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Sex modified the association between cognitive impairment and 1-year mortality in older adults with hip fractures

Zhi Yang, Yi-Dian Wang & Bin-Fei Zhang✉

To assess the role of sex-based influence on cognitive impairment and 1-year mortality in older adults with hip fractures. In this retrospective cohort study, we included older patients who experienced a hip fracture between 1 January 2015 and 30 September 2019. Demographic and clinical data of patients were obtained from original medical records. We contacted the patient's family members by telephone to record data on survival. The endpoint was all-cause mortality. Univariate and multivariate binary logistic regression models were used to build relationships between cognitive impairment and 1-year mortality. Overall, 2589 patients were included in this study, containing 835 males and 1754 females. One hundred five patients had cognitive impairment. The mean age was 79.60 (6.78) and 81.26 (5.84) years in the no cognitive and cognitive impairment groups. There were 286 (11.0%) patients who died after 1 year. Multivariate binary logistic regression showed that cognitive impairment was associated with increased 1-year mortality in hip fracture patients after correction for confounders (OR = 2.14, 95% CI: 1.2–3.82, *P* < 0.001). Also, the study found that cognitive impairment in male patients have an even higher 1-year mortality following hip fracture (OR = 5.96, 95% CI: 2.40–14.78, *P* < 0.0001). The interaction between males and females was *P* = 0.0171. The 1-year mortality was higher in older male patients with hip fractures and cognitive impairment. Cognitive impairment was associated with increased mortality in older adults with hip fractures. Notably, sex was a factor modifying this association, and male patients with cognitive impairment have an even higher 1-year mortality. Registration: ChiCTR2200057323.

Keywords Cognitive impairment, Hip fractures, Mortality, Sex

Hip fractures are a common cause of hospitalization and a significant cause of death among older people. The number of hip fracture patients is predicted to be 6.3 million by 2050[1]. The mortality rate at 1 year in the hip fracture population was 2.85 times, compared to the population without hip fracture[2]. Hip fractures have attracted widespread social attention.

Meanwhile, cognitive decline or impairment is a common phenomenon in elderly patients. It was reported that elderly patients experiencing cognitive decline or impairment account for 25–50% of hospital admissions[3]. Cognitive impairment can increase the incidence of associated complications and even endanger the lives of patients[4]. A systematic review assessed the impact of cognitive impairment on the quality of survival in older adults with hip fracture patients, which found that cognitive impairment was inversely related to patient health status and correlated with deterioration in health-related quality of life after hospital discharge[5]. Furthermore, cognitive impairment has significantly higher 12-month mortality and less functional recovery in hip fracture[6,7].

Also, several studies have shown that cognitive impairment is perceived differently according to sex[8,9]. In community-dwelling older adults, sex was found to be a significant influencing factor for cognitive impairment[10], and the male population was more likely to be cognitively impaired in hip fractures[11]. It was reported that men had more impaired cognitive scores in the Modified Mini-Mental State Examination, Hooper Visual Organization test, and Trail-making test within 22 days of hospital admission[11]. In addition, it was in males only that increased hip fracture risk was associated with mild stages of cognitive impairment[12], and males have a greater risk of mortality than females after hip fracture[13]. This evidence is a vital hypothesis that there is a sex-based difference in the association between cognitive impairment and mortality in hip fractures.

Department of Joint Surgery, Honghui Hospital, Xi'an Jiaotong University, No. 555 Youyi East Road, Beilin District, Xi'an 710054, Shaanxi Province, China. ✉email: zhangbf07@gmail.com

However, a detailed relationship between cognitive impairment and mortality in male and female patients with hip fractures has not been reported. Therefore, we aimed to determine the role of sex in modifying the association between cognitive impairment and 1-year mortality in older patients with hip fractures.

Materials and methods

Study design

This study was designed as a retrospective cohort study, and it was approved by the ethics committee of Honghui Hospital, Xi'an Jiaotong University (No. 202201009). The need for informed consent to participate was waived by the Institutional Review Board of Honghui Hospital. All human-related procedures followed the 1964 Declaration of Helsinki and its later amendments. The study has been reported according to the STROCSS 2021 guidelines[14].

Participants

We included the patients according to digital medical records and had a survival follow-up. Demographic and clinical data of patients were obtained from original medical records. The inclusion criteria were as follows: (1) age ≥ 65 years old; (2) a radiograph or computed tomography confirmed the diagnosis of a femoral neck or intertrochanteric fracture (ICD-10 S72.101, S72.000); (3) patients who were receiving surgical or conservative treatment in a hospital; (4) availability of clinical data when in the hospital; and (5) patients could be contacted by telephone. Patients who could not be contacted were excluded from this study[15,16].

Cognitive impairment was defined as meeting the diagnosis of Alzheimer's disease (ICD-10 G30). The diagnosis of Alzheimer's disease is based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association[17] and Diagnostic and Statistical Manual of Mental Disorders, fifth Edition[18]. The patients who have been diagnosed with Alzheimer's disease were defined as having cognitive impairment.

We used the events per variable method to calculate the sample size[19]. We predicted we would introduce ten variables in multivariable regression; thus, the sample size of cognitive impairment was at least 100. In addition, we set the power of the study to 0.8.

Hospital treatment

Patients were examined using blood tests and ultrasonography (assessing cardiac function and screening the deep vein thrombosis) to prepare for surgery. Intertrochanteric fractures are often treated with closed/open reduction and internal fixation (ORIF) with proximal femur nail anti-rotation. Femoral neck fractures are often treated with hemiarthroplasty (HA) or total hip arthroplasty (THA) according to the patient's age. Prophylaxis for deep vein thrombosis was initiated on admission. On discharge, patients were asked to return monthly to assess the union or function status of the fracture[15,16].

Follow-up

After discharge, family members of the patients were contacted by phone from January 2022 to March 2022 to record data on survival, survival time, and activities of daily living. The oral informed consent was obtained from all subjects and/or their legal guardian(s). The follow-up was conducted by two medical professionals with 2 weeks of training and a year of experience. Patients who could not be contacted were called twice more. When the family members of the patients also did not respond, we stopped and recorded the patients as lost to follow-up[15,16].

Study endpoint

The endpoint in this study was all-cause mortality after treatment. We defined all-cause mortality as death reported by the patient's family members.

Variables

The variables in our study were as follows: age, sex, occupation, history of allergy, injury mechanism, fracture classification, presence of hypertension, diabetes, coronary heart disease (CHD), arrhythmia, hemorrhagic stroke, ischemic stroke, cancer, associated injuries, cognitive impairment, chronic obstructive pulmonary disease (COPD), hepatitis and gastritis, time from injury to admission, time from admission to operation, duration of surgery, blood loss, infusion, transfusion, treatment, total time in hospital and follow-up, and 1-year mortality.

Statistical analysis

Continuous variables are reported as mean (standard deviation) (Gaussian distribution) or median (range, skewed distribution). Categorical variables are indicated as numbers with proportions. Differences between whether cognitive impairment was detected using chi-square analysis (categorical variables), one-way ANOVA (analysis of variance [normal distribution]), or Kruskal-Wallis H-test (skewed distribution). Univariate and multivariate binary logistic regression models examined the association between cognitive impairment and 1-year mortality. To further explore the role of sex modification on association, we also performed an interaction analysis.

All analyses were performed using statistical software packages R (http://www.R-project.org, R Foundation, Version 4.2.0) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions Inc., Boston, MA, USA, Version 4.2). A *P-value* < 0.05 (two-sided) was considered statistically significant.

Results

Patient characteristics

In this retrospective cohort study, we screened 2904 patients who had experienced a hip fracture between January 2015 and September 2019. Overall, 2589 study subjects met the inclusion criteria after excluding 315 (10.8%) patients lost to follow-up, as shown in Fig. 1. Of 2589 patients, there were 835 males and 1754 females. One hundred and five patients had cognitive impairment. The mean age was 79.60(6.78) and 81.26(5.84) years in the no cognitive and cognitive impairment groups. There were 286 (11.0%) patients with hip fractures who died after 1 year. The detailed demographic and clinical characteristics of all patients, including comorbidities, injury-related factors, treatment, hospitalization, and duration of follow-up, are presented in Table 1.

Univariate analysis of the association between variable and 1-year mortality

A univariate analysis was performed to identify potential confounders and the relationship between variables and 1-year mortality (Table 2). To more accurately examine the relationship between cognitive impairment and 1-year mortality in older patients with hip fracture, factors we need to adjust in multivariate analysis were identified as $P < 0.1$. Finally, age, sex, hospital stay, fracture classification, CHD, arrhythmia, time to admission, time to operation, ischemic stroke, cancer, and treatment strategy were identified as a confounding factor.

Multivariate analysis of cognitive impairment and 1-year mortality

We used three models (Table 3) to correlate cognitive impairment and 1-year mortality. Fully adjusted models showed that cognitive impairment was associated with increased 1-year mortality in older patients with hip fractures after controlling for confounding factors (OR = 2.14, 95% CI 1.20–3.82, $P < 0.001$). Mortality in older patients with hip fracture and cognitive impairment had an even higher 1-year mortality than those without cognitive impairment. The Kaplan-Meier survival curves are shown in Fig. 2.

The role of sex in the association between cognitive impairment and 1-year mortality

As shown in Table 4, the fully adjusted model showed that cognitive impairment was associated with increased 1-year mortality in male patients with hip fracture (OR = 5.96, 95% CI: 2.40-14.78, $P < 0.0001$) but not in females (OR = 1.08, 95% CI: 0.56–2.07, $P = 0.8246$). The *P*-value for interaction in the adjusted model was 0.0171. Older male patients with hip fractures and cognitive impairment had a higher 1-year mortality rate. In the stratified analysis, cognitive impairment was associated with increased mortality in males, but there was no association in females.

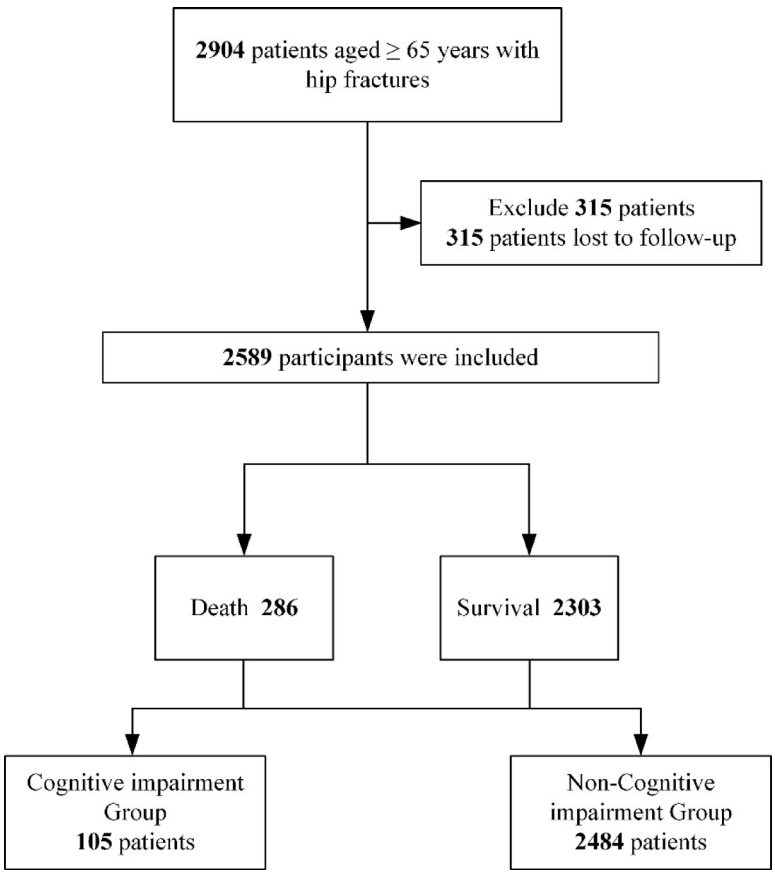

Fig. 1. The flow diagram.

Cognitive impairment	No	Yes	Standardize diff.	*P*-value*	*P*-value**
N	2484	105			
Age (year)	79.60 (6.78)	81.26 (5.84)	0.26 (0.07, 0.46)	0.014	0.006
Sex			0.24 (0.05, 0.44)	0.021	–
Male	812 (32.69%)	23 (21.90%)			
Female	1672 (67.31%)	82 (78.10%)			
Injury mechanism			0.26 (0.07, 0.46)	0.163	–
Falling	2401 (96.66%)	105 (100.00%)			
Accident	67 (2.70%)	0 (0.00%)			
Other	16 (0.64%)	0 (0.00%)			
Fracture classification			0.06 (– 0.13, 0.26)	0.538	–
Intertrochanteric fracture	1864 (75.04%)	76 (72.38%)			
Femoral neck fracture	620 (24.96%)	29 (27.62%)			
Hypertension	1221 (49.15%)	46 (43.81%)	0.11 (– 0.09, 0.30)	0.283	–
Diabetes	492 (19.81%)	20 (19.05%)	0.02 (– 0.18, 0.21)	0.848	–
CHD	1317 (53.02%)	61 (58.10%)	0.10 (– 0.09, 0.30)	0.307	–
Arrhythmia	843 (33.94%)	36 (34.29%)	0.01 (– 0.19, 0.20)	0.941	–
Hemorrhagic stroke	55 (2.21%)	2 (1.90%)	0.02 (– 0.17, 0.22)	0.832	–
Ischemic stroke	700 (28.18%)	56 (53.33%)	0.53 (0.33, 0.73)	< 0.001	–
Cancer	74 (2.98%)	1 (0.95%)	0.15 (– 0.05, 0.34)	0.225	–
Multiple injuries	179 (7.21%)	7 (6.67%)	0.02 (– 0.17, 0.22)	0.834	–
COPD	164 (6.60%)	6 (5.71%)	0.04 (– 0.16, 0.23)	0.719	–
Hepatitis	78 (3.14%)	4 (3.81%)	0.04 (– 0.16, 0.23)	0.701	–
Gastritis	45 (1.81%)	0 (0.00%)	0.19 (– 0.00, 0.39)	0.164	–
Treatment strategy			0.27 (0.07, 0.47)	0.067	–
Conservation	212 (8.53%)	16 (15.24%)			
ORIF	1660 (66.83%)	64 (60.95%)			
HA	577 (23.23%)	25 (23.81%)			
THA	35 (1.41%)	0 (0.00%)			
Time to admission (h)	80.90 (252.33)	102.6 (152.93)	0.10 (– 0.09, 0.30)	0.381	< 0.001
Time to operation (d)	4.28 (2.57)	4.49 (2.50)	0.08 (– 0.13, 0.30)	0.442	0.315
Operation time (min)	93.08 (36.09)	93.18 (32.41)	0.00 (– 0.21, 0.22)	0.979	0.813
Blood loss (mL)	240.98 (153.57)	252.05 (152.67)	0.07 (– 0.14, 0.29)	0.508	0.382
Infusion (mL)	1556.21 (382.72)	1552.30 (400.50)	0.01 (– 0.20, 0.22)	0.926	0.964
Stay in hospital (d)	8.93 (3.74)	8.71 (3.16)	0.06 (– 0.13, 0.26)	0.557	0.866
Follow-up (m)	39.27 (19.62)	28.15 (19.20)	0.57 (0.38, 0.77)	< 0.001	< 0.001
1-year mortality	262 (10.55%)	24 (22.86%)	0.33 (0.14, 0.53)	< 0.001	–

Table 1. Demographic and clinical characteristics ($N = 2589$). Mean + SD/N(%). *P*-value*: Non-parametric tests. *P*-value**: We used the Kruskal Wallis rank-sum test for continuous variables and Fisher's exact probability test for count variables with a theoretical number < 10. CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; ORIF, open reduction and internal fixation; HA, hemiarthroplasty; THA, total hip arthroplasty.

Discussion

This study found cognitive impairment was identified as a risk factor for 1-year mortality in older patients with hip fracture, which was confirmed by multivariate binary logistic regression analysis after adjusting for confounders. The cognitive impairment was associated with increased 1-year mortality 1.14 times (OR = 2.14) in patients with hip fractures compared to no cognitive impairment. After stratification of data by sex, we have found that sex influenced the association between cognitive impairment and 1-year mortality. The 1-year mortality was higher in males who suffered hip fractures and cognitive impairment (OR = 5.96, 95% CI: 2.40–14.78, $P < 0.0001$). The P-value for the interaction between males and females was $P = 0.0171$.

Numerous previous studies have shown that cognitive impairment is associated with poor outcomes, including limitations in activities of daily living and mobility, prolonged hospital stays, poorer health-related quality of life, and increased risk of hospitalization and death[20,21]. As described by Friedman et al., patients sustain hip fractures due to falls and bone fragility/osteoporosis, which can further impair gait, balance, proprioception, and skeletal muscle reduction[22]. The 1-year mortality rate following a hip fracture in older adults with cognitive impairment is as high as 39% [23]. Several factors may contribute to the elevated mortality rate, including but not limited to the following. Firstly, cognitively impaired patients are often associated with a variety of chronic diseases, such as cardiovascular disease[24] and diabetes[25], which increases the risk of surgery and anaesthesia. Secondly, these patients are more likely

	Statistics	OR (95%CI)	*P*-value
Age (year)	79.67 (6.75)	1.09 (1.07, 1.11)	< 0.0001
Sex			
Male	835 (32.25%)	1	
Female	1754 (67.75%)	0.65 (0.51, 0.84)	0.0010
Injury mechanism			
Falling	2506 (96.79%)	1	
Accident	67 (2.59%)	0.37 (0.12, 1.19)	0.0966
Other	16 (0.62%)	1.83 (0.52, 6.48)	0.3458
Fracture classification			
Intertrochanteric fracture	1940 (74.93%)	1	
Femoral neck fracture	649 (25.07%)	0.75 (0.56, 1.02)	0.0670
Hypertension	1267 (48.94%)	1.15 (0.90, 1.47)	0.2573
Diabetes	512 (19.78%)	1.09 (0.80, 1.47)	0.5882
CHD	1378 (53.23%)	1.62 (1.26, 2.09)	0.0002
Arrhythmia	879 (33.95%)	1.25 (0.97, 1.61)	0.0881
Hemorrhagic stroke	57 (2.20%)	1.74 (0.87, 3.48)	0.1180
Ischemic stroke	756 (29.20%)	1.28 (0.99, 1.66)	0.0634
Cancer	75 (2.90%)	1.72 (0.93, 3.17)	0.0815
Multiple injuries	186 (7.18%)	1.21 (0.77, 1.89)	0.4025
Cognitive impairment	105 (4.06%)	2.51 (1.57, 4.03)	0.0001
COPD	170 (6.57%)	1.35 (0.86, 2.12)	0.1879
Hepatitis	82 (3.17%)	1.69 (0.94, 3.05)	0.0801
Gastritis	45 (1.74%)	0.78 (0.28, 2.20)	0.6421
Time to admission (h)	81.78 (249.09)	1.00 (1.00, 1.00)	0.0513
Time to operation (d)	4.29 (2.57)	1.05 (1.00, 1.10)	0.0423
Treatment strategy			
Conservation	228 (8.81%)	1	
ORIF	1724 (66.59%)	0.23 (0.17, 0.32)	< 0.0001
HA	602 (23.25%)	0.23 (0.16, 0.34)	< 0.0001
THA	35 (1.35%)	0.07 (0.01, 0.49)	0.0080
Operation time (min)	93.08 (35.95)	1.00 (1.00, 1.00)	0.8223
Blood loss (mL)	241.41 (153.52)	1.00 (1.00, 1.00)	0.4813
Infusion (mL)	1556.06 (383.32)	1.00 (1.00, 1.00)	0.0629
Stay in hospital (d)	8.92 (3.72)	1.04 (1.01, 1.07)	0.0163

Table 2. Effects of factors on mortality measured by univariate analysis ($N = 2589$). OR (95% CI). *P*-value: Univariate binary logistic regression. CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; ORIF, open reduction and internal fixation; HA, hemiarthroplasty; THA, total hip arthroplasty.

Exposure	Non-adjusted	Adjust I	Adjust II
Cognitive impairment	2.51 (1.57, 4.03) 0.0001	2.46 (1.51, 4.00) 0.0003	2.14 (1.20, 3.82) 0.0099

Table 3. Univariate and multivariate results using the multivariate binary logistic regression model ($N = 2589$). Data in table: OR (95%CI) *P*-value. Outcome variable: 1-year mortality. Exposed variables: cognitive impairment. Minimally-adjusted for: age; sex. Fully-adjusted model adjust for: age; sex; stay in hospital; fracture classification; CHD; arrhythmia; time to admission; time to operation; ischemic stroke; cancer; treatment strategy.

to develop complications[26], such as delirium, infection, and pneumonia after surgery. Thirdly, these patients with cognitive impairment often suffer from malnutrition[27]. Fourth, cognitively impaired patients have poor medication compliance and complicated medication management[28]. In addition, patients with hip fractures may not receive adequate rehabilitation to meet their care needs after the onset of cognitive impairment[29–31], which in turn increases the 1-year mortality.

Cognitive impairment is a widespread comorbidity among hip fracture patients[5], with incidences of nearly 20% in Canada[32] and 13% in the United States[33,34]. Conversely, the prevalence of cognitive impairment is higher in patients with hip fractures compared to the general population, with 35–61% of hip fractures associated

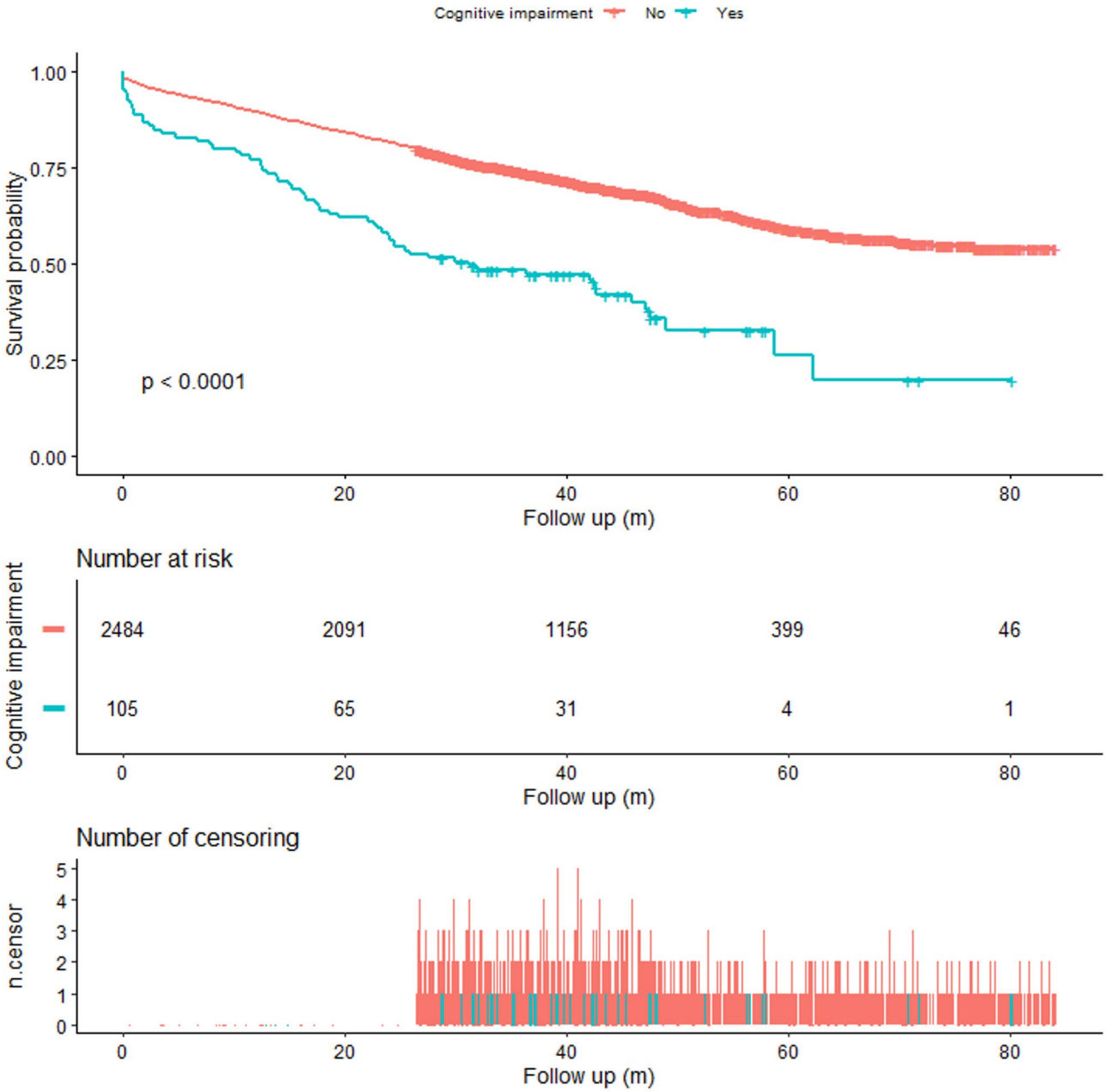

Fig. 2. Kaplan-Meier survival.

with widespread cognitive impairment[35]. The prevalence of cognitive impairment is 11% in this study, which is lower than in other studies[32–34] ; the main reason was that if these patients did not have obvious symptoms, they were difficult to detect with available tests and distinguish from other mental conditions. Consequently, the implementation of sensitive and accessible diagnostic tools becomes crucial for the early detection of cognitive decline.

In the general population, females (25.05%) have a higher rate of cognitive impairment than males (10.85%), according to a Chinese cohort study[36]. However, the prevalence of cognitive impairment in hip fractures was different in this situation. Gruber-Baldini found that males display more significant levels of cognitive impairment within the first 22 days of hip fracture than females in a prospective cohort study[11]. Thus, sex was a critical modified factor in the association between cognitive impairment and mortality in hip fractures. The higher mortality for men remained after controlling for cognitive impairment. Samuelsson et al.[37] identified a stronger sex effect on 4-month mortality among those with cognitive dysfunction, such that only 6% of men and 6% of women without cognitive dysfunction died. In comparison, 31% of men with cognitive dysfunction died compared to 19% of women with cognitive dysfunction. In fact, males were sicker with worse cognitive status and had higher weight and grip strength but lower total energy expenditure than females[38]. It was also reported that there were sex differences in the documentation of cognitive

Exposure	Sex	Crude	Adjusted model
Interaction analysis			
Cognitive impairment			
No	Male	Ref.	Ref.
Yes	Male	6.11 (2.63, 14.19) < 0.0001	5.96 (2.40, 14.78) 0.0001
No	Female	0.69 (0.53, 0.89) 0.0048	0.69 (0.53, 0.92) 0.0096
Yes	Female	1.25 (0.67, 2.35) 0.4778	1.08 (0.56, 2.07) 0.8246
P interaction		0.0235	0.0171
Stratified analysis			
	Male	6.11 (2.63, 14.19) < 0.0001	6.67 (2.60, 17.08) < 0.0001
	Female	1.83 (0.99, 3.39) 0.0539	1.55 (0.82, 2.94) 0.1748

Table 4. Effect of sex-modified cognitive impairment on 1-year mortality in older patients with hip fracture by interaction analysis and stratified analysis. Data in table: OR (95%CI) *P*-value. Outcome variable: 1-year mortality. Exposed variables: cognitive impairment. Effect modification factor: sex. Adjusted model adjust for: age (year); sex; stay in hospital (d); fracture classification; CHD; arrhythmia; time to admission (h); time to operation (d); ischemic stroke; cancer; treatment strategy.

impairment. Males had more cognitive impairment using direct testing. These reasons may be contributing to sex differences in recovery outcomes after hip fracture[35].

To identify confounding factors in the study and to draw reliable conclusions, we first identified the factors affecting hip fracture prognosis. Fracture classification, CHD, arrhythmia, ischemic stroke, cancer, and treatment strategies have been reported in previous studies as risk factors for hip fracture prognosis[21,39–42]. Furthermore, during the univariate analysis phase, we identified factors having a *P*-value < 0.1, including sex, length of hospital stay, time to admission, and time to operation. As for the treatment strategy, ORIF, HA, and THA were associated with low mortality compared to conservation. However, embolic events of varying intensity were seen during invasive intramedullary procedures, such as ORIF, HA, THA[43]. Thus, we controlled for the vast majority of confounding factors.

There are, of course, limitations to this study. Firstly, the causal relationship between cognitive impairment and prognosis could not yet be established in this study, and this will need to be further confirmed in future studies. Secondly, there was potential bias related to the diagnosis of cognitive impairment because the definition of cognitive impairment relies on the NINCDS-ADRDA criteria and the Diagnostic and Statistical Manual of Mental Disorders (fifth Edition), and we could not make a definite diagnosis again, such as neuropsychological tests or functional assessments. Thirdly, our study population was from western China, with geographical and ethnic limitations. This study's findings should be applied cautiously to populations from other regions.

Conclusions

The study showed that cognitive impairment was associated with increased mortality in older adults with hip fractures. Notably, sex was a factor modifying this association, and male patients with cognitive impairment have an even higher 1-year mortality.

Data availability

Xi'an Honghui Hospital implemented the data. According to relevant regulations, the data could not be shared but could be requested from the correspondence author.

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The authors declare no competing interests.

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Additional information
Correspondence and requests for materials should be addressed to B.-F.Z.

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