between patients who opted for additional treatment and patients who only received follow-up observation. However, the 5- and 8-year overall survival of high-risk patients with CCI ≥ 2 who received additional treatment was higher than those of patients who only received follow-up, but there was still no significant difference between the two groups. It provides a reasonable option to judge whether additional treatment is needed according to the risk of LNM and CCI score in the clinic. Therefore, we expect to apply CCI score to other advanced endoscopic procedures in elderly patients to formulate the most reasonable treatment.

The present study has several limitations. First, the sample size of this study is not large enough, especially group C, elderly patients with high-risk for EGAC after ESD often receive no additional treatment. Second, there are few studies on the effectiveness and safety of elderly EGAC patients after ESD. According to the prognosis of elderly patients with EGAC after ESD, the follow-up time required in this study is insufficient. Third, the additional treatment of patients with high risk of lymph node metastasis after ESD largely depends on the attending doctor. The indications and physical conditions of elderly EGAC patients have a greater impact on whether additional treatment is required. In addition, there are other uncertain factors such as age, family care, financial status, and patient treatment preferences (11, 25).

In conclusion, our study provides important evidence that the observation strategy without intervention after ESD for EGAC may be an acceptable or best option for elderly patients with CCI $\geq$ 2, as the additional treatment cannot effectively extend the life expectancy of patients. Furthermore, regardless of whether additional treatment after ESD in patients with EGAC, CCI $\leq$ 1 has a better survival condition than CCI $\geq$ 2.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The data sets generated and/or analyzed during the current study are not publicly available to ensure patient privacy, but are available from the corresponding author on reasonable request. Requests to access these datasets should be directed to Wenzhe Cao, caowenzhe301@163.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Ethics Review Committee of PLA General Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WC: conceptualization, formal analysis, methodology, software, and writing—original draft. SL: formal analysis, and writing—review and editing. ShaW: data curation. SheW: investigation and validation. YS: writing—review and editing and visualization. YH: conceptualization, funding acquisition, project administration, resources, and supervision. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.803113/full#supplementary-material

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Associations Between High-Sensitivity C-Reactive Protein and All-Cause Mortality Among Oldest-Old in Chinese Longevity Areas: A Community-Based Cohort Study

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Background: The association between high-sensitivity C-reactive protein (hsCRP) levels and all-cause mortality for the oldest-old (aged 80 years or older) remains unclear. We aimed to investigate the associations between hsCRP concentrations and the risks of all-cause mortality, and further identify the potential modifying factors affecting these associations among the oldest-old.

Methods: This prospective, community-based cohort study included 2,206 participants aged 80 years or older (median age 93.0 years) from the Healthy Aging and Biomarkers Cohort Study. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) with 95% confidential intervals (95% CIs) for all-cause mortality according to hsCRP quartiles and recommendation for relative risk categories of hsCRP levels (< 1.0, 1.0–3.0, and > 3.0 mg/L), with adjustment for sociodemographic information, lifestyle, physical examination, medical history, and other potential confounders.

Results: During a median follow-up period of 3.1 years (IQR: 1.6–3.9 years), 1,106 deaths were verified. After full adjustment for potential confounders, a higher hsCRP concentration was positively associated with an increased risk of all-cause mortality (P for trend < 0.001). Compared with the lowest quartile, the fully adjusted HRs of the second, third, and fourth quartiles were 1.17 (95% CI: 0.94, 1.46), 1.28 (95% CI: 1.01, 1.61), and 1.49 (95% CI: 1.20, 1.87), respectively. The association of hsCRP with all-cause mortality was modified by smoking status (P for interaction $= 0.011$), an increased risk of hsCRP with all-cause mortality showed among non-current smokers (HR: 1.17; 95% CI: 1.07, 1.28), but no significance was observed in current smokers (HR: 0.83; 95% CI: 0.66, 1.18).

Conclusions: Our study indicated that elevated hsCRP concentrations were associated with a higher risk of all-cause mortality among Chinese oldest-old. Future studies investigating additional factors of disease and aging processes are needed to obtain a better understanding of the mechanisms.

Keywords: high-sensitivity C-reactive protein, all-cause mortality, oldest-old, inflammation, aging, cohort study

BACKGROUND

Inflammation has been studied to be the role of a wide range of aging-related diseases (1), such as atherosclerosis and coronary artery disease (2), diabetes (3), Alzheimer's disease (4), and cancer (5). Inflammaging, a description of low-grade, chronic, systemic inflammation in aging, is a highly significant risk factor for both morbidity and mortality in elderly people, as most if not all age-related diseases share inflammatory pathogenesis (6, 7). Nevertheless, the precise etiology of inflammaging and its potential causal role in contributing to adverse health outcomes remain largely unknown (8). Chronic, low-grade elevations in markers of inflammation, such as high-sensitivity C-reactive protein (hsCRP), are potent risk factors for all-cause mortality (9).

CRP, an acute-phase protein produced predominantly by hepatocytes, is a sensitive and exquisitely systemic marker of inflammation (10). CRP has been commonly assayed for infections (11), in-hospital complications (12), prognosis influences (13), and aging-related health outcomes in clinical applications, especially cardiovascular and metabolic disease risk (14, 15). Higher hsCRP levels have been proposed as a predictor of all-cause mortality in many (16–28) but not all studies (29). Inconsistent results may exist due to sex, ethnic or age differences in the populations, and the strength of the association also varied across studies, from 1.14 to 3.64 (hazard ratios or relative risks). Moreover, these findings are based on the general population, but the oldest old adults (octogenarians, non-agenarians, and centenarians) remain underrepresented. The classic risk markers for disease and mortality might not be suitable in the oldest old population (30).

Therefore, we conducted the present study to prospectively examine whether hsCRP was associated with all-cause mortality among the oldest old adults based on datasets from the Healthy Aging and Biomarkers Cohort Study (HABCS).

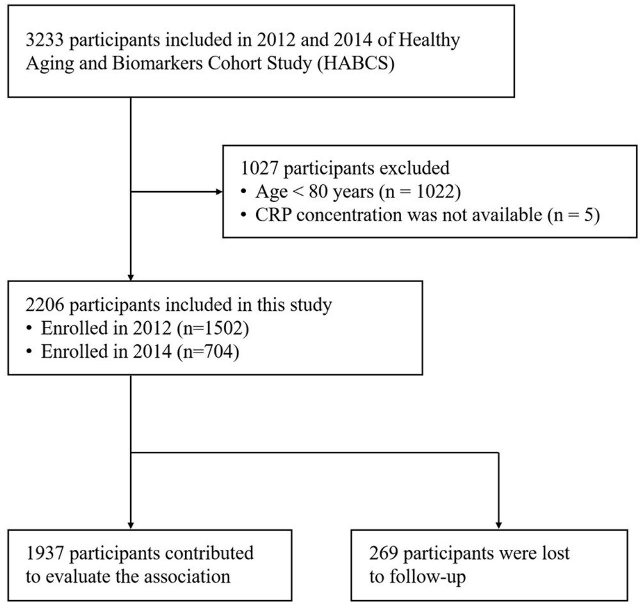

FIGURE 1 | Flowchart of participant enrollment.

METHODS

Design, Study Setting, and Participants

This is a prospective, community-based cohort study. Participants were recruited in 2012 and 2014 of HABCS from eight longevity areas selected by the Chinese Society of Gerontology. The densities of oldest old adults are higher (especially for centenarians) in longevity areas than in other areas. These areas include Chen Mai County (Hainan Province), Yong Fu County (Guangxi Province), Ma Yang County (Hunan Province), Zhong Xiang City (Hubei Province), Xia Yi County (He Nan Province), San Shui City (Guangdong Province), Lai Zhou City (Shandong Province), and Ru Dong County (Jiangsu Province). In this study, a total of 2206 participants were enrolled at baseline (1,506 in 2012 and 704 in 2014) and follow-up in 2014 and 2017, respectively. We included all adults aged 80 years or older with available results of CRP tests, and 269 participants were lost to follow-up (**Figure 1**). The study was approved by the Ethics Committee of Peking University and Duke University. All participants included in HABCS provided informed consent. More details of HABCS have been previously described (31).

Measurement of hsCRP

Venous blood samples were obtained from the participants by collecting in heparin anticoagulant vacuum tubes, before which participants were required to fast overnight. HsCRP concentration was generally measured through a high-sensitivity immunoturbidimetry assay, and all blood biochemistry tests were conducted by the central clinical lab at Capital Medical

Abbreviations: BMI, body mass index; CI, confidential interval; HABCS, Healthy Aging and Biomarkers Cohort Study; hsCRP, high-sensitivity C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; HR, hazard ratio; IQR, interquartile range; MMSE, Mini-Mental State Examination; SBP, systolic blood pressure; SOF, Study of Osteoporotic Fractures.

University in Beijing. The minimal detectable concentration of hsCRP was 0.11 mg/L.

Measurement of All-Cause Mortality

We verified the survival status of all participants at baseline during follow-up surveys in 2014 and 2017. The date of death was inquired and ascertained from family members or caregivers of the deceased. The survival time for participants was calculated from the date they enrolled in our study to the date of death. For the survivor, survival time was identified as right-censored at the date of the latest follow-up. Those who could not be found and contacted were recorded as "lost to follow-up."

Measurement of Covariates

Covariate information was collected via face-to-face structured questionnaires and biochemistry assays. Covariates in our analyses included sociodemographic information (age, sex, education, and residence), lifestyle (smoking status, alcohol consumption, exercise, and dietary habits), physical examination (body mass index [BMI], systolic blood pressure [SBP], and diastolic blood pressure [DBP]), medical history (hypertension, diabetes, and cardiovascular disease [CVD]), Mini-Mental State Examination (MMSE) score, frailty status, and biochemical indicators (plasma cholesterol, triglycerides, and fasting blood glucose).

Dietary habits include vegetable intake, fruit intake, and meat intake. For the frequencies of food intakes, "almost every day" or "often" were categorized into "often" and "occasionally" and "rarely or never" was categorized into "not often." For exercise, "yes" or "no" was determined from the question, "Do you do exercises regularly at present?." MMSE (32) is a practical scale for grading the cognitive state, and the oldest-old in China with MMSE scores below 24 could be defined as having a cognitive impairment (33). Frailty status was classified according to the Study of Osteoporotic Fractures (SOF) index (34) using three components as follows: (1) weight loss (BMI < 18.5 kg/m^2); (2) inability to rise from a chair without using arms; (3) reduced energy level, defined by a "yes" response to the question, "For at least the last 6 months have you been limited in activities people usually do, because of a health problem?"; the status was categorized as robust (no components), prefrail (1 component) or frail (2 or 3 components), which has been shown to be an applicable indicator of biological age in Chinese older adults (35). For the medical history, hypertension was defined as SBP$\geq$140 mmHg and/or DBP$\geq$90 mmHg based on 2018 Chinese guidelines for the management of hypertension (36); diabetes was defined as fasting blood glucose$\geq$7.0 mmol/L based on National guidelines for the prevention and control of diabetes in primary care (37) for the Chinese population; CVD was determined by the self-report of the participants.

Statistical Analysis

A table for baseline characteristics was generated using descriptive statistics stratified by hsCRP quartiles (mg/L). Continuous data were described by medians and interquartile ranges (IQR), and categorical data were described by frequencies and percentages (%). Hypotheses regarding differences in characteristics across quartiles of hsCRP were analyzed using linear regression for continuous variables and χ^2-tests for categorical variables.

Kaplan-Meier curves were generated for the quartiles of hsCRP concentrations, and log-rank tests were used to compare different quartile subgroups. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) with 95% confidential intervals (95% CIs) of mortality by hsCRP quartiles, with the lowest quartile (Q1) as the reference group. The Cox models were adjusted for potential confounders that may be associated with both hsCRP concentrations and mortality. The following three models with different adjustments were used: (1) the first model (model 1) tested the association between hsCRP and mortality, controlling for age and sex; (2) the second model (model 2) was further adjusted for other baseline characteristics, namely, education time (0 year or $\geq$1 year), residence status (rural or urban), smoking status (current or not current), alcohol consumption (current or not current), vegetable intake (often or not often), fruit intake (often or not often), meat intake (often or not often), and exercise (yes or no); and (3) the third adjusted model (model 3) was further adjusted for physical examination, disease status, and biochemical indicators. The aforementioned covariates included BMI (continuous), MMSE scores (continuous), frailty status (frail, prefrail, robust), hypertension (yes or no), diabetes (yes or no), CVD (yes or no), cholesterol (continuous), and triglycerides (continuous). Model 3 was considered to be fully adjusted. Tests of linear trends were performed by treating the median values for each quartile of hsCRP as a continuous variable. A supplementary analysis was also conducted based on the recommendation for relative risk categories of hsCRP levels (38), namely, < 1.0 mg/L (low risk), 1.0–3.0 mg/L (average risk), and > 3.0 mg/L (high risk).

The subgroup analyses of HRs for mortality by each 10 mg/L increase in hsCRP were performed according to sex (men or women), age (80+ years, 90+ years, and 100+ years), education, residence, smoking status, alcohol consumption, fruit intake, meat intake, vegetable intake, exercise, BMI ($<$18.5 kg/m^2, $\geq$18.5 and $<$24 kg/m^2, $\geq$24 kg/m^2), MMSE ($<$24 or $\geq$24), frailty status. Possible interaction effects were explored by groups from the abovementioned characteristics and a likelihood ratio test was performed to test for interactions by comparing the statistical fit of models with and without interaction terms in the fully adjusted model.

We also conducted sensitivity analyses to examine the robustness of our findings: (1) to exclude participants who died during the first 1 year of follow-up; (2) participants were divided by tertiles and quintiles of hsCRP concentrations.

Analyses were conducted using Stata version 14.0 (College Station, Texas). A $P < 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

Among 2,206 individuals, the median age of participants was 93 years (IQR: 86-100 years). A total of 1,417 were women (64.23%), and 1,905 were living in rural areas (87.19%). Baseline

TABLE 1 | Characteristics of participants by quartiles of high-sensitivity C-reactive Protein.

	Overall	High-sensitivity C-reactive Protein[a] (mg/L)				*P*
		Q1 ≥0.46	Q2 0.47–1.13	Q3 1.14–2.92	Q4 ≥2.93	
No. of participants	2,206	564	547	544	551	
Age, median (IQR), years	93 (86, 100)	93 (87, 100)	92 (85, 100)	92 (86, 100)	94 (88, 100)	0.389
Women, *n* (%)	1,417 (64.23)	405 (71.81)	344 (62.89)	336 (61.76)	332 (60.25)	<0.001
Residence, *n* (%)						0.102
Urban	280 (12.81)	64 (11.43)	58 (10.70)	78 (14.42)	80 (14.76)	
Rural	1,905 (87.19)	496 (88.57)	484 (89.30)	463 (85.58)	462 (85.24)	
Education time, years						0.706
0	1,714 (78.41)	444 (79.86)	417 (76.94)	424 (78.23)	429 (78.57)	
≥1	472 (21.59)	112 (20.14)	125 (23.06)	118 (21.77)	117 (21.43)	
Smoking status, *n* (%)						0.986
Current	220 (10.22)	56 (10.13)	53 (9.98)	54 (10.13)	57 (10.63)	
Not current	1,933 (89.78)	497 (89.87)	478 (90.02)	479 (89.87)	479 (89.37)	
Alcohol drinking status, *n* (%)						0.780
Current	254 (11.81)	68 (12.34)	67 (12.64)	61 (11.47)	58 (10.80)	
Not current	1,896 (88.19)	483 (87.66)	463 (87.36)	471 (88.53)	479 (89.20)	
Frequent vegetable intake, *n* (%)[b]	1,240 (57.57)	309 (55.98)	325 (61.21)	315 (59.10)	291 (54.09)	0.085
Frequent fruit intake, *n* (%)[b]	795 (36.75)	223 (40.11)	205 (38.46)	203 (37.94)	164 (30.43)	0.005
Frequent meat intake, *n* (%)[b]	1,024 (48.51)	251 (45.72)	271 (52.62)	277 (53.47)	225 (42.53)	<0.001
Habitual exercise, *n* (%)[c]	263 (12.51)	82 (15.27)	63 (12.14)	61 (11.66)	57 (10.90)	0.146
Medical history						
Hypertension, *n* (%)	841 (38.12)	254 (45.04)	201 (36.75)	191 (35.11)	195 (35.39)	<0.001
Diabetes, *n* (%)	189 (8.57)	34 (6.03)	38 (6.95)	58 (10.66)	36 (6.53)	0.005
CVD, *n* (%)	311 (14.10)	71 (12.59)	69 (12.61)	83 (15.26)	88 (15.97)	0.405
Frailty						0.002
Frail, *n* (%)	740 (33.54)	194 (34.40)	159 (29.07)	168 (30.88)	219 (39.75)	
Prefrail, *n* (%)	753 (34.13)	193 (34.22)	189 (34.55)	186 (34.19)	185 (33.58)	
Robust, *n* (%)	713 (32.32)	177 (31.38)	199 (36.38)	190 (34.93)	147 (26.68)	
MMSE scores, median (IQR)	25 (18, 28)	25 (17, 28)	26 (19, 28)	26 (19, 28)	24 (16, 28)	0.321
BMI, median (IQR), kg/m^2	20.00 (17.78, 22.81)	19.48 (17.58, 22.03)	20.41 (18.29, 23.45)	20.34 (18.03, 22.96)	19.93 (17.78, 22.75)	0.461
Systolic pressure, median (IQR), mmHg	140 (126, 160)	143 (130, 160)	140 (128, 160)	141.5 (127.5, 160)	140 (121, 155.5)	<0.001
Total cholesterol, median (IQR), mmol/L	4.31 (3.67, 5.02)	4.38 (3.68, 5.02)	4.33 (3.75, 5.02)	4.43 (3.78, 5.17)	4.07 (3.5, 4.83)	0.014
Triglycerides, median (IQR), mmol/L	0.86 (0.64, 1.19)	0.83 (0.61, 1.12)	0.88 (0.66, 1.23)	0.92 (0.67, 1.28)	0.84 (0.63, 1.17)	0.132
Glucose, median (IQR), mmol/L	4.68 (4.00, 5.45)	4.48 (3.89, 5.17)	4.71 (4.07, 5.45)	4.80 (4.10, 5.54)	4.69 (3.96, 5.67)	0.001

hsCRP, high-sensitivity C-reactive protein; CVD, cardiovascular disease; MMSE, Mini-Mental State Examination; BMI, body mass index.
[a] Quartiles of hsCRP: median (IQR), mg/L.
[b] "Frequent intake" was defined by the frequencies of "almost every day" or "often".
[c] "Habitual exercise" was defined as "exercise at present".

characteristics are summarized in **Table 1** by hsCRP quartiles. The median hsCRP concentration was 1.13 mg/L (IQR: 0.46–2.92 mg/L), with no significant associations with age or residence. Of those in the highest quartile of hsCRP, a greater proportion of the adults were women and frail, inclined to have less fruit and meat intakes, reported to have no hypertension or CVD, and tended to have lower levels of cholesterol and glucose.

HsCRP and All-Cause Mortality

During a median follow-up period of 3.1 years (IQR: 1.6–3.9 years), a total of 1,106 all-cause deaths occurred (men: 380; women: 726). **Figure 2** displays the Kaplan-Meier curves for all-cause mortality by quartiles of hsCRP. The log-rank tests showed significant differences in all-cause mortality among different levels of hsCRP ($P < 0.001$). **Table 2** presents the association between hsCRP and mortality. Compared to the lowest quartile, the fully adjusted HRs of the second, third, and fourth quartiles were 1.17 (95% CI: 0.94, 1.46), 1.28 (95% CI: 1.01, 1.61), and 1.49 (95% CI: 1.20, 1.87), respectively (**Table 2**). The risk of all-cause mortality increased with elevated hsCRP ($P < 0.001$). Compared to those with hsCRP <1.0 mg/L, individuals with hsCRP > 3.0 mg/L had a significantly higher risk (HR: 1.39; 95% CI: 1.14, 1.70) of all-cause mortality even after full adjustment.

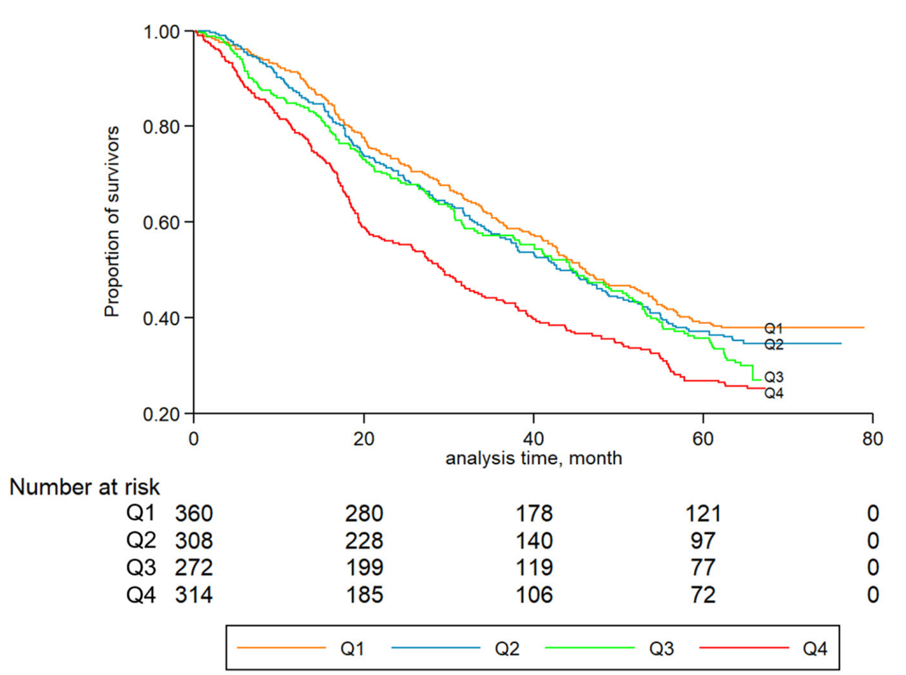

FIGURE 2 | Kaplan-Meier graphs for all-cause mortality by quartiles of CRP.

TABLE 2 | Association between hsCRP and all-cause mortality.

	Deaths/*N*	**HR [95% CI][a] for all-cause mortality**		
		Model 1	**Model 2**	**Model 3**
Quartiles of hsCRP				
Q1	263/491	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2	264/493	1.15 (0.94, 1.40)	1.10 (0.89, 1.36)	1.17 (0.94, 1.46)
Q3	271/483	1.27 (1.03, 1.55)	1.24 (1.00, 1.53)	1.28 (1.01, 1.61)
Q4	308/470	1.53 (1.27, 1.86)	1.50 (1.23, 1.84)	1.49 (1.20, 1.87)
P-trend		<0.001	<0.001	<0.001
Levels of hsCRP				
<1.0 mg/L	491/911	1.00 (reference)	1.00 (reference)	1.00 (reference)
1–3.0 mg/L	312/565	1.17 (0.98, 1.39)	1.18 (0.98, 1.41)	1.17 (0.96, 1.42)
>3.0 mg/L	303/461	1.45 (1.22, 1.71)	1.44 (1.21, 1.73)	1.39 (1.14, 1.70)
P-trend		<0.001	<0.001	0.001

[a]HR, hazard ratio; CI, confidence interval.
Model 1: adjusted for age, sex.
Model 2: adjusted for age, sex, education, residence, smoking, drinking, exercise, fruit intake, meat intake, vegetable intake.
Model 3: adjusted for age, sex, education, residence, smoking, drinking, exercise, fruit intake, meat intake, vegetable intake, BMI, MMSE, frailty, hypertension, diabetes, CVD, cholesterol, triglycerides.

Subgroup Analyses

Subgroup analyses stratified by major confounders are presented in **Table 3**. The HRs showed similar results with no significant differences across most subgroups defined by age, sex, education, residence, drinking status, vegetable intake, fruit intake, meat intake, exercise, BMI, frailty status, MMSE scores (all P for interaction > 0.05). However, a significant interaction from smoking status was noted ($P = 0.011$), where an increased risk of hsCRP with all-cause mortality showed among non-current smokers (HR: 1.17; 95% CI: 1.07, 1.28), but no significance was observed in current smokers (HR: 0.83; 95% CI: 0.66, 1.18).

Sensitivity Analyses

In the sensitivity analyses, we did not find notable changes in the results after excluding deaths during the first

TABLE 3 | Subgroup analyses for the hazard ratio of all-cause mortality for each 10 mg/L increase in hsCRP.

Subgroup	HR [95%CI][a]	P for interaction
Age		0.214
80+ years	1.02 (0.85, 1.23)	
90+ years	1.04 (0.93, 1.16)	
100+ years	1.23 (1.05, 1.45)	
Sex		0.135
Women	1.16 (1.04, 1.29)	
Men	0.98 (0.87, 1.10)	
Education time		0.226
0 year	1.11 (1.02, 1.20)	
≥1 year	0.92 (0.68, 1.24)	
Residence		0.418
Urban	0.95 (0.76, 1.18)	
Rural	1.10 (1.01, 1.19)	
Smoking status		0.011
Current	0.83 (0.66, 1.03)	
Not current	1.17 (1.07, 1.28)	
Drinking status		0.446
Current	0.98 (0.68, 1.40)	
Not current	1.08 (0.10, 1.17)	
Habitual exercise		0.820
Yes	1.02 (0.63 1.67)	
No	1.08 (1.00, 1.17)	
Vegetable intake		0.289
Often	1.16 (1.00, 1.34)	
Not often	1.05 (0.95, 1.16)	
Fruit intake		0.125
Often	1.18 (0.98, 1.43)	
Not often	1.03 (0.94, 1.13)	
Meat intake		0.646
Often	1.07 (0.89, 1.29)	
Not often	1.09 (1.00, 1.18)	
BMI		0.798
<18.5	1.14 (0.98, 1.32)	
≥18.5 and <24	1.04 (0.94, 1.16)	
≥24	0.99 (0.73, 1.35)	
MMSE scores		0.556
<24	1.10 (1.00, 1.21)	
≥24	1.05 (0.91, 1.21)	
Frailty		0.784
Frail	1.08 (0.95, 1.22)	
Prefrail	1.10 (0.97, 1.25)	
Robust	1.00 (0.81, 1.23)	

[a] *HR, hazard ratio; CI, confidence interval.*
HRs were adjusted for age, sex, education, residence, smoking, drinking, exercise, fruit intake, meat intake, vegetable intake, BMI, MMSE, frailty, hypertension, diabetes, CVD, cholesterol, triglycerides.

1 year of follow-up (**Supplementary Table 1**). Similar associations and trends were observed when participants were divided by tertiles (**Supplementary Table 2**) and quintiles (**Supplementary Table 3**) of hsCRP concentrations.

DISCUSSION

In this population-based study of the oldest old adults living in Chinese longevity areas, the participants with higher hsCRP concentrations had an increased risk of mortality, even after adjusting for potential confounders. The association of hsCRP with all-cause mortality was less likely to be modified by sociodemographic factors, physical examinations, biochemical indicators and most lifestyle factors, except for smoking status.

Our findings are consistent with previous studies demonstrating positive associations between hsCRP and all-cause mortality, which are significant at higher levels of the hsCRP distribution (16, 20–22, 24–26, 28). The estimated value might differ by ethnicity because Asian populations tend to have a lower hsCRP level than Western populations (39, 40). A study (41) with 11,623 middle-aged Chinese individuals categorized three groups based on hsCRP levels (< 1.0, 1.0–3.0, and > 3.0 mg/L) and obtained the result that the HR for all-cause mortality in the > 3.0 group was 2.64 (95% CI: 1.74, 4.01). This difference inferred that the estimate might wane with age or that the sample size of our current study was not sufficient to provide power to detect a difference.

It is also important to note that sex was not a modifier in our study. Some studies showed a positive association in both sexes (9, 24, 27), while significant differences appeared to exist in a single sex [mostly men (29, 42, 43)]. However, whether men or women were at a greater risk remains controversial (9, 24, 43, 44). The differential effect of hsCRP in predicting all-cause mortality risk by sex warrants further investigation. Smoking status is another novel point in which significant interaction was found. However, the estimate seemed to be stronger in non-smokers, though both stratifications showed no significant differences. One possibility is that inflammation adaption might occur in the human body during the period of habitual smoking, resulting in a lower hazard to current smokers than to those who did not smoke during the same period. Evidence showed that smoking cessation does not reduce CRP (45), or the time from smoking cessation may influence the concentrations (46). From another consideration, a limited sample size leads to a lack of statistical significance in the estimate, and even interaction exists. But in our study, we did not take this into account during grouping, which might cause misclassification bias. The interaction observed by smoking status warrants further research.

Potential limitations of the current study should be considered in evaluating our results. Our study was observational in nature, and we cannot rule out the possibility of reverse causality; therefore, hsCRP might also be a consequence of diseases rather than a cause. Moreover, the residual confounded by other unmeasured or unknown factors likely existed and potentially results were biased in an unknown direction despite our full adjustment in analyses, such as chronic diseases, which were self-reported thus residual confounding may still exist. The association might be partly affected by the loss to follow-up, which required further studies to verify this association. Additionally, since information on the subtype of death was not collected in the HABCS, in-depth analyses based on cause-specific mortality are necessary but unable to conduct. Finally, similar to most other studies, the fact that hsCRP was measured only once at baseline is a potential limitation because random fluctuation in this parameter over time would tend to increase the variance in the data; how trajectories of hsCRP may influence mortality remains undetermined.

Despite these limitations, this study has noteworthy strengths when compared to prior research. Above all, our findings were based on a prospective study with integrated and detailed baseline, outcome, and blood sample data. The robustness of the outcomes measured and the large sample size of the oldest old adults increases the relevance of our findings. For representativeness, it is believed that community-dwelling older adults are more typical due to the dominance of family care in Chinese society. A distinguishing feature of this study is that all of the longevity areas we investigated provided a distinct population of oldest old adults, which broadens the evidence from existing research with a unique age spectrum.

CONCLUSION

Our analyses indicated that elevated hsCRP concentrations are associated with a higher risk of all-cause mortality among the oldest-old adults. Future studies investigating additional factors of disease and aging processes are needed to conduct a better understanding of the mechanisms.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

CM, X-MS, and X-BW designed the study analysis. Z-JC, FZ, Y-BL, Y-LQ, and LL conducted HABCS and directed its implementation, including quality assurance and control, dataset management, and analytic strategy. Z-HL and F-RL contributed to data cleaning. Y-BL and Z-XY helped supervise the field activities. P-LC and Z-HL designed the study's analytic strategy, performed the statistical analyses, and had primary responsibility for writing the manuscript. P-LC, Z-HL, H-LY, XC, Y-FZ, and H-NL analyzed the data and prepared the manuscript. CM and X-MS are guarantors of the paper. All authors have critically commented on, revised the manuscript, and approved the final version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.824783/full#supplementary-material

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Association Between Fatigue and Falls Risk Among the Elderly Aged Over 75 Years in China: The Chain Mediating Role of Falls Efficacy and Lower Limb Function

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Background: Although fatigue has been shown to be strongly associated with falls risk, very few studies have focused on its mechanism involved in community-dwelling older subjects. The purpose of this study was to explore the relationship between fatigue and falls risk and its internal mechanism by constructing a chain mediation model.

Methods: A cross-sectional study design was adopted. A convenience sample of 270 older adults was recruited from July to October 2021 in an urban community, in Beijing, China. The participants completed the 14-item Fatigue Scale (FS-14), Falls Efficacy Scale International (FES-I), the Short Physical Performance Battery (SPPB) and Fall-Risk Self-Assessment Questionnaire (FRQ) to measure fatigue, falls efficacy, lower limb function and falls risk. The theory of unpleasant symptoms was used as a conceptual framework. Structural equation modeling (SEM) was utilized to test the hypothetical model.

Results: The overall fit of final model was found to be satisfactory: $\chi 2/df = 1.61$, $CFI = 0.971$, $TLI = 0.962$, $RMSEA = 0.049$ (*95% CI* 0.030/0.066) and $SRMR = 0.023$. Fatigue had a direct effect on falls risk ($\beta = 0.559$, $S.E. = 0.089$, *95% CI* 0.380/0.731), and it also had indirect effects on falls risk ($\beta = 0.303$, $S.E. = 0.072$, *95% CI* 0.173/0.460) through mediating factors. Falls efficacy and lower limb function were the main mediating variables, and there was a chain mediating effect ($\beta = 0.015$, $S.E. = 0.010$, *95% CI* 0.003/0.046).

Conclusions: Our study suggests that fatigue can influence falls risk among the elderly in China. There are many mediating paths between fatigue and falls risk. These results may help healthcare professionals to better understand the inherent relationship between fatigue and fall risk that may benefit older adults.

Keywords: aged, fatigue, accidental falls, lower extremity, self-efficacy

INTRODUCTION

A fall is defined as an incident in which a person suddenly and involuntarily came to rest upon the ground or surface lower than his/her original station (1). Although falls occur at all ages, older people are more vulnerable to be injured after a fall, creating functionality reduction, loss of independence and, in some cases, death. According to the World Health Organization's estimation, there are nearly 424,000 fatal falls each year (2), which has become a major public health problem all over the world. In China, falls occur in ∼13.5% of older adults aged 65 to 74 each year, and the rate increases to 18.3% for those in the 75 to 84 years. For adults aged 85 and older, 22.6% are at risk for falling (3). The occurrence of falls or falls risk depends on extrinsic factors and intrinsic factors. Fatigue has been listed as one main intrinsic factor among older adults (4, 5). Thus, a good way to reduce falls risk is to improve fatigue. However, as often in geriatrics, fatigue is often seen as a marker of aged-related accumulation of deficits (6), making it difficult to intervene against directly. Approaches that indirectly ease the impact of fatigue and falls risk, for instance interventions against mediating factors, may therefore be used instead. Does fatigue affect falls risk through other factors?

The Theory of Unpleasant Symptoms (TOUS), a middle-range theory, is proposed as a means for integrating existing information about a multitude of symptoms. It has three major components: influencing factors (give rise to or affect the nature of the symptom experience), symptoms (the individual is experiencing) and performance outcomes (the consequences of the symptom experience). Influencing factors are those physiologic, psychologic and situational factors that influence the: "occurrence, intensity, timing, distress level and quality of symptoms" (7). The TOUS is one mechanism for providing a diverse and holistic way to understand symptoms experience, including understanding the multidimensional nature of symptoms, as well as the factors influencing symptoms and the consequences of symptoms (8). Therefore, TOUS was chosen as the conceptual framework of our study. In the present study, fatigue was treated as symptoms, falls risk as performance outcomes, then lower limb function and falls efficacy as influencing factors.

Firstly, we hypothesized that lower limb function may be an important mediator variable. For one thing, fatigue may have an impact on lower limb function. A large body of evidences suggested that fatigue older adults experienced was significantly related to the decline of lower limb function, including walking speed, lower mobility and weaker strength (9, 10). Further, participants reporting frequent fatigue at early old age had slower chair rise (β −3.10 rep./min) and TUG speed (β −4.95 cm/s) when compared with those without fatigue (11). For another, lower limb function may have an impact on falls risk. The previous findings confirmed that lower limb strength and gait patterns differed between subjects with and without falls risk (12, 13). Another former study provided insight into the association between balance function and falls risk, concluding that there was an increasing trend across age group in terms of the prevalence of falls and perceived instability among older adults ($X^2 = 20.145$ and P-value < 0.001) (14). In conclusion, both fatigue and lower limb function can affect falls risk, while fatigue can predict lower limb function. Therefore, lower limb function may play an important intermediary role between fatigue and falls risk.

Secondly, we hypothesized that falls efficacy might be another important mediator. Falls efficacy measures older person's perceptions of his or her capabilities in not falling when performing some activities in different environments (15). Research on fatigue and falls efficacy showed that fatigue was significantly associated with falls efficacy (P-value ≤ 0.002) (16). Fatigued individuals reported significantly higher falls efficacy scale (FES) (P-value < 0.05), indicating less confidence in the performance of daily activities without falling (17). In terms of the relationship between falls efficacy and falls risk, researchers found that falls efficacy was observed to be a predictor of falls risk (18). Furthermore, lower falls efficacy was associated with higher falls incidence (19). The average FES score was significantly higher in fallers (19.2 ± 13.1 for fallers, 14.2 ± 8.3 for Non-fallers, P-value $= 0.001$) (20). All above mean that fatigue can affect an individual's falls risk by improving falls efficacy. Therefore, falls efficacy may also be an important mediator between fatigue and falls risk.

Thirdly, although the above analysis shows that lower limb function and falls efficacy may mediate the relationship between fatigue and falls risk among the elderly, this study holds that they do not simply play an independent mediating role but may also have a chain mediation effect. In addition to the direct effect of lower limb function and falls efficacy on the relationship between fatigue and falls risk mentioned, there is also a correlation between lower limb function and falls efficacy. As people age, the perceived loss of balance in static as well as dynamic situations and decreased muscle strength in daily life may induce lower falls efficacy (21, 22). On multivariate analyses, falls efficacy was independently associated with the Time Up and Go Test (TUG) ($OR = 1.080$, *95% CI* 1.034–1.128) and 4-Stage Balance Test score ($OR = 0.746$, *95% CI* 0.597–0.931), implying the relationship between the quality of gait and balance and falls efficacy (23). Therefore, we speculate that lower limb function can influence falls risk through falls efficacy.

To our knowledge, very few studies have assessed the link between fatigue and falls risk in community-dwelling older subjects. Will fatigue have an impact on falls risk through lower limb function and falls efficacy? There is a lack of in-depth research on the relationship of falls risk on fatigue through *lower limb function and falls efficacy*, especially the existence of the chain mediating mechanism of falls risk on fatigue through "*lower limb function and falls efficacy*". Based on these, we plan to construct a chain mediation model in order to explore the relationship between fatigue and falls risk and its internal mechanism this study. Our conceptual model illustrating the hypothesized relationships is presented in **Figure 1**.

Accordingly, we hypothesized that as:

H1. Fatigue will be statistically significant associated with lower limb function of the older adults.

H2. Fatigue will be statistically significant associated with falls efficacy of the older adults.

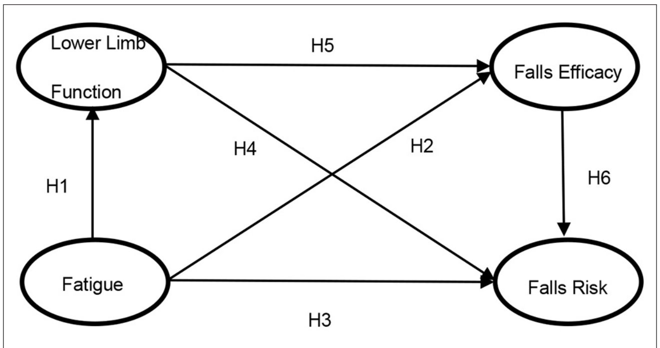

FIGURE 1 | Hypothesized Structural Equation Modeling (SEM).

H3. Fatigue will be statistically significant associated with falls risk of the older adults.

H4. Lower limb function will be statistically significant associated with falls risk of the older adults.

H5. Lower limb function will be statistically significant associated with falls efficacy of the older adults.

H6. Falls efficacy will be statistically significant associated with falls risk of the older adults.

MATERIALS AND METHODS

Design and Participants

Analysis was based on a cross-sectional study, which was conducted from July to October 2021 in an urban community, in Beijing, China. A convenience sample of older adults were selected to complete this face-to-face survey. Inclusion criteria were as follows: (a) 75 years of age or older, (b) ability to walk without or with a walking aid, (c) stable vital signs, (d) ability to communicate and understand effectively and (e) informed consent to participate voluntarily. The participants were excluded if they had been diagnosed with mental illness, dementia, reading or communication disabilities, or other forms of major disease. All participants could opt out of the survey at any time.

The balance between sample size and overall fit of structural equation modeling (SEM) was quite difficult. According to the research of Schumacker and Lomax, the sample size of most SEM studies is between 200 and 500 (24). Loehlin believed that in SEM model analysis, if the sample size did not reach more than 200, there should be at least 100 samples (25). Similarly, Mueller thought the sample size should be at least 100, and 200 was better (26). Therefore, the sample size of this study was at least 200.

The study was reported following the guidelines of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE). Ethical approval for this survey was obtained. This study also has been supported by a funding.

Instruments

The 14-item Fatigue Scale (FS-14) (27) is a self-rating scale containing 14 items. It is developed to reflect the severity of two different kinds of fatigue (physical fatigue and mental fatigue). The participants respond yes/no (yes = 1, no = 0) for each item, and the total scales range from 0 to 14 points. Higher scores indicate more severe fatigue symptoms. Cronbach's α ranged from 0.88 to 0.90 for all items.

Falls Efficacy Scale International (FES-I) (28), a 16-item instrument, is consisted of both easy and more complex physical and social activities. It assesses level of concern about falling when carrying out each activity on a four-point scale (1 = not at all concerned, 4 = very concerned). Higher total scores indicate more fear of falling. FES-I is suitable for use in a range of languages and cultural contexts, permitting direct comparison between studies and populations in different countries and settings. Cronbach's α varied from 0.90, 0.921 and 0.97 in German, Chinese and UK samples (29, 30).

The Short Physical Performance Battery (SPPB) (31) measures three components of lower limb function: standing balance, walking speed and chair stands. In the standing balance test, participants attempted to maintain three positions for 10 s each one after the other: side-by-side, semi-tandem and full tandem. Performances were scored as follows: 0: not attempted or tried but unable; 1: the side-by-side but not the semi-tandem for 10 s; 2: the semi-tandem for 10 s but the full tandem for <3 s; 3: the full tandem for 3 to 9 s; 4: the full tandem for 10 s. In the walking speed test, participants were required to walk an 8-foot walking course twice and time on the faster walk was recorded. Quartiles of time were scored as follows: 0: not complete; 1: $\geq$5.7 s; 2: 4.1 to 5.6 s; 3: 3.2 to 4.0 s; 4: $\leq$3.1 s. In the chair stands test, participants were asked to rise from a chair and sit down five times as quickly and safely as possible with their arms folded. Quartiles of time were scored as follows: 0: not complete; 1: $\geq$16.7 s; 2: 16.6 to 13.7 s; 3:13.6 to 11.2 s; 4: $\leq$11.1 s. The summary performance score ranging from 0 to 12 was created by summing each of the three tests. Cronbach's α was 0.76 for the total scale.

Fall-Risk Self-Assessment Questionnaire (FRQ) is a short, 12-item instrument specifically designed to assess their own fall risks for community dwelling seniors. It was revised by Rubenstein et al. (32) from Vivrette et al. (33). Its items require a yes/no response. The total score can be obtained by summing the total number of points for all "yes" responses (giving 2 points to questions 1 and 5 and 1 point to all other questions). Participants scoring $\geq$4 (maximum score of 14 with a minimum of 0) are considered to be at an indicated risk. The scale has been applied to Chinese older adults with good internal consistency, with Cronbach's α of 0.724 (34).

Data Collection

The participants were contacted and recruited through the staff of community health service station. The older adults who met the inclusion criteria were invited to participate in the investigation. Data were collected using structured questionnaires above. A custom-designed questionnaire was used to collect demographic data, including age, sex, ethnicity, marital status, education level, monthly income, financial burden, current dwelling status and current housing type. Due to the age of the participants, the survey was conducted in the form of face-to-face between the investigator and the respondent. To control the quality of survey, all researchers received uniform training before. After completion, the researcher checked whether the items were filled in completely. If there were any missing items, the researcher asked the participant to complete them immediately. The researcher thanked each participant and gave him or her a small gift as a reward after data collection.

Data Analyses

Descriptive statistics were used to summarize sample characteristics and variables. Correlations between the variables were assessed using Pearson's correlation coefficients. To ensure scientificity and validity of sample data, Harman's single-factor test was conducted to rule out possible common method variance bias (35). All the above statistical methods were completed using IBM SPSS Statistics version 26.0. Structural equation modeling (SEM) was used to test the overall model fit because it is based on a confirmatory approach, allows an examination of the relationships among the observed and latent variables in the hypothesized model and accounts for measurement error (Mplus version 7.4). Maximum likelihood (ML) was used for parameter estimation. Results of effects of variables for the structural model were presented with Estimate and S.E., as well as 95% Confidence Intervals (95% *CI*). Bootstrapping, a nonparametric resampling procedure, is an additional method advocated for testing mediation that does not impose the assumption of normality of the sampling distribution (36). The bootstrap test was sampled for 1,000 times in this study. The goodness of model fit was judged using several statistics including $\chi 2/df$ of 3 or less, root mean squared error of approximation (RMSEA) of 0.08 or less (37), standardized root mean squared residual (SRMR) of 0.08 or less (38), Comparative Fit Index (*CFI*) of 0.9 or more and Tucker-Lewis Index (*TLI*) of 0.9 or more. For all analyses, *P*-value < 0.05 was considered statistically significant.

RESULTS

General Characteristics of the Study Sample

A total of 270 participants met the inclusion criteria in this survey, and 12 participants withdrew for personal reasons during the study (**Figure 2**). Thus, 258 participants (106 males and 152 females) were analyzed, corresponding to a response rate of 95.6%. Their age ranged from 75 to 100 (Mean = 82.72, SD = 5.81). The 12 participants (4 males and 8 females) who withdrew ranged in age from 75 to 86 (Mean = 81.17, SD = 3.81). There is no difference between the sociodemographic characteristics of Non-responders and responders. **Table 1** shows the demographic characteristics of the study sample in detail.

Descriptive Statistics and Correlations of Variables

Harman's single-factor test showed that the maximum unrotated factor in this study could only explain 24.18% of the total variance (<40%), which indicated that the potential common method bias in the sample data was within an acceptable range. The correlations were analyzed to test for multicollinearity among the variables before hypothesis testing. **Table 2** presents the descriptive statistics and correlations of the variables. Specifically, a positive correlation was found between fatigue, falls efficacy and falls risk. Low limb function was negatively correlated with fatigue, falls efficacy and falls risk. The correlation coefficients of all the measurement variables in this study ranged from −0.399 to 0.575. Generally, when the absolute value of the correlation coefficient is <0.8, multicollinearity is not considered a problem.

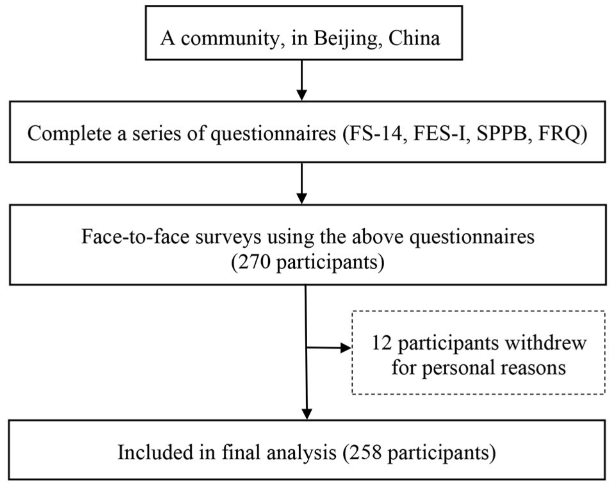

FIGURE 2 | Flow chart of survey process.

Hypothesized Model Tests

Figure 3 presents the final model with standardized path estimates. The overall fit of final model was found to be satisfactory: $\chi 2/df = 1.61$, $CFI = 0.971$, $TLI = 0.962$, $RMSEA = 0.049$ (*95% CI* 0.030/0.066) and $SRMR = 0.023$. **Table 3** shows the decomposition of direct and indirect effects of each factor in the structural model. Through bootstrap test, all of our 6 hypothesized paths were supported. There were one direct path (H3) and three statistically significant indirect paths (H1 to H4, H2 to H6 and H1 to H5 to H6). The effect of fatigue on falls risk was divided into direct effect ($\beta = 0.559$, $S.E. = 0.089$, *95% CI* 0.380/0.731) and total indirect effect ($\beta = 0.303$, $S.E. = 0.072$, *95% CI* 0.173/0.460). Proportion analysis showed that the indirect effect through falls efficacy was largest (67.8%), followed by lower limb function (27.1%), and lower limb function and falls efficacy (5.1%).

DISCUSSION

As for these hypotheses, fatigue, lower limb function, falls efficacy, and falls risk had significant relationships with each other in our sample. In addition, as far as we know this study is the first to examine the underlying internal mechanism of fatigue on falls risk among the elderly in China. We found that fatigue had direct and indirect effects on falls risk through multiple mediations, while verifying the role of lower limb function and falls efficacy on the chain of mediators that act in this relationship.

To our knowledge, very few studies have assessed the link between fatigue and risk of fall in community-dwelling older subjects. As expected, fatigue was a significant risk factor for falling in older population, as demonstrated by the previous

TABLE 1 | Demographics of the study sample.

Variables	Categories	Respondents (*N* = 258)	Non-respondents (*N* = 12)	*P*-value
Age (years)	75 84	163 (63.2)	9 (75.0)	0.486
	85 94	88 (34.1)	3 (25.0)	
	≥95	7 (2.7)	0	
Sex	Male	106 (41.1)	4 (33.3)	0.594
	Female	152 (58.9)	8 (66.7)	
Ethnicity	Han Chinese	241 (93.4)	12 (100.0)	0.359
	Minority	17 (6.6)	0	
Marital status	Married	217 (84.1)	9 (75.0)	0.458
	Unmarried, divorced or widowed	41 (15.9)	3 (25.0)	
Education level	Elementary school or less	15 (5.9)	1 (8.3)	0.377
	Middle school	39 (15.1)	0	
	High school	62 (24.0)	3 (25.0)	
	University and above	142 (55.0)	8 (66.7)	
Monthly income (RMB)	Up to 1,000	13 (5.0)	1 (8.3)	0.386
	1,001–3,000	32 (12.4)	1 (8.3)	
	3,001–5,000	65 (25.2)	5 (41.7)	
	At least 5,000	148 (57.4)	5 (41.7)	
Financial burden	No burden	144 (55.8)	6 (50.0)	0.915
	Mild	68 (26.4)	5 (41.7)	
	Moderate	33 (12.8)	0	
	Heavy	13 (5.0)	1 (8.3)	
Current dwelling status	Living alone	27 (10.5)	3 (25.0)	0.322
	Not living alone	231 (89.5)	9 (75.0)	
Current housing type	Bungalow	9 (3.5)	0	0.807
	Walk-up apartment	83 (32.2)	4 (33.3)	
	Elevator apartment	166 (64.3)	8 (66.7)	

RMB, Renminbi.

TABLE 2 | Descriptive statistics and correlation coefficients among variables in respondents (*N* = 258).

	Scale range	Mean (SD)	1	2	3	4
1 Fatigue	0–14	7.64 (3.21)	1			
2 Lower Limb Function	0–12	9.13 (2.65)	−0.246**	1		
3 Falls Efficacy	16–64	23.20 (7.52)	0.483**	−0.362**	1	
4 Falls Risk	0–14	5.23 (3.04)	0.563**	−0.399**	0.575**	1

** *Correlation is significant at the 0.01 level (two-tailed).*

study (39). The direct relationship between fatigue and falls risk we reported has been testified in a systematic review (5). Similarly, recent findings suggested that the severity of fatigue was associated with the risk of falls for community dwelling older adults even after adjustment for possible confounding factors, which is consist with our findings (40). This implies that the importance of fatigue in predicting incidence or risk of falls is applicable to Chinese older adults. Furthermore, among all multiple paths from fatigue to falls risk, mediating the path through falls efficacy was found to be dominant in this study (β = 0.205, *S.E.* = 0.063, *95% CI* 0.104/0.344). Falls efficacy originated from self-efficacy theory (SET) (41), which referred to an individual's perception of capabilities at avoiding falls during essential, nonhazardous activities of daily living (42). In consideration of falls risk in older persons, falls efficacy should not be underestimated. Our result tended to support that the assessment of falls efficacy may be nearly a specific tool to assess falls risk. Meanwhile, there are relatively few studies that directly examine the relationship between fatigue and falls efficacy, our findings also provide evidence that improving fatigue can facilitate falls efficacy in one's personal life, thereby reducing falls risk.

Our research showed through the results of the Bootstrap test program for the intermediary effect that fatigue can affect falls risk among Chinese older adults through lower limb function, which affected through part of the intermediary effect of falls efficacy. In other words, lower limb function partly affected falls risk by influencing falls efficacy. This verified H1 to H5 to h6 that "*lower limb function and falls efficacy*" played a chained intermediary role between fatigue and falls risk, which showed that people with less fatigue are more likely to have better lower limb function, leading to higher falls efficacy, to promote falls risk among the elderly in China. From the perspective of gerontology, the weakness of physiological function made the elderly more susceptible to fatigue, which in turn affects the range of lower limb motion to some extent (20). On the other hand, reduced capacity to produce strength in the lower limbs was an important fall predictor among older adults because the capacity to recover balance depended on the magnitude and rate of joint torques that was produced (43). All of these changes in lower limb function had a significant impact on falls efficacy in older adults. That is to say, older adults with poorer lower limb function have lower falls efficacy (44), meaning less confidence in the activities they engage in. Then, the elderly with low falls efficacy tend to limit their own activities in daily activities (45), which gradually reduces lower limb function, thus entering a vicious cycle, namely "poor lower limb function–reduced falls efficacy–worse lower limb function". In general, fatigue can affect falls risk through lower limb function and falls efficacy in our sample.

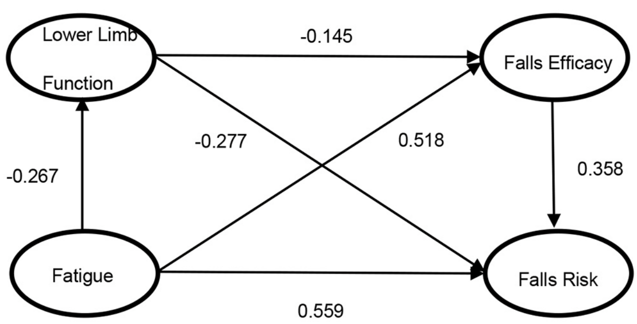

FIGURE 3 | Graphical representations of Final Structural Equation Modeling (SEM).

This study also has some limitations. First, due to some objective factors, we adopted a cross-sectional study design, which prevented us from exploring a potential causal relationship. Although existing studies have provided a solid foundation, the current results can be enriched and expanded through further longitudinal studies. Second, although we used a series of questionnaires, we may still miss some potential influencing factors. Future work should incorporate other relevant factors actively to complete a more comprehensive exploration of structural equation modeling. Third, according to the sociodemographic data, our participants had higher education level, more monthly income, and lower medical burden, which may be related to the city in which the study was conducted. The samples for this study were contacted and recruited from an urban community in Beijing, China. As we all know, Beijing is the capital of China, and the elderly who settled here may have superior material conditions to take care of their own health. In the next, we plan to carry out a wider range of survey to improve the generalizability of our findings. Finally, there may be some threats because the independent variables and outcomes are all self-reported. For example, the participants in this study were aged 75 years and above, who were prone to memory loss, so recall bias may occur when filling in the self-report questionnaires. Additionally, when answering research questions, a person may feel the need to answer in a way that conforms to social norms, which could lead to the emergence of social desirability biases. Future work needs to consider the combination of quantitative and qualitative research, so as to better understand how Chinese older adults understand fatigue and falls risk with minimal bias.

CONCLUSION

In conclusion, this study investigates how fatigue influences falls risk among the elderly in China. There

TABLE 3 | Decomposition of Effects of Variables in Structural Equation Modeling ($N = 258$).

Variables in the model	***Estimate***	***S.E.***	***95% Confidence interval***
Direct effect			
H1 Lower Limb Function on Fatigue	−0.267	0.089	−0.434/−0.071
H2 Falls Efficacy on Fatigue	0.518	0.050	0.415/0.616
H3 Falls Risk on Fatigue	0.559	0.089	0.380/0.731
H4 Falls Risk on Lower Limb Function	−0.277	0.084	−0.427/−0.097
H5 Falls Efficacy on Lower Limb Function	−0.145	0.069	−0.300/−0.020
H6 Falls Risk on Falls Efficacy	0.358	0.094	0.188/0.544
Indirect effect			
Falls Risk on Fatigue through *Lower Limb Function*	0.082	0.039	0.024/0.174
Falls Risk on Fatigue through *Falls Efficacy*	0.205	0.063	0.104/0.344
Falls Risk on Fatigue through *Falls Efficacy and Lower Limb Function*	0.015	0.010	0.003/0.046
Total indirect effect	0.303	0.072	0.173/0.460

are many mediating paths between fatigue and falls risk. Falls efficacy and lower limb function were the main mediating variables. Specifically, the results also confirmed a chain mediation model. According to our results, the development and implementation of intervention strategies focusing on lower limb function and falls efficacy may be helpful to reduce the risk of falls for older adults in China. These results may help healthcare professionals to better understand the inherent relationship between fatigue and fall risk that may benefit older adults.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Chinese PLA General Hospital Medical Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YH conceived the idea with HP. HP supervised the project. YH drafted the manuscript. HZ revised the manuscript. All authors contributed to collect the data and do the data analysis. All authors contributed to the article and approved the submitted version.

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Prevalence of and Factors Associated With Nutritional Supplement Use Among Older Chinese Adults: A Nationwide Cross-Sectional Study in China

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Objective: This study identified the prevalence of nutritional supplement (NS) use among older Chinese adults and explored the factors associated with NS use in this population.

Methods: We used data from 11,089 Chinese men and women aged ≥ 65 years from the 2018 Chinese Longitudinal Healthy Longevity Survey. The chi-square test was used to examine the differences in demographics, health status and lifestyles at different levels. Multivariate logistic regression was used to assess the association between NS use and demographic and lifestyle characteristics.

Results: Twelve percent of Chinese adults aged 65 years and above used NS. In terms of the type of supplement used, the most commonly used was calcium (8.49%), followed by protein (2.73%) and multivitamins (2.40%). In terms of demographic characteristics, women, older people, urban residents with other marital status, higher educational level, better living conditions and better lifestyle habits showed a greater use of some kinds of NS to varying degrees. Factors associated with the use of any NS included female gender [OR = 1.71, 95% confidence intervals (95% CI): 1.09–1.44], age 85–94 (OR = 1.30, 95% CI: 1.08–1.58), urban household registration (*hukou*) (OR = 1.25, 95% CI:1.46–2.00), higher education (primary school and middle school: OR = 1.32, 95% CI:1.14–1.52; high school and above: OR = 1.56, 95% CI:1.25–1.94), average and poor living standard (average: OR = 0.64, 95% CI:0.56–0.73; poor: OR = 0.42, 95% CI:0.32–0.55), poor health status (OR = 1.36, 95% CI:1.13–1.63), former smoking (OR = 1.33, 95% CI:1.11–1.60), and having exercise habits (former exercise: OR = 2.24, 95% CI:1.83–2.74; current exercise: OR = 2.28, 95% CI:2.00–2.61). Women reported taking 2–3 kinds of NSs, and more than 50% of NS users reported taking supplements often.

Conclusion: This study provides information on the current prevalence of NS use among older Chinese adults, and it clarifies the association of NS use with demographic, lifestyle and other factors. Providing scientifically based health guidance on NS use for older people is crucial to promoting their health.

Keywords: nutritional supplement use, older adults, prevalence, associated factors, China

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INTRODUCTION

Due to economic development and changing lifestyles, individuals are increasingly interested in health, wellbeing and self-care (1), especially older people who have greater health care needs and a greater concern for their health. A specific manifestation is their more widespread use of dietary supplements (2). A study of nutritional supplement (NS) use in China from 2010 to 2012 showed that participants aged 60 years and older had the highest rate of NS use among all age groups over 6 years (3).

Although scholars have conducted comprehensive studies on the role of NS in health, little is known about its prevalence, especially among older Chinese adults. Currently, most studies by Chinese scholars on NS use have been conducted in children and pregnant and lactating women, such as the effect of NSs on anemia in children (4) and the use of NSs in pregnant and lactating women (5, 6). Some scholars have studied the use of NSs in older adults with diseases (7), but studies on NS use in the older population are relatively scarce, and the results vary widely. A study by Gong on the use of NSs in China from 2010 to 2012 found that the rate of overall nutrient supplement use among people aged 60 years and older was 1.75% (3), while another 2017 resident survey on NS behaviors concluded that 45.6% of the elderly population had consumed NSs (8). On the one hand, the NS market in China has shown rapid growth over the past 20 years (9). In China, NSs are classified as a health food (10), meaning that supplement products, including vitamins, minerals and amino acids, can be purchased without a prescription, allowing for increased sales and industry expansion through advertising by sellers in the health care industry (11). However, such health-related promotion can also put consumers at risk, which especially affects the most vulnerable populations (12). On the other hand, as health literacy has increased (13, 14), the population has become skeptical of products that are marketed as "health buys." The results from an interview study with older people in Chinese communities showed that many older participants did not trust the marketing of NSs and did not believe that these products would help to improve their health (15). "The Scientific Consensus on the Use of Nutrient Supplements among Chinese Residents" guides residents on the possible negative effects of excessive supplementation (16). Based on the above industry background and the health perceptions of the population, the available evidence does not yet give us an up-to-date picture of NS use in the older populations in China.

To fill the gaps in the literature, the purpose of this study was to examine NS use in the elderly population in China based on a nationwide survey of older adults and to explore the current prevalence of specific NS use and the factors associated with it.

METHODS

Data Source

The data in this study were collected from the Chinese Longitudinal Healthy Longevity Survey (CLHLS), which involved a large-scale, household-based open cohort study. The CLHLS survey sampling covers ∼85% of the total population in China, targeting a substantial amount of centenarians, nonagenarians, and octogenarians, with a targeted random sampling method. It was carried out in eight survey waves during the years 1998–2018 by conducting face-to-face interviews. Each respondent was interviewed by well-trained investigators. It was reported with high reliability and validity in the analyses of health measures, which exceeded widely used criteria (17). More details of the 2018 wave CLHLS data are available in the review by Zheng (18). Detailed instructions about the database are available on the website of Peking University Center for Healthy Aging and Development http://chads.nsd.pku.edu.cn/sjzx/index.htm (accessed on 10 August 2021). The data were made available through an agreement with the Center and can be downloaded from the following website: https://opendata.pku.edu.cn/dataset.xhtml?persistentId= doi: 10.18170/DVN/WBO7LK. We extracted cross-sectional data from the 2018 wave of the CLHLS because information on NS use among older people was only included in 2018 survey. A total of 15,874 respondents was obtained. **Figure 1** displays the exclusion of respondents who did not meet the criteria with incomplete or missing data. A total of 11,089 participants with complete data were included in the analysis. Institutional Review Board (IRB) approval was waived, as our study used secondary data from the public domain.

Measures

Information about nutritional supplements was collected by asking the following questions: "Do you usually take a nutritional supplement?" If the participant answered "yes," further questions were asked, "Do you take (1) protein, (2) calcium, (3) iron, (4) zinc, (5) multivitamin, (6) vitamin A/D, (7) docosahexaenoic acid (DHA) (8) others?" and "How often do you take each kind of nutritional supplement?" Respondents answered each of nutritional supplement with a "yes" or "no" answer, followed by a selection of "seldom/ sometimes/ often" to each NS if the answer is "yes."

All covariates used in the analysis were self-reported data obtained from face-to-face interviews. Gender was categorized as a binary variable: male or female; age was categorized as a categorical variable: 65–74, 75–84, 85–94, 95 years old and above; according to the current type of household registration (*hukou*), older adults were categorized as urban and rural, a binary variable; marital status was divided into married and others (including divorced, widowed and never married) as a binary variable; the educational level was divided into illiterate, primary school and middle school, high school and above, as a categorical variable; the living standard was based on the question "How do you rate your economic status compared with others in your local area?" This question was divided into three groups (very good/good, fair, bad/very bad, as a categorical variable). Health status was defined as the participant's self-rated health scale and was divided into three groups as a categorical variable: very good/good, fair, bad/very bad. Sleep quality was based on self-reported sleep quality (very good/good, fair, bad/very bad, as a categorical variable). The classification of smoking status, drinking status, and exercise status was based on the following questions: "Do you smoke/drink alcohol/do exercises regularly at present?" and "Did you smoke/drink alcohol/do exercises

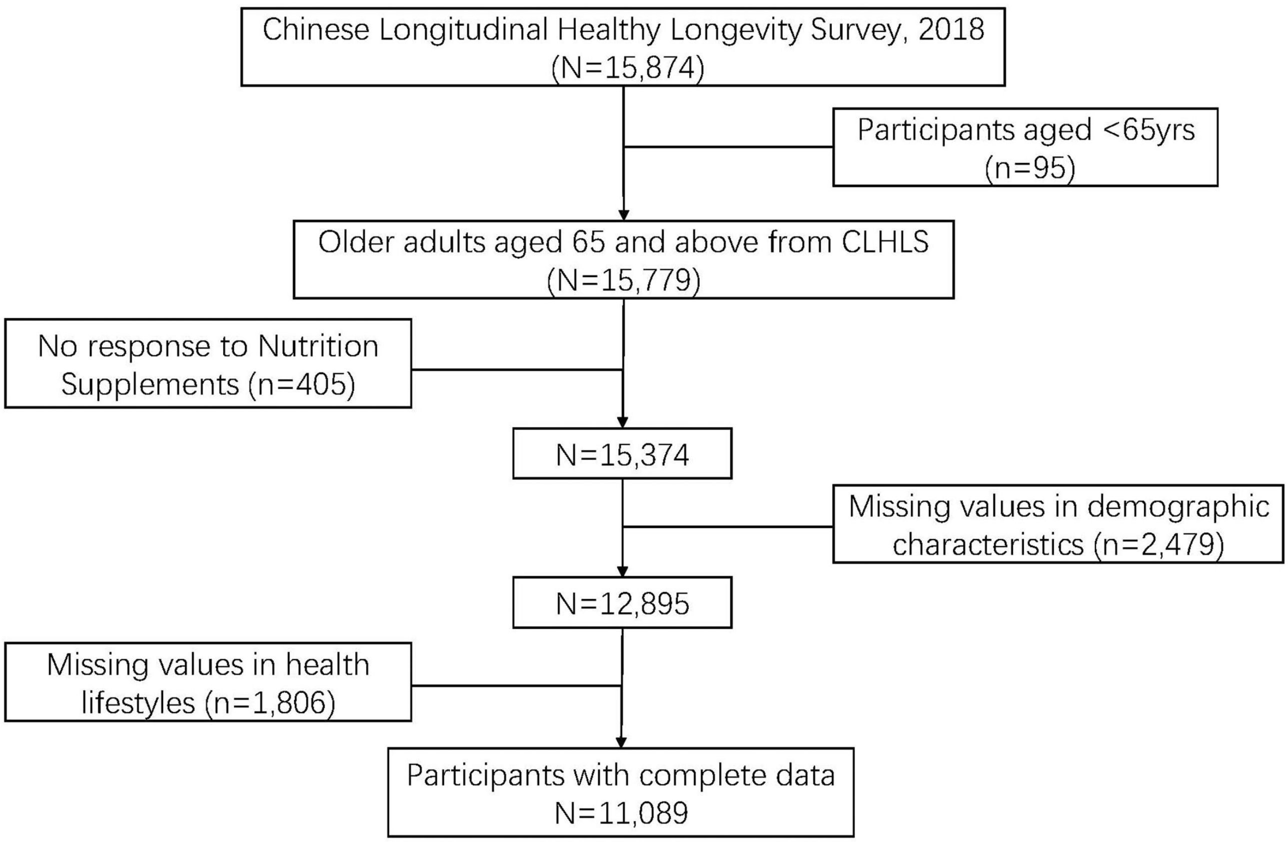

FIGURE 1 | Flowchart of sample screening for study inclusion.

regularly in the past?" It was further divided into three groups: never, former, and current (**Supplementary Table 1**).

Statistical Analysis

The usage rate of NSs was described by the rate and 95% confidence intervals (95% CI). The chi-square test was used to examine the differences in NS use in different demographics, health statuses, and lifestyles. Multivariate logistic regression was used to assess the association between NS use and demographic and lifestyle characteristics. Odds ratios (ORs) and 95% CIs were reported in the results of regression analysis. The regression results were two-tailed with a level of significance of 0.05 ($p < 0.05$). All statistical analyses were performed using STATA 14.0.

RESULTS

Prevalence and Types of NSs Used by Older Adults

Table 1 shows the prevalence and types of NSs used by older adults. A total of 12.28% of the respondents reported using NSs. In terms of the type of NS used, the most commonly used was calcium (8.49%), followed by protein (2.73%) and multivitamins (2.40%); there was less than a 1% probability of iron, zinc, or DHA being used. In terms of demographic characteristics, a larger proportion of females reported using NSs (13.36% in females vs. 10.94% in males, $P < 0.001$), especially calcium (9.6% in females vs. 7.13% in males, $P < 0.001$). The proportion of older adults taking protein, iron, and multivitamins showed an overall increase with age, but the oldest age group had the lowest proportion of calcium use. A greater proportion of urban residents reported using NSs in all categories. Compared with married people, people with other marital statuses had a higher rate of protein usage (2.08% in married people vs. 3.25% in others, $P < 0.001$). The proportion of older adults taking NSs increased with educational level in all categories. Older adults with good living conditions also used more NSs. NS use in older adults was associated with health status, particularly taking calcium and zinc. Older adults with better or worse sleep quality used more NSs but did not show significant differences in specific categories. Smokeless tobacco users who had quit had the highest rate of using NSs, while current smokers had the lowest use, especially for protein, calcium, multivitamins, vitamins A and D and others. The relationship between alcohol drinking and NS use was shown for protein and iron, and again, those drinkers who had quit alcohol drinking had the highest use, and current drinkers had the lowest; for older people with past or current exercise

TABLE 1 | Prevalence (%, 95% confidence interval) and types of NSs used by older adults.

Variables		n	Any NSs	Protein	Calcium	Iron	Zinc	Multivitamin	Vitamin A/D	DHA	Others
Total		11,089	12.28 (11.68–12.91)	2.73 (2.44–3.05)	8.49 (7.98–9.03)	0.84 (0.68–1.03)	0.78 (0.62–0.96)	2.40 (2.12–2.70)	1.89 (1.65–2.16)	0.58 (0.44–0.74)	1.98 (1.73–2.26)
Gender	Male	4,953	10.94 (10.09–11.85)	2.71 (2.27–3.20)	7.13 (6.43–7.88)	0.95 (0.70–1.26)	0.83 (0.59–1.12)	2.38 (1.98–2.85)	1.94 (1.57–2.36)	0.69 (0.48–0.96)	1.92 (1.55–2.34)
	Female	6,136	13.36 (12.52–14.24)	2.75 (2.36–3.20)	9.60 (8.87–10.36)	0.75 (0.55–1.00)	0.73 (0.54–0.98)	2.41 (2.04–2.83)	1.86 (1.54–2.23)	0.49 (0.33–0.70)	2.04 (1.70–2.42)
Age,y	65–74	2,731	11.64 (10.46–12.91)	1.68 (1.24–2.24)	8.79 (7.75–9.91)	0.40 (0.20–0.72)	0.44 (0.23–0.77)	1.72 (1.27–2.28)	1.50 (1.08–2.03)	0.55 (0.31–0.90)	1.57 (1.14–2.12)
	75–84	3,034	12.52 (11.37–13.76)	2.08 (1.60–2.64)	8.83 (7.85–9.90)	0.86 (0.56–1.25)	0.76 (0.48–1.14)	2.44 (1.92–3.05)	1.94 (1.48–2.50)	0.63 (0.38–0.98)	1.94 (1.48–2.50)
	85–94	2,738	13.48 (12.22–14.81)	3.4 (2.75–4.15)	9.24 (8.18–10.39)	1.06 (0.71–1.52)	0.95 (0.06–1.39)	2.78 (2.19–3.46)	2.37 (1.84–3.02)	0.69 (0.42–1.08)	2.34 (1.80–2.98)
	≥95	2,586	11.41 (10.21–12.70)	3.91 (3.19–4.73)	7 (6.05–8.05)	1.04 (0.69–1.52)	0.97 (0.63–1.42)	2.67 (2.08–3.36)	1.74 (1.27–2.32)	0.43 (0.21–0.76)	2.09 (1.57–2.72)
Hukou	Rural	7,836	9.98 (9.21–10.66)	2.12 (1.81–2.46)	7.68 (7.10–8.29)	0.54 (0.39–0.72)	0.5 (0.35–0.68)	1.05 (0.83–1.30)	1.05 (0.83–1.30)	0.20 (0.12–0.33)	1.26 (1.03–1.54)
	Urban	3,253	17.83 (16.53–19.19)	4.21 (3.55–4.96)	10.45 (9.42–11.55)	1.57 (1.17–2.06)	1.44 (1.06–1.92)	5.66 (4.89–6.51)	3.93 (3.29–4.66)	1.48 (1.09–1.95)	3.72 (3.10–4.43)
Marital status	Married	4,896	12.01 (11.11–12.95)	2.08 (1.70–2.52)	8.31 (7.55–9.12)	0.88 (0.64–1.18)	0.71 (0.50–0.99)	2.45 (2.04–2.92)	1.84 (1.48–2.25)	0.61 (0.41–0.87)	1.98 (1.61–2.41)
	Others	6,193	12.5 (11.68–13.35)	3.25 (2.82–3.72)	8.64 (7.95–9.37)	0.81 (0.60–1.06)	0.82 (0.61–1.08)	2.36 (1.99–2.77)	1.94 (1.61–2.31)	0.55 (0.38–0.77)	1.99 (1.65–2.37)
Education level	Illiterate	5,224	10.16 (0.94–11.02)	2.32 (1.93–2.76)	7.68 (6.97–8.43)	0.52 (0.34–0.75)	0.52 (0.34–0.75)	1.19 (0.91–1.52)	1.15 (0.88–1.48)	0.31 (0.18–0.50)	1.42 (1.11–1.78)
	Primary and middle school	4,792	13.11 (12.16–14.09)	2.82 (2.37–3.33)	8.81 (8.02–9.64)	0.83 (0.60–1.13)	0.69 (0.47–0.97)	2.59 (2.16–3.08)	1.94 (1.57–2.37)	0.54 (0.35–0.79)	2.19 (1.80–2.65)
	High school and above	1,073	18.92 (16.62–21.39)	4.38 (3.24–5.78)	11.09 (9.27–13.12)	2.42 (1.59–3.53)	2.42 (1.59–3.53)	7.46 (5.96–9.19)	5.31 (4.05–6.83)	2.05 (1.29–3.09)	3.82 (2.76–5.15)
Living standard	Very good/good	2,168	18.68 (17.06–20.39)	4.75 (3.89–5.73)	12.32 (10.96–13.77)	1.80 (1.28–2.45)	1.71 (1.20–2.34)	4.61 (3.77–5.58)	3.64 (2.90–4.52)	1.29 (0.86–1.86)	2.95 (2.28–3.75)
	Fair	7,801	11.25 (10.56–11.98)	2.35 (2.02–2.71)	7.88 (7.30–8.50)	0.65 (0.49–0.86)	0.59 (0.43–0.79)	2.01 (1.71–2.35)	1.54 (1.28–1.84)	0.44 (0.30–0.61)	1.87 (1.58–2.20)
	Bad/very bad	1,120	7.05 (5.62–8.71)	1.52 (0.89–2.42)	5.36 (4.12–6.84)	0.27 (0.06–0.78)	0.27 (0.05–0.78)	0.80 (0.37–1.52)	0.98 (0.49–1.75)	0.18 (0.02–0.64)	0.89 (0.43–1.64)
Health status	Very good/good	5,203	12.68 (11.79–13.62)	2.94 (2.50–3.44)	8.76 (8.01–9.57)	1.00 (0.75–1.31)	1.00 (0.75–1.31)	2.52 (2.11–2.98)	2.00 (1.64–2.42)	0.69 (0.49–0.96)	1.92 (1.57–2.33)

(Continued)

TABLE 1 | Continued

Variables		*n*	Any NSs	Protein	Calcium	Iron	Zinc	Multivitamin	Vitamin A/D	DHA	Others
	Fair	4,319	11.30 (10.37–12.28)	2.45 (2.01–2.96)	7.76 (6.98–8.59)	0.72 (0.49–1.02)	0.63 (0.41–0.91)	2.32 (1.89–2.81)	1.74 (1.37–2.17)	0.46 (0.28–0.71)	2.01 (1.62–2.48)
	Bad/very bad	1,567	13.66 (11.99–15.46)	2.81 (2.05–3.75)	9.64 (8.22–11.21)	0.64 (0.31–1.17)	0.45 (0.18–0.92)	2.23 (1.56–3.09)	1.98 (1.35–2.80)	0.51 (0.22–1.00)	2.11 (1.45–2.94)
Sleep quality	Very good/good	5,775	12.85 (12.00–13.74)	2.79 (2.38–3.25)	8.59 (7.88–9.34)	0.85 (0.63–1.12)	0.83 (0.61–1.10)	2.39 (2.01–2.82)	1.97 (1.63–2.37)	0.48 (0.32–0.70)	2.20 (1.84–2.61)
	Fair	3,616	11.06 (10.06–12.13)	2.43 (1.96–2.99)	8.21 (7.34–9.16)	0.80 (0.54–1.15)	0.69 (0.45–1.02)	2.41 (1.93–2.96)	1.77 (1.37–2.25)	0.66 (0.43–0.99)	1.69 (1.29–2.16)
	Bad/very bad	1,698	12.96 (11.39–14.65)	3.18 (2.40–4.13)	8.78 (7.47–10.22)	0.88 (0.50–1.45)	0.77 (0.41–1.31)	2.41 (1.74–3.26)	1.88 (1.29–2.65)	0.71 (0.37–0.12)	1.88 (1.29–2.65)
Smoke	Never	7,674	12.51 (11.78–13.27)	2.70 (2.35–3.08)	8.70 (8.08–9.36)	0.85 (0.65–1.08)	0.82 (0.63–1.05)	2.44 (2.10–2.81)	1.97 (1.67–2.30)	0.69 (0.52–0.90)	2.11 (1.81–2.46)
	Former	1,694	14.17 (12.54–15.92)	3.78 (2.92–4.80)	9.15 (7.82–10.62)	1.12 (0.68–1.75)	0.89 (0.50–1.46)	3.07 (2.30–4.01)	2.54 (1.84–3.40)	0.30 (0.10–0.69)	2.18 (1.54–3.00)
	Current	1,721	9.41 (8.07–10.89)	1.86 (1.28–2.61)	6.91 (5.76–8.22)	0.52 (0.24–0.99)	0.46 (0.20–0.91)	1.57 (1.04–2.27)	0.93 (0.53–1.51)	0.35 (0.13–0.76)	1.22 (0.76–1.86)
Drink	Never	8,104	12.64 (11.92–13.38)	2.81 (2.46–3.20)	8.65 (8.05–9.28)	0.80 (0.06–1.02)	0.72 (0.54–0.92)	2.44 (2.12–2.80)	1.92 (1.64–2.25)	0.58 (0.43–0.77)	2.07 (1.77–2.41)
	Former	1,320	12.20 (10.48–14.08)	3.56 (2.63–4.71)	8.03 (6.62–9.63)	1.44 (0.87–2.24)	1.29 (0.75–2.05)	2.58 (1.79–3.58)	2.27 (1.54–3.23)	0.38 (0.12–0.88)	2.12 (1.41–3.05)
	Current	1,665	10.63 (9.19–12.21)	1.68 (1.12–2.42)	8.11 (6.84–9.52)	0.54 (0.25–1.02)	0.66 (0.33–1.18)	2.04 (1.42–2.84)	1.44(0.93–2.14)	0.72 (0.37–1.26)	1.44 (0.93–2.14)
Exercise	Never	6,595	8.10 (7.45–8.78)	1.91 (1.59–2.27)	5.72 (5.17–6.30)	0.44 (0.30–0.63)	0.35 (0.22–0.52)	1.24 (0.99–1.54)	1.05 (0.08–1.32)	0.26 (0.15–0.41)	1.12 (0.88–1.41)
	Former	861	19.62 (17.03–22.44)	4.53 (3.24–6.14)	13.12 (10.94–15.56)	1.97 (1.15–3.14)	2.21 (1.33–3.42)	5.11 (3.74–6.80)	3.72 (2.56–5.21)	0.93 (0.40–1.82)	3.37 (2.27–4.80)
	Current	3,633	18.14 (16.90–19.43)	3.80 (3.20–4.47)	12.44 (11.39–13.56)	1.29 (0.95–1.72)	1.21 (0.88–1.62)	3.85 (3.25–4.53)	3.00 (2.47–3.61)	1.07 (0.76–1.46)	3.22 (2.67–3.85)

TABLE 2 | Logistic regression analysis of factors associated with NSs use.

Variables		Any NSs		Protein		Calcium		Iron		Zinc		Multivitamin		Vitamin A/D		DHA		Others	
		OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Gender	Female	1.71**	1.46–2.00	1.25	0.92–1.70	1.79**	1.49–2.17	1.33	0.78–2.28	1.36	0.78–2.38	1.87**	1.35–2.60	1.36	0.95–1.96	0.69	0.37–1.27	1.35	0.94–1.92
Age,y	75–84	1.09	0.92–1.28	1.18	0.79–1.75	0.97	0.80–1.18	2.43*	1.18–5.00	1.84	0.90–3.79	1.59*	1.08–2.33	1.29	0.85–1.95	1.12	0.55–2.26	1.31	0.87–1.97
	85–94	1.30**	1.08–1.58	2.06**	1.37–3.08	1.08	0.87–1.35	3.85**	1.80–8.27	2.66*	1.23–5.74	2.34**	1.54–3.56	1.76*	1.12–2.76	1.26	0.58–2.75	1.87**	1.20–2.92
	≥95	1.18	0.95–1.46	2.70**	1.75–4.18	0.83	0.65–1.06	4.96**	2.14–11.51	3.05**	1.31–7.12	2.88**	1.80–4.61	1.46	0.86–2.47	0.91	0.35–2.37	2.03**	1.22–3.36
Hukou	Urban	1.25**	1.09–1.44	1.31*	1.00–1.72	0.95	0.80–1.12	1.29	0.78–2.12	1.19	0.71–2.00	2.86**	2.11–3.87	2.05**	1.48–2.86	3.95**	2.06–7.58	1.90**	1.39–2.59
Marital status	Others	1.04	0.90–1.21	1.23	0.91–1.66	1.09	0.92–1.29	0.68	0.41–1.14	0.96	0.56–1.65	0.88	0.64–1.20	1.14	0.81–1.60	1.27	0.69–2.34	0.91	0.65–1.27
Education level	Primary and middle school	1.32**	1.14–1.52	1.40*	1.04–1.88	1.14	0.96–1.35	1.68	0.95–2.95	1.40	0.78–2.52	2.16**	1.52–3.06	1.55*	1.06–2.26	1.09	0.54–2.20	1.46*	1.03–2.07
	High school and above	1.56**	1.25–1.94	1.70*	1.11–2.61	1.27	0.98–1.66	3.49**	1.72–7.05	3.66**	1.79–7.46	3.91**	2.55–5.99	2.80**	1.74–4.48	1.98	0.87–4.51	1.70*	1.05–2.74
Living standard	Fair	0.64**	0.56–0.73	0.59**	0.45–0.77	0.65**	0.55–0.76	0.54**	0.34–0.84	0.53**	0.33–0.84	0.66**	0.50–0.87	0.60**	0.44–0.81	0.54*	0.32–0.93	0.84	0.61–1.15
	Bad/very bad	0.42**	0.32–0.55	0.42**	0.25–0.73	0.44**	0.33–0.60	0.30*	0.09–1.01	0.35	0.10–1.19	0.40*	0.20–0.82	0.51*	0.26–0.99	0.34	0.08–1.50	0.50	0.25–1.01
Health status	Fair	1.02	0.89–1.17	0.96	0.73–1.25	1.00	0.85–1.17	0.78	0.48–1.24	0.70	0.43–1.15	1.02	0.77–1.35	0.99	0.72–1.36	0.73	0.41–1.31	1.26	0.93–1.71
	Bad/very bad	1.36**	1.13–1.63	1.10	0.76–1.59	1.35**	1.10–1.67	0.70	0.34–1.44	0.50	0.22–1.15	1.05	0.70–1.58	1.18	0.76–1.83	0.87	0.38–1.99	1.45	0.94–2.22
Sleep quality	Fair	0.92	0.81–1.06	1.00	0.76–1.32	1.03	0.88–1.21	1.21	0.75–1.96	1.12	0.68–1.86	1.19	0.89–1.58	1.02	0.74–1.41	1.84*	1.04–3.26	0.80	0.58–1.11
	Bad/very bad	1.01	0.85–1.21	1.29	0.93–1.80	1.01	0.82–1.24	1.30	0.70–2.39	1.18	0.62–2.26	1.09	0.75–1.58	0.99	0.65–1.50	1.88	0.92–3.88	0.83	0.55–1.25
Smoke	Former	1.33**	1.11–1.60	1.42*	1.01–2.00	1.28*	1.03–1.60	0.93	0.50–1.71	0.72	0.37–1.41	1.26	0.87–1.84	1.15	0.76–1.74	0.29*	0.11–0.77	0.96	0.63–1.47
	Current	0.96	0.78–1.18	0.92	0.61–1.41	0.99	0.78–1.26	0.70	0.32–1.52	0.58	0.26–1.31	0.97	0.61–1.53	0.58	0.33–1.03	0.47	0.18–1.18	0.71	0.43–1.19
Drink	Former	0.97	0.79–1.18	1.17	0.82–1.68	0.97	0.76–1.23	1.97*	1.09–3.56	2.32**	1.25–4.32	1.17	0.77–1.77	1.26	0.80–1.96	0.94	0.35–2.51	1.10	0.70–1.72
	Current	0.95	0.79–1.15	0.65*	0.42–0.99	1.11	0.89–1.37	0.78	0.37–1.65	1.20	0.59–2.41	1.04	0.69–1.56	0.92	0.58–1.48	1.50	0.73–3.05	0.84	0.53–1.34
Exercise	Former	2.24**	1.83–2.74	1.62*	1.10–2.38	2.43**	1.92–3.08	2.71**	1.43–5.14	4.21**	2.19–8.09	2.04**	1.37–3.03	2.08**	1.33–3.26	1.90	0.78–4.59	1.93**	1.22–3.05
	Current	2.28**	2.00–2.61	2.01**	1.53–2.63	2.87**	1.96–2.67	2.29**	1.38–3.82	2.70**	1.55–4.68	2.14**	1.58–2.90	2.07**	1.48–2.89	2.35**	1.26–4.39	2.51**	1.82–3.47

Reference group in each variable is omitted. OR, odds ratio; CI, confidence interval. * $P < 0.05$, ** $P < 0.01$.

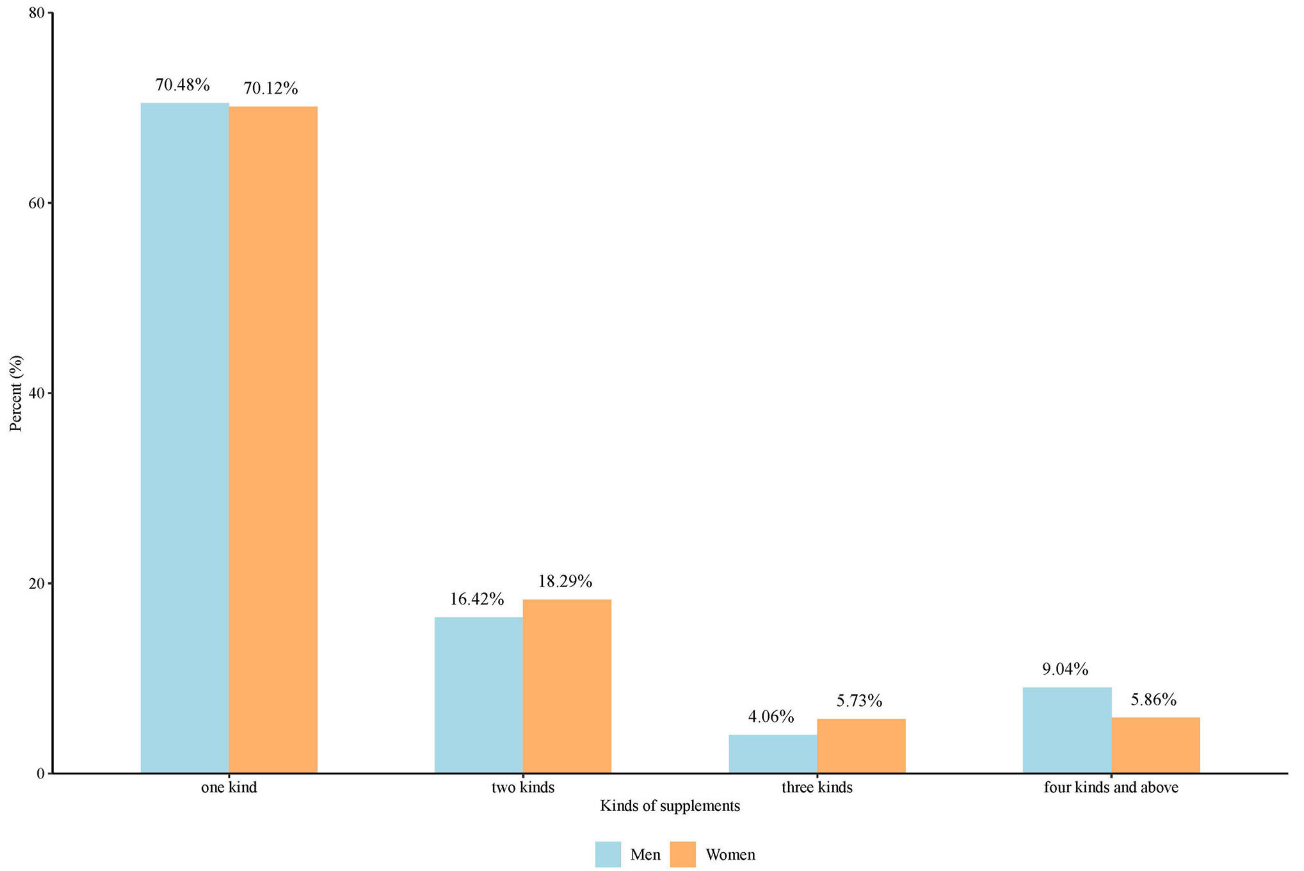

FIGURE 2 | Distribution of the number of supplements taken by gender.

habits, NS use was higher in all categories compared to those who never exercised.

Factors Associated With NS Use

Table 2 shows the results of the multivariate logistic regression examining the factors associated with NS use. The results displayed are for nine full models with all features entered into the logistic regression. Factors associated with the use of any NS included female gender, age 85–94, urban *hukou*, higher education, average and poor living standards, poor health status, former smoking, and exercise habits (former or current exercise). Factors associated with the use of protein included those aged over 85, urban *hukou*, higher education, average and poor living standard, former smoking, current drinking, and exercise habits (former or current exercise). Factors associated with the use of calcium included female gender, average and poor living standards, poor health status, former smoking, and exercise habits (former or current exercise). Factors associated with the use of iron included those aged over 75, high school education and above, average living standard, former smoking, and exercise habits (former or current exercise). Factors associated with the use of zinc included those aged over 85, high school education and above, average living standard, former drinking, and exercise habits (former or current exercise). Factors related to the use of multivitamins included female gender, those aged over 75, urban *hukou*, higher education, average and poor living standards, and exercise habits (former or current exercise). Factors related to the use of vitamins A and D included those aged 85–94 years, urban *hukou*, higher education, average and poor living standards, and exercise habits (former or current exercise). Factors related to DHA use included urban *hukou*, average living standard, average sleep quality, former smoking, and current exercise. Factors related to the use of other NSs included those aged over 85, urban *hukou*, higher education, and exercise habits (former or current exercise).

Distribution of NSs Taken

Figure 2 illustrates the distribution between men and women of the number of supplements taken, with 70.48% of males and 70.12% of females users taking only one NS; 9.04% of males and 5.86% of females took more than four or more NSs. There was a difference in the number of supplements taken by males and females, but the result was only statistically significant at the 10% level ($\chi^2 = 7.113$, $P = 0.068$).

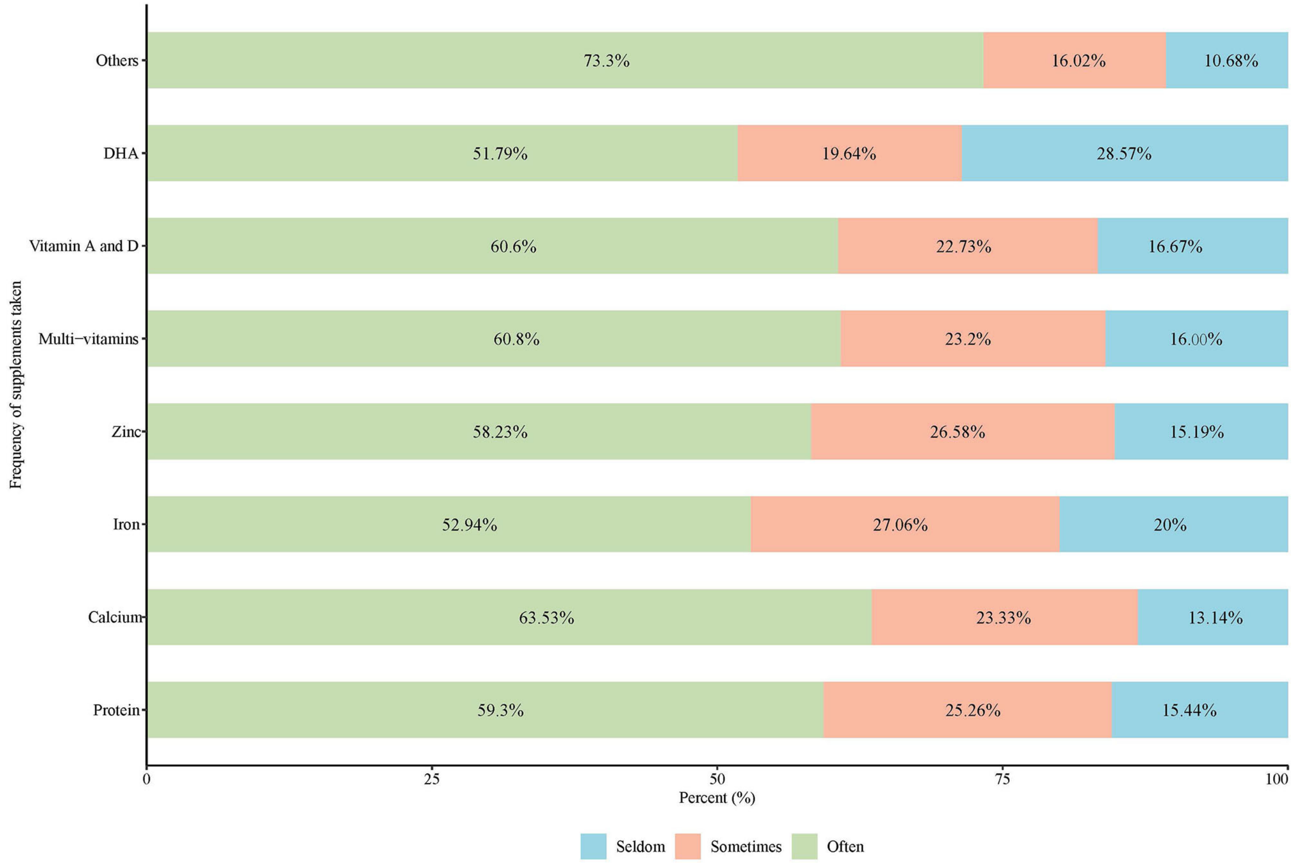

FIGURE 3 | Distribution of the supplements taken by frequency.

More than 50% of NS users reported taking supplements often, with the top three most common types being others, calcium, and multivitamins. DHA and iron were used less frequently (**Figure 3**).

DISCUSSION

This study analyzed the use of NSs and associated factors among older Chinese adults aged 65 years and above. The results of the study showed that the probability of any NS use among older Chinese adults was 12.28%, significantly higher than the 1.75% among those aged 60 years and above reported by China Health and Nutrition Survey (CHNS) in 2010–2012(3) but still lower than the overall prevalence reported in developed countries, such as the United States, the NS use rate for those aged 60 years and above was 74.3% in 2017–2018(19). Previous studies reported that in Australian National Health Survey, the proportion of people aged 70 and over using NS was 52.7% in 2011–2012, and 49.5% in 2014–2015(20, 21). This may be because dietary guidelines in China prioritize adequate dietary sources of nutrients and do not recommend NSs for the general population (3, 22). The difference in prevalence is modest compared to older people in other Asian countries. South Korea reported 16.3% of the population aged 65 years and above using vitamin-mineral supplements in 2007–2008 (23), and Japan reported that the NS use proportion was 12.6% among males and 17.0% among females aged 70 years and above (24).

Our study showed that women used NSs, such as calcium and multivitamins, more often than men. This result is consistent with previous studies that have shown a higher interest in NS use among female consumers (25–27). Some researchers attribute this to women being more concerned than men about their health, as they feel more responsible for the wellbeing of other family members (2). It may also due to gender differences in genetic, epigenetic and hormonal mechanisms that lead to osteoporosis and iron deficiency anemia (IDA) being more prevalent in women (28–30). Older adults are more likely to use supplements such as protein, iron, zinc and multivitamins, and other studies have reported a significant linear increase in NS use in older age groups (24), which may be related to the increased health problems people face as they age. Higher levels of purchasing power and greater awareness of health care resulted in higher rates of NS use among urban than rural older adults (3). In addition, as in other studies, NSs were used more by older people who were well-educated and who had better living conditions (31, 32).

NS use also varied by health status and health awareness. This study showed that older people who rated themselves as having poor health were more likely to use NSs, which is consistent with the results of other Chinese studies (3, 33), but some researchers have reported opposite results, with a UK study finding that participants who considered their health to be good or excellent were more likely to use NSs than those who reported fair or poor health (34). As we mentioned earlier, the recommendations of the Chinese dietary guidelines possibly led older people who rated themselves as having good health to be more likely to obtain nutrients from their diet. The increased use of DHA among older adults with fair sleep quality compared to those with good sleep quality is because omega-3 polyunsaturated fatty acids, which include docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are beneficial for sleep (35). Several studies have shown that NS users tend to maintain a healthy lifestyle, such as a balanced diet and regular exercise (32, 34, 36). We found that former smokers were more likely to use NSs, including protein and calcium, and that former smokers increased supplement use, possibly to minimize the adverse effects of their previous habits on their health (27, 37). Past alcohol consumption was associated with the use of iron and zinc, and we suggest that this may be because most older people could not clearly distinguish between the effects of iron (a possible prooxidant) and zinc (a possible antioxidant) on cardiovascular disease and choose to avoid taking these supplements during periods of alcohol consumption (38). In addition, people with exercise habits, whether they currently exercise or not, had a higher probability of using a NS.

In terms of categories, the most common NS used by older Chinese people was calcium, followed by protein, which may be closely related to aging. The aging process is often characterized by unintended loss of muscle (sarcopenia) and bone (osteoporosis), and protein and calcium intake are factors often considered in the prevention or treatment of chronic osteoporosis and sarcopenia (39), with protein supplements and resistance exercise improving muscle function in frail older people (40). Due to differences in dietary habits, the Chinese choose to consume related nutrients more often through calcium supplements rather than in food (41). Apart from that, a large proportion of the Chinese population is at risk for inadequate intake of zinc, iron and vitamins (3), but this may be overlooked due to metabolic adjustments (42) and because there are no obvious clinical signs or symptoms of these deficiencies (43). Compared to other NSs, this study showed that the rate of iron and zinc intake in the elderly was <1%.

Notably, among respondents using NSs, the difference between men and women in terms of kinds of NSs taken was only statistically significant at the 10% level, with women preferring to take NSs in combination but controlling the overall quantity taken. In addition, those using NSs also showed a consistent pattern, with over 50% of supplement users reporting regular supplement use to maintain long-term organ-specific function (e.g., bone, heart, prostate protection) (44).

Our study analyzed the use of NS among older people aged 65 years and above in China. Although the results showed a relatively low rate of NS use in China, compared with rates reported in previous studies, the rate of NS use among older adults has increased, despite the different survey samples, since older adults are more likely to use supplements to maintain and promote health. However, as we have mentioned, inappropriate use of supplements may lead to adverse outcomes (44). In addition, with increasing health literacy, respondents expressed uncertainty about the usefulness of these supplements (45). Therefore, how do we provide scientifically based health guidance to older people that addresses their needs in the future? A recent systematic review showed that community pharmacists lack knowledge about NSs globally (46), suggesting that we should make NS-related health workers sufficiently knowledgeable about NSs to provide accurate information to users. At the same time, in the context of health policy and the development of general practitioners (GPs) in China, the management of people's health in the community by GPs should be strengthened, and personalized guidance should be provided to the elderly according to their health conditions and related needs, especially on the types of NSs to be taken and the frequency of taking them. As users of NSs are more likely to have a lower socioeconomic status, targeted NS guidance has benefits in reducing health inequalities and may also reduce adverse events due to inappropriate use (45).

Several potential limitations of this study should be noted. First, the cross-sectional design does not help us explore the trend of NS use among older adults in China. Although the database we used is a longitudinal survey, surveys of NSs started in 2018, and we hope in the future to be able to conduct tracking and comparative studies of trends in the use of NS among older people over time. In addition, due to the limitations of the data, our measurement of NSs is not comprehensive, and there is no information on specifications, quantities, etc., to help us calculate the intake of each nutrient. In particular, measures of NS utilization and self-rating questions such as living standards and health status were self-reported and could suffer from bias. Besides, factors including physical diseases, insurance, financial support need to be further explored in the future.

CONCLUSION

The results of this study showed that the probability of using any NS among older Chinese adults was 12.28%. The most common NSs used by older Chinese individuals were calcium and protein. Women used NSs like calcium and multivitamins more often than men. Older people were more likely to use supplements like protein, iron, zinc and multivitamins. Older people with high levels of education, good living conditions and those who rated their health as poor were more likely to use NSs. Former smokers were more likely to use protein and calcium, past alcohol consumption was associated with iron and zinc use, and those with an exercise habit were more likely to use any of the NSs. More women reported taking 2–3 NSs, and more than 50% of NS users reported taking supplements often. This study provides information on the current prevalence of NS among older adults in China and the association with demographics, lifestyle and other factors. How to provide scientifically based health guidance on NS use for older people remains crucial in promoting their health in the future.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. The data of CLHLS 2018 is publicly available by application through http://chads.nsd.pku.edu.cn/sjzx/index.htm.

ETHICS STATEMENT

The CLHLS study was approved by Research Ethics Committees of Peking University (IRB00001052–13074). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WD performed and interpreted statistical analysis and drafted manuscript writing. ZS and RB supported manuscript writing and contributed to the study design for the study. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.822087/full#supplementary-material

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Association Between Triglyceride–Glucose Index and the Risk of Type 2 Diabetes Mellitus in an Older Chinese Population Aged Over 75 Years

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Background: The association between the triglyceride–glucose (TyG) index and type 2 diabetes mellitus (T2DM) in older adults has not been fully understood. This research aims to explore the association between the TyG index and the incidence of T2DM in an older Chinese population aged over 75 years.

Methods: This longitudinal analysis study was performed based on a database from a health check screening program in China. The participants were stratified based on the quintile ranges of the TyG index (Q1 to Q5 groups). T2DM was defined as fasting plasma glucose (FPG) $\geq$ 7.00 mmol/L and/or self-reported T2DM. The cumulative incidences of T2DM in various quintile groups were estimated by the Kaplan–Meier method. The Cox proportional hazard model was used to examine the independent impact of the TyG index on the risk of T2DM during the follow-up period. Subgroup analysis was performed by gender and BMI to further validate the credibility of the results.

Results: During the follow-up period, a total of 231 new-onset T2DM cases were recorded among the 2,571 individuals aged over 75 years. After adjusting confounding factors, elevated TyG index independently indicated a higher risk of T2DM (HR = 1.89; 95% CI, 1.47–2.44; $p < 0.01$). Higher TyG index quintile groups (Q3 to Q5) also presented with a higher risk of T2DM (hazard ratio (HR) = 1.36, 1.44, and 2.12, respectively) as compared with the lowest quintile group (Q1). Subgroup analysis showed that increased TyG index led to a higher risk of T2DM with HR = 2.35 (95% CI, 1.73–3.19), 1.90 (95% CI, 1.27–2.83), 2.95 (95% CI, 1.94–4.50), and 1.72 (95% CI, 1.25–2.35) in male subgroup, female subgroup, BMI < 24 kg/m^2 subgroup, and BMI $\geq$ 24 kg/m^2 subgroup, respectively.

Conclusions: Triglyceride–glucose index independently correlated with the risk of incident T2DM in Chinese adults aged over 75 years. The TyG index might be useful in monitoring T2DM in the older populations.

Keywords: triglyceride–glucose index, type 2 diabetes mellitus, risk, older adults, body mass index

INTRODUCTION

Type 2 diabetes mellitus (T2DM) has been considered as a risk equivalent for cardiovascular disease and all-cause mortality, which imposes a remarkable economic burden on patients and societies (1, 2). In recent decades, the prevalence of patients with T2DM has significantly increased, especially in developing countries (3). Chinese adults, especially older adults, have experienced a distinct transition of diet patterns and a tremendous rise in the incidence of obesity, which is also a major trigger for the development of T2DM (4, 5). In line with the statistics by the International Diabetes Federation (6), China has the largest population of patients with T2DM, approaching 114.4 million in 2017. Currently, epidemiological investigation reveals that there exist over 400 million patients with diabetes in the world, and this figure is estimated to increase to 700 million by 2045. T2DM is a leading cause of morbidity and mortality in the geriatric population. Other concomitant diseases in older patients with T2DM, such as renal dysfunction, heart failure, stroke, dementia, muscle loss, cognitive impairment, and osteoporosis, also contribute to the difficulty in T2DM management. However, the specific characteristics of geriatric T2DM have not been given due attention in previous studies. Hence, regular health checks, early identification of T2DM, and early intervention are the major important factors to prevent the development of T2DM and its related complications so as to improve the quality of life of older adults. Besides, surveillance of T2DM needs to be individualized in this age group, keeping in mind the benefit to risk ratio. Thus, a simple and cost-effective predictor is warranted for detecting individuals in the older population with a high risk of T2DM.

The main risk factors of T2DM include an unhealthy diet, obesity, sedentary behaviors, and reduced physical activity (7). The insulin resistance (IR) and dysfunction of islet β-cell are the pivotal pathophysiological pathways of T2DM (8, 9). IR is presented as insulin-dependent organic cells that respond inappropriately to insulin stimulation (10) and may occur as early as ∼20 years prior to the definite diagnosis (9, 11). Moreover, the aging-related pathophysiological changes in older adults can lead to enhanced susceptibility of T2DM and carbohydrate intolerance, which are due to the decrease in insulin secretion following glucose load and also the aggravation in IR in tissues (12). A recent research suggested that IR was more significantly related to the onset of diabetes mellitus in the Chinese population than β-cell dysfunction (13). IR is associated with multiple metabolic abnormalities that include dyslipidemia and hyperglycemia (10).

In brief, the evaluation of IR status is necessary to identify high-risk population of T2DM. The typical methods to assess IR, such as hyperglycemic clamp and the homeostasis model assessment of IR (HOMA-IR), are costly and time-consuming for routine medical examination and large-scale epidemiological investigations. However, regular health checkup requires noninvasive and cost-effective tests to identify those with a greater risk of T2DM. Recently, the triglyceride–glucose (TyG) index, calculated by the formula ln(fasting triglycerides(mg/dl)*fasting blood glucose (mg/dL)/2) (14), has been found to be associated with several commonly used alternate predictors of IR that include hyperglycemic clamp and HOMA-IR (14–16). It has also been considered as a candidate indicator for defining the status of metabolic health (17). Moreover, recent evidence suggests that the TyG index is highly correlated with arterial stiffness in both healthy individuals and patients with hypertension (18, 19) and could predict the risk of adverse cardiovascular events in the T2DM population (20).

In the consideration of the feature of the TyG index as a credible and surrogate indicator of IR, it might also be a potential predictor of T2DM. Compared with insulin-based indices, the TyG index could be easier to obtain and calculate for clinical investigators, and several epidemiologic studies have indicated that the TyG index is related to the risk of incident T2DM in Asian and European countries (20–29). However, the outcomes were inconclusive and controversial as a result of either the cross-sectional design (30), limited population scale (29), or confined study population such as normal-weight adults (21, 31). Nonetheless, the association between the TyG index and incident T2DM has not been investigated in older adults. Therefore, in our study, data were downloaded freely from a public database based on a population cohort in China, and a longitudinal analysis was performed. We aimed to explore the relationship of the TyG index with the risk of developing incident T2DM in an older Chinese population aged over 75 years.

METHODS

Research Design

We downloaded the original database sorted by Chen et al. (32) from the DATADRYAD website (www.datadryad.org), where original databases can be freely obtained by others. The original database was designed based on a population cohort from 2010 to 2016 in China with a median follow-up of 3.1 years, and the data were acquired for the public database established by the Rich Healthcare Group (32). The inclusion criteria for the participants in the database were as follows: (1) at least 20 years old; (2) followed up for at least 2 years; and (3) with available data of body mass index (BMI) and fasting plasma glucose (FPG) value. In the study by Chen et al., the population cohort investigation was approved by the Rich

Healthcare Group Review Board (32), and thus, ethics approval was not required in this longitudinal analysis. According to the statement in the study by Chen et al. (32), the authors permitted others to perform secondary analysis based on their work non-commercially. Therefore, their database was used in this longitudinal analysis without infringing the authors' rights. Since several previous studies reported that 75 years old is considered a watershed for the significant deterioration of many of the body systems and also the development of diseases such as T2DM, hypertension, and cardiovascular or cerebrovascular diseases, we only included participants over 75 years old to investigate the incident T2DM in an older Chinese population. The following patients were excluded: (1) participants with missing TyG index measurements; (2) patients lost to follow-up; (3) patients with visit intervals <2 years; and (4) patients with extreme BMI values (<15 kg/m^2 or >55 kg/m^2) (32). Then, the general information, biochemical test results, and the incidence of T2DM of the participants were acquired. Based on these data, the association between the TyG index and the risk of incident T2DM was investigated.

Definitions

The endpoint of the study was the diagnosis of T2DM during the follow-up period or during the last visit. The definition of incident T2DM in the research by Chen et al. (32) was FPG ≥ 7.00 mmol/L and/or self-reported T2DM by the patients.

Data Acquisition

In the database offered by Chen et al. (32), the baseline examinations were performed by using the standardized spreadsheet to acquire the participant's general information and by testing the laboratory indices under the fasting status. The following data were recorded and analyzed: (1) basic information and anthropometric indices that include age, gender, blood pressure, weight (kg), height (m), and BMI [calculated as weight (kg)/height (m2)]; (2) laboratory parameters that include triglyceride, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, endogenous creatinine clearance rate, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and FPG; (3) sociodemographic parameters such as smoking history and alcohol intake; and (4) the study endpoint (incident T2DM).

Statistical Analysis

The missing values of the variables were supplemented using multiple imputations prior to statistical analysis, based on a multiple of replications and a chained equation approach modality in the R language. For quantitative variables, values are shown as mean ± standard deviation, and the differences between groups were compared *via* the one-way analysis of variance (ANOVA) method. For qualitative variables, data are presented as numbers (percentages), and the significance of differences between groups was analyzed through the chi-square test.

To explore the association of different TyG index values with the risk of T2DM onset, patients aged over 75 years were stratified into five groups according to the quintile values of the TyG index of all participants, namely, Q1, Q2, Q3, Q4, and Q5 groups. The independent impact of the TyG index as a continuous variable or as a hierarchical variable (Q1, Q2, Q3, Q4, and Q5 groups) on the risk of incident T2DM was evaluated *via* the Cox proportional hazard model. The crude (univariate) model only included the TyG index. Model I was adjusted for gender, age, and BMI. Model II (fully adjusted model) was adjusted for gender, age, BMI, systolic blood pressure, alanine aminotransferase, and blood urea nitrogen. The *p*-Values of the Cox regression analysis and corresponding hazard ratios with 95% confidence intervals (CIs) were recorded and presented. The log-rank test was performed to compare the T2DM risks among TyG index quintile groups, and the Kaplan–Meier curves for T2DM onset were applied for generating cumulative event rates. Given the potential confounding effects of gender and BMI, the gender-stratified as well as BMI-stratified (cutoff value, 24 kg/m2) multivariate Cox regression proportional hazards models were analyzed, with adjustment for gender, age, BMI, systolic blood pressure, alanine aminotransferase, and blood urea nitrogen. A subgroup analysis was performed by gender and BMI to further validate the results. As is known, a higher BMI is associated with a greater risk of T2DM. According to the criteria of weight for adults issued by the National Health and Family Planning Commission of the People's Republic of China, BMI ≥ 24 kg/m^2 is considered overweight (33). Therefore, we divided BMI as < 24 kg/m^2 and ≥ 24 kg/m^2 in this study based on a Chinese population (33).

Data analysis and plotting were performed using R language (version 4.1.0; R Foundation for Statistical Computing) and SAS version 9.2 (SAS Institute Inc, Cary, NC). The *p*-value < 0.05 from the two-sided hypothesis test was considered statistically significant.

RESULTS

Baseline Characteristics and the Incidence of T2DM of the Included Participants

A total of 2,571 participants aged over 75 years were included in this longitudinal analysis. **Table 1** shows the baseline characteristics of the included participants stratified by quintile of the TyG index.

The average age of the study population was 79.68 ± 4.06 years, and 63.6% of them were men.

Participants in the higher quintile groups of TyG index (Q2, Q3, Q4, and Q5) showed higher levels of BMI, systolic blood pressure, diastolic blood pressure, fasting blood glucose, total cholesterol, triglyceride, low-density lipoprotein, and alanine aminotransferase and lower levels of high-density lipoprotein, blood urea nitrogen, creatinine clearance rate, and smoking frequency as compared to Q1 group.

During the follow-up period, 231 cases of T2DM were identified with an incidence of 9%. As shown in **Table 1** and **Figure 1**, a total of 33 (6.4%), 27 (5.3%), 44 (8.6%), 49 (9.5%), and 78 (15.1%) cases of T2DM were observed in Q1, Q2, Q3, Q4, and Q5 groups, respectively.

TABLE 1 | Baseline characteristics of the participants.

Variable	All participants (2,571)	TyG index					*P* value
		Q1 (514)	Q2 (514)	Q3 (513)	Q4 (515)	Q5 (515)	
Age	79.68 (4.06)	80.15 (4.39)	79.73 (4.17)	79.77 (4.04)	79.39 (3.77)	79.38 (3.85)	0.013
Gender							<0.001
Male	1,634 (63.6)	379 (73.7)	352 (68.5)	314 (61.2)	293 (56.9)	296 (57.5)	
Female	937 (36.4)	135 (26.3)	162 (31.5)	199 (38.8)	222 (43.1)	219 (42.5)	
Bmi	23.96 (3.18)	22.73 (3.06)	23.57 (3.28)	23.89 (3.16)	24.54 (2.97)	25.08 (2.89)	<0.001
Tyg index	8.60 (0.51)	7.90 (0.22)	8.33 (0.08)	8.59 (0.08)	8.86 (0.08)	9.33 (0.26)	<0.001
Systolic blood pressure	130.37 (12.18)	128.73 (13.09)	129.53 (12.34)	130.31 (12.18)	131.46 (11.70)	131.80 (11.31)	<0.001
Diastolic blood pressure	76.29 (8.93)	75.42 (8.66)	75.59 (8.90)	76.15 (9.04)	77.34 (9.26)	76.94 (8.63)	0.001
Fasting blood glucose	5.14 (0.47)	4.98 (0.46)	5.08 (0.44)	5.14 (0.46)	5.22 (0.44)	5.30 (0.47)	<0.001
Total cholesterol	5.01 (0.73)	4.72 (0.70)	4.91 (0.73)	5.08 (0.73)	5.11 (0.68)	5.23 (0.71)	<0.001
Triglyceride	1.51 (0.83)	0.70 (0.15)	1.04 (0.13)	1.33 (0.15)	1.71 (0.21)	2.79 (0.87)	<0.001
High-density lipoprotein	1.38 (0.24)	1.44 (0.24)	1.41 (0.24)	1.40 (0.24)	1.35 (0.23)	1.30 (0.23)	<0.001
Low-density lipoprotein	2.90 (0.54)	2.72 (0.51)	2.87 (0.54)	2.98 (0.55)	2.99 (0.52)	2.94 (0.55)	<0.001
Alanine aminotransferase	17.00 [13.30, 22.00]	15.50 [12.33, 19.50]	16.35 [13.20, 21.37]	16.20 [13.00, 21.50]	18.00 [14.00, 22.35]	18.00 [15.00, 24.30]	<0.001
Aspartate aminotransferase	24.00 [21.00, 28.25]	24.00 [21.00, 28.00]	24.00 [21.00, 28.10]	23.50 [20.70, 28.00]	24.80 [21.00, 28.00]	24.80 [21.50, 29.20]	0.060
Blood urea nitrogen	5.08 (0.92)	5.20 (0.90)	5.06 (0.93)	5.06 (0.91)	5.01 (0.92)	5.08 (0.91)	0.016
Creatinine clearance rate	75.09 (11.89)	76.08 (11.34)	75.32 (11.63)	74.71 (12.15)	73.98 (12.20)	75.37 (12.07)	0.060
Type 2 diabetes mellitus	231 (9.0)	33 (6.4)	27 (5.3)	44 (8.6)	49 (9.5)	78 (15.1)	
Smoking							0.001
Every day	716 (27.8)	176 (34.2)	145 (28.2)	146 (28.5)	123 (23.9)	126 (24.5)	
Occasionally	119 (4.6)	21 (4.1)	34 (6.6)	16 (3.1)	23 (4.5)	25 (4.9)	
None	1,736 (67.5)	317 (61.7)	335 (65.2)	351 (68.4)	369 (71.7)	364 (70.7)	
Drinking							0.185
Every week	40 (1.6)	4 (0.8)	13 (2.5)	10 (1.9)	8 (1.6)	5 (1.0)	
Occasionally	291 (11.3)	67 (13.0)	60 (11.7)	58 (11.3)	46 (8.9)	60 (11.7)	
None	2,240 (87.1)	443 (86.2)	441 (85.8)	445 (86.7)	461 (89.5)	450 (87.4)	

Unadjusted and Adjusted Cox Proportional Hazard Models of Incident T2DM

The independent impact of the TyG index on the risk of incident T2DM was evaluated using the unadjusted (univariate) and adjusted (multivariate) Cox proportional hazard models. The variables added to the different adjusted models were selected based on the results of an univariate analysis. The effect sizes of the TyG index, including hazard ratio (HR) and 95% CIs, are depicted in **Table 2**. Higher TyG index increased the hazard of T2DM development (HR = 1.89; 95% CI, 1.47–2.44) after adjusting for gender, age, BMI, systolic blood pressure, alanine aminotransferase, and blood urea nitrogen. As for sensitivity analysis, the quintile of the TyG index was used as a categorical variable, and the hazard ratio as well as the *p*-value for the trend of T2DM risk were calculated. The hazard ratio of T2DM in the whole adjusted model was 1.97 (95% CI, 1.45–2.66; $p < 0.01$).

Subgroup Analysis

Table 3 shows the subgroup analysis for the association between the TyG index and T2DM development after adjusting for gender, age, BMI, systolic blood pressure, alanine aminotransferase, and blood urea nitrogen. Subgroups were stratified based on gender (male and female) and BMI (< 24 kg/m^2 and ≥ 24 kg/m^2). The results suggested that an elevated risk of incident T2DM stably existed in the different subgroups in Q3, Q4, and Q5 groups as compared to the Q1 group (HR > 1 for all), and there were statistical significances for the Q5 group vs. Q1 group ($p < 0.05$ in all subgroups). When analyzed as a continuous variable, the elevation of TyG index resulted in an increased risk of incident T2DM by 2.35-folds (95% CI, 1.73–3.19; $p < 0.01$), 1.90-folds (95% CI, 1.27–2.83; $p < 0.01$), 2.95 (95% CI, 1.94–4.50; $p <0.001$), and 1.72-folds (95% CI, 1.25–2.35; $p < 0.01$) in the male subgroup, the female subgroup, BMI < 24 kg/m^2 subgroup, and BMI ≥ 24 kg/m^2 subgroup, respectively.

DISCUSSION

This longitudinal analysis study showed that increased TyG index was independently associated with a higher risk of incident T2DM in an apparently healthy older population aged over 75 years in China (HR = 1.89; 95% CI, 1.47–2.44; $p < 0.01$). As compared to the individuals with the lowest quintile of the TyG index, participants with the top quintile of the TyG index presented with a 2.1-fold higher risk of T2DM onset (Q5 vs. Q1: adjusted HR = 2.12; 95% CI, 1.39–3.24; $p < 0.01$). Besides, the results of subgroup analysis demonstrated that this association existed in spite of difference in gender (male or female) or BMI (< 24 kg/m^2 or ≥ 24 kg/m^2), which indicates that the conclusions were robust and the TyG index was applicable for the older subjects. Additionally, stronger correlations were discovered in male individuals and in individuals with BMI < 24 kg/m^2.

The TyG index is a product derived from triglyceride and fasting blood glucose and has been found to be a potential biomarker for IR in previous epidemiological investigations (14, 34–36). Guerrero-Romero et al. found not only a considerably high sensitivity (96.5%) but alsoa satisfactory specificity (85.0%) of the TyG index for detecting IR in a Mexican population (15). The TyG index also had better performance than HOMA in a Brazilian investigation by Vasques et al. (37). In accordance with the results of this study, some previous investigations also suggested that an increased TyG index might be associated with a higher risk of future T2DM onset in multiple regions in Asia and Europe (22, 28, 29, 38). A previous Chinese cohort study also found the consistent results in individuals with normal BMI (21). Thus, the relationship between the TyG index and T2DM risk among older Chinese individuals has been rarely investigated in previous studies. Since this study was carried out based on a large cohort of 2,571 apparently healthy old adults aged over 75 years with all range of BMI values in China, it is applicable to a considerably wide range of the older population and provides a reliable basis for further clinical promotion and practice.

Type 2 diabetes mellitus is characterized by islet β-cell dysfunction and IR (39). Notably, the TyG index might also be a predictor for the susceptibility of β-cells to the cytotoxic effect of glucose and lipid. Islet β-cell is known to be vulnerable to oxidative stress due to limited antioxidant enzyme ability, and oxidative stress has been found to be involved in the pathogenesis and progression of T2DM (40, 41). Moreover, emerging evidence has found that certain antioxidant supplementation could modulate lipid metabolism and enhance insulin sensitivity (42–44). Increased blood glucose contents also induce reactive oxygen species production in islet β-cells, which in turn leads to glucose toxicity and dysregulated function of β-cells, thus promoting IR and T2DM (40, 41). Besides, the dysfunction of pancreatic β-cells can also be induced by long-term exposure to triglyceride, which might be caused by continuously elevated free fatty acid levels (45, 46). Therefore, to a certain extent, the TyG index reflects the transformation of physiological modulation and metabolic regulation of the body and is closely associated with the probability of the onset and progression of T2DM.

To further explore the substantial correlations between independent and dependent variables in the onset of T2DM, we performed subgroup analysis and explored potential interactions. In this study, gender and BMI were taken as grouped variables, and more significant correlations were found in male individuals and those with BMI ≥ 24 kg/m^2. This hazard ratio was relatively larger in male participants, which was inconsistent with the cohort investigation by Zhang et al. (21). This discordance might be partially due to the different age distributions in our study population, which were all aged > 75 years. With the aging process in older adults, the lipid deposition in hepatocytes in men might have different patterns as compared to women (47, 48). On the other hand, it is well known that obese individuals are heterogenous from lean ones and are usually considered to be

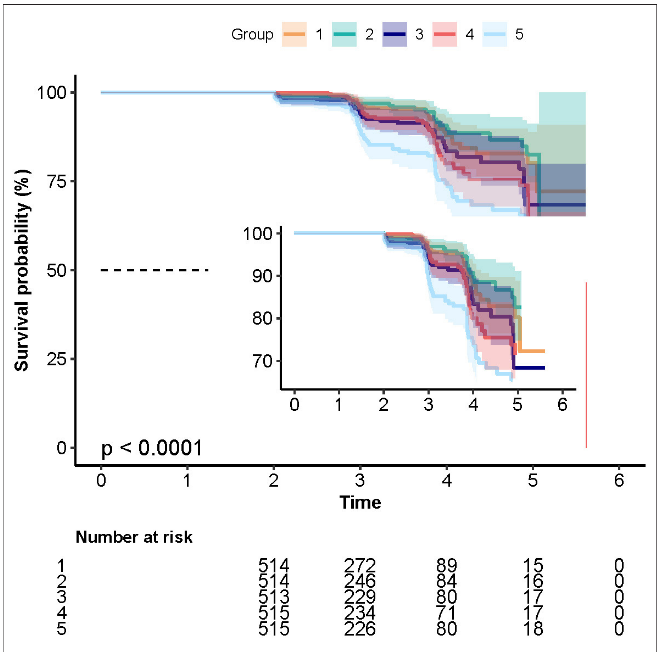

FIGURE 1 | The Kaplan–Meier curves depicting the cumulative incident type 2 diabetes mellitus (T2DM) in different quintile groups (Q1 to Q5) of triglyceride-glucose (TyG) index. Each color of lines indicates a quintile group. The color range indicates the 95% confidence internval (CI) range of cumulative incidence of T2DM at a different follow-up time.

TABLE 2 | Multivariate analysis for the relationship between TyG index and incident T2DM.

	Hazard ratio, 95% CI and *P* value		
	Crude	**Model I**	**Model II**
TyG index	2.21 (1.74, 2.82) < 0.01	1.98 (1.54, 2.55) < 0.01	1.89 (1.47, 2.44) < 0.01
TyG index quintiles			
Q1	1	1	1
Q2	0.88 (0.53, 1.46) 0.62	0.84 (0.51, 1.41) 0.52	0.83 (0.50, 1.39) 0.48
Q3	1.52 (0.97, 2.39) 0.07	1.39 (0.88, 2.20) 0.15	1.36 (0.86, 2.14) 0.19
Q4	1.69 (1.08, 2.62) 0.02	1.49 (0.95, 2.34) 0.08	1.44 (0.92, 2.27) 0.11
Q5	2.67 (1.77, 4.01) < 0.01	2.24 (1.47, 3.42) < 0.01	2.12 (1.39, 3.24) < 0.01
P for trend	2.35 (1.76, 3.14) < 0.01	2.05 (1.52, 2.77) < 0.01	1.97 (1.45, 2.66) < 0.01

TABLE 3 | Subgroup analysis.

Confounding factor category	Serum TyG index quintiles					HR for TG/HDL-C as continuous variable	*P* for trend	*P* for interaction
	Q1	Q2	Q3	Q4	Q5			
Gender								0.39
Male	1	0.70 (0.37, 1.30) 0.26	1.10 (0.61, 1.96) 0.76	1.53 (0.90, 2.61) 0.12	2.69 (1.66, 4.36) < 0.01	2.35 (1.73, 3.19) < 0.01	2.57 (1.78, 3.72) < 0.01	
Female	1	1.47 (0.59, 3.66) 0.41	1.08 (1.09, 5.48) 0.03	1.40 (0.91, 4.73) 0.08	1.26 (1.24, 5.99) 0.01	1.90 (1.27, 2.83) < 0.01	1.88 (1.18, 3.02) < 0.01	
BMI								0.045
<24	1	0.66 (0.31, 1.42) 0.289	1.30 (0.66, 2.57) 0.44	1.44 (0.72, 2.88) 0.30	3.83 (2.14, 6.87) < 0.01	2.95 (1.94, 4.50) <0.001	3.25 (2.01, 5.25) < 0.01	
≥24	1	1.03 (0.50, 2.08) 0.95	1.50 (0.79, 2.83) 0.22	1.55 (0.83, 2.88) 0.17	1.90 (1.05, 3.45) 0.03	1.72 (1.25, 2.35) < 0.01	1.68 (1.15, 2.45) < 0.01	

more susceptible to T2DM. However, in the subgroups according to the cutoff value of BMI, TyG index showed a significantly positive correlation with the risk of future T2DM, and lean individuals presented with a higher hazard of future T2DM risk with increased TyG index (BMI < 24 kg/m^2, HR $= 2.95$, $p < 0.001$; BMI ≥ 24 kg/m^2, HR $= 1.72$, $p < 0.01$). A possible reason for this inconsistency from expectation was that the mechanism of the TyG index promoting T2DM in various BMI populations might be diverse. The increased risk of T2DM in obese populations with high TyG index might be mainly caused by aggravated IR, whereas in the lean population, the dysfunction of β-cells induced by glycotoxicity and lipotoxicity should be attributed to. Taken together, according to the results of the subgroup analysis, the TyG index showed a higher sensitivity for estimating the risk of T2DM in the male population and those with normal BMI. Thus, it might be a useful index for monitoring the risk of T2DM onset, especially in older male populations without obesity. For instance, the TyG index could be calculated and provided for individuals at regular health checks with the corresponding explanations such as "low/moderate/high risk of T2DM" and suggestions such as "re-check within 3/6/12 months at endocrine clinic."

The present research has several strengths. First, this investigation is performed based on a large cohort study with age >75 years, and thus, the results are specifically applicable and dependable for the older population. The other similar clinical observations either had a relatively small population or the age of the sample tended to be diverse. Second, we have taken the TyG index as both a ranked categorical variable and as a continuous variable, and sensitivity calculation and trend examination were both performed to enhance the credibility of the conclusion. There are also a few limitations to this study. First, T2DM was diagnosed based on fasting blood glucose without the data of glycosylated hemoglobin (HbA1c) and oral glucose tolerance test, which might result in the underestimated incidence of T2DM. Second, due to the lack of data on insulin levels and HbA1c, the comparison of the TyG index and HOMA-IR or HbA1c in predicting T2DM risk is not available in this study. Finally, since this cohort research was conducted in China, the findings of this study need to be validated in other races and a worldwide range of populations.

CONCLUSION

The present investigation suggests that increased TyG index is independently associated with a higher risk of T2DM onset in the older Chinese population aged over 75 years. Moreover, the results in this study extend our knowledge that the TyG index appears to be more sensitive for evaluating the risk of T2DM in men as well as in lean individuals. The TyG index might thus be a useful tool for detecting individuals at A high risk of developing T2DM, especially in men without obesity.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical approval was not provided for this study on human participants because the ethics approval was obtained in the previous research by Chen et al. (32) and was no longer needed for the current study. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

QL and SY contributed to the conception and design of the research. YL, LD, LM, and YH acquired the data from the database. LL, DK, NL, and ML performed the statistical analysis. XF, HL, and JL drafted the manuscript. All authors contributed to the article and approved the submitted version.

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Serum Lipid Profiles and All-Cause Mortality: A Retrospective Single Center Study on Chinese Inpatient Centenarians

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Objectives: To analyze the serum lipid profiles and investigate the relationship between the lipoprotein cholesterol levels and all-cause mortality in Chinese inpatient centenarians.

Design: Retrospective study.

Methods: Centenarians aged 100 years and older were admitted from January 2010 to January 2021 in our hospital. All centenarians completed a follow up visit till April 2021 of all-cause mortality and serum lipid profiles, including total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) levels. Cox proportional hazard models were used to assess the association between lipid profiles and all-cause mortality.

Results: (1) These 121 centenarians on average were 100.85 ± 1.37 years old (100∼107 years), including 114 males and 7 females. (2) The rate of treatment with lipid-lowering drugs was 69.4%, and the lipid-lowering drugs were mainly statins (63.6%). (3) The results of serum lipid profiles were as follows: TC 3.90 ± 0.69 mmol/L, TG 1.36 ± 0.55 mmol/L, HDL-C 1.14 ± 0.24 mmol/L, and LDL-C 2.05 ± 0.46 mmol/L. (4) The median follow-up time was 589 days (95% CI: 475, 703), and the all-cause mortality rate was 66.1%. (5) Multivariable analysis showed that higher TC level (HR = 1.968, 95% CI = 1.191–3.253, P = 0.008), lower LDL-C level (HR = 0.379, 95% CI = 0.212–0.677, P = 0.001) was independent factors contributed to all-cause mortality. Sensitivity analysis showed that the above results were stable. The therapy and complication morbidity did not present significant publication bias.

Conclusions: The serum lipid profiles of Chinese inpatient centenarians were lower than those of the previous studies. Low LDL-C level was associated with an increased risk of all-cause mortality, which may indicate that more intensive lowering of LDL-C had a potential adverse effect on all-cause mortality for centenarians.

Keywords: centenarians, lipid-lowering drugs, mortality, risk factor, lipid profiles

INTRODUCTION

The global population is aging, which leads to an increasing burden of age-related cardiology diseases. Centenarians are a specific group with different lipoprotein cholesterol levels compared with those of ordinary elderly people. Atherosclerotic cardiovascular disease (ASCVD) and its clinical manifestations, are the leading causes of morbidity and mortality throughout the world. Lipid levels, especially LDL-C level, have been well established as an important risk factor of ASCVD for decades (1). Evidence has shown that statins could reduce total cardiovascular events, which can improve the prognosis of the elderly patients. What's more, lowering LDL-C level by intensified statin therapy provides incremental additional reduction in cardiovascular risk (2). While studies have shown that (3, 4) the relationship between dyslipidemia and the risk of death will gradually weaken with age, some studies (5–8) have found no association between LDL-C level and the risk of all-cause mortality; lower LDL-C level is not always associated with greater benefit. An excessive low level of LDL-C might be negatively correlated with all-cause mortality (9, 10).

However, contradicting results were reported in the magnitude of the reductions in individual mortality and cardiovascular end points among the elderly patients, especially centenarians. Therefore, the purpose of this study is to analyze the serum lipid profiles and evaluate the relationship between the lipid levels and all-cause mortality in the single center inpatient centenarians.

MATERIALS AND METHODS

Study Population

Centenarians aged 100 years or above and with available clinical data were admitted in our hospital from January 2010 to January 2021, among whom 121 centenarians were qualified for final statistical analysis. The main inclusion criteria into final analysis were (1) the clinical data and laboratory examinations were sufficient; (2) the participants could be successfully followed up successfully till the end point event.

The missing data were excluded for analysis. The key exclusion criteria were as followings: (1) with recent acute coronary syndrome; (2) receiving hemodialysis therapy; (3) Poorly control of blood pressure and glucose; (4) in a serious or critical conditions.

According to "2016 Chinese Guideline for the Management of Dyslipidemia in Adults" (11), the diagnostic criteria for dyslipidemia: ① Hypercholesteremia: total cholesterol (TC) $\geq$ 6.20 mmol/L; ② Hypertriglyceridemia: triglycerides (TG) $\geq$ 2.3 mmol/L; ③ Combined hyperlipidemia: TC $\geq$6.20 mmol/L and TG $\geq$ 2.3 mmol/L; ④ Low level of high-density lipoprotein cholesterol (HDL-C): HDL-C $\leq$ 1.0 mmol/L; ⑤ Dyslipidemia: over 1 type of the above conditions.

Study Design

The clinical data of all admitted participants were exported from Electronic Medical Record, including age, gender, BMI, smoking history, drinking history, comorbid diseases, lipid-lowering drugs, etc. Participants were classified as non-smokers, or current smokers. Non-smokers were defined as adults who had not smoked at least 100 cigarettes in their lifetime, current smokers were defined as adults who had smoked at least 100 cigarettes and were currently smoking. Drinkers were defined as an average alcohol ingestion of $\geq$30 g/day. BMI was calculated as body weight divided by the square of the height (kg/m^2). Each chronic disease was defined as described previously. The serum lipid profiles were detected by the immunoturbidimetric method in the biochemical laboratory of our hospital using Roche reagents. TC, TG, LDL-C, HDL-C levels were all recorded till the end of the study.

Methods through outpatient visiting, rehospitalization and telephone, all admitted participants were retrospectively followed up on the day of examination and ended

at the first occurrence of endpoint event, or in April 2021. The time scale for Cox model was 10 years. The endpoint event was defined as all-cause death, referring to the death of any causes that occurred during the follow-up period.

Statistical Analysis

Continuous variables were presented as mean $\pm$ standard deviation, and categorical variables were presented as frequency and percentages.

The final lipid profile levels were calculated according to the average of multiple lipid values during the whole follow-up period. Baseline characteristics between groups were compared by *t*-test or rank sum test for non-normal distribution data, and by Chi-square test for categorical variables.

The survival curves were estimated by the standard Kaplan-Meier estimator, and multivariable Cox models were estimated to investigate associations between serum lipid profiles and all-cause mortality, also used to estimate the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of the endpoint events. HR and 95% CIs were obtained by using multivariable Cox models, while beta coefficient (B) and *P*-values were calculated by using linear regression analyses.

The analysis stratified by the lipid-lowering therapy was used to show the association and check whether the findings would be consistent with the whole patients. The Chi-square test was used for the analyses.

The centenarians' data within the recent 5 years were used to evaluate the potential bias, and sensitivity analysis was used to evaluate the stability of the results. The Kaplan-Meier and multivariable Cox models were used for sensitivity analysis.

All statistical analyses were performed with SPSS 22.0 software. A *p*-value of $<$0.05 was considered as significant difference.

RESULTS

The Baseline Features of the Inpatient Centenarians

A total of 121 centenarians, including 114 males and seven females, were eligible for this study. Centenarians on average were 100.85 $\pm$ 1.37 years (range: 100–107 years), the majority

TABLE 1 | The baseline features of inpatient centenarians.

Items	Total (*n* = 121)	Dyslipidemia group (*n* = 37)	Normal group (*n* = 84)	*P-value*
Age (years)	100.85 ± 1.37	100.92 ± 1.44	100.82 ± 1.35	0.72
BMI (kg/m^2)	22.72 ± 3.18	22.84 ± 3.46	22.66 ± 3.07	0.79
Gender (M/F)	114/7	37/0	77/7	0.099
Smokers [*n* (%)]	2 (1.7)	2 (5.4)	0 (0)	0.092
Drinkers [*n* (%)]	11 (9.1)	5 (13.5)	6 (7.1)	0.308
CHD [*n* (%)]	102 (84.3)	30 (81.1)	72 (85.7)	0.519
Hypertension [*n* (%)]	97 (80.2)	29 (78.4)	68 (81.0)	0.744
DM [*n* (%)]	49 (40.5)	16 (43.2)	33 (39.3)	0.683
Cancer [*n* (%)]	38 (31.4)	9 (24.3)	29 (34.5)	0.265
Lipid-lowering	84 (69.4)	29 (78.4)	55 (65.5)	0.156
Drugs [*n* (%)]				
Statins [*n* (%)]	77 (63.6)	24 (64.9)	53 (63.1)	0.852
Fibrates [*n* (%)]	3 (2.5)	2 (5.4)	1 (1.2)	0.221
Niacin [*n* (%)]	1 (0.8)	1 (2.7)	0 (0)	0.306
Ezetimibe [*n* (%)]	2 (1.7)	1 (2.7)	1 (1.2)	0.52
Policosanol [*n* (%)]	3 (2.5)	2 (5.4)	1 (1.2)	0.221

BMI, body mass index; CHD, coronary heart disease; DM, diabetes mellitus. P-value is for comparison between dyslipidemia group and normal group.

TABLE 2 | The serum lipid levels between the two groups.

Items	Total (*n* = 121)	Dyslipidemia group (*n* = 37)	Normal group (*n* = 84)	*P-value*
TC (mmol/L)	3.90 ± 0.69	3.74 ± 0.71	3.97 ± 0.68	0.09
TG (mmol/L)	1.36 ± 0.55	1.70 ± 0.62	1.22 ± 0.44	0.00
HDL-C (mmol/L)	1.14 ± 0.24	0.88 ± 0.14	1.26 ± 0.18	0.00
LDL-C (mmol/L)	2.05 ± 0.46	2.05 ± 0.48	2.04 ± 0.46	0.89

TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. P-value is for comparison between dyslipidemia group and normal group.

of centenarians (94.2%) were male. The rate of current smokers and alcoholic drinkers were 1.7 and 9.1% respectively. 84.3% of the patients had coronary heart disease, 80.2% with hypertension, 31.4% with cancer, and 40.5% with diabetes mellitus. There were 37 cases (30.6%) diagnosed as dyslipidemia, and 70.5% of the patients using lipid-lowering drugs (seen in **Table 1**).

The Serum Lipid Levels of Inpatient Centenarians

The serum lipid levels of these 121 centenarians were as follows: TC 3.90 ± 0.69 mmol/L, TG 1.36 ± 0.55 mmol/L, HDL-C 1.14 ± 0.24 mmol/L, LDL-C 2.05 ± 0.46 mmol/L.

Centenarians were divided into two groups by the difference of having dyslipidemia or not. Compared with normal group, the TG level in the dyslipidemia group was significantly higher, while the HDL-C level was significantly lower (both $P < 0.05$). There were no significant differences in TC and LDL-C levels between the two groups (**Table 2**).

Associations of LDL-C Level With All-Cause Mortality

The follow-up duration ranged from 21 days to 2,535 days, and the median follow-up time was 589 days (95% CI: 475, 703). A total of 80 out of 121 centenarians died during this period, leading to an all-cause mortality rate of 66.1%. So far, 41 cases (33.9%) were still alive. The median follow-up was 521 days (95% CI: 234, 808), and 615 days (95% CI: 494,736) for the dyslipidemia and the normal group, respectively. The Kaplan–Meier survival curves for all-cause mortality in the dyslipidemia group and the normal group were shown in **Figure 1**, indicating no significant difference of the survival probability in the two groups ($P = 0.526$).

The analysis stratified by the lipid-lowering therapy was used to show the association and check whether the findings would be consistent between the two groups. The Chi-square test showed there was no significant difference of all-cause mortality between the lipid lowering drugs non-users and lipid lowering drugs users ($P = 0.468$), and the Kaplan–Meier survival curves showed the same result (**Figure 2**).

Multivariable analysis was adjusted by age, BMI, coronary heart disease, diabetes mellitus, hypertension, cancer and the lipid-lowering therapy. We found that TC level in centenarians was a risk factor (HR = 1.968, 95% CI = 1.191–3.253, P = 0.008) for all-cause death, while LDL-C level (HR = 0.379, 95% CI = 0.212–0.677, P = 0.001) was the protective factor for all-cause death (see **Table 3**). It suggested that low LDL-C level might be associated with an increased risk of all-cause in centenarians.

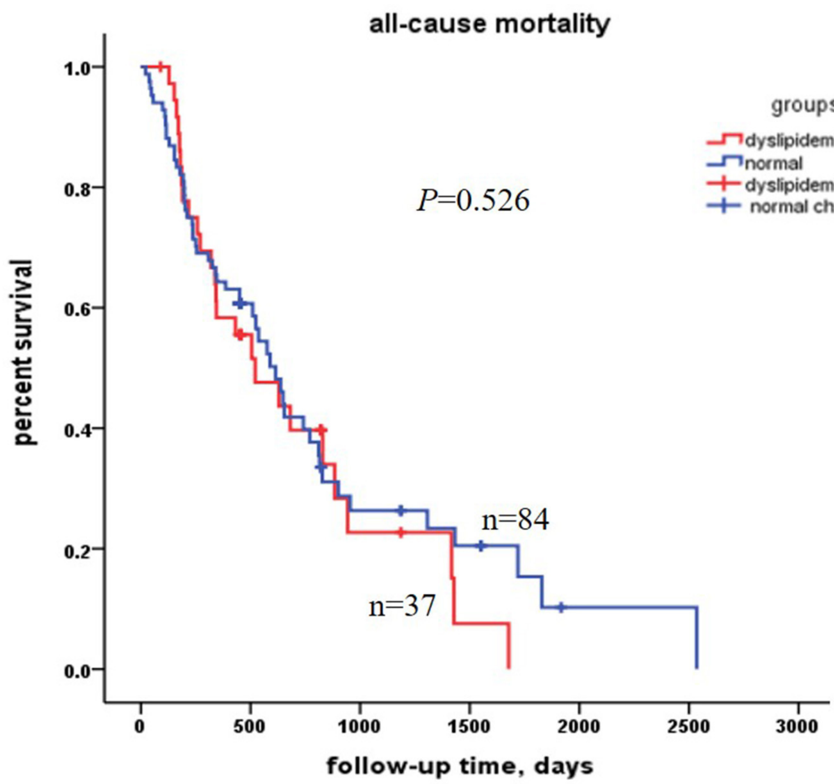

FIGURE 1 | Kaplan–Meier survival curves estimation for all-cause mortality in the 121 centenarians. There was no significant difference between the dyslipidemia centenarians and the normal centenarians.

Results of the Sensitivity Analysis

There were 90 out of 121 centenarians from the recent 5 years, from2016 to 2021. The 90 centenarians were also divided into two groups: dyslipidemia group and normal group. There were 49 out of 90 centenarians died during this period, leading to an all-cause mortality rate of 54.4%. The Kaplan–Meier survival curves were showed in **Figure 3**. The multivariable analysis showed that TC level was a risk factor and LDL-C level was the protective factor for all-cause death, which were the same as the whole 121 centenarians (see **Table 4**). The analyses stratified by the lipid-lowering therapy were undertaken to check the findings, and the results were consistent with the two groups. Sensitivity analysis showed that the above results were stable.

DISCUSSION

In this study, the average levels of TC, TG, LDL-C and HDL-C in inpatient centenarians were 3.90 ± 0.69 mmol/L, 1.36 ± 0.55 mmol/L, 2.05 ± 0.46 mmol/L and 1.14 ± 0.24 mmol/L, respectively. Previous studies have shown that the incidence of dyslipidemia in Chinese adults was 26.3–42.65% (12, 13). The latest research on distribution characteristics of blood lipid profile in Hainan centenarians (14) showed that the median levels of TC, TG, LDL-C and HDL-C were 4.60 mmol/L, 1.05 mmol/L, 2.77 mmol/L and 1.41 mmol/L, respectively, and the prevalence of dyslipidemia was 19.1%. Centenarians in Hainan were all community populations, while centenarians in our study were all from hospital. The levels of TC and LDL-C in this study were lower comparing to the previous studies, which may be related to multiple reasons, such as the coexistence of chronic diseases in hospitalized patients, combination effect of lipid-lowering drugs and other non-drug therapies.

In this study, 69.4% of centenarians had taken lipid-lowering drugs in hospital, and the lipid-lowering drugs were mainly statins (63.6%). Statins are known to reduce LDL-C level by roughly 50% and, decrease cardiovascular risks, which were recommended for primary and secondary drugs for preventions of ASCVD (11). Previous studies have shown that the treatment rate of lipid-lowering drugs in China was only 5∼14.5% (12). However, the use of statins in patients with acute coronary syndrome in China have increased greatly in recent years (15). The treatment rate of lipid-lowering drugs was higher than previous studies mainly related to the better compliance of drugs in hospital, which indicated that the treatment rate of lipid-lowering drugs for the elderly can be improved by strengthening publicity, education and supervision.

We investigated the relationship between LDL-C level and 10 years all-cause mortality among inpatient centenarians in this study. We found that LDL-C level was a protective factor for all-cause death (HR = 0.379, 95% CI = 0.212–0.677, P = 0.001). And the sensitivity analysis showed that our results were stable. Previous studies have generally focused on that more

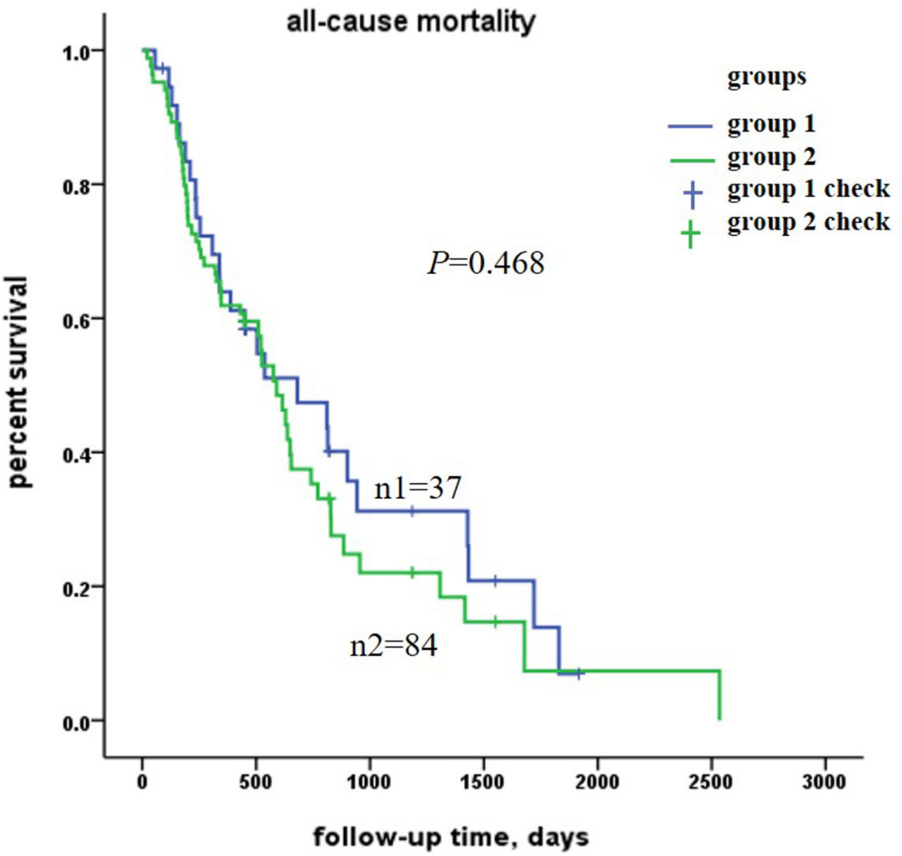

FIGURE 2 | Kaplan–Meier survival curves estimation for all-cause mortality in the 121 centenarians. There was no significant difference between group 1 and group 2. Group 1 was for lipid lowering drugs non-users, Group 2 was for lipid lowering drugs users.

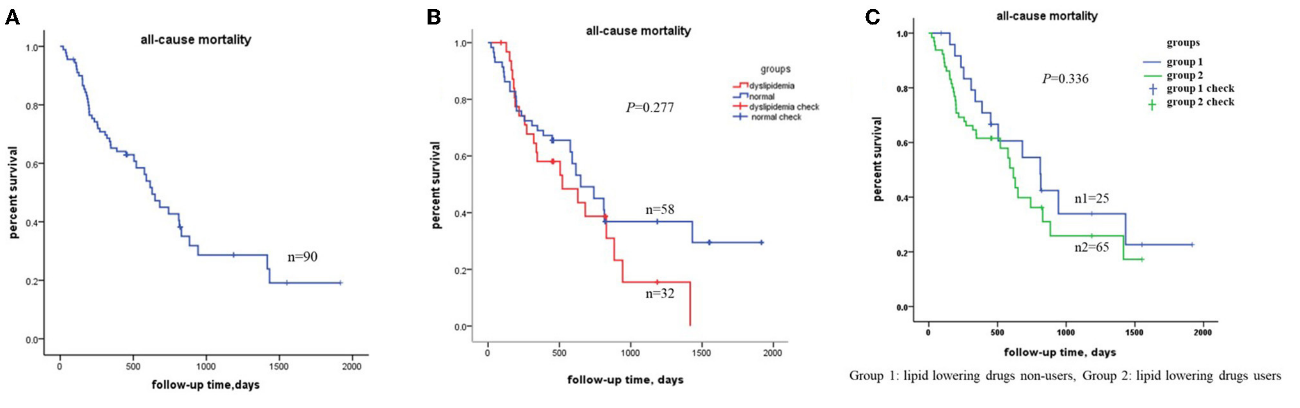

FIGURE 3 | Kaplan–Meier survival curves estimation in the 90 centenarians from recent 5 years (from 2016 to 2021). **(A)** The total all-cause mortality in the 90 centenarians; **(B)** the total all-cause mortality between the dyslipidemia group and normal group; **(C)** the all-cause mortality stratified by the lipid-lowering therapy. Group 1 was for lipid lowering drugs non-users, Group 2 was for lipid lowering drugs users. Both $P > 0.05$, which indicated the same results as the whole centenarians.

intensive LDL-C lowering can reduce the risk of all-cause and cardiovascular mortality for ASCVD patients (16). The lipid status and the association between LDL-C level and all-cause mortality in inpatient centenarians are still poorly evaluated. Studies have confirmed that lowering of LDL-C with standard statin regimens can reduce the risk of occlusive vascular events in ASCVD patients. More intensive lowering of LDL-C level with statin therapy also produced definite further reductions

TABLE 3 | The multivariate analysis in 121 centenarians.

Items	B	SE	Wald	Sig.	HR	95.0% CI	
						lower	upper
Age	−1.768	1.064	2.761	0.097	0.171	0.021	1.374
BMI	−0.039	0.040	0.950	0.330	0.962	0.890	1.040
Smoking	0.910	1.056	0.741	0.389	2.483	0.313	19.685
Drinking	−0.324	0.415	0.610	0.435	0.723	0.321	1.631
TC	0.677	0.256	6.983	0.008	1.968	1.191	3.253
TG	−0.033	0.309	0.011	0.916	0.968	0.528	1.772
HDL-C	−1.267	0.749	2.860	0.091	0.282	0.065	1.223
LDL-C	−0.971	0.296	10.756	0.001	0.379	0.212	0.677
Cancer	0.519	0.260	3.992	0.046	1.680	1.010	2.796
CHD	0.201	0.370	0.296	0.587	1.223	0.592	2.527
Hypertension	0.414	0.350	1.398	0.237	1.513	0.762	3.006
DM	0.302	0.249	1.478	0.224	1.353	0.831	2.203
Lipid-lowering therapy	0.080	0.283	0.079	0.778	1.083	0.622	1.886

BMI, body mass index; TC, total cholesterol; TG, triglyceride; HDL-C„ high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CHD, coronary heart disease; DM, diabetes mellitus.

TABLE 4 | The multivariable analysis in the 90 centenarians from the recent 5 years.

Items	B	SE	Wald	Sig.	HR	95.0% CI	
						lower	upper
TC	0.754	0.377	4.008	0.045	2.126	1.016	4.451
TG	0.421	0.388	1.180	0.277	1.524	0.713	3.258
HDL-C	−0.478	0.875	0.299	0.585	0.620	0.112	3.444
LDL-C	−1.615	0.464	12.137	0.000	0.199	0.080	0.493

TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. The analysis was adjusted by age, BMI, coronary heart disease, diabetes mellitus, hypertension, cancer, and the lipid-lowering therapy.

in the incidence of cardiac events (8, 17). A meta-analysis of 34 studies (16) showed that intensive lipid-lowering therapy is beneficial to the end points. In this meta-analysis, compared with less intensive LDL-C lowering, more intensive reduction was associated with a greater benefit to cardiovascular mortality in patients with higher baseline LDL-C levels. But this association was not found when baseline LDL-C level was $<$ 100 mg/dl. The direct association of LDL-C level with all-cause mortality was still unclear. A nationwide representative longitudinal study based on the data from the China Health and Retirement Longitudinal Study (CHARLS), found some different results from previous studies (18); this study demonstrated that middle-aged and elderly Chinese men with very low LDL-C level had an increased risk of all-cause mortality. Similarly, a Chinese recent study (19) of 6,941 elderly people showed that the ratio of LDL-C/HDL-C level had a U-shaped relationship with all-cause mortality in hypertensive patients over 65-year-old, suggesting that both lower and higher LDL-C/HDL-C ratios will all increase the all-cause mortality. In addition, previous study showed the LDL-C level of 3.6 mmol/L (140 mg/ dl) may have the lowest risk of all-cause mortality (20). Recently, a study form Korean (21) in the elderly population found LDL-C level was not correlated with cardiovascular death and all-cause death, indicating high LDL-C level may not be a risk factor for CVD in the elderly individuals.

CONCLUSION

The results in our study proved the point that "lowest was not the best", suggesting the potential harmful effect of more intensive lowering of LDL-C on all-cause mortality, which indicates that special attention should be paid to the inpatient centenarians on proper LDL-C level. However, prospective and well-designed cohort studies are still needed to validate the relationship between LDL-C level and mortality in centenarians.

STUDY LIMITATIONS

There were some limitations in this study. (1) The association between LDL-C level and mortality of subgroups could not be analyzed due to the small sample size of centenarians in a single center; centenarians from multiple-center should be continuously admitted to expand the sample size to verify the reliability of the results. (2) The centenarians were often complicated by physical comorbidity and polypharmacy, and we were failed to collect all the drugs details so that we can't analyze the confounding factors. However, the study is still ongoing, and further analysis should be carried out when the sample size is qualified. Then we will check the correlation between combination of different drugs and all-cause mortality.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Chinese PLA General Hospital Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XZ, LF, and QJS: conceptualization. XZ, YXH, and JHL: patients enrolling. XZ, JHL, HJW, SSS, TS, and XLD: data collecting and follow-up. XZ and WHX: statistical analysis. XZ: writing—original draft and funding acquisition. XZ, QJS, LF, and JC: writing—review and editing. All authors contributed to the article and approved the submitted version.

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Pilot study of peripheral blood chemokines as biomarkers for atrial fibrillation-related thromboembolism and bleeding in elderly patients

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Background: The scoring systems currently used to identify the potential for thrombosis and bleeding events in high-risk atrial fibrillation patients have certain limitations. The aim of this pilot study was to identify inflammatory chemokines with potential utility as sensitive biomarkers for the risk of thrombosis and bleeding in elderly patients with non-valvular atrial fibrillation.

Methods: From January 1, 2014, to December 31, 2017, 200 consecutive elderly patients with atrial fibrillation (average age: 87.6 ± 7.7 years) were enrolled and followed up for 2 years to observe thromboembolic (arterial and venous) and bleeding events. Serum was collected upon enrollment, and the baseline levels of 27 chemokines were analyzed. During the 2-year follow-up, 12 patients were lost to follow-up. Among the 188 patients, there were 32 cases (17.0%) of AF-related thrombosis, 36 cases (19.1%) of arterial thrombosis, and 35 cases (18.6%) of major bleeding events.

Results: Among 188 patients, 30 patients without clinical events (control group), 23 with arterial thrombosis, 15 with atrial fibrillation-related venous thromboembolism, and 12 with major bleeding were selected and randomly matched to compare chemokine levels. The baseline levels of interleukin-6, interleukin-10, vascular cell adhesion molecule-1, chemokine C-C-motif ligand, B-lymphocyte chemoattractant 1, interleukin-4, E-selectin, fractalkine, C-X-C motif chemokine 12, and granulocyte chemotactic protein 2 were found to differ statistically among the four groups ($p < 0.05$). Compared with that in the control group, the level of interleukin-4 in patients with atrial fibrillation-related thrombosis, arterial thrombosis, or major bleeding increased by 53-fold (0.53 vs. 0.01 pg/ml), 17-fold (0.17 vs. 0.01 pg/ml), and 19-fold (0.19 vs. 0.01 pg/ml), respectively. Compared with that in the control group, the level of interleukin-6 in patients with arterial thrombosis increased by six-fold (39.78 vs. 4.98 pg/ml).

Conclusions: Among elderly patients with atrial fibrillation at high risk of thromboembolism and bleeding, the baseline levels of interleukin-6, interleukin-4, and E-selectin were significantly increased in those that experienced thrombosis and bleeding events during the 2-year follow-up, indicating that these chemokines may serve as potential biomarkers for an increased risk of thrombosis and bleeding in this population.

Clinical trial registration number: ChiCTR-OCH-13003479.

KEYWORDS

atrial fibrillation, chemokine, elderly, thromboembolism, bleeding

Background

The incidence of atrial fibrillation (AF) increases significantly with age (1, 2). In the last decade, the burden of AF and AF-related stroke/thrombotic events in China increased significantly, but the rate of anticoagulation therapy prescribed for patients with AF in China was significantly lower than that in Europe and America, especially among elderly patients (2, 3). The risk of ischemic stroke, AF-related venous thrombosis, and acute myocardial infarction might coexist in elderly patients with AF (4, 5). The risk of thromboembolism in patients with AF can be effectively reduced by anticoagulation therapy. However, the dysfunction of organs such as the liver and kidney, presence of other diseases such as hypertension, diabetes, and atherosclerosis, and use of multiple medications that predispose elderly patients with AF to concomitant thromboembolism and bleeding (6, 7), which often leads to death or severe disability, profoundly affects the quality of life (8).

The current clinical risk scoring systems for thromboembolism are $CHADS_2$ [congestive heart failure, hypertension, age of 75 years, diabetes, stroke (doubled)] and CHA_2DS_2-VASc [congestive heart failure, hypertension, age of 75 years (doubled), diabetes mellitus, stroke or transient ischemic attack (doubled), vascular disease, age of 65–74 years, female sex)]; whereas that for bleeding is HAS-BLED [hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (>65 years), drugs/alcohol concomitance]. In these systems, there are overlaps among clinical factors such as hypertension, previous stroke, and age, and the utility of these systems for identifying thrombosis and bleeding risk in high-risk patients with AF is limited (9–11).

Previous studies showed that chemokines play an important role in inflammation and atherosclerosis (12, 13). However, the relationship between chemokines and the prognosis of AF remains unclear. It has been suggested that when AF is associated with a hypercoagulable state, the levels of some cytokines are elevated. Gizatulina et al. found that blood concentration of growth differentiation factor 15 (GDF-15) as a predictor of left atrial/left atrial appendage (LA/LAA) thrombosis in patients with non-valvular atrial fibrillation (14). A systematic review and meta-analysis including five studies involving 22,928 patients and concerning the association between IL-6 and thromboembolic events in AF showed that higher level of IL-6 in AF patients is related to long-term thromboembolic events including stroke (RR 1.44, CI 95% 1.09–1.90, $p = 0.01$) and a higher risk of long-term bleeding risk (RR 1.36, CI 95% 1.06–1.74, $p = 0.02$) (15). So Inflammatory chemokines might serve as sensitive biomarkers for guiding the clinical management of anticoagulation treatment (16–19). This prospective study aimed to identify chemokines with potential utility as sensitive biomarkers in patients with AF at high risk of thromboembolism and bleeding.

Abbreviations: AF, atrial fibrillation; CHADS2, congestive heart failure, hypertension, age of 75 years, diabetes, stroke (doubled); CHA2DS2-VASc, congestive heart failure, hypertension, age of 75 years (doubled), diabetes mellitus, stroke or transient ischemic attack (doubled), vascular disease, age of 65 to 74 years, female sex; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (> 65 years), drugs/alcohol concomitance; NAP2, neutrophil activating protein-2; ICAM-1, intercellular cell adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; PF, platelet factor; MIG, monokine induced by interferon-r; BCA-1, B-lymphocyte chemoattractant 1; RANTES, regulated on activation normal T cell expressed and secreted; MIP, monocyte chemoattractant protein; TNF, tumor necrosis factor; IL, interleukin; GCP2, granulocyte chemotactic protein 2; ENA-78, epithelial neutrophil activating peptide-78; IP-10, interferon-inducible protein-10; MCP-1, monocyte chemoattractant protein-1; TARC, thymus and activation-regulated chemokine; CCL19, chemokine C-C-motif ligand; SDF1, stromal cell-derived factor 1; CXCL12, C-X-C motif chemokine 12; I-TAC, interferon-inducible T cell alpha chemoattractant; sE, selsoluble E-selectin; Th2 lymphocytes, T helper lymphocytes.

Methods

Study population

This was a prospective observational cohort study (clinical trial registration number: ChiCTR-OCH-13003479). Between January 1, 2014, and December 31, 2015, 200 consecutive elderly patients (all aged over 75 years) with non-valvular AF at the General Hospital of the Chinese People's Liberation Army were enrolled (average age: 87.6 ± 7.7 years). The study was approved by the Medical Ethics Committee of the General Hospital of the People's Liberation Army (approval number: S2013-064-02).

The inclusion criteria for patients in the AF group (including new onset, paroxysmal, persistent, and permanent AF, as confirmed by electrocardiogram or 24 h Holter monitor) were age ≥75 years and at least one AF attack recorded in the year prior to the study. Patients or patients' relatives provided written consent. The exclusion criteria were age ≤75 years, rheumatic heart disease, biological or mechanical valve replacement or mitral valve repair, serious uncontrolled infection, and an AF attack recorded more than 1 year before the study.

Clinical data collection

Clinical data were collected at the baseline and during follow-up by experienced attending cardiologists. The baseline clinical data of enrolled patients were as follows: name, gender, age, type of AF (new onset, paroxysmal, persistent, or permanent), systolic blood pressure, diastolic blood pressure, smoking and drinking history, disease history (such as ischemic stroke, hypertension, diabetes, congestive heart failure, peripheral vascular disease, and renal/liver dysfunction), and medication status [including the use of antiplatelet drugs (aspirin and clopidogrel) and anticoagulation drugs (warfarin and novel oral anti-coagulants)]. Follow-up data including medication status and clinical endpoints were collected through medical records, telephone interviews, and questionnaires.

Two hundred elderly patients with AF were followed up for 2 years to observe thromboembolic (both arterial and venous thrombosis) and bleeding events. AF-related thrombotic events included ischemic stroke, lower extremity deep venous thrombosis, and thrombosis of other systems (including mesenteric thrombosis and venous catheter-related thrombosis). Arterial thrombosis was defined as acute myocardial infarction and unstable angina. Clinically relevant major bleeding events included a decrease in hemoglobin of more than 2 g/L, the need for a blood transfusion or hospitalization, bleeding in major organs, and fatal bleeding. Non-clinically relevant major bleeding events included chronic bleeding and a decrease in hemoglobin of <2 g/L. Minor bleeding events included subcutaneous hematoma, gastrointestinal bleeding (below the standard for major bleeding), and blood sputum (20). Data collection was completed for 188 patients; 12 patients were lost to follow-up, the loss to follow-up rate is 6%.

Measurement of chemokine levels

Two milliliters of fasting blood was drawn from all patients in the early morning on the day of enrollment. Blood samples were collected using EDTA anticoagulant vessels and then centrifuged at 4,000 rpm for 8 min (room temperature). Plasma was separated and stored at −80°C for batch analysis. The Aimplex method (Beijing Kuang Bo Biotechnology Limited by Share Ltd., Beijing, China) was used to detect 27 chemokines of the chemokine family, including neutrophil activating protein-2 (NAP2), P-selectin, E-selectin, intercellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), platelet factor 4 (PF4), monokine induced by interferon-r (MIG), B-lymphocyte chemoattractant 1 (BCA-1), regulated on activation normal T cell expressed and secreted (RANTES), monocyte chemoattractant protein (MIP)-3beta, MIP-1beta, tumor necrosis factor (TNF)-alpha, interleukin (IL)-1beta, IL-2, IL-4, IL-6, granulocyte chemotactic protein 2 (GCP2), IL-10, epithelial neutrophil activating peptide 78 (ENA-78), interferon-inducible protein-10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), thymus and activation-regulated chemokine (TARC), chemokine C-C-motif ligand (CCL19), stromal cell-derived factor 1 [(SDF1; also known as C-X-C motif chemokine 12 (CXCL12)], fractalkine, and interferon-inducible T cell alpha chemoattractant (I-TAC). For each inflammatory chemokine, the intragroup error was <6%, while the intergroup error was <8%.

Statistics

Continuous variables were expressed as the median [interquartile range (IQR)] if the data were non-normally distributed, or as the mean ± standard deviation (SD; ± SD) if the data were normally distributed (Kolmogorov-Smirnov criteria). The Kruskal-Wallis test was used to compare non-parametric data. Two-way ANOVA was used to compare data with a normal distribution. Qualitative data were expressed as percentages. A $p < 0.05$ was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics version 19.0 (SPSS, Inc., Chicago, IL, USA).

Results

Baseline clinical characteristics and risk of thrombosis and bleeding

The clinical characteristics of 188 patients with AF are presented in Table 1. This cohort was predominantly elderly

TABLE 1 Baseline clinical characteristics of 188 elderly patients with AF at high risk of thromboembolism and bleeding.

Characteristic	Patients with AF ($n = 188$)
Age, mean (SD) (years)	87.6 (7.7)
Male, *n* (%)	174 (92.55)
Systolic blood pressure, mean (SD) (mmHg)	133.82 (13.65)
Diastolic blood pressure, mean (SD) (mmHg)	69.91 (10.62)
Smoking history, *n* (%)	90 (47.87)
Drinking history, *n* (%)	88 (46.81)
Type of AF, *n* (%)	
New onset AF, *n* (%)	7 (3.72)
Paroxysmal AF, *n* (%)	117 (62.23)
Persistent AF, *n* (%)	13 (6.91)
Permanent AF, *n* (%)	51 (27.13)
Comorbidities	
Hypertension, *n* (%)	135 (71.81)
Coronary heart disease, *n* (%)	143 (76.06)
Old myocardial infarction, *n* (%)	38 (20.21)
Hyperlipidemia, *n* (%)	41 (21.81)
Type 2 diabetes, *n* (%)	64 (34.04)
Congestive heart failure, *n* (%)	44 (23.40)
Stroke, *n* (%)	84 (44.68)
Peripheral vascular disease, *n* (%)	26 (13.83)
Renal dysfunction, *n* (%)	48 (25.53)
Liver dysfunction, *n* (%)	4 (2.13)
Anemia, *n* (%)	41 (21.81)
Past bleeding history, *n* (%)	39 (65.42)
Current bleeding, *n* (%)	15 (7.99)
Risk of fall, *n* (%)	68 (36.17)
CHA_2DS_2-VASc, mean (SD)	5.1 (1.6)
HAS-BLED, mean (SD)	3.4 (1.2)
Anticoagulation therapy	
Warfarin, *n* (%)	10 (5.32)
Rivaroxaban, *n* (%)	25 (13.30)
Clopidegrel, *n* (%)	78 (41.49)
Aspirin, *n* (%)	74 (39.36)

AF, atrial fibrillation; SD, standard deviation; CHA2DS2-VASc: congestive heart failure, hypertension, age 75 years (doubled), diabetes mellitus, stroke or transient ischemic attack (doubled), vascular disease, age 65 to 74 years, and female sex; HAS-BLED: hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (65 years), drugs/alcohol concomitance.

(aged 75–98 years, average age: 87.6 ± 7.7 years) male patients (92.6%). This cohort of elderly patients with AF was at high risk of thromboembolism [CHA_2DS_2-VASc (mean ± SD): 5.1 ± 1.6] and bleeding [HAS-BLED (mean ± SD): 3.4 + 1.2].

Among 188 elderly patients with AF, the number of patients on warfarin, rivaroxaban, clopidegrel, and aspirin were 10 (5.32%), 25 (13.30%), 78 (41.49%), and 74 (39.36%) respectively.

TABLE 2 Adverse clinical events in 188 elderly patients with AF at high risk of thromboembolism and bleeding during 2-year follow-up.

Adverse event	Case #	Incidence (%)
AF-related thromboembolism		
Ischemic stroke	8	4.26
Lower extremity deep venous thrombosis	19	10.11
Other-system thrombosis	5	2.66
Arterial thrombosis		
Acute myocardial infarction	22	11.70
Unstable Angina	14	7.45
Bleeding		
Cerebral hemorrhage	8	4.26
Clinically relevant major bleeding	18	9.57
Non-clinically relevant major bleeding	9	4.79
Minor bleeding	36	19.15
All-cause death	54	28.72

AF, atrial fibrillation; Other-system thrombosis: mesenteric thrombosis, venous catheter-related thrombosis, etc.; Clinically relevant major bleeding: hemoglobin decreased more than 2 g/L, the need for blood transfusion or hospitalization, or bleeding in major organs, fatal bleeding, etc.; Non-clinically relevant major bleeding: chronic bleeding, hemoglobin decreased less than 2 g/L; Minor bleeding: subcutaneous hematoma, gastrointestinal bleeding (less than the standards of major bleeding), blood sputum, etc.

Clinical outcomes of elderly patients with AF during follow-up

During the 2-year follow-up, among the 188 patients, there were 32 cases (17.0%) of AF-related thrombosis (including ischemic stroke, deep-vein thrombosis, and thrombosis of other systems), 36 cases (19.1%) of arterial thrombosis,35 cases (18.6%) of major bleeding events (including hemorrhagic stroke and other clinical major bleeding events), and 36 cases (19.2%) of minor bleeding. There were 54 cases (28.7%) of all-cause death (Table 2).

Association between chemokines and AF-related arterial thrombosis, venous thrombosis, and bleeding events

Thirty high-risk patients with AF but not exhibiting clinical adverse events (control group), 23 with arterial thrombosis (unstable angina and acute myocardial infarction), 15 with AF-related venous thrombosis, and 12 with major bleeding were selected and matched randomly to analyze the 27 chemokines. The baseline levels of IL-6, IL-10, VCAM-1, CCL19, BCA-1, IL-4, E-selectin, fractalkine, CXCL12, and GCP2 were found to differ statistically among the control, arterial thrombosis, AF-related venous thrombosis, and major bleeding groups ($p <$ 0.05). Compared with those in the control group, the levels of IL-4 in patients with AF-related venous thrombosis, arterial thrombosis, or major bleeding events increased by 53- (0.53 vs.

0.01 pg/ml), 17- (0.17 vs. 0.01 pg/ml) and 19-fold (0.19 vs. 0.01 pg/ml), respectively. Compared with those in the control group, the levels of IL-6 in patients with arterial thrombosis increased by six-fold (39.78 vs. 4.98 pg/ml; Table 3).

Discussions

Chemokines and AF-related stroke

Accumulating data indicate that endothelial dysfunction, platelet activation, and coagulation factor activation caused by inflammation might cause patients with AF to enter a prothrombotic state (21–23). The upregulation of inflammatory factors such as IL-6 and IL-8 are related to endothelial dysfunction, platelet activation, and active thrombosis (21, 22). Experimental studies have demonstrated that the IL-6-induced expression of tissue factor and von Willebrand factor is involved in platelet activation, possibly driven by platelet-monocyte interactions (24, 25). Patients with increased levels of IL-6 are more likely to have thrombus formation in the left atrial appendage (21, 22). Moreover, Pinto et al. (26) found that elevated levels of IL-6, von Willebrand factor, and TNF-alpha are significant predictors of stroke, based on a 3-year follow-up of 373 patients with AF. IL-6 is also an independent predictor of the composite endpoint of stroke or death in patients with AF (27) and is associated with worse outcomes after ischemic stroke (28).

IL-6 and AF-related thrombosis

The patients with AF in our study were at high risk of both thromboembolism and bleeding and were much older than the patients enrolled in these previous studies. We found that the levels of IL-6 increased significantly in patients with arterial thrombosis and AF-related thrombosis during the 2-year follow-up; our results were consistent with the previous findings. Interestingly, we also found that the expression of IL-6 was significantly increased in patients with AF with major bleeding. This result was consistent with the findings of the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy Study) trial, in which an independent relationship was identified between IL-6 and a higher risk of stroke and major bleeding independent of clinical risk factors, even after adjusting for cardiovascular biomarkers to attenuate the prognostic value (29).

E-selectin/VCAM-1 and AF-related thrombosis/bleeding

Under normal physiological conditions, soluble E-selectin (sE-sel) is not expressed on the surface of endothelial cells (30). Under pathological conditions, increased expression of E-selectin on the surface of endothelial cells can mediate the activation of endothelial cells and the adhesion of leukocytes, which may play a role in the process of thrombosis (31). However, data regarding whether sE-sel contributes to the risk of thromboembolism in patients with AF remains limited and confusing. For instance, Freestone et al. (32) found that compared to patients with sinus rhythm, patients with AF have elevated levels of sE-sel, and low baseline sE-sel levels predict the successful maintenance of sinus rhythm at 6 months of follow-up (33). In contrast, another study conducted by Freestone et al. (34) indicated that in patients with systolic heart failure, the differences between plasma sE-sel levels in patients with AF and those in patients with normal sinus rhythm were not significant.

Similar to the first study by Freestone et al., a study by Krishnamoorthy et al. (35) of 423 patients with non-valvular AF followed up for 19 months showed that elevated levels of sE-sel were associated with an increased risk of clinical adverse events (acute myocardial infarction, ischemic stroke, and all-cause mortality). However, Roldán et al. (36) found no association between sE-sel levels and inflammation or abnormal thrombogenesis in 191 consecutive patients with chronic non-rheumatic AF who were not receiving anticoagulation therapy. However, plasma levels of sE-sel were significantly decreased ($p < 0.01$) after oral anticoagulation therapy.

In the Bruneck study (37), a prospective population-based cohort study with a 20-year follow-up ($n = 909$), the levels of soluble VCAM-1 were significantly associated with incident AF (hazard ratio: 1.49; 95% confidence interval, CI: 1.26–1.78, $p < 0.001$ with a Bonferroni correction for both values); even after adjusting for age and sex, the association was still significant. However, the association with E-selectin levels was insignificant (after a Bonferroni correction in unadjusted and age- and sex-adjusted analyses).

Our results showed that the levels of E-selectin were significantly increased in the major bleeding and AF-related thrombosis groups, compared with those in patients without thromboembolic and bleeding events. Furthermore, the levels of VCAM-1 were different significantly among control group vs. arterial thrombosis, venous thrombosis, and major bleeding groups ($p < 0.05$). Further *in vivo* and *in vitro* studies are needed to investigate whether increased E-selectin levels, which reflect endothelial activation and platelet aggregation, initiate AF and AF-related thrombosis or are simply a consequence of AF-accompanied cardiovascular disease and adverse clinical events.

IL-4/IL-10 and AF-related thrombosis/bleeding

IL-4 and IL-10, secreted by type II T helper lymphocytes (Th2 lymphocytes), can inhibit the synthesis and expression of proinflammatory markers such as IL-6, IL-8, and TNF by

TABLE 3 Levels of chemokines in elderly patients with AF and different adverse clinical events.

Chemokine	Control ($n = 30$)		Arterial thrombosis ($n = 23$)		AF related venous thromboembolism ($n = 15$)		Major bleeding ($n = 12$)		*p*
IL-6, pg/ml	4.98	(3.05–10.49)	9.21	(3.75–20.82)	13.86	(7.36–21.81)	39.78	(10.06–182.96)	**<0.001**
IL-10, pg/ml	3.73	(3.24–4.78)	4.52	(3.98–6.64)	4.75	(3.28–7.35)	6.31	(4.01–15.00)	**0.01**
VCAM-1, ng/ml	358.53	(292.39–474.19)	438.93	(282.19–463.42)	468.53	(325.93–561.71)	643.97	(374.09–1079.54)	**0.02**
CCL19, pg/ml	95.25	(66.70–109.48)	106.21	(76.52–133.43)	99.41	(72.17–143.85)	132.18	(97.36–196.46)	**0.03**
BCA-1, pg/ml	5.54	(3.96–9.18)	6.31	(4.34–10.11)	6.55	(5.06–13.86)	9.41	(54.61–5.68)	**0.04**
IL-4, pg/ml	0.01	(0.01–0.17)	0.19	(0.01–1.90)	0.53	(0.02–1.67)	0.17	(0.01–0.93)	**0.04**
E-selectin, ng/ml	8.59	(5.62–13.06)	9.94	(5.92–12.76)	5.34	(3.74–11.79)	15.52	(8.37–21.94)	**0.04**
Fractalkine, ng/ml	32.16	(24.51–37.63)	34.14	(27.28–45.05)	35.24	(24.96–44.69)	51.12	(32.18–101.47)	**0.05**
CXCL12, pg/ml	2.32	(1.57–4.48)	2.84	(1.85–6.52)	3.91	(2.80–10.49)	4.16	(3.04–9.23)	**0.05**
GCP2, pg/ml	22.22	(16.42–33.03)	23.93	(20.24–28.40)	25.81	(23.71–28.95)	32.07	(25.39–45.66)	**0.05**
MCP-1, pg/ml	73.27	(51.28–93.71)	74.43	(56.64–92.80)	71.53	(64.98–98.77)	124.82	(80.63–193.93)	0.06
PF4, ng/ml	6.62	(0.44)	6.49	(0.68)	6.65	(0.42)	7.04	(1.23)	0.08
IP-10, pg/ml	36.34	(25.66–50.51)	33.16	(24.17–49.65)	40.79	(36.42–73.35)	48.82	(38.67–59.12)	0.11
TNF-alpha, pg/ml	0.13	(0.01–0.57)	0.37	(0.01–1.03)	0.01	(0.01–1.57)	0.31	(0.01–1.12)	0.12
I-TAC, pg/ml	6.16	(4.26–15.60)	6.01	(4.57–9.47)	6.92	(4.10–16.77)	6.59	(3.72–15.61)	0.12
MIG, ng/ml	0.28	(0.08)	0.27	(0.07)	0.28	(0.10)	0.34	(0.11)	0.14
ICAM-1, ng/ml	282.25	(113.22)	310.42	(156.41)	326.69	(134.32)	379.35	(160.31)	0.17
IL-2, pg/ml	3.26	(2.48–3.69)	3.08	(2.51–4.49)	3.44	(2.85–4.49)	3.21	(2.16–5.40)	0.23
IL-1beta, pg/ml	0.02	(0.01–0.02)	0.02	(0.02–0.02)	0.02	(0.02–0.02)	0.02	(0.02–2.51)	0.27
IL-8, pg/ml	61.48	(23.36–113.33)	59.12	(27.01–156.94)	97.03	(48.58–213.75)	112.39	(66.39–199.48)	0.43
NAP2, ng/ml	18.26	(3.29)	17.79	(3.94)	16.54	(4.68)	18.01	(3.67)	0.54
ENA-78, ng/ml	1.55	(1.03)	1.59	(1.08)	1.66	(0.83)	1.24	(0.86)	0.59
MIP-1alpha, pg/ml	20.59	(17.44–37.44)	29.17	(13.84–38.16)	26.95	(25.58–45.28)	41.70	(28.20–53.25)	0.67
MIP-3beta, pg/ml	92.69	(27.91)	106.95	(44.31)	114.26	(47.65)	175.61	(137.92)	0.75
P-selectin, ng/ml	80.95	(28.23)	82.81	(29.37)	77.47	(32.47)	87.00	(34.90)	0.79
TARC, pg/ml	41.52	(18.99–74.24)	44.42	(18.54–93.56)	31.28	(9.99–108.72)	30.01	(14.52–83.02)	0.82
RANTES, ng/ml	2.34	(0.29)	2.24	(0.33)	2.38	(0.45)	2.75	(1.02)	0.84

AF, atrial fibrillation; IL, interleukin; VCAM-1, vascular cell adhesion molecule-1; CCL19, chemokine C–C-motif ligand; BCA-1, B-lymphocyte chemoattractant 1; CXCL12, C–X–C motif chemokine 12, also known as stromal cell-derived factor 1 (SDF1); GCP2, granulocyte chemotactic protein 2; MCP-1, monocyte chemoattractant protein-1; PF4, platelet factor 4; IP-10, interferon–inducible protein-10; TNF–alpha, tumor necrosis factor-alpha; I-TAC, interferon-inducible T cell alpha chemoattractant; MIG, monokine induced by interferon-r; ICAM-1; intercellular cell adhesion molecule-1; NAP2, neutrophil activating protein-2; ENA-78, epithelial neutrophil activating peptide 78; MIP, monocyte chemoattractant protein; TARC, thymus and activation–regulated chemokine; RANTES, regulated on activation normal T cell expressed and secreted. Median ± quartile: IL-6, IL-10, VCAM-1, CCL19, BCA-1, IL-4, E-selectin, fractalkine, CXCL12, GCP2, MCP-1, IP-10, TNF-alpha, I-TAC, IL-2, IL-1beta, IL-8, MIP-3beta, TARC. Mean ± standard deviation: PF4, MIG, ICAM-1, NAP2, ENA-78, MIP-1alpha, P-selectin, RANTES. Continuous variables were expressed as the median [interquartile range (IQR)] if the data were non-normally distributed, or as the mean ± standard deviation (SD; — X± SD) if the data were normally distributed (Kolmogorov-Smirnov criteria). The bold value represents $p < 0.05$.

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inhibiting type I T helper lymphocytes and stimulating B and Th2 lymphocytes, thus reducing the inflammatory response (38). The IL-10-592A/C polymorphism is associated with AF, and people of Han Chinese descent with the A allele are at an increased risk of AF (39). Henningsen et al. (30) did not find significant differences in either the genotypic or allelic frequency of IL-10-1082 between patients with AF and the control group, although the expression of inflammation and cell adhesion molecules in a rat model of venous thrombosis was inhibited by viral IL-10 gene transfer (40), and the IL-10-1082A/G polymorphism is associated with the risk of deep venous thrombosis (41). A C582T polymorphism in the IL-4 gene [odds ratio, OR ¼: 1.40, 95% CI: 1.13–1.73, p ¼: 0.003)] was found to be an independent predictor of thromboembolic stroke (42).

In our study, we did observe significantly higher baseline levels of IL-4 and IL-10 in patients with thromboembolic or bleeding events during the 2-year follow-up, compared to those in patients without these adverse events. Especially, compared to those in the patients without adverse events, the baseline levels of IL-4 in patients with venous thrombosis during follow-up increased by 53-fold. It suggested that IL-4 and IL-10 may highly be associated with the progression of AF-related adverse events. However, IL-4 levels could be associated with some medical setting, such as scleroderma, multiple sclerosis, chronic sinusitis, inflammatory bowel diseases, bronchial asthma, atopic dermatitis (43–45). Although we excluded patients with rheumatic heart disease and serious uncontrolled infection, other disease didn't be excluded, which needed to be explored further.

Possible mechanisms

There is a close relationship between inflammation, platelet activation and AF. Inflammatory cytokines play a certain role in the maintenance and prognosis of AF (46). Inflammation leads to cardiac endothelial damage or dysfunction, and promotes the aggregation of platelets, and the activation fibrinolytic protein and clotting factors (47). At the same time, the reconstruction of atrial anatomy cause by AF provides the environment for platelet aggregation and blood coagulation which promotes thrombosis (48). Chemokines, to a certain extent, is involved in inflammation, angiogenesis and necrosis, which is a key mediator of inflammation-related cell migration (49). Studies suggests that pro-inflammatory cytokines, such as IL-1β, IL-6, and IL-8, promote a pro-coagulant state through the induction of tissue factor. Anti-inflammatory cytokines, including IL-2, IL-4, and IL-10, act to reduce coagulation induced by other pro-inflammatory factors (50). Additionally, the cytokines IL-4, IL-6, IL-8, IL-10, and IL-1β were all significantly elevated in massive PE patients in comparison to those with low-risk and submassive PE, indicating the overwhelming inflammatory response with larger embolism (51). It is found that the polymorphisms of IL-4−589C/T and IL-13 intron 3C/T were associated with the increased risk of VTE among women, while IL-6 174C/G was found to make men susceptible to the VTE event (51). When compared with patients with lacunar infarct, those with cardioembolic stroke were shown to have significantly increased levels of proinflammatory cytokines such as IL-1β and IL-6 (51). The mechanisms of chemokines with increased levels in patients that experienced thrombosis and bleeding events during the 2-year follow-up in our study should be further studied *in vivo* and *in vitro*.

Limitations

There were several limitations in this study. Although there were 18.6% patients on anticoagulation, the anticoagulant may impact the thromboembolism and bleeding event. Moreover, this was single-center study and most of patients enrolled in Beijing, the result cannot be generalized other population. Given the small sample in this study, there were not exactly matched for age and sex, which possibility caused the bias. In addition, we were unable to perform multivariate regression analysis after adjusting the confounders. The temporal changes in the chemokines and their effect on clinical outcomes in patients with AF will be examined in our future analysis. Additionally, we did not compare differences in chemokines among different types of AF, due to the limited number of subjects.

Conclusion

In summary, among the 27 chemokines screened in our study, IL-6, IL-4, and E-selectin exhibited significantly increased levels in the study group that experienced thrombosis and bleeding events.

Data availability statement

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

Ethics statement

This study was approved by Medical Ethics Committees of the Chinese PLA General Hospital (Reference Number: S2013-064-02). The patients/participants provided their written informed consent to participate in this study.

Author contributions

YG conceived and designed the study. YG, HW, and MT analyzed and interpreted the data and wrote the report. YG supervised the work. MT and HW engaged in cohort assignment for participants. MT, HS, HW, XM, MG, QC, FL, QZ, YS, and YG reviewed and interpreted the results, commented on the report, contributed to revisions, and read and approved the final version. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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