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Elevated albumin: a protective factor against mortality in geriatric hip fracture patients

Hai Huang[1], Yao Liu[2*] and Bin-Fei Zhang[3]

Abstract

Introduction To evaluate the association between albumin concentration at admission and mortality in elderly patients with hip fractures.

Methods Elderly patients with hip fractures were screened between Jan 2015 and Sep 2019. Demographic and clinical characteristics of the patients were collected. Linear and nonlinear multivariate Cox regression models were used to identify the association between albumin concentration at admission and mortality. All analyses were performed using EmpowerStats and the R software.

Results This retrospective cohort study included 2387 patients who met the study criteria. The mean follow-up was 37.64 months. The albumin concentration was 37.72 ± 4.03 g/L. Multivariate Cox regression showed that albumin concentration was associated with mortality in geriatric patients with hip fracture (Hazard Ratio [HR] = 0.94, 95% confidence intervals [CI]:0.92–0.96, $P < 0.0001$). Compared to the low albumin group (< 35 g/L), the medium group (≥ 35 g/L and < 40 g/L) decreased mortality risk by 29% (HR = 0.71, 95%CI:0.59–0.86, $P = 0.0003$), and the high group (≥ 40 g/L) decreased mortality risk by 38% (HR = 0.62, 95%CI:0.49–0.79, $P < 0.0001$). In addition, the test for a linear trend (*P* for trend) also showed a linear correlation in the different models. No saturation or threshold effect was observed in the nonlinear association. The sensitivity analysis used propensity score matching, and the results were stable.

Conclusion The albumin concentrations at admission were associated with mortality in geriatric hip fractures, and it could be considered a predictor for the risk of mortality. (ChiCTR2200057323)

Keywords Albumin concentration, Mortality, Elderly patients, Hip fracture, Cox regression

Introduction

Proximal femur fractures are a common consequence of osteoporosis, and we refer collectively to them as "hip fractures". They are a global challenge for healthcare systems, patients, and their families [1, 2]. The hip fracture incidences were estimated to be 14.2 million in 2019 [3], and the total annual number of hip fractures nearly doubled from 2018 to 2050 [4]. The mean overall one-year mortality rate is 22% [5].

Many risk factors and indicators are related to patient prognosis [6, 7]. Albumin is the most abundant plasma protein in humans. It is only produced by the

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liver, and the full extent of its metabolic function is not known in detail [8]. A previous study demonstrated a progressive reduction in serum albumin concentration with age between 0.12 and 0.15 g/L per year in the elderly population [9], and the mean levels of albumin in community-dwelling and hospitalized were 41.13 g/L and 36.04 g/L, respectively [8]. Albumin is considered a poor marker as a nutritional indicator, as stated in guidelines such as ESPEN [10], and is thought to be an indicator of disease severity [11–14]. Detection of hypoalbuminemia and medical intervention could decrease the complication rates and improve the prognosis [15, 16].

In geriatric patients with hip fractures, hypoalbuminemia is a powerful independent risk factor for mortality following a surgical procedure in comparison with patients with normal albumin concentration [17]. Further, it was reported that albumin levels < 38 g/L were associated with a higher risk of postoperative infections in hip fractures [8]. A meta-analysis by Li et al. [18] concluded that low serum albumin level was the sole indicator of increased risk of in-hospital death, postoperative complications, and mortality following hip fracture surgery. Malafarina et al. also concluded that an early nutritional intervention could improve recovery [16].

Previous research has established correlations between hypoalbuminemia and post-fracture mortality in hip fracture patients. Nevertheless, the existing evidence regarding the precise association patterns between admission albumin levels and mortality risk within the geriatric hip fracture population is still incomplete, especially when it comes to longitudinal outcomes. To bridge this knowledge gap, we carried out a large-scale cohort study with a follow-up period more than three years. The aim was to systematically assess the relationship between admission albumin concentrations and all-cause mortality in elderly hip fracture patients. Our study specifically examined the hypothesis that this association exhibits either linear or non-linear characteristics. We aimed to potentially unearth crucial insights into the prognostic value of albumin for mortality risk in this vulnerable group.

Materials and methods

Study design

This retrospective cohort study included elderly adults with hip fractures from 1 Jan 2015 to 30 Sep 2019 at the largest trauma center in northwestern China.

The Ethics Committee of the Honghui Hospital, Xi'an Jiaotong University approved this retrospective study (No. 202201009). All human-related procedures were performed in accordance with the 1964 Declaration of Helsinki and its later amendments. The study has been reported according to the STROCSS 2021 guidelines [19]. The oral informed consent was obtained from all subjects and/or their legal guardians.

Participants

Demographic and clinical data of the patients were obtained from their original medical records. The inclusion criteria were as follows:1) age ≥ 65 years; 2) X-ray or computed tomography diagnosis of the femoral neck, intertrochanteric, or subtrochanteric fracture; 3) participants who were receiving surgical or conservative treatment in the hospital; 4) availability of clinical data in the hospital; and 5) patients or their families contacted via telephone. Patients who could not be contacted were excluded. Figure 1 shows a flow chart of the study.

Hospital treatment

Patients underwent blood examinations prior to the surgery. Intertrochanteric fractures are often chosen for closed/open reduction and internal fixation (ORIF) of the proximal femoral nail anti-rotation [20–22] and less arthroplasty [23]. 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 at admission. As for the patients with conservative treatment, we would give skin traction to stabilize the fracture for union, and we transferred them to the department of internal medicine to adjust the body condition. Patients were advised to visit for monthly follow-ups at discharge to assess fracture union or function. During the hospitalization, the patients received the orthogeriatric co-management strategy [24].

Follow-up

After discharge, patients' family members were contacted by telephone from Jan 2022 to Mar 2022 to record data on survival, survival time, and activities of daily living. Telephone follow-up was conducted by two medical professionals with two weeks of training and one year of experience. We tried twice for patients who could not be contacted on the first attempt. When the family members of the patients did not respond, we stopped and recorded the patients as lost to follow-up.

Endpoint events

The endpoint event in this study was all-cause mortality after treatment. We defined all-cause mortality as any death reported by patient family members, including intraoperative, intensive care, hospital, and follow-up deaths.

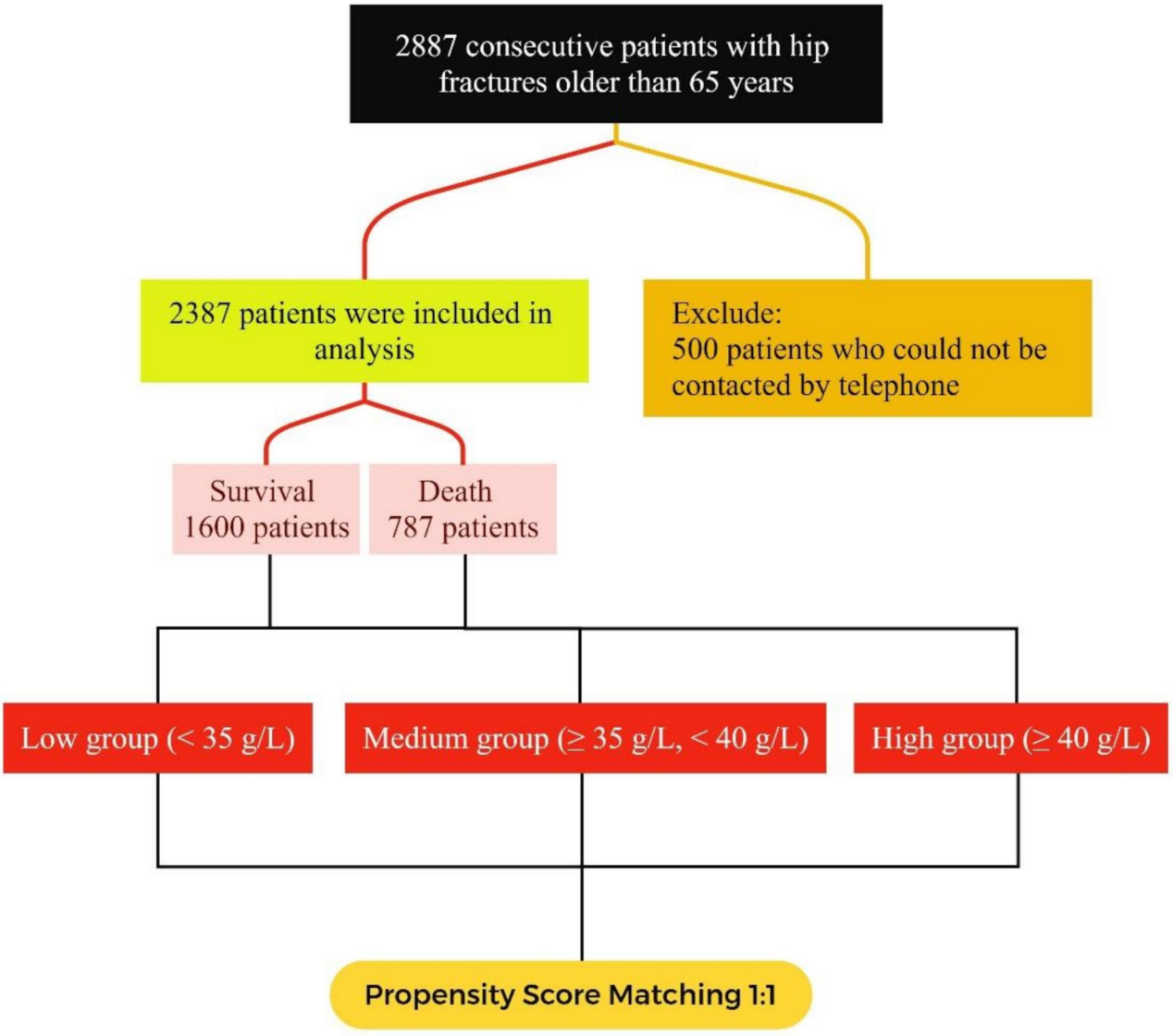

Fig. 1 Study flow chart

Variables

The following variables were collected in this study: age, sex, occupation, history of allergy, injury mechanism, fracture classification, hypertension, diabetes mellitus, coronary heart disease (CHD), arrhythmia, hemorrhagic stroke, ischemic stroke, cancer, associated injuries, dementia, chronic obstructive pulmonary disease (COPD), hepatitis, gastritis, age-adjusted Charlson comorbidity index (aCCI) [25], time from injury to admission, time from admission to surgery, admission albumin concentration, operation time, blood loss, infusion, transfusion, treatment strategy, time in hospital, and follow-up. Occupations included retirement, farmers, and others. Injury mechanisms included falls, accidents, and others. Blood loss was defined as the total blood loss during the surgery. The infusion was defined as the total volume of liquid used in the operation. Transfusion was defined as the total volume of red blood cells used during the surgery. The treatment strategy was divided into the conservation and surgery groups (ORIF/HA/THA).

The albumin concentration at admission was defined as the result of a blood test at admission. The dependent variable was all-cause mortality, and the independent variable was albumin concentration at admission. Other variables were categorized as potentially confounding factors.

Statistics analysis

Data are expressed as mean (standard deviation) (Gaussian distribution) or median (min, max) (skewed distribution) for continuous variables and as numbers

and percentages for categorical variables. χ^2 (categorical variables), one-way ANOVA test (normal distribution), or Kruskal-Wallis H test (skewed distribution) were used to detect differences among different albumin concentrations (tertiles). To examine the association between albumin concentration and mortality, we constructed three distinct models using univariate and multivariate Cox proportional hazards regression models, including a non-adjusted model (no covariates were adjusted), a minimally adjusted model (only sociodemographic variables were adjusted), and a fully adjusted model (all covariates presented in the study were adjusted). The effect sizes with 95% confidence intervals (CI) were recorded. Because Cox proportional hazards regression model-based methods are often suspected to be unable to deal with nonlinear models, the nonlinearity between admission albumin concentration and mortality was addressed using a Cox proportional hazards regression model with cubic spline functions and smooth curve fitting (penalized spline method). If nonlinearity was detected, we first calculated the inflection point using a recursive algorithm and then constructed a two-piecewise Cox proportional hazards regression model on both sides of the inflection point.

To test the robustness of our results, we performed a sensitivity analysis. We converted albumin into a categorical variable according to the tertiles and calculated the *P* for trend to verify the results of albumin as a continuous variable and to examine the possibility of nonlinearity. In addition, propensity score matching (PSM) was introduced to compare matched groups, and we adjusted for confounding factors in PSM models.

All analyses were performed using statistical software packages R (http://www.R-project.org, The R F oundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions Inc., Boston, MA, USA). Hazard ratios (HR) and 95%CI were calculated. A *P* value of < 0.05 (two-sided) was considered statistically significant.

Results

Patient characteristics

From the initial 2887 consecutive participants who had hip fractures between Jan 2015 and Sep 2019, we enrolled 2387 participants who met the study criteria. The mean follow-up was 37.64 months (ranged from 0.00 to 78.21 months for total patients, ranged from 0.00 to 69.89 months for death patients, ranged from 26.48 to 78.21 months for survival patients). There were 47 deaths in hospital totally. During follow-up, 787 (33%) patients died for all-cause reasons. The albumin concentration was 37.72 ± 4.03 g/L. We divided the patients into three groups according to their albumin concentration. Table 1 lists the patients' demographic and clinical characteristics, including comorbidities, factors associated with injuries, and treatment.

Most patients (91.83%) received surgical treatment, and 195 patients (8.17%) received conservative treatment because of poor status, comorbidities, or refusal to undergo surgery. The albumin concentration at admission was 35.91 ± 4.45 g/L in the conservation group and 37.88 ± 3.95 g/L in the operation group ($P < 0.001$).

Univariate analysis of the association between variates and mortality

We performed univariate analysis to identify potential confounding factors and the relationship between variables and mortality (Table 2). According to the criteria of $P < 0.1$, the following variables were considered in the multivariate Cox regression: age, sex, injury mechanism, fracture classification, aCCI, CHD, arrhythmia, ischemic stroke, cancer, dementia, COPD, hepatitis, time to operation, treatment strategy, operation time, infusion, and transfusion.

Multivariate analysis between admission albumin concentration and mortality

We used three models (Table 3) to correlate albumin concentrations at admission and mortality. Stable linear regression was observed when the albumin concentration was a continuous variable. The fully adjusted model showed a mortality risk decrease of 6% (HR = 0.94, 95% CI:0.92–0.96), $P < 0.0001$) when albumin concentration increased by 1 g/L and after controlling for confounding factors. When albumin concentration was used as a categorical variable, we found statistically significant differences among the three models ($P < 0.05$). Compared to the low albumin group (< 35 g/L), the medium group (≥ 35 g/L and < 40 g/L) decreased mortality risk by 29% (HR = 0.71, 95% CI:0.59–0.86, $P = 0.0003$), and the high group (≥ 40 g/L) decreased mortality risk by 38% (HR = 0.62, 95% CI:0.49–0.79, $P < 0.0001$). In addition, the *P* for trend showed a linear correlation in the three models ($P < 0.0001$).

In addition, we divided the age into 65 ≤ age<75, 75 ≤ age<85, and age ≥ 85 subgroups. The age-stratified analysis in the fully-adjusted model showed that the preoperative albumin level was not associated with mortality (HR = 0.95, 95% CI:0.91–1.01, $P = 0.0893$) in 65 ≤ age<75 patients but associated with the mortality in 75 ≤ age<85 patients (HR = 0.94, 95% CI:0.91–0.97, $P = 0.0001$) and 85 ≤ age patients (HR = 0.94, 95% CI:0.91–0.98, $P = 0.0010$).

Table 1 The demographic and clinical characteristics ($N = 2387$)

Admission Albumin (g/L)	Low group (< 35 g/L)	Medium group (≥ 35 g/L, < 40 g/L)	High group (≥ 40 g/L)	*P*-value	*P*-value*
No. of patients	521	1179	687		
Age (years)	81.63 ± 6.87	79.89 ± 6.51	77.29 ± 6.61	< 0.001	< 0.001
Sex				0.068	-
Male	181 (34.74%)	399 (33.84%)	201 (29.26%)		
Female	340 (65.26%)	780 (66.16%)	486 (70.74%)		
Occupation				0.703	-
Retirement	293 (56.24%)	692 (58.69%)	401 (58.37%)		
Farmer	127 (24.38%)	287 (24.34%)	158 (23.00%)		
Other	101 (19.39%)	200 (16.96%)	128 (18.63%)		
History of allergy				0.309	-
No	495 (95.01%)	1138 (96.52%)	657 (95.63%)		
Yes	26 (4.99%)	41 (3.48%)	30 (4.37%)		
Injury mechanism				0.729	-
Falling	501 (96.16%)	1144 (97.03%)	662 (96.36%)		
Accident	14 (2.69%)	28 (2.37%)	20 (2.91%)		
Other	6 (1.15%)	7 (0.59%)	5 (0.73%)		
Fracture classification				< 0.001	-
Intertrochanteric fracture	414 (79.46%)	877 (74.39%)	414 (60.26%)		
Femoral neck fracture	89 (17.08%)	272 (23.07%)	261 (37.99%)		
Subtrochanteric fracture	18 (3.45%)	30 (2.54%)	12 (1.75%)		
aCCI				< 0.001	-
2	6 (1.15%)	38 (3.22%)	60 (8.73%)		
3	65 (12.48%)	225 (19.08%)	174 (25.33%)		
4	218 (41.84%)	495 (41.98%)	254 (36.97%)		
5	151 (28.98%)	293 (24.85%)	139 (20.23%)		
6	65 (12.48%)	98 (8.31%)	44 (6.40%)		
7	14 (2.69%)	25 (2.12%)	14 (2.04%)		
8	2 (0.38%)	4 (0.34%)	2 (0.29%)		
9	0 (0.00%)	1 (0.08%)	0 (0.00%)		
Hypertension				0.052	-
No	285 (54.70%)	608 (51.57%)	328 (47.74%)		
Yes	236 (45.30%)	571 (48.43%)	359 (52.26%)		
Diabetes Mellitus				0.018	-
No	429 (82.34%)	955 (81.00%)	525 (76.42%)		
Yes	92 (17.66%)	224 (19.00%)	162 (23.58%)		
CHD				0.282	-
No	231 (44.34%)	572 (48.52%)	324 (47.16%)		
Yes	290 (55.66%)	607 (51.48%)	363 (52.84%)		
Arrhythmia				0.004	-
No	318 (61.04%)	813 (68.96%)	468 (68.12%)		
Yes	203 (38.96%)	366 (31.04%)	219 (31.88%)		
Hemorrhagic stroke				0.95	-
No	509 (97.70%)	1154 (97.88%)	673 (97.96%)		
Yes	12 (2.30%)	25 (2.12%)	14 (2.04%)		
Ischemic stroke				0.438	-
No	361 (69.29%)	835 (70.82%)	499 (72.63%)		
Yes	160 (30.71%)	344 (29.18%)	188 (27.37%)		
Cancer				0.015	-
No	496 (95.20%)	1147 (97.29%)	673 (97.96%)		
Yes	25 (4.80%)	32 (2.71%)	14 (2.04%)		
Associated injuries				0.007	-
No	468 (89.83%)	1107 (93.89%)	644 (93.74%)		
Yes	53 (10.17%)	72 (6.11%)	43 (6.26%)		

Table 1 (continued)

Admission Albumin (g/L)	Low group (< 35 g/L)	Medium group (≥ 35 g/L, < 40 g/L)	High group (≥ 40 g/L)	*P*-value	*P*-value*
Dementia				< 0.001	-
No	482 (92.51%)	1136 (96.35%)	671 (97.67%)		
Yes	39 (7.49%)	43 (3.65%)	16 (2.33%)		
COPD				< 0.001	-
No	480 (92.13%)	1088 (92.28%)	667 (97.09%)		
Yes	41 (7.87%)	91 (7.72%)	20 (2.91%)		
Hepatitis				0.025	-
No	495 (95.01%)	1150 (97.54%)	665 (96.80%)		
Yes	26 (4.99%)	29 (2.46%)	22 (3.20%)		
Gastritis				0.834	-
No	512 (98.27%)	1161 (98.47%)	674 (98.11%)		
Yes	9 (1.73%)	18 (1.53%)	13 (1.89%)		
Treatment strategy				< 0.001	-
Conservation	76 (14.59%)	85 (7.21%)	34 (4.95%)		
ORIF	354 (67.95%)	832 (70.57%)	401 (58.37%)		
HA	89 (17.08%)	254 (21.54%)	228 (33.19%)		
THA	2 (0.38%)	8 (0.68%)	24 (3.49%)		
Albumin (g/L)	32.12 ± 2.36	37.53 ± 1.40	42.31 ± 1.98	< 0.001	< 0.001
Time to admission (hours)	135.35 ± 274.20	77.37 ± 280.78	41.58 ± 181.27	< 0.001	< 0.001
Time to operation (days)	4.67 ± 2.91	4.25 ± 2.53	4.11 ± 2.25	0.001	0.002
Operation time (mins)	98.48 ± 43.34	92.83 ± 36.22	95.02 ± 34.22	0.025	0.053
Blood loss (mL)	257.62 ± 171.59	248.40 ± 158.33	230.66 ± 147.45	0.015	0.254
Infusion (mL)	1558.55 ± 417.30	1552.06 ± 387.20	1598.42 ± 368.85	0.053	0.003
Transfusion (U)	1.56 ± 1.30	1.18 ± 1.26	0.79 ± 1.16	< 0.001	< 0.001
Follow-up (months)	33.75 ± 20.39	38.72 ± 18.51	38.74 ± 16.64	< 0.001	< 0.001
In-hospital mortality	11 (2.11%)	21 (1.78%)	15 (2.18%)	0.805	-
Mortality				< 0.001	-
Survival	261 (50.10%)	804 (68.19%)	535 (77.87%)		
Dead	260 (49.90%)	375 (31.81%)	152 (22.13%)		

Mean + SD/N(%). *P*-value*: For continuous variables, we used the Kruskal Wallis rank-sum test and Fisher's exact probability test for count variables with a theoretical number of < 10

aCCI, age-adjusted Charlson Comorbidity Index; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; ORIF, open reduction and internal fixation; HA, hemiarthroplasty; THA, total hip arthroplasty

Curve fitting

As shown in Fig. 2, there was a smooth curve between albumin concentration at admission and mortality after adjusting for confounding factors. We compared two fitting models to explain this association (Table 4). Unfortunately, we found no saturation or threshold effect.

Propensity score matching (PSM)

To test the robustness of our results, we performed sensitivity analysis using PSM, as shown in Tables 5, 6 and 7; Fig. 3. One thousand three hundred eighty patients (57.8%) were successfully matched (Table 5**and** Fig. 3). Age and aCCI treatment did not match between the two groups (Table 6). We found the results were stable in the multivariate Cox regression under the PSM and PSM-adjusted models (Table 7).

Discussion

Preoperative health status is a critical predictor of postoperative outcomes in elderly patients [26]. We found a linear association between the serum albumin concentration and mortality in geriatric patients with hip fractures. The higher the albumin concentration, the lower the mortality rate. This detailed result showed a mortality risk decrease of 6% (HR = 0.94) when albumin concentration increased by 1 g/L after controlling for confounding factors. Compared to albumin concentration < 35 g/L, the medium group (≥ 35 g/L and < 40 g/L) could decrease the mortality risk by 29% (HR = 0.71), and the high group (≥ 40 g/L) could decrease the mortality risk by 38% (HR = 0.62). In addition, preoperative albumin level was not associated with mortality in 65 ≤ age<75 patients but associated with mortality in patients 75 ≤ age.

These findings suggest albumin can be used as a risk stratification metric, with 35 g/L being a crucial

Table 2 Effects of factors on mortality measured by univariate analysis ($N = 2387$)

Factors	Statistics	HR (95%CI)	*P*-value
Age (year)	79.52 ± 6.80	1.08 (1.07, 1.09)	< 0.0001
Sex			
Male	781 (32.72%)	1.0	
Female	1606 (67.28%)	0.73 (0.63, 0.84)	< 0.0001
Occupation			
Retirement	1386 (58.06%)	1.0	
Farmer	572 (23.96%)	0.93 (0.78, 1.10)	0.3965
Other	429 (17.97%)	0.88 (0.72, 1.06)	0.1775
History of allergy			
No	2290 (95.94%)	1.0	
Yes	97 (4.06%)	0.93 (0.64, 1.35)	0.7158
Injury mechanism			
Falling	2307 (96.65%)	1.0	
Accident	62 (2.60%)	0.24 (0.11, 0.54)	0.0006
Other	18 (0.75%)	1.60 (0.83, 3.09)	0.1593
Time to admission (hours)	79.73 ± 256.62	1.00 (1.00, 1.00)	0.1107
Fracture classification			
Intertrochanteric fracture	1705 (71.43%)	1.0	
Femoral neck fracture	622 (26.06%)	0.86 (0.72, 1.03)	0.0920
Subtrochanteric fracture	60 (2.51%)	0.69 (0.43, 1.12)	0.1348
aCCI			
2	104 (4.36%)	1.0	
3	464 (19.44%)	2.81 (1.22, 6.46)	0.0148
4	967 (40.51%)	6.77 (3.02, 15.19)	< 0.0001
5	583 (24.42%)	9.31 (4.14, 20.92)	< 0.0001
6	207 (8.67%)	11.78 (5.17, 26.84)	< 0.0001
7	53 (2.22%)	15.71 (6.54, 37.77)	< 0.0001
8	8 (0.34%)	29.32 (9.45, 91.03)	< 0.0001
9	1 (0.04%)	31.74 (3.82, 263.93)	0.0014
Hypertension			
No	1221 (51.15%)	1.0	
Yes	1166 (48.85%)	1.12 (0.97, 1.29)	0.1133
Diabetes Mellitus			
No	1909 (79.97%)	1.0	
Yes	478 (20.03%)	0.99 (0.83, 1.18)	0.8672
CHD			
No	1127 (47.21%)	1.0	
Yes	1260 (52.79%)	1.35 (1.17, 1.55)	< 0.0001
Arrhythmia			
No	1599 (66.99%)	1.0	
Yes	788 (33.01%)	1.31 (1.14, 1.51)	0.0002
Hemorrhagic stroke			
No	2336 (97.86%)	1.0	
Yes	51 (2.14%)	1.11 (0.70, 1.77)	0.6561
Ischemic stroke			
No	1695 (71.01%)	1.0	
Yes	692 (28.99%)	1.44 (1.24, 1.67)	< 0.0001
Cancer			
No	2316 (97.03%)	1.0	
Yes	71 (2.97%)	1.79 (1.29, 2.50)	0.0005
Associated injuries			
No	2219 (92.96%)	1.0	
Yes	168 (7.04%)	0.93 (0.70, 1.24)	0.6313

Table 2 (continued)

Factors	Statistics	HR (95%CI)	*P*-value
Dementia			
No	2289 (95.89%)	1.0	
Yes	98 (4.11%)	2.81 (2.17, 3.65)	< 0.0001
COPD			
No	2235 (93.63%)	1.0	
Yes	152 (6.37%)	1.54 (1.20, 1.97)	0.0006
Hepatitis			
No	2310 (96.77%)	1.0	
Yes	77 (3.23%)	1.46 (1.04, 2.06)	0.0274
Gastritis			
No	2347 (98.32%)	1.0	
Yes	40 (1.68%)	0.97 (0.57, 1.65)	0.9122
Albumin concentration (g/L)	37.72 ± 4.03	0.91 (0.89, 0.92)	< 0.0001
Time to operation (days)	4.29 ± 2.54	1.03 (1.00, 1.06)	0.0427
Treatment strategy			
Conservation	195 (8.17%)	1.0	
ORIF	1587 (66.49%)	0.30 (0.25, 0.36)	< 0.0001
HA	571 (23.92%)	0.32 (0.26, 0.41)	< 0.0001
THA	34 (1.42%)	0.06 (0.02, 0.25)	< 0.0001
Operation time (mins)	94.63 ± 37.26	1.00 (1.00, 1.00)	0.0849
Blood loss (mL)	245.09 ± 158.31	1.00 (1.00, 1.00)	0.5711
Infusion (mL)	1567.08 ± 388.57	1.00 (1.00, 1.00)	0.0003
Transfusion (U)	1.14 ± 1.27	1.06 (1.00, 1.13)	0.0344

aCCI, age-adjusted Charlson Comorbidity Index; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; ORIF, open reduction and internal fixation; HA, hemiarthroplasty; THA, total hip arthroplasty; HR, Hazard ratios; CI, confidence intervals

Table 3 Multivariate results by Cox regression (*N* = 2387)

Exposure	Non-adjusted model	Minimally-adjusted model	Fully-adjusted model
Admission albumin	0.92 (0.90, 0.94) < 0.0001	0.93 (0.91, 0.95) < 0.0001	0.94 (0.92, 0.96) < 0.0001
Age Stratified Analysis			
65 ≤ age<75	0.91 (0.88, 0.95) < 0.0001	0.92 (0.88, 0.96) 0.0002	0.95 (0.91, 1.01) 0.0893
75 ≤ age<85	0.91 (0.89, 0.93) < 0.0001	0.92 (0.90, 0.95) < 0.0001	0.94 (0.91, 0.97) 0.0001
age ≥ 85	0.93 (0.91, 0.96) < 0.0001	0.94 (0.91, 0.97) < 0.0001	0.94 (0.91, 0.98) 0.0010
Admission albumin tertiles			
Low group (< 35 g/L)	Ref	Ref	Ref
Medium group (≥ 35 g/L, < 40 g/L)	0.56 (0.48, 0.66) < 0.0001	0.63 (0.54, 0.74) < 0.0001	0.71 (0.59, 0.86) 0.0003
High group (≥ 40 g/L)	0.39 (0.32, 0.48) < 0.0001	0.52 (0.42, 0.64) < 0.0001	0.62 (0.49, 0.79) < 0.0001
P **for trend**	< 0.0001	< 0.0001	< 0.0001

Data in table: HR (95%CI) *P*-value

Outcome variable: mortality

Exposed variables: admission albumin concentration

Minimally-adjusted adjust for: age; sex

Fully-adjusted model adjust for: age; sex; injury mechanism; fracture classification; aCCI; CHD; arrhythmia; ischemic stroke; cancer; dementia; COPD; hepatitis; time to operation; treatment strategy; operation time; infusion; transfusion

clinical threshold, thus justifying more rigorous albumin level monitoring in this patient group. There are some implications for clinical practice: Firstly, it is necessary to standardize albumin monitoring in the routine assessment of elderly hip fracture patients, especially those ≥ 75 years old. Secondly, it is necessary to set 35 g/L as the intervention threshold. For patients with albumin < 35 g/L, it is necessary to start personalized nutritional support or albumin supplementation plans and prioritize fixing potential nutritional deficits (like low protein intake) and occult blood loss. Thirdly, it is necessary to integrate albumin levels into preoperative risk assessment tools to predict long-term prognosis. In the future, prospective randomized controlled trials should be conducted to validate the impact of albumin supplementation on mortality and elucidate the causal relationship. Secondly, the study should explore the clinical significance and the optimal

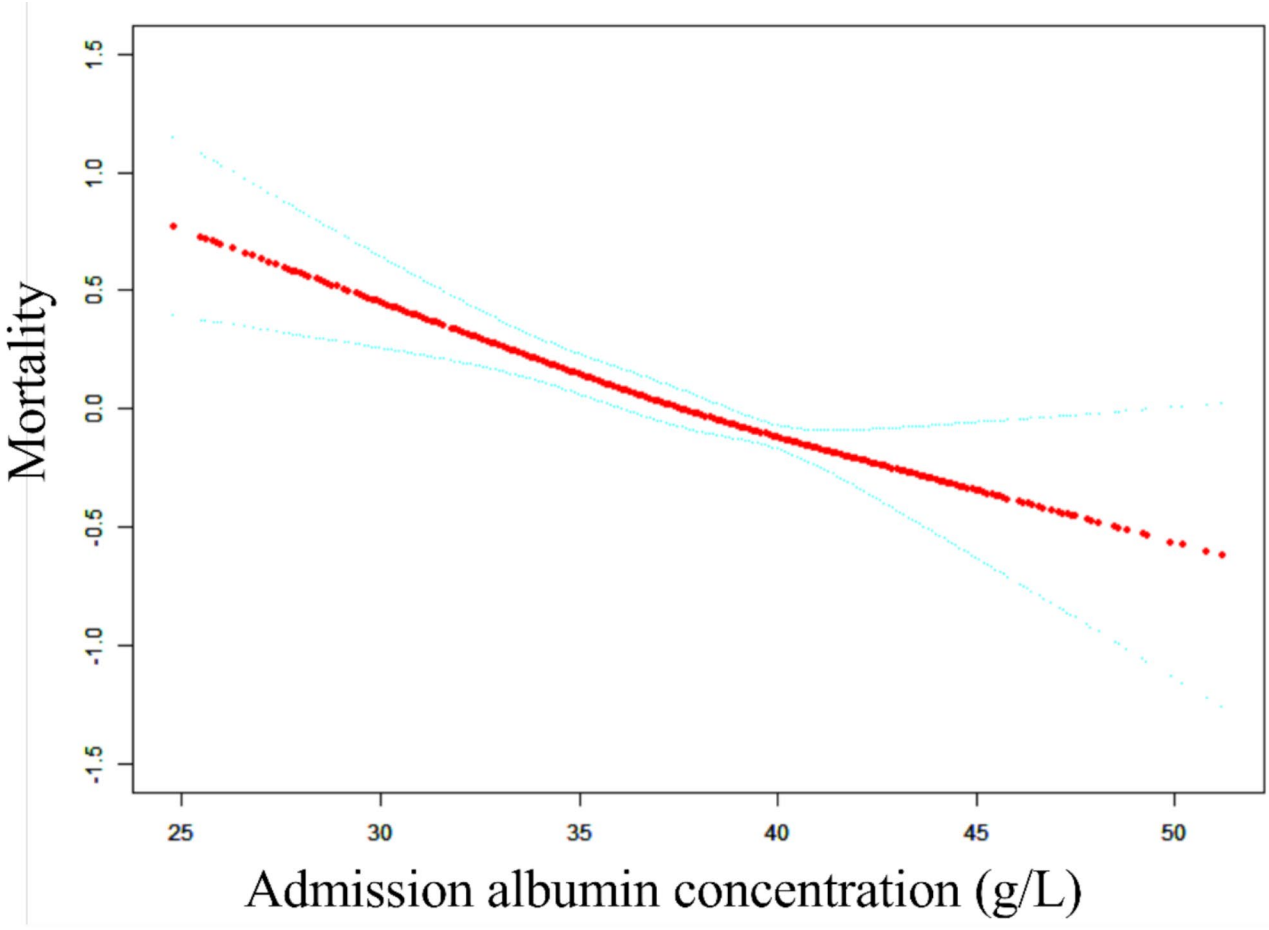

Fig. 2 Curve fitting between admission albumin concentration and mortality. Adjusted for age; sex; injury mechanism; fracture classification; aCCI; CHD; arrhythmia; ischemic stroke; cancer; dementia; COPD; hepatitis; time to operation; treatment strategy; operation time; infusion; transfusion

Table 4 Nonlinearity of admission albumin concentration (g/L) versus mortality ($N = 2387$)

Outcome	HR (95%CI) *P*-value
Fitting model by stand linear regression	0.94 (0.92, 0.96) < 0.0001
Fitting model by two-piecewise linear regression	
Inflection point	31
< 31	1.00 (0.88, 1.14) 0.9786
> 31	0.93 (0.91, 0.96) < 0.0001
P for log-likelihood ratio test	0.322

Adjust for: age; sex; injury mechanism; fracture classification; aCCI; CHD; arrhythmia; ischemic stroke; cancer; dementia; COPD; hepatitis; time to operation; treatment strategy; operation time; infusion; transfusion

intervention window of dynamic albumin changes, such as the acute decline following hip fractures.

Several retrospective, prospective studies and systematic reviews have revealed associations between albumin concentration at admission and mortality or postoperative complications [17, 27–37] in geriatric patients with hip fractures. All previous studies showed that low serum albumin concentration was associated with later mortality or complications, and all reported associations were linear, or a group of low albumin concentration was related to a high rate of mortality or complications. A retrospective study by Dhingra et al. [33] found that low serum albumin levels were associated with a higher incidence of mortality in 95 geriatric patients with femoral neck fractures. A retrospective study by Miyanishi et al. [29] found that a serum albumin concentration < 36 g/L on admission was a predictive factor for mortality after hip fracture surgery in 129 hip joints (OR = 5.85). In the largest sample size retrospective cohort study, Bohl et al. [17] found that the prevalence of hypoalbuminemia was 45.9%, and hypoalbuminemia was a powerful independent risk factor for mortality following a surgical procedure for geriatric hip fracture. Additionally, the authors reported that patients with hypoalbuminemia had a higher risk of sepsis, pneumonia, and unplanned intubation. Pimlott et al. [28] pointed out that the association between low serum albumin levels

Table 5 Propensity score parameter list

The variables used in calculating the propensity score	**Age; sex; injury mechanism; fracture classification; aCCI; CHD; arrhythmia; ischemic stroke; cancer; dementia; COPD; hepatitis; time to operation; operation; operation time; infusion; transfusion**
Propensity score algorithm	Cox regression model
C-statistical	0.6597
Matching method	Greedy matching within specified caliper distances
Metric Distances	0.05
Matching ratio	1:1
Use of replacement	With replacement
Matching sample size	No. of mortality = 1: 690 cases No. of mortality = 0: 690 cases Total 1380 cases

and in-hospital mortality (OR = 2.44) remained statistically significant in a prospective cohort study. Ko et al. [32] reported that the albumin level (OR = 2.87) was associated with a higher mortality risk in a larger cohort of 1841 patients. In the field of geriatric hip fractures, two systematic reviews assessed the negative effect of low albumin levels on prognosis. Li et al. [18] reported that low serum albumin levels were an indicator of increased risk of in-hospital death, complications, and total mortality. In the studies mentioned above, the authors did not consider the duration of follow-up. As a retrospective cohort study, our study provided a long follow-up time. In our study, the average follow-up was 37.64 months (more than 3 years), and the longest follow-up was 84.19 months. Previous prospective studies by Pimlott et al. [28] and Ko et al. [32] did not report follow-up data. Thus, to our knowledge, this study is the first to provide follow-up data and hazard ratio values to describe survival analysis and the slope of the survival curve.

Previous studies provide various definitions of low albumin levels. Low albumin concentration was defined as < 35 g/dL in Canadians by Pimlott et al. [28] and Americans by Bohl et al. [17], and < 32 g/dL in South Korea by Ko et al. [32], and < 36 g/L in Japanese individuals by Malafarina et al. [16]. At the beginning of the variable descriptions, we divided the study population into < 35 g/L, ≥ 35 g/L and < 40 g/L, and ≥ 40 g/L. In the 35 g/L group, the incidence of hypoalbuminemia was 21.83%. In the multivariate analysis, we not only built the association by albumin as a continuous variable and categorical variable but also provided a test for linear trend, the null hypothesis being that there is no linear trend between albumin concentration and group order. The value of *P* for the trend shows positive findings.

Our study is the first to explain a stable linear association using multivariate Cox regression. Although previous studies have reported a progressive reduction in serum albumin concentration associated with ageing [9, 38, 39], a meta-analysis showed that the average level of albumin in the community (41.13 g/L) was assessed in older people [8]. However, serum albumin concentration rapidly declined when a hip fracture occurred. In our study, the albumin concentration at admission was 37.72 g/L, indicating an approximate loss of 3.4 g/L. The reason for the acute loss of albumin remains unclear. It is possible that hidden blood loss was the main reason, as described by Liu et al., who reported that albumin level < 30 g/L at admission was associated with a greater likelihood of more hidden blood loss [40]. According to our results, increased albumin concentration was associated with decreased mortality. Future studies were needed to conduct the randomized controlled trial, showing the effect of albumin supplementation on hip fracture.

Inflammation and nutritional status play important roles in the development of mortality [41, 42]. Serum albumin concentration is an important marker of nutritional status and the inflammatory response [43, 44]. Therefore, the potential mechanism of association between hypoalbuminemia and mortality in hip fracture was pre-injury chronic inflammation and nutritional status. Previous studies have reported that lower serum albumin concentrations [8, 45] were associated with an increased risk of incident chronic disease and mortality in the general population. In addition, the inflammatory response would increase after the injury [46] and duration of the operation [47]. Therefore, we hypothesized that the integration of albumin may reflect inflammation, malnutrition, and other abnormalities throughout the lifespan and could be associated with all-cause and cause-specific mortality.

Our study was designed as a retrospective cohort, and 500 patients were lost to follow-up. In the analysis, we found that patients who were lost to follow-up were randomized, and most of the variables in Table 1 were comparable between the present and absent groups. Furthermore, we included patients admitted before September 2019 to avoid the effect of COVID-19 on

Table 6 The balance test of PSM

Variables	Survival (690)	Mortality (690)	Standardized difference	*P* value
Age (year)	83.22 ± 4.54	81.87 ± 6.29	0.25 (0.14, 0.35)	< 0.001*
Sex			0.09 (-0.01, 0.20)	0.09
Male	226 (32.75%)	256 (37.10%)		
Female	464 (67.25%)	434 (62.90%)		
Occupation			0.12 (0.01, 0.22)	0.09
Retirement	442 (64.06%)	414 (60.00%)		
Farmer	127 (18.41%)	160 (23.19%)		
Other	121 (17.54%)	116 (16.81%)		
History of allergy			0.03 (-0.08, 0.13)	0.617
No	673 (97.54%)	670 (97.10%)		
Yes	17 (2.46%)	20 (2.90%)		
Injury mechanism			0.08 (-0.02, 0.19)	0.314
Falling	675 (97.83%)	677 (98.12%)		
Accident	12 (1.74%)	7 (1.01%)		
Other	3 (0.43%)	6 (0.87%)		
Fracture classification			0.11 (0.00, 0.22)	0.123
Intertrochanteric fracture	511 (74.06%)	534 (77.39%)		
Femoral neck fracture	171 (24.78%)	143 (20.72%)		
Subtrochanteric fracture	8 (1.16%)	13 (1.88%)		
aCCI			0.39 (0.28, 0.49)	< 0.001*
2	2 (0.29%)	8 (1.16%)		
3	14 (2.03%)	73 (10.58%)		
4	317 (45.94%)	303 (43.91%)		
5	254 (36.81%)	209 (30.29%)		
6	86 (12.46%)	74 (10.72%)		
7	15 (2.17%)	20 (2.90%)		
8	2 (0.29%)	3 (0.43%)		
Hypertension			0.05 (-0.06, 0.15)	0.36
No	329 (47.68%)	346 (50.14%)		
Yes	361 (52.32%)	344 (49.86%)		
Diabetes			0.04 (-0.07, 0.15)	0.459
No	547 (79.28%)	558 (80.87%)		
Yes	143 (20.72%)	132 (19.13%)		
CHD			0.03 (-0.08, 0.13)	0.626
No	316 (45.80%)	307 (44.49%)		
Yes	374 (54.20%)	383 (55.51%)		
Arrhythmia			0.00 (-0.10, 0.11)	0.955
No	449 (65.07%)	448 (64.93%)		
Yes	241 (34.93%)	242 (35.07%)		
Hemorrhagic stroke			0.00 (-0.11, 0.11)	1
No	678 (98.26%)	678 (98.26%)		
Yes	12 (1.74%)	12 (1.74%)		
Ischemic stroke			0.02 (-0.08, 0.13)	0.688
No	462 (66.96%)	469 (67.97%)		
Yes	228 (33.04%)	221 (32.03%)		
Cancer			0.05 (-0.05, 0.16)	0.327
No	667 (96.67%)	660 (95.65%)		
Yes	23 (3.33%)	30 (4.35%)		
Associated injuries			0.05 (-0.06, 0.15)	0.373
No	643 (93.19%)	651 (94.35%)		
Yes	47 (6.81%)	39 (5.65%)		
Dementia			0.06 (-0.05, 0.16)	0.297
No	655 (94.93%)	646 (93.62%)		

Table 6 (continued)

Variables	Survival (690)	Mortality (690)	Standardized difference	*P* value
Yes	35 (5.07%)	44 (6.38%)		
COPD			0.03 (-0.08, 0.13)	0.602
No	643 (93.19%)	638 (92.46%)		
Yes	47 (6.81%)	52 (7.54%)		
Hepatitis			0.00 (-0.11, 0.11)	1
No	665 (96.38%)	665 (96.38%)		
Yes	25 (3.62%)	25 (3.62%)		
Gastritis			0.00 (-0.11, 0.11)	1
No	677 (98.12%)	677 (98.12%)		
Yes	13 (1.88%)	13 (1.88%)		
Time to admission (h)	94.38 ± 314.44	85.11 ± 157.26	0.04 (-0.07, 0.14)	0.489
Operation			0.09 (-0.01, 0.20)	0.236
ORIF	508 (73.62%)	535 (77.54%)		
HA	180 (26.09%)	153 (22.17%)		
THA	2 (0.29%)	2 (0.29%)		
Operation time (mins)	90.04 ± 32.51	91.54 ± 33.14	0.05 (-0.06, 0.15)	0.394
Blood loss (mL)	237.07 ± 157.23	242.80 ± 142.73	0.04 (-0.07, 0.14)	0.479
Infusion (mL)	1502.74 ± 345.87	1509.04 ± 371.50	0.02 (-0.09, 0.12)	0.744
Transfusion (U)	1.24 ± 1.25	1.30 ± 1.24	0.05 (-0.06, 0.15)	0.377
Time to operation (d)	4.26 ± 2.41	4.51 ± 2.85	0.09 (-0.01, 0.20)	0.082

* Variables were not successfully matched

Table 7 Multivariate results by Cox regression

Exposure	Non-adjusted model	Minimally-adjusted model	Fully-adjusted model	PSM model	PSM-adjusted model
Admission albumin	0.91 (0.89, 0.92) < 0.0001	0.93 (0.91, 0.95) < 0.0001	0.94 (0.92, 0.96) < 0.0001	0.96 (0.93, 0.99) 0.0046	0.95 (0.92, 0.98) 0.0042

Data in table: HR (95% CI) *P*-value

Outcome variable: mortality

Exposed variables: albumin

Adjust variables in the PSM-adjusted model: age, aCCI

prognosis [48, 49]. During the analysis, to explore the real relationship between the two factors, we not only carried out linear regression using different adjusted models but also changed the continuous variable of albumin to a categorical variable or performed a trend test for the result. Additionally, we considered confounders in earlier studies [14, 30, 50], adjusted the factor of $P < 0.1$ in the univariate analysis, and comprehensively considered the variables that needed adjustment. The age-stratified analysis showed that the preoperative albumin level was not associated with mortality in 65 ≤ age<75 patients but associated with mortality in patients 75 ≤ age. Phillips reported that in middle-aged men, serum albumin decreased with age [50]. In this study, there were 583, 1226, and 578 patients in 65 ≤ age<75, 75 ≤ age<85, and age ≥ 85 subgroups, and the mean albumin levels were 39.0 ± 4.3, 37.8 ± 3.8, 36.4 ± 3.9 g/L and the mortality rates were 101 (17.3%), 395 (32.2%) and 291 (50.3%), respectively. The higher age with lower albumin level was associated with higher mortality.

In addition, we explored the association with the curve relationship and found no threshold or saturation effect, which supplements the stability of the linear association. We also performed sensitivity analysis using PSM to test the robustness of our results. One thousand three hundred eighty patients were matched successfully, and the results remained stable.

It was noted that there were 195 patients received conservative treatment, and there were 130 (66.7%) deaths. The reasons for conservative treatment were the poor status to support operation or the refusal of operation from patients' families. Therefore, surgery-specific variables (e.g., time to operation, operation time, blood loss, infusion, transfusion, etc.) are unsuitable for conservative cases. When we excluded these conservative patients, the adjusted model also showed a mortality risk decrease of 6% (HR = 0.94) when albumin increased by 1 g/L.

Our study had some limitations. First, because of the retrospective design, loss to follow-up was inevitable. To obtain a prognosis, we attempted thrice to

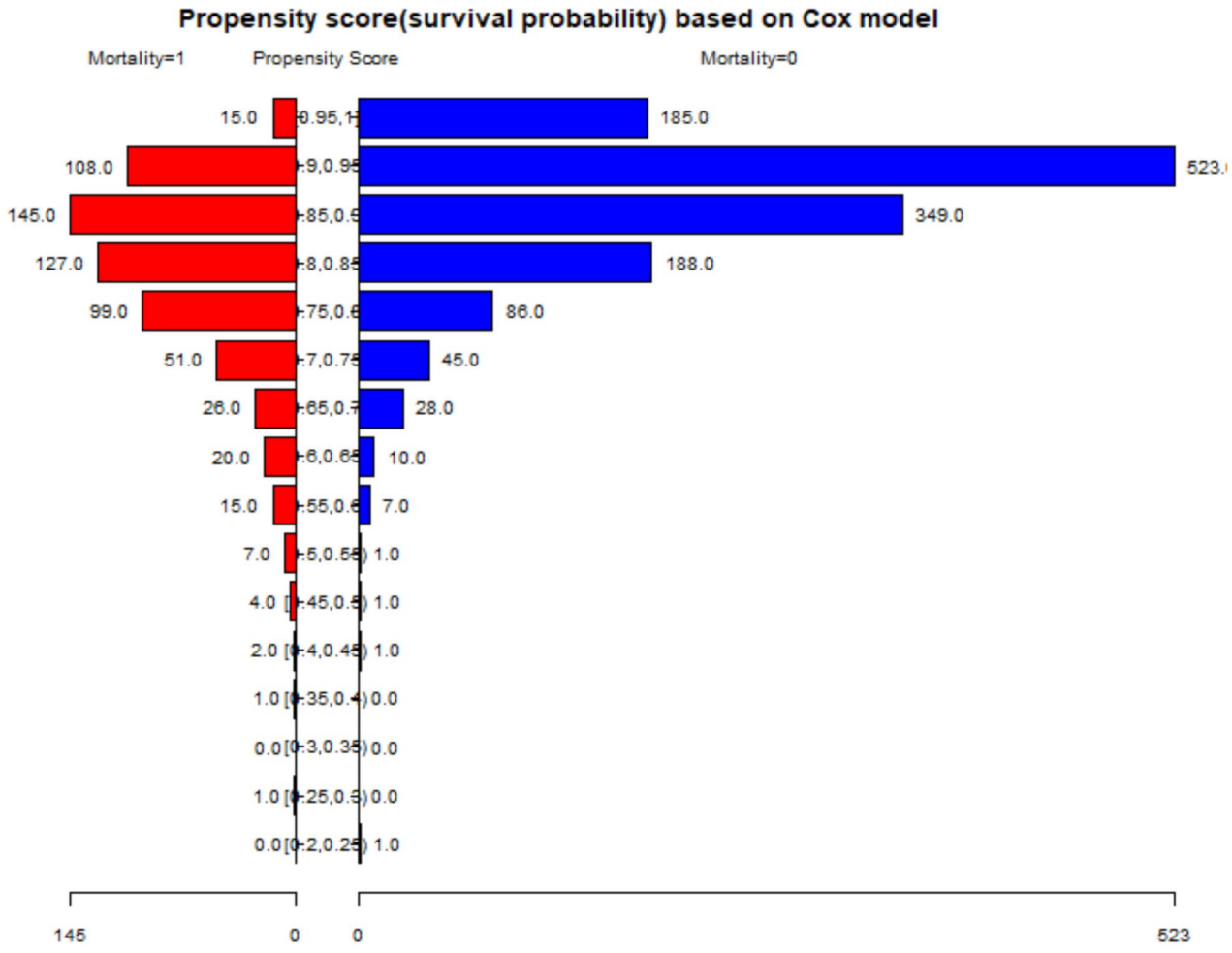

Fig. 3 The PSM of two groups under propensity score based on the Cox model

establish contact with the patients who failed to return for follow-up. Second, our analysis had many potential confounders related to mortality. However, these data did not include body mass index, C-reactive protein, pre-injury walking level, or other reported mortality-related factors. The reason was that we did not get the data in the early digital medical system (body mass index and pre-injury walking level), or the surgeons did not have the C-reactive protein test at admission. It is important to analyze whether hypoalbuminemia is the cause or an intermediate factor, including various variables, in order to establish appropriate treatment in the future. Third, our study was designed as a single center, and the external validity of the results needs to be considered in the future.

In conclusion, albumin concentration is associated with mortality in geriatric patients with hip fractures, and it could be considered a predictor for the risk of mortality.

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Author contributions
According to the definition given by the International Committee of Medical Journal Editors (ICMJE), the authors listed above qualify for authorship based on making one or more of the substantial contributions to the intellectual content of the following: Conceived and designed the study: Yao Liu, Bin-Fei Zhang. Performed the study: Hai Huang, Bin-Fei Zhang. Analyzed the data: Hai Huang, Yao Liu, Bin-Fei Zhang. Wrote the manuscript: Hai Huang. All authors reviewed the manuscript.

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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.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee of the Honghui Hospital, Xi'an Jiaotong University (No. 202201009).

Consent for publication
Not applicable.

Consent to publish
The work described has not been published before (except in the form of an abstract or as part of a published lecture, review, or thesis); it is not under consideration for publication elsewhere, and all co-authors have approved its publication.

Competing interests
The authors declare no competing interests.

Registered information
This study is registered on the website of the Chinese Clinical Trial Registry (ChiCTR: ChiCTR2200057323).

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