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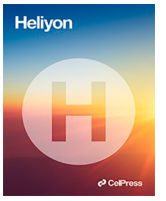

Research article

# Serum cystatin C as a biomarker to predict all-cause mortality in geriatrics hip fracture

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ABSTRACT

*Background:* Cystatin C, a low-molecular-weight protein, belongs to cysteine protease inhibitors produced primarily by nucleated cells. Its serum concentration, independent of sex, age, or muscle mass, is a good predictor of renal dysfunction in older adults. This study evaluated the association between all-cause mortality and preoperative cystatin C levels in hip fractures.

*Materials and methods:* Data describing the demographic and clinical characteristics of the patients were gathered specifically from older individuals who had suffered hip fractures. The study used linear and non-linear multivariate Cox regression models to investigate the association between preoperative cystatin C levels and mortality. The analyses were conducted using the R and EmpowerStats software.

*Results:* In total, two thousand three hundred and ninety-four patients were included in this study. A total of 790 patients (33 %) died of all causes. The mean follow-up was 37.62 months. The preoperative cystatin C was 0.91 ± 0.41 mg/L. Linear multivariate Cox regression analysis revealed a significant association between preoperative cystatin C level and death, with a hazard ratio (HR) of 2.19 (95 % confidence interval [CI]: 1.72–2.79, $P < 0.0001$). Nevertheless, the correlation between the variables was inconsistent. A cystatin C concentration of 1.62 mg/L marked a significant change in the non-linear relationship. A preoperative cystatin C level below 1.62 mg/L was found to be significantly linked with an increased risk of mortality (HR = 2.60, 95 % CI: 1.92–3.52, $P < 0.0001$). The mortality reached its highest point when the preoperative cystatin C level was greater than 1.62 mg/L. After that, the mortality risk did not increase further (HR = 1.54, 95 % CI: 0.98–2.42, $P = 0.0588$). The non-linear relationship remained consistent in the propensity score-matching sensitive analysis.

*Conclusions:* The study found a non-linear relationship between preoperative cystatin C levels and mortality in geriatric hip fractures. This suggests that preoperative cystatin C can be used as a predictor of the risk of death. The registration number is ChiCTR2200057323.

## 1. Introduction

The prevalence of geriatric hip fractures increases with the increasing population of older individuals worldwide [1,2]. The reported one-year mortality rate was 22%–33 % [3,4]. Surgeons have used many treatment strategies to decrease mortality and improve prognoses, such as accelerated surgery [5], general anesthesia [6], nutritional intake [7], and surgical choice [8]. However, these

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**List of Abbreviations**

| | |
|---|---|
| aCCI | age-adjusted Charlson comorbidity index |
| CHD | coronary heart disease |
| CI | confidence interval |
| COPD | chronic obstructive pulmonary disease |
| HR | Hazard ratio |
| PSM | propensity score matching |

strategies do not improve prognosis. Several factors affect the pathophysiology of geriatric hip fractures.

Cystatin C is a small protein that falls into a category of cysteine protease inhibitors. It is mostly produced by cells with a nucleus. Due of its low molecular weight, it can be readily filtered. Crucially, the level of the substance in the blood is not affected by gender, age, or muscle mass, and it is a reliable indicator of kidney problems in older individuals [9,10].

Cystatin C, an underexplored biomarker, has implications beyond renal function [11,12] and is linked to frailty status in older men [13,14]. Elevated levels of cystatin C in the general population have been linked to a higher risk of cardiovascular disease [15–17]. Additionally, cystatin C levels have been identified as a new predictor of prognosis in non-ST-elevation acute coronary syndrome [18]. Hart et al. proposed that elevated levels of cystatin C could serve as a potential biomarker for failed aging, characterized by a higher susceptibility to frailty and mortality [14]. Bai et al. included cystatin C as a component in a biological age formula, as they found it to be a biomarker of aging [19].

Cystatin C serves as both a risk factor for hip fracture [20] and as a predictor of postoperative complications in the context of hip fracture [21]. Nevertheless, the association between serum cystatin C levels and the prognosis of patients with hip fractures is not yet well understood. This study is a prospective cohort study that aims to determine the effect of cystatin C in hip fractures. Hence, this investigation examined the impact of serum cystatin C levels on patient death during an extended period of observation. Our hypothesis posited that there would exist either a linear or non-linear correlation between preoperative cystatin C levels and mortality.

## 2. Materials and methods

### 2.1. Study design

This study involved the enrollment of elderly individuals who experienced a hip fracture between January 1, 2015, and September 30, 2019, at the largest trauma center in Northwest China.

The Ethics Committee of our Hospital (No. 202201009) has granted approval for this prospective investigation. All human-related protocols adhered to the 1964 Declaration of Helsinki and its subsequent revisions. The study was conducted in accordance with the STROCSS 2021 requirements [22]. All subjects participating in the study provided verbal consent after being told about the investigation.

### 2.2. Participants

The demographic and clinical characteristics of the patients were extracted from their original medical records. The criteria for inclusion were as follows: 1) Patients aged 65 years or older; 2) Patients diagnosed with a femoral neck, intertrochanteric, or subtrochanteric fracture through X-ray or computed tomography; 3) Patients receiving either surgical or conservative treatment in the hospital; 4) Availability of clinical data during hospitalization; and 5) Patients who can be reached by telephone. Patients that were unreachable were excluded from this investigation.

### 2.3. Hospital treatment

Upon admission, blood tests were conducted to assess the levels of Cystatin C. We quantified the concentration of cystatin C in serum samples using the method of Immunoturbidimetry. Intertrochanteric fractures are commonly managed with closed or open reduction and internal fixation (ORIF) using a proximal femoral nail anti-rotation. Femoral neck fractures are commonly managed by either hemiarthroplasty (HA) or total hip arthroplasty (THA), depending on the patient's age. Prophylactic measures to prevent deep vein thrombosis were started at admission. Upon discharge, patients were asked to return every month to assess fracture union or function.

### 2.4. Follow-up

Following discharge, telephone interviews were conducted with patients' family members between January 2022 and March 2022 to collect data on survival, survival duration, and daily living activities. Two healthcare practitioners, who underwent a two-week training program and have one year of practical experience, carried out telephone follow-up consultations. We made two attempts to reach patients who were unreachable on the initial contact. In the event that the patients' family members did not provide a

**Table 1**
The Demographic and clinical characteristics of patients in this study (N = 2394).

| Cystatin C tertiles | Low | Middle | High | *P*-value | *P*-value* |
|---|---|---|---|---|---|
| **No. of patients** | 764 | 845 | 785 | | |
| **Cystatin C (mg/L)** | 0.59 ± 0.08 | 0.81 ± 0.07 | 1.33 ± 0.46 | <0.001 | <0.001 |
| **Creatinine (umol/L)** | 54.45 ± 11.63 | 65.15 ± 14.96 | 93.56 ± 51.48 | <0.001 | <0.001 |
| **Age (year)** | 76.36 ± 6.40 | 79.89 ± 6.26 | 82.26 ± 6.47 | <0.001 | <0.001 |
| **Sex** | | | | <0.001 | – |
| Male | 198 (25.92 %) | 301 (35.62 %) | 290 (36.94 %) | | |
| Female | 566 (74.08 %) | 544 (64.38 %) | 495 (63.06 %) | | |
| **Occupation** | | | | 0.948 | – |
| Retirement | 437 (57.20 %) | 486 (57.51 %) | 463 (58.98 %) | | |
| Farmer | 190 (24.87 %) | 204 (24.14 %) | 183 (23.31 %) | | |
| Other | 137 (17.93 %) | 155 (18.34 %) | 139 (17.71 %) | | |
| **History of allergy** | | | | 0.792 | – |
| No | 730 (95.55 %) | 812 (96.09 %) | 755 (96.18 %) | | |
| Yes | 34 (4.45 %) | 33 (3.91 %) | 30 (3.82 %) | | |
| **Injury mechanism** | | | | 0.045 | – |
| Falling | 731 (95.68 %) | 813 (96.21 %) | 770 (98.09 %) | | |
| Accident | 28 (3.66 %) | 23 (2.72 %) | 12 (1.53 %) | | |
| Other | 5 (0.65 %) | 9 (1.07 %) | 3 (0.38 %) | | |
| **Fracture classification** | | | | <0.001 | – |
| Intertrochanteric fracture | 494 (64.66 %) | 603 (71.36 %) | 615 (78.34 %) | | |
| Femoral neck fracture | 252 (32.98 %) | 222 (26.27 %) | 146 (18.60 %) | | |
| Subtrochanteric fracture | 18 (2.36 %) | 20 (2.37 %) | 24 (3.06 %) | | |
| **aCCI** | | | | <0.001 | – |
| 2 | 71 (9.29 %) | 28 (3.31 %) | 6 (0.76 %) | | |
| 3 | 224 (29.32 %) | 152 (17.99 %) | 88 (11.21 %) | | |
| 4 | 272 (35.60 %) | 358 (42.37 %) | 337 (42.93 %) | | |
| 5 | 143 (18.72 %) | 211 (24.97 %) | 235 (29.94 %) | | |
| 6 | 46 (6.02 %) | 72 (8.52 %) | 88 (11.21 %) | | |
| 7 | 6 (0.79 %) | 18 (2.13 %) | 30 (3.82 %) | | |
| 8 | 1 (0.13 %) | 6 (0.71 %) | 1 (0.13 %) | | |
| 9 | 1 (0.13 %) | 0 (0.00 %) | 0 (0.00 %) | | |
| **Hypertension** | | | | <0.001 | – |
| No | 427 (55.89 %) | 439 (51.95 %) | 357 (45.48 %) | | |
| Yes | 337 (44.11 %) | 406 (48.05 %) | 428 (54.52 %) | | |
| **Diabetes** | | | | 0.066 | – |
| No | 590 (77.23 %) | 689 (81.54 %) | 636 (81.02 %) | | |
| Yes | 174 (22.77 %) | 156 (18.46 %) | 149 (18.98 %) | | |
| **CHD** | | | | <0.001 | – |
| No | 403 (52.75 %) | 409 (48.40 %) | 316 (40.25 %) | | |
| Yes | 361 (47.25 %) | 436 (51.60 %) | 469 (59.75 %) | | |
| **Arrhythmia** | | | | <0.001 | – |
| No | 557 (72.91 %) | 554 (65.56 %) | 486 (61.91 %) | | |
| Yes | 207 (27.09 %) | 291 (34.44 %) | 299 (38.09 %) | | |
| **Hemorrhagic stroke** | | | | 0.121 | – |
| No | 754 (98.69 %) | 826 (97.75 %) | 763 (97.20 %) | | |
| Yes | 10 (1.31 %) | 19 (2.25 %) | 22 (2.80 %) | | |
| **Ischemic stroke** | | | | 0.168 | – |
| No | 557 (72.91 %) | 597 (70.65 %) | 538 (68.54 %) | | |
| Yes | 207 (27.09 %) | 248 (29.35 %) | 247 (31.46 %) | | |
| **Cancer** | | | | 0.198 | – |
| No | 738 (96.60 %) | 817 (96.69 %) | 769 (97.96 %) | | |
| Yes | 26 (3.40 %) | 28 (3.31 %) | 16 (2.04 %) | | |
| **Associated injuries** | | | | 0.813 | – |
| No | 709 (92.80 %) | 784 (92.78 %) | 734 (93.50 %) | | |
| Yes | 55 (7.20 %) | 61 (7.22 %) | 51 (6.50 %) | | |
| **Dementia** | | | | 0.8 | – |
| No | 736 (96.34 %) | 811 (95.98 %) | 751 (95.67 %) | | |
| Yes | 28 (3.66 %) | 34 (4.02 %) | 34 (4.33 %) | | |
| **COPD** | | | | 0.082 | – |
| No | 728 (95.29 %) | 789 (93.37 %) | 727 (92.61 %) | | |
| Yes | 36 (4.71 %) | 56 (6.63 %) | 58 (7.39 %) | | |
| **Hepatitis** | | | | 0.092 | – |
| No | 749 (98.04 %) | 814 (96.33 %) | 757 (96.43 %) | | |
| Yes | 15 (1.96 %) | 31 (3.67 %) | 28 (3.57 %) | | |
| **Gastritis** | | | | 0.321 | – |
| No | 755 (98.82 %) | 830 (98.22 %) | 768 (97.83 %) | | |
| Yes | 9 (1.18 %) | 15 (1.78 %) | 17 (2.17 %) | | |
| **Treatment strategy** | | | | <0.001 | – |

(*continued on next page*)

**Table 1** (*continued*)

| Cystatin C tertiles | Low | Middle | High | *P*-value | *P*-value* |
|---|---|---|---|---|---|
| Conservation | 35 (4.58 %) | 62 (7.34 %) | 100 (12.74 %) | | |
| ORIF | 486 (63.61 %) | 569 (67.34 %) | 540 (68.79 %) | | |
| HA | 221 (28.93 %) | 205 (24.26 %) | 142 (18.09 %) | | |
| THA | 22 (2.88 %) | 9 (1.07 %) | 3 (0.38 %) | | |
| **Time to admission (h)** | 70.82 ± 257.00 | 83.71 ± 279.23 | 85.29 ± 228.64 | 0.475 | <0.001 |
| **Time to operation (d)** | 4.03 ± 2.35 | 4.27 ± 2.40 | 4.59 ± 2.85 | <0.001 | <0.001 |
| **Operation time (mins)** | 95.28 ± 36.98 | 93.35 ± 34.76 | 95.74 ± 40.17 | 0.421 | 0.745 |
| **Blood loss (mL)** | 242.59 ± 156.70 | 238.39 ± 154.36 | 255.51 ± 170.25 | 0.116 | 0.558 |
| **Infusion (mL)** | 1609.04 ± 378.92 | 1555.10 ± 393.87 | 1537.47 ± 391.41 | 0.002 | <0.001 |
| **Transfusion (U)** | 0.95 ± 1.24 | 1.13 ± 1.26 | 1.38 ± 1.29 | <0.001 | <0.001 |
| **Stay in hospital (d)** | 8.37 ± 3.53 | 8.78 ± 3.36 | 9.42 ± 3.87 | <0.001 | <0.001 |
| **Follow up (months)** | 38.01 ± 15.87 | 38.60 ± 18.11 | 36.19 ± 21.14 | 0.025 | 0.033 |
| **Mortality** | | | | <0.001 | – |
| Survival | 614 (80.37 %) | 580 (68.64 %) | 410 (52.23 %) | | |
| Dead | 150 (19.63 %) | 265 (31.36 %) | 375 (47.77 %) | | |

*P*-value*: for variables that have a continuous range of values, we used the Kruskal-Wallis rank-sum test. In the case of variables that have a count of occurrences and a theoretical number of less than 10, we utilized Fisher's exact probability test.

response, we ceased our efforts and documented the patients as having been lost to follow-up.

### 2.5. Endpoint events

The endpoint event in this study was all-cause mortality.

### 2.6. Variables in this study

The variables recorded in this study included age, gender, occupation, allergy history, injury mechanism, fracture classification, hypertension, diabetes, coronary heart disease, arrhythmia, hemorrhagic stroke, ischemic stroke, cancer, associated injuries, dementia, chronic obstructive pulmonary disease (COPD), hepatitis, gastritis, age-adjusted Charlson comorbidity index (aCCI), time from injury to admission, time from admission to surgery, preoperative cystatin C levels, surgery duration, blood loss, infusion, transfusion, treatment, hospital stay duration, and follow-up.

### 2.7. Statistics analysis

Continuous variables are typically presented as the mean ± standard deviation when they follow a Gaussian distribution, or as the median together with the range when they have a skewed distribution. Categorical variables are represented numerically using proportions. The study employed chi-square test for categorical variables, one-way ANOVA for variables with normal distribution, and Kruskal-Wallis H test for variables with skewed distribution to identify disparities among various preoperative cystatin C levels. We employed univariate and multivariate Cox proportional hazards regression models, specifically three models, to examine the correlation between preoperative cystatin C level and death. In order to assess the reliability of our findings, we conducted a sensitivity analysis. We transformed the preoperative cystatin C into a categorical variable. We used the statistical significance (P-value) to assess the trend and investigate the potential presence of nonlinearity by using preoperative cystatin C as a continuous variable. We used a Cox proportional hazards regression model with cubic spline functions and smooth curve fitting (using the penalized spline method) to account for the nonlinearity between preoperative cystatin C and mortality. Upon detecting nonlinearity, we proceeded to compute the inflection point using a recursive approach. Next, we developed a two-piecewise Cox proportional hazards regression model for each side of the inflection point. Furthermore, we implemented propensity score matching (PSM) to create matched groups, and we accounted for confounding factors in the PSM models.

The statistical analyses were conducted using the R software program (http://www.R-project.org, R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions Inc., Boston, MA, USA). Calculations were performed to determine the hazard ratios (HR) and 95 % confidence intervals (CI). A P-value less than 0.05 (two-sided) was deemed to indicate statistical significance.

## 3. Results

### 3.1. Patient characteristics

Out of the initial 2887 participants who experienced hip fractures from January 2015 to September 2019, we selected and included 2394 people who satisfied the study requirements. The average preoperative cystatin C level was 0.91 ± 0.41 mg/L, ranging from 0.16 to 6.62 mg/L. The average duration of follow-up was 37.62 months, with a range of 0.03–77.96 months. Out of the entire patient population, 790 individuals (33 %) died of various causes. We categorized the cystatin C concentration into three distinct groups. Table 1 presents the demographic and clinical profiles of all 2394 patients, encompassing comorbidities, factors linked to injuries, and

**Table 2**
The factors on mortality in univariate analysis (N = 2394).

| | Statistics | HR (95 % CI) | *P*-value |
|---|---|---|---|
| **Age (year)** | 79.54 ± 6.81 | 1.08 (1.07, 1.09) | <0.0001 |
| **Sex** | | | |
| Male | 789 (32.96 %) | 1.0 | |
| Female | 1605 (67.04 %) | 0.73 (0.63, 0.84) | <0.0001 |
| **Occupation** | | | |
| Retirement | 1386 (57.89 %) | 1.0 | |
| Farmer | 577 (24.10 %) | 0.93 (0.79, 1.11) | 0.4239 |
| Other | 431 (18.00 %) | 0.87 (0.72, 1.05) | 0.1458 |
| **History of allergy** | | | |
| No | 2297 (95.95 %) | 1.0 | |
| Yes | 97 (4.05 %) | 0.93 (0.64, 1.35) | 0.7107 |
| **Injury mechanism** | | | |
| Falling | 2314 (96.66 %) | 1.0 | |
| Accident | 63 (2.63 %) | 0.24 (0.11, 0.53) | 0.0005 |
| Other | 17 (0.71 %) | 1.43 (0.71, 2.87) | 0.3140 |
| **Time to admission (h)** | 80.12 ± 256.37 | 1.00 (1.00, 1.00) | 0.1459 |
| **Fracture classification** | | | |
| Intertrochanteric fracture | 1712 (71.51 %) | 1.0 | |
| Femoral neck fracture | 620 (25.90 %) | 0.85 (0.72, 1.02) | 0.0808 |
| Subtrochanteric fracture | 62 (2.59 %) | 0.72 (0.45, 1.14) | 0.1623 |
| **aCCI** | | | |
| 2 | 105 (4.39 %) | 1.0 | |
| 3 | 464 (19.38 %) | 2.80 (1.22, 6.45) | 0.0152 |
| 4 | 967 (40.39 %) | 6.83 (3.05, 15.32) | <0.0001 |
| 5 | 589 (24.60 %) | 9.51 (4.23, 21.36) | <0.0001 |
| 6 | 206 (8.60 %) | 12.20 (5.36, 27.81) | <0.0001 |
| 7 | 54 (2.26 %) | 15.95 (6.65, 38.24) | <0.0001 |
| 8 | 8 (0.33 %) | 29.79 (9.60, 92.47) | <0.0001 |
| 9 | 1 (0.04 %) | 32.29 (3.88, 268.47) | 0.0013 |
| **Hypertension** | | | |
| No | 1223 (51.09 %) | 1.0 | |
| Yes | 1171 (48.91 %) | 1.13 (0.98, 1.30) | 0.0835 |
| **Diabetes** | | | |
| No | 1915 (79.99 %) | 1.0 | |
| Yes | 479 (20.01 %) | 0.99 (0.83, 1.18) | 0.8943 |
| **CHD** | | | |
| No | 1128 (47.12 %) | 1.0 | |
| Yes | 1266 (52.88 %) | 1.34 (1.16, 1.54) | <0.0001 |
| **Arrhythmia** | | | |
| No | 1597 (66.71 %) | 1.0 | |
| Yes | 797 (33.29 %) | 1.31 (1.13, 1.51) | 0.0003 |
| **Hemorrhagic stroke** | | | |
| No | 2343 (97.87 %) | 1.0 | |
| Yes | 51 (2.13 %) | 1.11 (0.70, 1.77) | 0.6556 |
| **Ischemic stroke** | | | |
| No | 1692 (70.68 %) | 1.0 | |
| Yes | 702 (29.32 %) | 1.45 (1.25, 1.67) | <0.0001 |
| **Cancer** | | | |
| No | 2324 (97.08 %) | 1.0 | |
| Yes | 70 (2.92 %) | 1.84 (1.32, 2.56) | 0.0003 |
| **Associated injuries** | | | |
| No | 2227 (93.02 %) | 1.0 | |
| Yes | 167 (6.98 %) | 0.94 (0.71, 1.25) | 0.6721 |
| **Dementia** | | | |
| No | 2298 (95.99 %) | 1.0 | |
| Yes | 96 (4.01 %) | 2.85 (2.19, 3.70) | <0.0001 |
| **COPD** | | | |
| No | 2244 (93.73 %) | 1.0 | |
| Yes | 150 (6.27 %) | 1.57 (1.23, 2.02) | 0.0003 |
| **Hepatitis** | | | |
| No | 2320 (96.91 %) | 1.0 | |
| Yes | 74 (3.09 %) | 1.49 (1.06, 2.11) | 0.0219 |
| **Gastritis** | | | |
| No | 2353 (98.29 %) | 1.0 | |
| Yes | 41 (1.71 %) | 0.94 (0.56, 1.60) | 0.8282 |
| **Time to operation (d)** | 4.29 ± 2.54 | 1.03 (1.00, 1.06) | 0.0274 |
| **Treatment strategy** | | | |
| Conservation | 197 (8.23 %) | 1.0 | |

(*continued on next page*)

**Table 2** (*continued*)

| | Statistics | HR (95 % CI) | *P*-value |
|---|---|---|---|
| ORIF | 1595 (66.62 %) | 0.29 (0.24, 0.36) | <0.0001 |
| HA | 568 (23.73 %) | 0.32 (0.25, 0.40) | <0.0001 |
| THA | 34 (1.42 %) | 0.06 (0.02, 0.25) | <0.0001 |
| **Blood loss (mL)** | 245.15 ± 160.35 | 1.00 (1.00, 1.00) | 0.5930 |
| **Infusion (mL)** | 1567.52 ± 389.18 | 1.00 (1.00, 1.00) | 0.0002 |
| **Operation time (mins)** | 94.74 ± 37.25 | 1.00 (1.00, 1.00) | 0.0846 |
| **Transfusion (U)** | 1.15 ± 1.28 | 1.07 (1.01, 1.13) | 0.0262 |
| **Stay in hospital (d)** | 8.86 ± 3.61 | 1.03 (1.01, 1.05) | 0.0008 |
| **Cystatin C (mg/L)** | 0.91 ± 0.41 | 1.70 (1.56, 1.86) | <0.0001 |
| **Creatinine (umol/L)** | 71.05 ± 35.45 | 1.00 (1.00, 1.00) | <0.0001 |

treatment approaches.

### 3.2. Univariate analysis

We conducted a univariate analysis to detect possible confounding factors and examine the association between variables and mortality. The results are presented in Table 2. The multivariate Cox regression analysis considered the following variables based on the criteria of $P < 0.1$: age, sex, injury mechanism, fracture classification, aCCI, hypertension, CHD, arrhythmia, ischemic stroke, cancer, dementia, COPD, hepatitis, time to operation, treatment strategy, operation time, infusion, transfusion, length of hospital stay, and creatinine.

### 3.3. Multivariate analysis

We used three models (Table 3) to establish a correlation between preoperative cystatin C levels and mortality. Linear regression was obtained when the concentration of cystatin C was treated as a continuous variable. The fully adjusted model, after accounting for all relevant covariates, revealed a 119 % increase in the risk of mortality (HR = 2.19, 95 % CI: 1.72–2.79, $P < 0.0001$) for every 1 mg/L rise in cystatin C concentration. When we categorized the cystatin C concentration, we observed statistically significant differences among the groups in all three models ($P < 0.0001$). Furthermore, the P-value for the trend demonstrated a significant linear association in all three models ($P < 0.0001$).

Nevertheless, we observed a deceleration in the rate of change in the high subgroup of cystatin C concentration (Table 3). The presence of this instability suggests the potential for a non-linear association.

### 3.4. Non-linear association

Fig. 1 demonstrates a curving relationship between the preoperative cystatin C level and mortality, even after accounting for confounding factors. We compared two fitting models to elucidate this correlation (Table 4). Remarkably, we detected a point of change in the curvilinear. A preoperative cystatin C level below 1.62 mg/L was found to be significantly linked with an increased risk of mortality (HR = 2.60, 95%CI: 1.92–3.52, $P < 0.0001$). The mortality reached its highest point when the preoperative cystatin C level was greater than 1.62 mg/L. After that, the mortality risk did not increase further (HR = 1.54, 95%CI: 0.98–2.42, $P = 0.0588$). Nevertheless, males and females had no discernible statistical inflection point, respectively.

**Table 3**
Multivariate results by cox regression (N = 2394).

| Exposure | Non-adjusted model | Minimally-adjusted model | Fully-adjusted model |
|---|---|---|---|
| **Cystatin C (mg/L)** | 1.70 (1.56, 1.86) <0.0001 | 1.57 (1.40, 1.75) <0.0001 | 2.19 (1.72, 2.79) <0.0001 |
| **Cystatin C group** | | | |
| Low | Ref | Ref | Ref |
| Middle | 1.59 (1.30, 1.94) <0.0001 | 1.22 (1.00, 1.50) 0.0545 | 1.10 (0.88, 1.38) 0.4080 |
| High | 2.57 (2.13, 3.11) <0.0001 | 1.71 (1.40, 2.09) <0.0001 | 1.55 (1.23, 1.96) 0.0002 |
| ***P* for trend** | <0.0001 | <0.0001 | <0.0001 |

**Data in table**: HR (95 % CI) *P*-value.
**Outcome variable**: mortality.
**Exposed variables**: cystatin C.
**Minimally-adjusted model was adjusted for**: age; sex.
**Fully-adjusted model was adjusted for:** age, sex, injury mechanism, fracture classification, aCCI, hypertension, CHD, arrhythmia, ischemic stroke, cancer, dementia, COPD, hepatitis, time to operation, treatment strategy, operation time, infusion, transfusion, length in hospital and creatinine.

### 3.5. Propensity score matching (PSM)

In order to assess the strength and reliability of our findings, we conducted a sensitivity analysis using PSM, as depicted in Fig. 2 and Tables 5–7. A total of 1206 patients, accounting for 50.37 % of the sample, were successfully matched (Fig. 2; Table 5). The age and aCCI variables were not consistent between the two groups, as indicated in Table 6. The multivariate Cox regression results remained consistent in both the PSM and PSM-adjusted models, as shown in Table 7.

Fig. 3 displays the Kaplan-Meier survival curve. The death rate was significantly greater ($P < 0.0001$) in the three subgroups with elevated preoperative cystatin C levels.

## 4. Discussion

A non-linear relationship was seen between preoperative cystatin C levels and mortality. A concentration of 1.62 mg/L marked a point where the saturation effect changed. When the concentration of cystatin C was below 1.62 mg/L, there was a 160 % increase in mortality (HR = 2.60) for every 1 mg/L rise in cystatin C concentration. When the concentration of cystatin exceeded 1.62 mg/L, the mortality reached its highest point, and there was no further increase in the death rate. Therefore, it serves as a valuable indication for accurately forecasting mortality in practical applications.

Several research in the field of serum cystatin C has found connections between serum cystatin C and several health conditions, including ischemic stroke [23], peripheral artery disease [24], thyroid diseases [25], cardiovascular disease [26], and female hip fracture [20,27,28]. Serum cystatin C is a widely used marker for assessing kidney function, with high levels of sensitivity and specificity. Cystatin C served as a significant indicator of the glomerular filtration rate in elderly individuals. Cystatin C, a biomarker that goes beyond renal function, has received limited attention in research [11,12,15–18] and recent investigations have found associations between cystatin C and a frailty state [13,14,19]. According to Chen et al., cystatin C levels were found to be a useful predictor of the risk of postoperative pneumonia in older persons after hip fracture surgery [21]. Several observational studies have indicated a correlation between kidney function and the likelihood of death following hip fractures. Jonsson et al. determined that patients with hip fractures who had reduced renal function had a higher risk of mortality, even after considering other known risk factors. Furthermore, the link between mortality and renal function was particularly pronounced for cystatin C [29]. A study conducted by Gulin et al. revealed that poor renal function was identified as a separate risk factor for mortality in a group of 236 patients with hip fractures (HR = 0.972) [30].

This study investigates the correlation between cystatin C levels and mortality in elderly individuals with hip fractures. In this work, we built a correlation using curve fitting and identified a point of saturation. Our research demonstrates a correlation between cystatin C levels and the likelihood of death within a moderate timeframe in individuals with hip fractures. Elevated levels of Cystatin C were correlated with greater mortality rates. Therefore, the amount of serum cystatin C was a predictor of death that was not influenced by other factors. Our findings offer a new viewpoint on the prognostic significance of preoperative cystatin C. This necessitates more investigation into the pathophysiology and notable alterations in renal function following hip fractures in older individuals.

In order to investigate potential confounding variables in this study, we identified parameters that have an impact on mortality. Table 2 displays the primary determinants influencing the prognosis. Previous studies have identified several risk variables, including age [31], sex [4], fracture classification [31], aCCI [32], CHD [33], arrhythmia [34,35], cancer [36], dementia [37], COPD [38], time to operation [39], treatment strategy [40], transfusion [41] and hospital stay [42]. Furthermore, our study revealed significant correlations between mortality and injury mechanism, operation time, and infusion, as determined by the criteria of $P < 0.1$. We included the variable of cystatin C level, which has been specifically related to ischemic stroke [23]. Hence, numerous potential confounding factors were taken into account in this investigation.

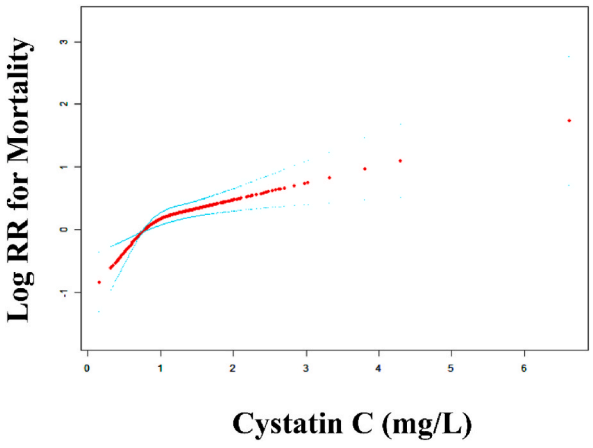


**Fig. 1.** Curve fitting between preoperative cystatin C and mortality.

**Table 4**
The nonlinearity association of cystatin C and mortality (N = 2394).

| Outcome | Total | Male | Female |
|---|---|---|---|
| **Fitting model by stand linear regression** | 2.19 (1.72, 2.79) <0.0001 | 2.42 (1.63, 3.62) <0.0001 | 1.79 (1.30, 2.48) 0.0004 |
| **Fitting model by two-piecewise linear regression** | | | |
| **Inflection point** | 1.62 | 1.62 | 1.62 |
| **< Inflection point** | 2.60 (1.92, 3.52) <0.0001 | 2.84 (1.72, 4.70) <0.0001 | 1.94 (1.22, 3.09) 0.0049 |
| **> Inflection point** | 1.54 (0.98, 2.42) 0.0588 | 1.80 (0.90, 3.60) 0.0982 | 1.61 (0.91, 2.84) 0.1015 |
| ***P* for log-likelihood ratio test** | 0.040 | 0.253 | 0.629 |

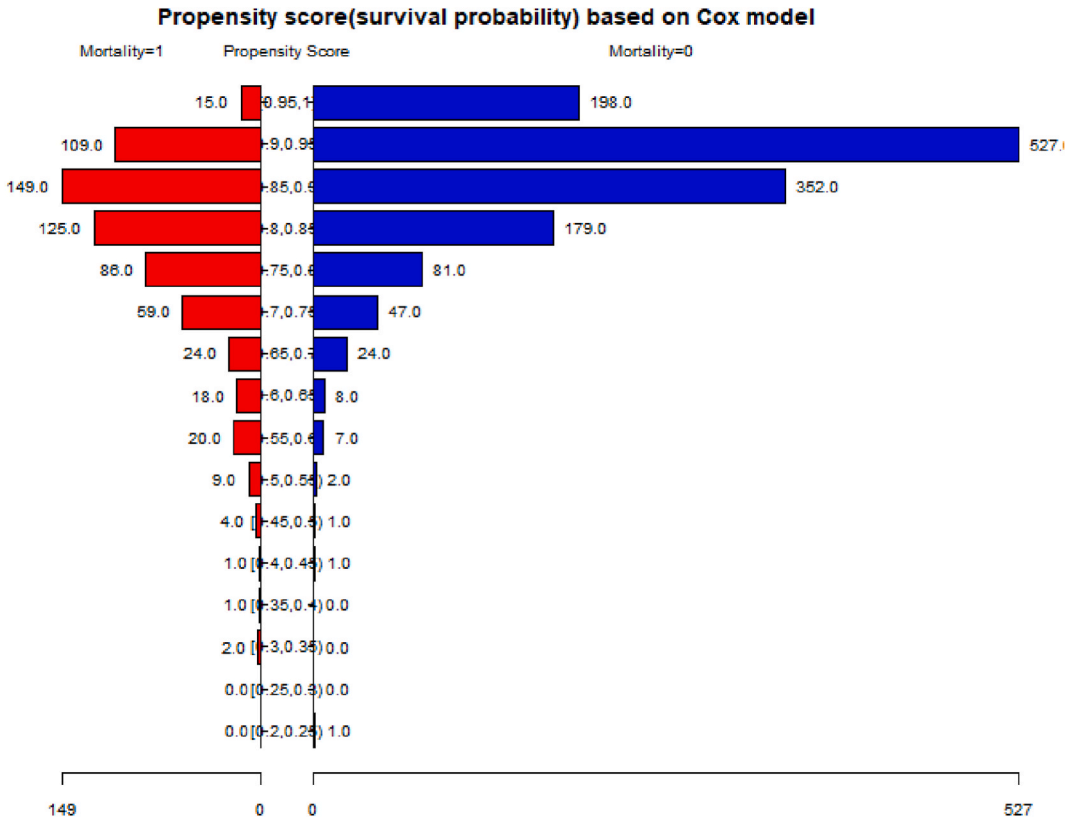


**Fig. 2.** The PSM of two groups.

**Tables 5**
PSM list.

| The variables used in calculating the propensity score | All the variables in this study |
|---|---|
| Propensity score algorithm | Cox regression model |
| C-statistical | 0.716 |
| 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: 603 cases |
| | No. of mortality = 0: 603 cases |
| | Total 1206 cases |

It is important to note that elevated levels of cystatin C are linked not only to higher mortality rates in hip fracture patients, but also to the mortality of patients with "shrunken pore syndrome" or other "selective glomerular filtration syndromes." These syndromes are characterized by a decrease in the ratio of cystatin C to creatinine in the estimated glomerular filtration rate (eGFR), without any non-renal factors affecting cystatin C or creatinine [29,43–45].

**Tables 6**
The balance test of PSM (N = 1206).

| Variables | Survival (603) | Dead (603) | Standardized diff. | *P*-value |
|---|---|---|---|---|
| **Age (year)** | 83.18 ± 4.68 | 81.96 ± 6.31 | 0.2199 | 0.0001[a] |
| **Sex** | | | 0.0551 | 0.37 |
| Male | 213 (35.3) | 229 (38) | | |
| Female | 390 (64.7) | 374 (62) | | |
| **Occupation** | | | | 0.0437 |
| Retirement | 384 (63.7) | 360 (59.7) | 0.0819 | |
| Farmer | 107 (17.7) | 142 (23.5) | 0.1438 | |
| Other | 112 (18.6) | 101 (16.7) | 0.0479 | |
| **History of allergy** | | | 0.0289 | 0.7384 |
| No | 586 (97.2) | 583 (96.7) | | |
| Yes | 17 (2.8) | 20 (3.3) | | |
| **Injury mechanism** | | | | 0.5767 |
| Falling | 591 (98) | 592 (98.2) | 0.0121 | |
| Accident | 9 (1.5) | 6 (1) | 0.0449 | |
| Other | 3 (0.5) | 5 (0.8) | 0.0409 | |
| **Fracture classification** | | | | 0.3042 |
| Intertrochanteric fracture | 441 (73.1) | 456 (75.6) | 0.057 | |
| Femoral neck fracture | 155 (25.7) | 136 (22.6) | 0.0737 | |
| Subtrochanteric fracture | 7 (1.2) | 11 (1.8) | 0.0547 | |
| **aCCI** | | | | <0.0001[a] |
| 2 | 0 (0) | 6 (1) | 0.1418 | |
| 3 | 14 (2.3) | 63 (10.4) | 0.3371 | |
| 4 | 267 (44.3) | 260 (43.1) | 0.0234 | |
| 5 | 229 (38) | 191 (31.7) | 0.1326 | |
| 6 | 78 (12.9) | 65 (10.8) | 0.0667 | |
| 7 | 13 (2.2) | 16 (2.7) | 0.0325 | |
| 8 | 2 (0.3) | 2 (0.3) | 0 | |
| **Hypertension** | | | 0.0398 | 0.5264 |
| No | 292 (48.4) | 304 (50.4) | | |
| Yes | 311 (51.6) | 299 (49.6) | | |
| **Diabetes** | | | 0.0741 | 0.2244 |
| No | 471 (78.1) | 489 (81.1) | | |
| Yes | 132 (21.9) | 114 (18.9) | | |
| **CHD** | | | 0.0067 | 0.9539 |
| No | 276 (45.8) | 274 (45.4) | | |
| Yes | 327 (54.2) | 329 (54.6) | | |
| **Arrhythmia** | | | 0.0105 | 0.9035 |
| No | 394 (65.3) | 397 (65.8) | | |
| Yes | 209 (34.7) | 206 (34.2) | | |
| **Hemorrhagic stroke** | | | 0.038 | 0.6597 |
| No | 591 (98) | 594 (98.5) | | |
| Yes | 12 (2) | 9 (1.5) | | |
| **Ischemic stroke** | | | 0.0283 | 0.6678 |
| No | 401 (66.5) | 409 (67.8) | | |
| Yes | 202 (33.5) | 194 (32.2) | | |
| **Cancer** | | | 0.06 | 0.372 |
| No | 583 (96.7) | 576 (95.5) | | |
| Yes | 20 (3.3) | 27 (4.5) | | |
| **Associated injuries** | | | 0.0357 | 0.6199 |
| No | 566 (93.9) | 571 (94.7) | | |
| Yes | 37 (6.1) | 32 (5.3) | | |
| **Dementia** | | | 0.0507 | 0.4507 |
| No | 573 (95) | 566 (93.9) | | |
| Yes | 30 (5) | 37 (6.1) | | |
| **COPD** | | | 0.0063 | 1 |
| No | 558 (92.5) | 557 (92.4) | | |
| Yes | 45 (7.5) | 46 (7.6) | | |
| **Hepatitis** | | | 0.0263 | 0.7612 |
| No | 579 (96) | 582 (96.5) | | |
| Yes | 24 (4) | 21 (3.5) | | |
| **Gastritis** | | | 0.0116 | 1 |
| No | 590 (97.8) | 591 (98) | | |
| Yes | 13 (2.2) | 12 (2) | | |
| **Treatment strategy** | | | | 0.3601 |
| ORIF | 439 (72.8) | 458 (76) | 0.0722 | |
| HA | 163 (27) | 143 (23.7) | 0.0763 | |
| THA | 1 (0.2) | 2 (0.3) | 0.0333 | |
| **Time to admission (h)** | 97.83 ± 334.16 | 86.72 ± 234.14 | 0.0385 | 0.5037 |

(*continued on next page*)

**Tables 6** (*continued*)

| Variables | Survival (603) | Dead (603) | Standardized diff. | *P*-value |
|---|---|---|---|---|
| **Time to operation (d)** | 4.39 ± 2.53 | 4.47 ± 2.78 | 0.0318 | 0.581 |
| **Transfusion (U)** | | | | 0.6729 |
| 0 | 262 (43.4) | 254 (42.1) | 0.0268 | |
| 1 | 2 (0.3) | 2 (0.3) | 0 | |
| 2 | 295 (48.9) | 300 (49.8) | 0.0166 | |
| 3 | 0 (0) | 2 (0.3) | 0.0816 | |
| 4 | 39 (6.5) | 43 (7.1) | 0.0264 | |
| 6 | 4 (0.7) | 2 (0.3) | 0.0472 | |
| 8 | 1 (0.2) | 0 (0) | 0.0576 | |
| **Blood loss (mL)** | 242.44 ± 157.93 | 244.78 ± 143.88 | 0.0155 | 0.7882 |
| **Infusion (mL)** | 1519.14 ± 361.83 | 1512.75 ± 374.07 | 0.0173 | 0.7633 |
| **Operation time (mins)** | 91.88 ± 34.28 | 92.10 ± 33.49 | 0.0064 | 0.9114 |
| **Stay in hospital (d)** | 9.06 ± 3.69 | 9.04 ± 3.43 | 0.0065 | 0.9099 |
| **Creatinine (umol/L)** | 75.00 ± 46.00 | 75.52 ± 31.44 | 0.0133 | 0.8177 |
| **Follow up (months)** | 46.33 ± 13.54 | 22.61 ± 16.03 | 1.599 | <0.0001 |

For continuous variables: (N) Mean ± SD, Standardized difference = abs(Mean1−Mean0)/sqrt((S1+S2)/2). For categorical variables: N (%), Standardized difference = abs(P1–P0)/sqrt((P1*(1-P1) + P0*(1-P0))/2) Use subset of data.

[a] Variables were not successfully matched.

**Tables 7**

Multivariate results in PSM(N = 1206).

| Outcome: | Fully-adjusted model | PSM model | PSM-adjusted model |
|---|---|---|---|
| **Fitting model by stand linear regression** | 2.19 (1.72, 2.79) <0.0001 | 1.22 (1.06, 1.40) 0.0060 | 1.23 (1.07, 1.42) 0.0034 |
| **Fitting model by two-piecewise linear regression** | | | |
| **Inflection point** | 1.62 | 1.59 | 1.57 |
| **<Inflection point** | 2.60 (1.92, 3.52) <0.0001 | 1.55 (1.18, 2.04) 0.0016 | 1.69 (1.27, 2.24) 0.0003 |
| **>Inflection point** | 1.54 (0.98, 2.42) 0.0588 | 0.98 (0.71, 1.34) 0.8834 | 0.93 (0.66, 1.29) 0.6510 |
| ***P* for log-likelihood ratio test** | 0.040 | 0.040 | 0.012 |

**Data in table**: HR (95 % CI) *P*-value; **Outcome variable:** mortality; **Exposed variables:** cystatin C; **Adjusted variables in PSM-adjusted model:** age, aCCI.

The average duration of follow-up in the current study was 37.62 months. Despite a 17.0 % loss to follow-up in our prospective trial, we discovered that the patients who were lost to follow-up exhibited similar demographic features to those who remained, indicating that the missing data was randomly distributed. In addition, we incorporated patients who were hospitalized prior to September 2019 in order to mitigate the impact of COVID-19 on admissions [46,47], and we verified that death was not attributed to COVID-19. In order to evaluate the correlation between cystatin C concentration and mortality, we conducted a linear regression analysis using an adjusted model. We took into account the factors that were previously examined in studies [4,23,31–42]. We adjusted for the factor with a significance level of $P < 0.1$ in the univariate analysis, and we thoroughly considered the variables that required adjustment. More precisely, we used a sensitivity analysis of the trend test within the linear model. Furthermore, due to the irregular HR interval of the model, we took into account the curve relationship and identified a clinical saturation impact and inflection point. Curve fitting was a more appropriate method than linear fitting for elucidating the correlation between preoperative cystatin C levels and mortality. More precisely, we used PSM analysis in the non-linear model and observed a high level of stability in the non-linear relationship.

There were certain constraints in our investigation. Due to the prospective design, loss to follow-up was unavoidable. In order to ascertain a prognosis, we made three attempts to communicate with patients who were unable to make phone calls. Furthermore, due to the absence of approximately 50 % of data in the postoperative cystatin C and creatinine, we were unable to include these variables in the analysis. In addition, a small number of patients experienced postoperative acute renal injury at our trauma hospital. We must investigate the correlation between postoperative renal function and mortality in the future.

To summarize, there is a non-linear relationship between preoperative cystatin C levels and mortality in geriatric hip fractures. Therefore, preoperative cystatin C can be taken as a predictor for the risk of death.

## Ethics approval and consent to participate

The Ethics Committee of the Honghui Hospital, Xi'an Jiaotong University approved this study (No. 202201009).

## Registered information

The study was registered with the Chinese Clinical Trial Registry (ChiCTR) with the identification number ChiCTR2200057323.

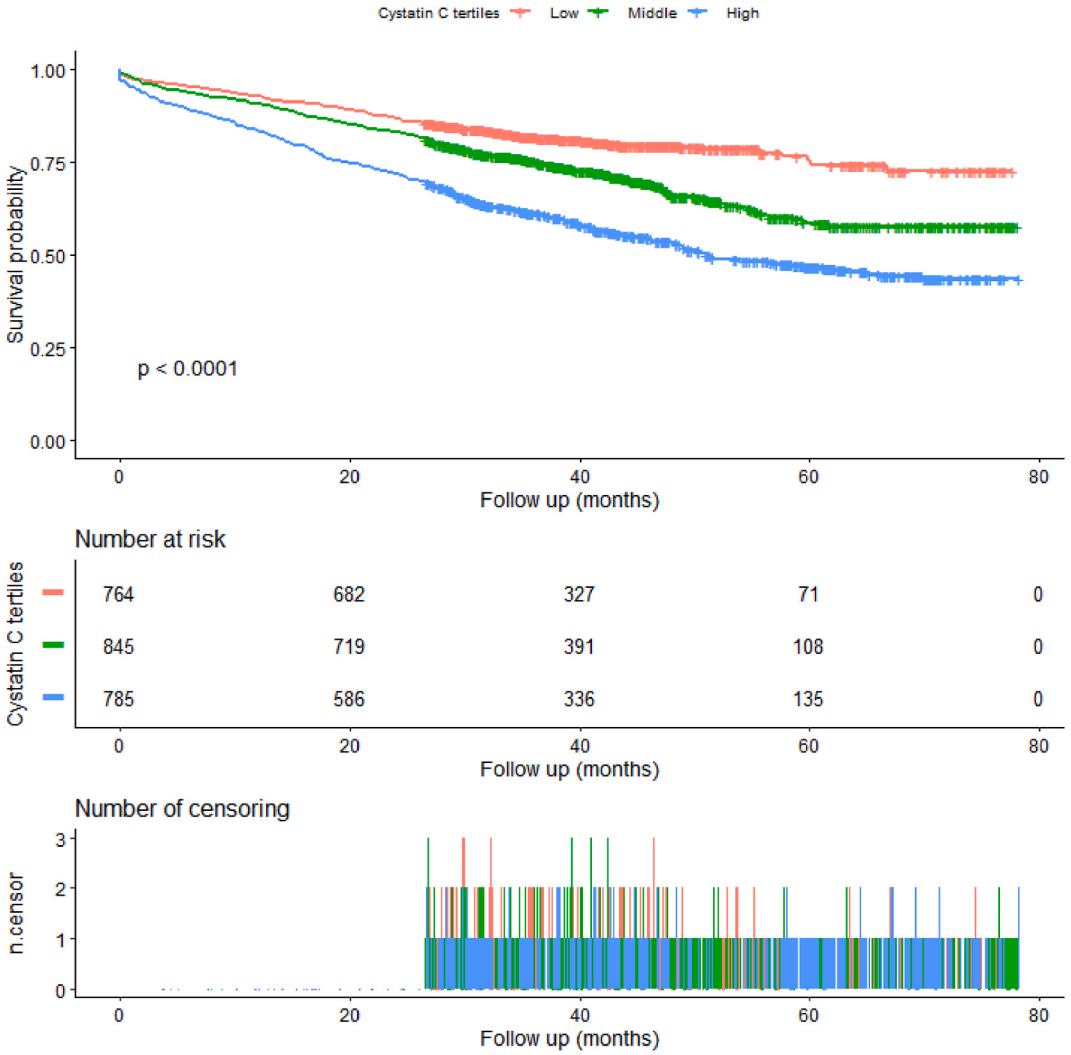


**Fig. 3.** Kaplan-Meier survival.

## Consent for publication

Not applicable.

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## Data availability statement

Xi'an Honghui Hospital provided the data. According to relevant regulations, the data cannot be shared but could request from the correspondence author.

## CRediT authorship contribution statement

**Bin-Fei Zhang:** Data curation, Formal analysis, Funding acquisition, Investigation, Methodology. **Lin Liu:** Data curation. **Ke Xu:** Data curation. **Peng Xu:** Data curation, Investigation, Methodology.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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