Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Association between serum uric acid-to-creatinine ratio and all-cause mortality in patients with coronary heart disease

Liwen Jiang
The First Affiliated Hospital of Shantou University Medical College
Jiaxin Xiao
The First Affiliated Hospital of Shantou University Medical College
Mengyue Lin
The First Affiliated Hospital of Shantou University Medical College
Pan Chen
The First Affiliated Hospital of Shantou University Medical College
Jiasheng Wen
The First Affiliated Hospital of Shantou University Medical College
Junshuang Tang
The First Affiliated Hospital of Shantou University Medical College
Shaobin Li
The First Affiliated Hospital of Shantou University Medical College
Sirui Han
The First Affiliated Hospital of Shantou University Medical College
Shiwan Wu
Shantou University Medical College
Haoxian Tang
The First Affiliated Hospital of Shantou University Medical College
Xiulian Deng
The First Affiliated Hospital of Shantou University Medical College
Bing Wang
Guangdong Aviation Satellite Technology Co., Ltd
XiaoQi Xiao
Guangdong Aviation Satellite Technology Co., Ltd
Xuerui Tan
doctortxr@126.com

The First Affiliated Hospital of Shantou University Medical College
Yequn Chen
The First Affiliated Hospital of Shantou University Medical College

Research Article

Keywords: Serum uric acid-to-creatinine ratio, all-cause mortality, coronary heart disease, two-stage Cox regression, nonlinear relationship

Posted Date: June 3rd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9402300/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

The serum uric acid-to-creatinine ratio (UCR), an indicator of renal function, has been linked to adverse cardiovascular outcomes. This study aimed to evaluate the association between UCR and the risk of all-cause mortality in patients with coronary heart disease (CHD).

Methods

This longitudinal cohort study included patients with CHD who were admitted to the First Affiliated Hospital of Shantou University Medical College between January 2020 and April 2024. Restricted cubic spline (RCS) analysis, multivariate Cox regression models, and threshold effect analyses were used to assess the association between UCR and mortality risk.

Results

A total of 5,850 patients with CHD were included, with a mean age of 66.5 ± 10.9 years. During a median follow-up period of 487.5 days (interquartile range [IQR]: 240–833), 501 (8.6%) deaths occurred. RCS analysis revealed a U-shaped relationship between UCR and all-cause mortality risk, with patients having a UCR range of 3.5 to 6.5 showing the lowest mortality risk. Multivariate Cox regression models indicated that patients with UCR < 3.5 had a 46% higher mortality risk (HR = 1.46, 95% CI: 1.18–1.81), while those with UCR ≥ 6.5 had a 56% higher mortality risk (HR = 1.56, 95% CI: 1.13–2.15). A negative association between UCR and all-cause mortality risk was observed in patients with UCR < 4.418 (HR = 0.77, 95% CI: 0.68–0.88), whereas a positive association was observed in those with UCR ≥ 4.418 (HR = 1.21, 95% CI: 1.06–1.38).

Conclusion

A U-shaped relationship was observed between UCR and all-cause mortality risk in patients with CHD. The findings suggest that UCR may serve as a prognostic indicator of CHD.

1. Introduction

Coronary artery disease (CAD) remains the leading cause of death worldwide and has consistently accounted for the highest proportion of cardiovascular disease mortality over the years[1, 2]. Coronary heart disease (CHD), characterized by coronary atherosclerosis, leads to vascular stenosis or occlusion, resulting in myocardial hypoxia and ischemia[3]. According to the Global Burden of Disease reports, the number of global cardiovascular disease cases increased by 252 million between 1990 and 2019, with deaths rising from 12.1 million to 18.6 million, among which ischemic heart disease was the leading cause of death[4]. With the rapid development of the global economy and population aging, the prevalence and mortality of CHD have

declined in developed countries[5], but continue to rise in many low-income and developing nations[6, 7], imposing a substantial burden on national health systems and economic growth.

Smoking, hypertension, hyperglycemia, and hyperlipidemia have long been recognized as major risk factors for CHD[8–11]. In recent years, serum uric acid (SUA) levels have also gained attention[12], though the evidence regarding their association with all-cause mortality remains inconsistent. Some studies have suggested a positive linear correlation[13, 14], while others have reported nonlinear associations[15–17]. For example, Yan et al., found a U-shaped relationship between SUA levels and all-cause mortality in patients with CHD[18]. Additionally, a negative association has been observed between SUA levels and all-cause and cardiovascular mortality in patients undergoing hemodialysis[19].

SUA, the final product of purine metabolism in humans, is primarily excreted by the kidneys[20], and is strongly influenced by renal function[21]. Serum creatinine (SCr), a commonly used indicator of renal function[22], is closely associated with cardiovascular diseases, such as heart failure, hypertension, and CHD[23, 24]. Combining SUA with SCr yields a new index, the uric acid-to-creatinine ratio (UCR), which more accurately reflects uric acid metabolism after adjusting for renal function[25]. Previous studies have demonstrated associations between UCR and conditions such as non-alcoholic fatty liver disease (NAFLD), metabolic syndrome, and ischemic stroke[26–28]. Furthermore, several studies have suggested that UCR is a better predictor of disease outcomes than SUA alone[29]. However, limited research has examined the association between UCR and all-cause mortality in patients with CHD. Therefore, this cohort study aimed to investigate the association between UCR and all-cause mortality in patients with CHD.

2. Materials and methods

2.1 Study Design and Population

This study was based on the CHD cohort data from the Eastern Guangdong Health and Disease Cohort Platform (EGHDCP). This cohort included patients diagnosed with CHD at the First Affiliated Hospital of Shantou University Medical College between January 2020 and April 2024. Figure 1 illustrates the population screening process. A total of 15,542 patients were screened. After excluding patients with missing SUA, SCr, or other essential data, 8,400 patients were deemed eligible. Among them, 2,550 patients without follow-up data were excluded, leaving 5,850 individuals for the final analysis.

2.2 Data collection

Baseline data of patients, including demographic characteristics, laboratory indicators, medication use, and comorbidities, were extracted from the clinical electronic management system of EGHDCP-CHD. The following variables were included: demographic characteristics including age, sex, smoking status (never, former, or now); laboratory indicators including systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose (FPG), homocysteine (HCY), blood urea nitrogen (BUN), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein (TP), albumin (ALB), globulin

(GLB), alkaline phosphatase (ALP); medication use including α-blockers, β-blockers, calcium channel blockers (CCB), statins, antiplatelet agents, anticoagulants, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), uric acid lowering drug, and diuretics; comorbidities including hypertension, diabetes, ischemic stroke, left heart failure, and renal dysfunction, which were identified based on diagnoses in the medical records. Among them, hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg or current use of antihypertensive medications. Diabetes was diagnosed based on medical history, laboratory results (FPG ≥ 7.0 mmol/L or glycosylated hemoglobin [HbA1c] ≥ 6.5%) or current use of antidiabetic therapy.

2.3 Exposure and outcome

The UCR was calculated as SUA (μmol/L)/SCr (μmol/L). Restricted cubic spline (RCS) analysis was used to determine the cutoff values for grouping. Based on the intersection point between the shaded area (95% CI) and the line of HR = 1 in the results, the study population was divided into three groups: UCR < 3.5, 3.5–6.5, and ≥ 6.5. The outcome measure of this study was all-cause mortality. In the EGHDCP-CHD cohort, if patients died during hospitalization, the time of death was recorded; for participants who did not die during hospitalization, their survival status was collected through regular telephone follow-ups.

2.4 Statistical analysis

Baseline characteristics of the study population were described according to the UCR groups. Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range [IQR]), depending on their distribution, while categorical variables were expressed as frequencies (percentages). One-way analysis of variance, the Kruskal–Wallis H test, and the chi-square test were used to compare differences among groups.

To examine the association between UCR and all-cause mortality risk, multivariate Cox regression models were constructed using UCR as a categorical variable and adjusted for potential confounding factors. Model 1 adjusted for age, sex and smoking status. Model 2 further considered DBP, HCY, BUN, TC, TG, HDL-C, AST, ALT, TP, ALB, GLB, ALP. Model 3 additionally adjusted for comorbidities (hypertension, diabetes, ischemic stroke, left heart failure, renal dysfunction) and medication use (α-blockers, β-blockers, CCB, statins, antiplatelet agents, ACEI, diuretics). Considering the nonlinear relationship between UCR (as a continuous variable) and mortality risk identified in the RCS analysis, a threshold effect analysis was conducted using the two-stage Cox regression method. Furthermore, stratified analyses were performed to explore the heterogeneity of the association between UCR and all-cause mortality, including gender (male or female), age (< 60 years or ≥ 60 years), β-blockers (yes or no), CCB (yes or no), statins (yes or no), ARB (yes or no), antiplatelet agents (yes or no), diuretics (yes or no), hypertension (yes or no), and diabetes (yes or no). A series of sensitivity analyses were also conducted, excluding participants with estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2, hyperuricemia (male > 420 μmol/L or female > 360 μmol/L), either hyperuricemia or eGFR < 60 mL/min/1.73 m^2, ischemic stroke, or left heart failure, to assess the robustness of the findings.

All statistical analyses were performed using the R Statistical Software (http://www.R-project.org, The R Foundation) and Free Statistics software version 2.2.0. A two-sided test with $P < 0.05$ was considered statistically significant.

3. Results

A total of 5,850 patients with CHD were included in the study. The mean age was 66.5 ± 10.9 years, and 2,184 (37.3%) were women. The mean UCR was 4.4 ± 1.7. The proportions of patients with hypertension and diabetes were 63.6% and 39.9%, respectively, while 552 (9.4%) participants had renal dysfunction. During a median follow-up period of 487.5 days (IQR: 240–833), the all-cause mortality rate in the total population was 8.6% (n = 501) (Table 1).

Table 1
Baseline characteristics of the study population

Variables	Total (n = 5,850)	UCR			*P*-value
		< 3.5 (n = 1,544)	[3.5, 6.5) (n = 3,760)	≥ 6.5 (n = 546)	
Age (years)	66.5 ± 10.9	69.2 ± 11.1	65.9 ± 10.5	63.4 ± 12.0	< 0.001
Sex, male, n (%)	3666 (62.7)	1081 (70.0)	2348 (62.4)	237 (43.4)	< 0.001
Smoke status, n (%)					< 0.001
Never	3814 (65.2)	1000 (64.8)	2411 (64.1)	403 (73.8)	
Former	633 (10.8)	193 (12.5)	396 (10.5)	44 (8.1)	
Now	1403 (24.0)	351 (22.7)	953 (25.3)	99 (18.1)	
Systolic blood pressure (mmHg)	139.1 ± 23.4	142.1 ± 25.5	138.2 ± 22.6	137.1 ± 22.0	< 0.001
Diastolic blood pressure (mmHg)	83.3 ± 14.1	83.5 ± 14.8	83.3 ± 13.7	82.5 ± 14.7	0.407
Comorbidities, n (%)					
Hypertension	3719 (63.6)	1082 (70.1)	2307 (61.4)	330 (60.4)	< 0.001
Diabetes	2334 (39.9)	793 (51.4)	1354 (36.0)	187 (34.2)	< 0.001
Ischemic stroke	642 (11.0)	202 (13.1)	386 (10.3)	54 (9.9)	0.008
Left heart failure	571 (9.8)	227 (14.7)	283 (7.5)	61 (11.2)	< 0.001
Renal dysfunction	552 (9.4)	348 (22.5)	177 (4.7)	27 (4.9)	< 0.001
Medication, n (%)					
α-blockers	662 (11.3)	318 (20.6)	295 (7.8)	49 (9.0)	< 0.001
β-blockers	3665 (62.6)	958 (62.0)	2365 (62.9)	342 (62.6)	0.844
ACEI	1208 (20.6)	279 (18.1)	836 (22.2)	93 (17.0)	< 0.001
ARB	2463 (42.1)	694 (44.9)	1523 (40.5)	246 (45.1)	0.004
Calcium channel blockers	2337 (39.9)	725 (47.0)	1399 (37.2)	213 (39.0)	< 0.001
Diuretics	2113 (36.1)	733 (47.5)	1155 (30.7)	225 (41.2)	< 0.001
Statins	4997 (85.4)	1304 (84.5)	3249 (86.4)	444 (81.3)	0.003
Anticoagulants	4303 (73.6)	1088 (70.5)	2781 (74.0)	434 (79.5)	< 0.001

Data are shown as mean ± standard deviation (SD) or median (IQR) for continuous variables and proportions (%) for categorical variables. ARB, angiotensin receptor blockers; ACEI, angiotensin-converting enzyme inhibitors; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SUA, serum uric acid; SCr, serum creatinine; UCR, uric acid-to-creatinine ratio.

Variables	Total (n = 5,850)	UCR			*P*-value
		< 3.5 (n = 1,544)	[3.5, 6.5) (n = 3,760)	≥ 6.5 (n = 546)	
Antiplatelet agents	4611 (78.8)	1201 (77.8)	2995 (79.7)	415 (76.0)	0.076
Uric acid lowering drug	381 (6.5)	100 (6.5)	208 (5.5)	73 (13.4)	< 0.001
Laboratory indicators					
Homocysteine (μmol/L)	13.4 (10.7, 16.8)	15.1 (11.7, 19.7)	13.1 (10.6, 16.1)	12.2 (9.9, 14.6)	< 0.001
Fasting plasma glucose (mmol/L)	6.4 ± 2.7	6.9 ± 3.5	6.2 ± 2.4	6.2 ± 2.4	< 0.001
Blood urea nitrogen (mmol/L)	6.1 (4.8, 7.7)	7.6 (5.5, 12.2)	5.8 (4.7, 7.1)	5.4 (4.4, 6.7)	< 0.001
Total cholesterol (mmol/L)	4.7 ± 1.4	4.5 ± 1.4	4.8 ± 1.3	5.0 ± 1.4	< 0.001
Triglyceride (mmol/L)	1.2 (0.9, 1.8)	1.2 (0.9, 1.7)	1.2 (0.9, 1.8)	1.4 (1.0, 2.0)	< 0.001
HDL-C (mmol/L)	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	< 0.001
LDL-C (mmol/L)	2.9 ± 1.0	2.7 ± 1.1	2.9 ± 1.0	3.0 ± 1.0	< 0.001
AST (U/L)	22.0 (17.6, 29.4)	22.0 (17.0, 30.7)	21.9 (17.7, 29.0)	22.7 (18.2, 30.5)	0.098
ALT (U/L)	21.1 (14.6, 32.8)	18.8 (12.5, 30.7)	21.5 (15.0, 32.6)	24.3 (16.6, 36.8)	< 0.001
Total protein (g/L)	65.5 ± 7.3	63.4 ± 7.9	66.3 ± 6.8	66.6 ± 8.0	< 0.001
Albumin (g/L)	37.8 ± 4.7	35.8 ± 5.0	38.5 ± 4.3	38.5 ± 5.0	< 0.001
Globulin (g/L)	28.0 ± 4.5	28.0 ± 4.6	27.9 ± 4.4	28.3 ± 4.4	0.064
Alkaline phosphatase (U/L)	78.0 (64.0, 96.2)	79.9 (64.1, 100.4)	77.0 (63.7, 94.5)	79.8 (66.7, 96.9)	< 0.001
SUA (μmol/L)	405.1 ± 128.4	340.1 ± 136.7	411.9 ± 105.3	542.4 ± 127.7	< 0.001
SCr (μmol/L)	86.6 (72.3, 107.0)	113.1 (87.1, 195.0)	83.5 (71.7, 98.4)	69.3 (61.2, 78.3)	< 0.001
UCR	4.4 ± 1.7	2.5 ± 0.9	4.8 ± 0.8	7.6 ± 1.2	< 0.001
All-cause mortality, n (%)	501 (8.6)	242 (15.7)	210 (5.6)	49 (9.0)	< 0.001

Data are shown as mean ± standard deviation (SD) or median (IQR) for continuous variables and proportions (%) for categorical variables. ARB, angiotensin receptor blockers; ACEI, angiotensin-converting enzyme inhibitors; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SUA, serum uric acid; SCr, serum creatinine; UCR, uric acid-to-creatinine ratio.

3.1 Exploration of group cutoffs and baseline characteristics

We first explored the potential relationship using RCS analysis, which revealed a nonlinear U-shaped relationship between UCR and all-cause mortality (*P* for non-linearity < 0.001, Fig. 2). Accordingly, the population was divided into three groups according to UCR levels: < 3.5, 3.5–6.5, and ≥ 6.5, with the second group serving as the reference category.

Table 1 presents the baseline characteristics of patients in each UCR group. The mean UCR values for the three groups were 2.5 ± 0.9, 4.8 ± 0.8, and 7.6 ± 1.2, and the corresponding all-cause mortality rates were 15.7%, 5.6%, and 9.0% (*P* < 0.001). Patients with a lower UCR were older and had a higher proportion of males than the reference group. They also exhibited higher levels of elevated levels of SBP, HCY, FPG, BUN, ALP, and SCr, as well as lower levels of TC, LDL-C, ALT, TP, ALB, and SUA. Statistically significant differences were observed among the three groups regarding comorbidities and medication use.

3.2 Association between UCR and all-cause mortality risk

Both the low and high UCR groups showed increased risks of all-cause mortality among patients with CHD (Table 2). In the crude model, patients with a lower UCR (< 3.5) had a 2-fold higher risk of mortality (HR = 3.00, 95% CI: 2.49–3.61), while those with a higher UCR (≥ 6.5) had an 83% higher risk (HR = 1.83, 95% CI: 1.34–2.50). After adjusting for potential confounding factors, including demographic variables, laboratory parameters, comorbidities, and medication use, the associations were attenuated but remained significant. Individuals with a lower UCR had a 46% higher risk, and those with a higher UCR had a 56% higher risk of mortality compared to the reference group (Table 2).

Table 2
Association between UCR and all-cause mortality in patients with coronary heart disease

UCR	Crude model		Model 1		Model 2		Model 3	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
< 3.5	3.00 (2.49 ~ 3.61)	< 0.001	2.29 (1.90 ~ 2.77)	< 0.001	1.47 (1.19 ~ 1.81)	< 0.001	1.46 (1.18 ~ 1.81)	< 0.001
[3.5, 6.5)	Reference		Reference		Reference		Reference	
≥ 6.5	1.83 (1.34 ~ 2.50)	< 0.001	2.09 (1.53 ~ 2.87)	< 0.001	1.85 (1.35 ~ 2.54)	< 0.001	1.56 (1.13 ~ 2.15)	0.007

Results were derived from Cox regression. Model 1 adjusted for age, sex, smoking status. Model 2 further adjusted for diastolic blood pressure, homocysteine, blood urea nitrogen, total cholesterol, triglyceride, HDL-C, AST, ALT, total protein, albumin, globulin, and alkaline phosphatase. Model 3 was adjusted for the variables in model 2 plus comorbidities and medication use, including hypertension, diabetes, ischemic stroke, left heart failure, renal dysfunction, α-blockers, β-blockers, calcium channel blockers, statins, antiplatelet agents, ACEI, and diuretics. ACEI, angiotensin-converting enzyme inhibitors; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL-C, high-density lipoprotein cholesterol; UCR, uric acid-to-creatinine ratio.

3.3 Nonlinear relationship and two-piecewise Cox models

A significant nonlinear, U-shaped relationship between UCR and all-cause mortality risk was observed (*P* for non-linearity < 0.001, Fig. 2). We further examined this association using two-piecewise Cox proportional hazards models. As expected, the mortality risk decreased as the UCR increased when the value was lower than 4.418 (HR = 0.77, 95% CI: 0.68–0.88), whereas the risk increased when the UCR was higher than 4.418 (HR = 1.21, 95% CI: 1.06–1.38). Furthermore, the two-stage regression model exhibited superior performance compared to the one-way regression model (*P* for likelihood ratio test < 0.001, Table 3).

Table 3
Threshold effect analysis of UCR on all-cause mortality

UCR	**Fully adjusted model**	
	HR (95% CI)	***P*-value**
< 4.418	0.77 (0.68 ~ 0.88)	< 0.001
≥ 4.418	1.21 (1.06 ~ 1.38)	0.005
Likelihood Ratio test	-	< 0.001

Results were derived from two-stage Cox regression. Fully adjusted model included age, sex, smoking status, diastolic blood pressure, homocysteine, blood urea nitrogen, total cholesterol, triglyceride, HDL-C, AST, ALT, total protein, albumin, globulin, alkaline phosphatase, hypertension, diabetes, ischemic stroke, left heart failure, renal dysfunction, α-blockers, β-blockers, calcium channel blockers, statins, antiplatelet agents, ACEI, and diuretics. ACEI, angiotensin-converting enzyme inhibitors; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL-C, high-density lipoprotein cholesterol; UCR, uric acid-to-creatinine ratio.

3.4 Subgroup analysis and sensitivity analysis

The results of the subgroup analyses (Fig. 3) showed that the association between UCR and all-cause mortality risk was consistent across subgroups defined by sex, age, β-blockers, CCB, statins, hypertension, and diabetes status. Significant interactions were observed in the ARB, antiplatelet agents, and diuretics subgroups. The association between UCR and mortality risk was stronger in patients using ARB or antiplatelet agents and in those not taking diuretics. Sensitivity analyses, excluding individuals with eGFR < 30 mL/min/1.73 m^2, hyperuricemia, either hyperuricemia or eGFR < 60 mL/min/1.73 m^2, ischemic stroke, or left heart failure, confirmed the robustness of the main results, showing that both low and high UCR were associated with an increased risk of all-cause mortality (Table 4).

Table 4
Sensitivity analyses for the association between UCR and all-cause mortality in patients with coronary heart disease

UCR	Crude Model		Model 1		Model 2		Model 3	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Exclude eGFR < 30 mL/min/1.73 m^2 (n = 5,431)								
< 3.5	2.09 (1.67 ~ 2.60)	< 0.001	1.55 (1.23 ~ 1.94)	< 0.001	1.28 (1.01 ~ 1.61)	0.039	1.35 (1.07 ~ 1.71)	0.012
[3.5, 6.5)	Reference		Reference		Reference		Reference	
≥ 6.5	1.87 (1.37 ~ 2.56)	< 0.001	2.22 (1.62 ~ 3.05)	< 0.001	2.04 (1.48 ~ 2.81)	< 0.001	1.69 (1.22 ~ 2.34)	0.002
Exclude hyperuricemia (n = 3,022)								
< 3.5	2.45 (1.87 ~ 3.21)	< 0.001	1.83 (1.39 ~ 2.42)	< 0.001	1.41 (1.06 ~ 1.89)	0.020	1.41 (1.05 ~ 1.90)	0.024
[3.5, 6.5)	Reference		Reference		Reference		Reference	
≥ 6.5	3.77 (1.38 ~ 10.26)	0.010	4.90 (1.79 ~ 13.39)	0.002	6.07 (2.19 ~ 16.82)	0.001	5.87 (2.10 ~ 16.43)	0.001
Exclude hyperuricemia or eGFR < 60 mL/min/1.73 m^2 (n = 2,640)								
< 3.5	1.74 (1.26 ~ 2.39)	0.001	1.28 (0.92 ~ 1.79)	0.138	1.11 (0.79 ~ 1.55)	0.559	1.18 (0.83 ~ 1.67)	0.354
[3.5, 6.5)	Reference		Reference		Reference		Reference	
≥ 6.5	3.72 (1.37 ~ 10.15)	0.010	4.90 (1.79 ~ 13.42)	0.002	7.36 (2.61 ~ 20.78)	< 0.001	6.56 (2.28 ~ 18.87)	< 0.001
Exclude ischemic stroke (n = 5,208)								

Model 1 adjusted for age, sex, smoking status. Model 2 further adjusted for diastolic blood pressure, homocysteine, blood urea nitrogen, total cholesterol, triglyceride, HDL-C, AST, ALT, total protein, albumin, globulin, alkaline phosphatase. Model 3 was adjusted for the variables in model 2 plus comorbidities and medication use, including hypertension, diabetes, ischemic stroke, left heart failure, renal dysfunction, α-blockers, β-blockers, calcium channel blockers, statins, antiplatelet agents, ACEI, and diuretics. ACEI, angiotensin-converting enzyme inhibitors; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL-C, high-density lipoprotein cholesterol; UCR, uric acid-to-creatinine ratio.

UCR	Crude Model		Model 1		Model 2		Model 3	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Exclude eGFR < 30 mL/min/1.73 m^2 (n = 5,431)								
< 3.5	2.80 (2.28 ~ 3.45)	< 0.001	2.18 (1.76 ~ 2.70)	< 0.001	1.33 (1.05 ~ 1.68)	0.018	1.35 (1.06 ~ 1.72)	0.016
[3.5, 6.5)	Reference		Reference		Reference		Reference	
≥ 6.5	1.70 (1.20 ~ 2.42)	0.003	1.93 (1.35 ~ 2.75)	< 0.001	1.69 (1.18 ~ 2.42)	0.004	1.43 (1.00 ~ 2.06)	0.053
Exclude left heart failure (n = 5,279)								
< 3.5	2.86 (2.30 ~ 3.56)	< 0.001	2.18 (1.75 ~ 2.73)	< 0.001	1.40 (1.10 ~ 1.79)	0.007	1.39 (1.08 ~ 1.78)	0.011
[3.5, 6.5)	Reference		Reference		Reference		Reference	
≥ 6.5	1.82 (1.26 ~ 2.62)	0.001	2.15 (1.49 ~ 3.12)	< 0.001	2.09 (1.44 ~ 3.03)	< 0.001	1.85 (1.27 ~ 2.69)	0.001

Model 1 adjusted for age, sex, smoking status. Model 2 further adjusted for diastolic blood pressure, homocysteine, blood urea nitrogen, total cholesterol, triglyceride, HDL-C, AST, ALT, total protein, albumin, globulin, alkaline phosphatase. Model 3 was adjusted for the variables in model 2 plus comorbidities and medication use, including hypertension, diabetes, ischemic stroke, left heart failure, renal dysfunction, α-blockers, β-blockers, calcium channel blockers, statins, antiplatelet agents, ACEI, and diuretics. ACEI, angiotensin-converting enzyme inhibitors; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL-C, high-density lipoprotein cholesterol; UCR, uric acid-to-creatinine ratio.

4. Discussion

This cohort study revealed a U-shaped relationship between UCR and the risk of all-cause mortality in patients with CHD, indicating that both lower and higher UCR levels were associated with increased mortality risk. Furthermore, using a two-piecewise Cox regression analysis, we observed that the direction of the association changed when a cutoff value of 4.418 was applied. These findings suggest that UCR could serve as a useful indicator for evaluating the prognosis of patients with CHD, and maintaining a moderate UCR level may be beneficial.

SUA is the final product of purine metabolism, and its stable SUA levels depend on a dynamic balance of exogenous dietary intake, endogenous production, renal excretion, and reabsorption[20]. Creatinine, a product of muscle metabolism, is commonly used to assess kidney function.[22] Previous studies have demonstrated associations between UCR and metabolic syndrome, cognitive function, and NAFLD[26, 27, 30]. The relationship between UCR and cardiovascular diseases has also gained increasing attention, with evidence showing that

UCR is associated with all-cause mortality in the general adult population[31]. A study based on the NHANES database reported a reverse-J-shaped relationship between UCR and mortality risk in patients with hypertension[32], which aligns with our findings. Conversely, a small-sample retrospective study found that a higher UCR was independently associated with an increased risk of all-cause mortality in elderly patients undergoing hemodialysis[29]. This discrepancy may be attributed to differences in study populations. It could be speculated that patients undergoing hemodialysis tended to have severe renal dysfunction; therefore, the UCR level and the damage mechanism would have changed.

Few studies have specifically examined the relationship between UCR and CHD. Some investigations have reported a U-shaped association between SUA levels and all-cause mortality in patients with CHD[18, 33]. A study involving 330 elderly patients with acute myocardial infarction showed that a lower UCR was associated with an increased risk of adverse in-hospital outcomes, including cardiovascular events and all-cause mortality[34]. This observation may be explained by UCR accounting for renal function effects, or by differences between patients with a single acute myocardial infarction and the broader CHD population. Because UCR reflects both uric acid excretion and reabsorption, it provides a more comprehensive assessment of prognosis. However, whether UCR is superior to SUA alone remains uncertain and warrants further investigation.

In this study, UCR and all-cause mortality showed significant interactions with ARB, antiplatelet agents, and diuretics. ARB use was associated with an increased mortality risk when UCR was low, and the opposite pattern was observed when UCR was high. Conversely, diuretic use increased the risk of mortality when UCR was high and reduced it when UCR was low. Certain ARB medications can inhibit uric acid transporters in the renal proximal convoluted tubules[35, 36], thereby decreasing the reabsorption of SUA and enhancing its excretion, ultimately leading to lower SUA levels. In contrast, diuretic use reduces blood volume and activates the renin-angiotensin-aldosterone system, which increases uric acid reabsorption and circulating SUA levels[37–39]. Furthermore, the association between UCR and mortality persisted even after excluding individuals with hyperuricemia and elevated creatinine levels, indicating that in patients with normal SUA and SCr levels, UCR levels should still be considered for prognostic assessment.

Although this study demonstrates an association between UCR and all-cause mortality in patients with CHD, the mechanism underlying this nonlinear relationship remains unclear. UCR reflects SUA levels after accounting for renal function, and hyperuricemia is known to be associated with hypertension, diabetes, and various metabolic syndromes[40]. A possible mechanism is that SUA possesses both antioxidant and pro-oxidant properties[41]. When SUA levels rise, urate accumulation in tissues can trigger inflammation, oxidative stress, and activation of the renin-angiotensin system in endothelial cells, resulting in endothelial dysfunction[42, 43]. Additionally, elevated SUA inhibits endothelial nitric oxide production[44], reducing antioxidant defense and increasing mortality risk in patients with CHD. Low SUA levels can also have adverse effects[45], reflecting reduced antioxidant capacity and impaired free radical scavenging[46]. Elevated free radical levels can exacerbate oxidative stress, eventually increasing the risk of death. Further research is warranted to elucidate and confirm these underlying mechanisms.

To our knowledge, this study is the first to investigate the association between UCR and the risk of all-cause mortality in patients with CHD. However, several limitations should be acknowledged. First, as a single-center observational cohort study, the generalizability of our findings is limited, and the inherent nature of observational designs restricts causal inference. Second, the absence of data on dietary intake and nutritional status may have introduced potential bias. Third, despite adjusting for multiple covariates, the influence of residual or unmeasured confounders cannot be entirely excluded.

5. Conclusion

In summary, this study identified a significant U-shaped nonlinear relationship between UCR and the risk of all-cause mortality in patients with CHD, with a tipping point of 4.418. UCR may serve as a valuable prognostic marker in this population, and maintaining a moderate UCR level could help reduce mortality risk.

Abbreviations

UCR uric acid-to-creatinine ratio, CHD coronary heart disease, RCS restricted cubic spline, CAD coronary artery disease, SUA serum uric acid, SCr serum creatinine, NAFLD non-alcoholic fatty liver disease, EGHDCP Eastern Guangdong Health and Disease Cohort Platform, SBP systolic blood pressure, DBP diastolic blood pressure, FPG fasting plasma glucose, HCY homocysteine, BUN blood urea nitrogen, TC total cholesterol, TG triglyceride, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, AST aspartate aminotransferase, ALT alanine aminotransferase, TP total protein, ALB albumin, GLB globulin, ALP alkaline phosphatase, CCB calcium channel blockers, ACEI angiotensin-converting enzyme inhibitors, ARB angiotensin receptor blockers, HbA1c glycosylated hemoglobin, SD standard deviation, IQR interquartile range, eGFR estimated glomerular filtration rate.

Declarations

Ethics approval and consent to participate: This study was conducted in accordance with the Declaration of Helsinki. CHD sub-cohort from the Eastern Guangdong Health and Disease Cohort Platform (EGHDCP-CHD) research was approved by the Medical Ethics Committee of the First Affiliated Hospital of Shantou University Medical College (Project ID: B-2025-012). Written informed consent was obtained from all participants.

Clinical trial number: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: The datasets generated and/or analysed during the current study are not publicly available due to institutional data sharing policy restrictions but are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: This study was supported by National Natural Science Foundation of China (No. 82073659); Guangdong Province Science and Technology Special Fund (2022-124-6); Guangdong Provincial Innovation Team (2024KCXTD019).

Authors' contributions: Conceptualization, LWJ, JXX, MYL, YQC, and XRT; Methodology, LWJ, JXX, and MYL; Formal analysis, LWJ, JXX, and MYL; Data Curation, LWJ, JXX, MYL, HXT, XLD, BW, and XQX; Writing-Original Draft Preparation, LWJ, JXX and MYL; Writing-Review & Editing, LWJ, MYL, PC, JSW, JST, SBL, SRH, SWW, YQC, and XRT.

Acknowledgement: Not applicable.

References

1. Nichols M, Townsend N, Scarborough P, Rayner M. Cardiovascular disease in Europe 2014: epidemiological update. Eur Heart J. 2014;35(42):2950–9.
2. Roth GA, Mensah GA, Fuster V. The Global Burden of Cardiovascular Diseases and Risks: A Compass for Global Action. J Am Coll Cardiol. 2020;76(25):2980–1.
3. Falk E. Pathogenesis of Atherosclerosis. J Am Coll Cardiol. 2006;47(8):C7–12.
4. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton AZ, Benjamin EJ, Benziger CP, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: Update From the GBD 2019 Study. J Am Coll Cardiol. 2020;76(25):2982–3021.
5. Wilmot KA, O'Flaherty M, Capewell S, Ford ES, Vaccarino V. Coronary Heart Disease Mortality Declines in the United States From 1979 Through 2011: Evidence for Stagnation in Young Adults, Especially Women. Circulation. 2015;132(11):997–1002.
6. Mi Y, Xue Z, Qu S, Yin Y, Huang J, Kou R, Wang X, Luo S, Li W, Tang Y. The economic burden of coronary heart disease in mainland China. Public Health. 2023;224:140–51.
7. Zhu KF, Wang YM, Zhu JZ, Zhou QY, Wang NF. National prevalence of coronary heart disease and its relationship with human development index: A systematic review. Eur J Prev Cardiol. 2016;23(5):530–43.
8. Fuchs FD, Whelton PK. High Blood Pressure and Cardiovascular Disease. Hypertension. 2020;75(2):285–92.
9. Hindy G, Wiberg F, Almgren P, Melander O, Orho-Melander M. Polygenic Risk Score for Coronary Heart Disease Modifies the Elevated Risk by Cigarette Smoking for Disease Incidence. Circ Genom Precis Med. 2018;11(1):e001856.
10. Janjusevic M, Fluca AL, Gagno G, Pierri A, Padoan L, Sorrentino A, Beltrami AP, Sinagra G, Aleksova A. Old and Novel Therapeutic Approaches in the Management of Hyperglycemia, an Important Risk Factor for Atherosclerosis. Int J Mol Sci 2022, 23(4).
11. Ripatti P, Rämö JT, Mars NJ, Fu Y, Lin J, Söderlund S, Benner C, Surakka I, Kiiskinen T, Havulinna AS, et al. Polygenic Hyperlipidemias and Coronary Artery Disease Risk. Circ Genom Precis Med. 2020;13(2):e002725.
12. Braga F, Pasqualetti S, Ferraro S, Panteghini M. Hyperuricemia as risk factor for coronary heart disease incidence and mortality in the general population: a systematic review and meta-analysis. Clin Chem Lab Med. 2016;54(1):7–15.
13. Wang R, Song Y, Yan Y, Ding Z. Elevated serum uric acid and risk of cardiovascular or all-cause mortality in people with suspected or definite coronary artery disease: A meta-analysis. Atherosclerosis. 2016;254:193–9.

14. Zhao G, Huang L, Song M, Song Y. Baseline serum uric acid level as a predictor of cardiovascular disease related mortality and all-cause mortality: a meta-analysis of prospective studies. Atherosclerosis. 2013;231(1):61–8.
15. Cho SK, Chang Y, Kim I, Ryu S. U-Shaped Association Between Serum Uric Acid Level and Risk of Mortality: A Cohort Study. Arthritis Rheumatol. 2018;70(7):1122–32.
16. Crawley WT, Jungels CG, Stenmark KR, Fini MA. U-shaped association of uric acid to overall-cause mortality and its impact on clinical management of hyperuricemia. Redox Biol. 2022;51:102271.
17. Hu L, Hu G, Xu BP, Zhu L, Zhou W, Wang T, Bao H, Cheng X. U-Shaped Association of Serum Uric Acid With All-Cause and Cause-Specific Mortality in US Adults: A Cohort Study. J Clin Endocrinol Metab 2020, 105(1).
18. Yan X, Gong J, Wang Z, Wu Q, Qi C, Wang F. Serum uric acid was non-linearly associated with the risk of all-cause and cardiovascular death in individuals with coronary heart disease: a large prospective cohort study. Front Endocrinol (Lausanne). 2023;14:1278595.
19. Latif W, Karaboyas A, Tong L, Winchester JF, Arrington CJ, Pisoni RL, Marshall MR, Kleophas W, Levin NW, Sen A, et al. Uric acid levels and all-cause and cardiovascular mortality in the hemodialysis population. Clin J Am Soc Nephrol. 2011;6(10):2470–7.
20. Copur S, Demiray A, Kanbay M. Uric acid in metabolic syndrome: Does uric acid have a definitive role? Eur J Intern Med. 2022;103:4–12.
21. Mijailovic NR, Vesic K, Borovcanin MM. The Influence of Serum Uric Acid on the Brain and Cognitive Dysfunction. Front Psychiatry. 2022;13:828476.
22. Chen X, Jin H, Wang D, Liu J, Qin Y, Zhang Y, Zhang Y, Xiang Q. Serum creatinine levels, traditional cardiovascular risk factors and 10-year cardiovascular risk in Chinese patients with hypertension. Front Endocrinol (Lausanne). 2023;14:1140093.
23. Freedman BI, Iskandar SS, Appel RG. The link between hypertension and nephrosclerosis. Am J Kidney Dis. 1995;25(2):207–21.
24. Kazory A. The Congestion-Creatinine Interplay in Acute Heart Failure: Time to Move Up to the Next Level. Am J Med. 2020;133(3):259–60.
25. Li M, Gu L, Yang J, Lou Q. Serum uric acid to creatinine ratio correlates with β-cell function in type 2 diabetes. Diabetes Metab Res Rev. 2018;34(5):e3001.
26. Cao T, Tong C, Halengbieke A, Ni X, Tang J, Zheng D, Guo X, Yang X. Serum uric acid to creatinine ratio and metabolic syndrome in middle-aged and elderly population: Based on the 2015 CHARLS. Nutr Metab Cardiovasc Dis. 2023;33(7):1339–48.
27. Sookoian S, Pirola CJ. The serum uric acid/creatinine ratio is associated with nonalcoholic fatty liver disease in the general population. J Physiol Biochem. 2023;79(4):891–9.
28. Xu J, Jiang X, Liu Q, Liu J, Fang J, He L. Lower serum uric acid to serum creatinine ratio as a predictor of poor functional outcome after mechanical thrombectomy in acute ischaemic stroke. Eur J Neurol. 2024;31(7):e16296.
29. Ding Z, Fan Y, Yao C, Gu L. The association between the serum uric acid to creatinine ratio and all-cause mortality in elderly hemodialysis patients. BMC Nephrol. 2022;23(1):177.

30. Chen G, Tong L, Ye Q. Association between the serum uric acid/serum creatinine ratio and cognitive function in older adults: NHANES in the United States. Sci Rep. 2024;14(1):16312.
31. She D, Xu W, Liu J, Zhang Z, Fang P, Li R, Kong D, Xuan M, Liu Q, Pan MY, et al. Serum Uric Acid to Creatinine Ratio and Risk of Metabolic Syndrome in Patients with Overweight/Obesity. Diabetes Metab Syndr Obes. 2023;16:3007–17.
32. Zeng Y, Chen Y, Li J, Chen L. Nonlinear association between the serum uric acid-to-creatinine ratio and all cause mortality in patients with hypertension: a ten-year cohort study using the NHANES database. Sci Rep. 2024;14(1):31423.
33. Zheng Y, Ou J, Huang D, Zhou Z, Dong X, Chen J, Liang D, Liu J, Liu Y, Chen J, et al. The U-Shaped Relationship Between Serum Uric Acid and Long-Term All-Cause Mortality in Coronary Artery Disease Patients: A Cohort Study of 33,034 Patients. Front Cardiovasc Med. 2022;9:858889.
34. Jiang L, Jin J, He X, Hu X, Guo L, Chen G, Zhou Y. The association between serum uric acid / serum creatinine ratio and in-hospital outcomes in elderly patients with acute myocardial infarction. BMC Cardiovasc Disord. 2024;24(1):52.
35. Hamada T, Ichida K, Hosoyamada M, Mizuta E, Yanagihara K, Sonoyama K, Sugihara S, Igawa O, Hosoya T, Ohtahara A, et al. Uricosuric action of losartan via the inhibition of urate transporter 1 (URAT 1) in hypertensive patients. Am J Hypertens. 2008;21(10):1157–62.
36. Nakashima M, Uematsu T, Kosuge K, Kanamaru M. Pilot study of the uricosuric effect of DuP-753, a new angiotensin II receptor antagonist, in healthy subjects. Eur J Clin Pharmacol. 1992;42(3):333–5.
37. Ben Salem C, Slim R, Fathallah N, Hmouda H. Drug-induced hyperuricaemia and gout. Rheumatology (Oxford). 2017;56(5):679–88.
38. Misra D, Zhu Y, Zhang Y, Choi HK. The independent impact of congestive heart failure status and diuretic use on serum uric acid among men with a high cardiovascular risk profile: a prospective longitudinal study. Semin Arthritis Rheum. 2011;41(3):471–6.
39. Weinman EJ, Eknoyan G, Suki WN. The influence of the extracellular fluid volume on the tubular reabsorption of uric acid. J Clin Invest. 1975;55(2):283–91.
40. Chen Y, Li H, Cai Y, Wang K, Wang Y. Anti-hyperuricemia bioactive peptides: a review on obtaining, activity, and mechanism of action. Food Funct. 2024;15(11):5714–36.
41. Gherghina ME, Peride I, Tiglis M, Neagu TP, Niculae A, Checherita IA. Uric Acid and Oxidative Stress-Relationship with Cardiovascular, Metabolic, and Renal Impairment. Int J Mol Sci 2022, 23(6).
42. Kushiyama A, Nakatsu Y, Matsunaga Y, Yamamotoya T, Mori K, Ueda K, Inoue Y, Sakoda H, Fujishiro M, Ono H, et al. Role of Uric Acid Metabolism-Related Inflammation in the Pathogenesis of Metabolic Syndrome Components Such as Atherosclerosis and Nonalcoholic Steatohepatitis. Mediators Inflamm. 2016;2016:8603164.
43. Yu MA, Sánchez-Lozada LG, Johnson RJ, Kang DH. Oxidative stress with an activation of the renin-angiotensin system in human vascular endothelial cells as a novel mechanism of uric acid-induced endothelial dysfunction. J Hypertens. 2010;28(6):1234–42.
44. Roumeliotis S, Roumeliotis A, Dounousi E, Eleftheriadis T, Liakopoulos V. Dietary Antioxidant Supplements and Uric Acid in Chronic Kidney Disease: A Review. Nutrients 2019, 11(8).

45. Horsfall LJ, Nazareth I, Petersen I. Serum uric acid and the risk of respiratory disease: a population-based cohort study. Thorax. 2014;69(11):1021–6.
46. Dhanesha N, Vázquez-Rosa E, Cintrón-Pérez CJ, Thedens D, Kort AJ, Chuong V, Rivera-Dompenciel AM, Chauhan AK, Leira EC, Pieper AA. Treatment with Uric Acid Reduces Infarct and Improves Neurologic Function in Female Mice After Transient Cerebral Ischemia. J Stroke Cerebrovasc Dis. 2018;27(5):1412–6.

Figures

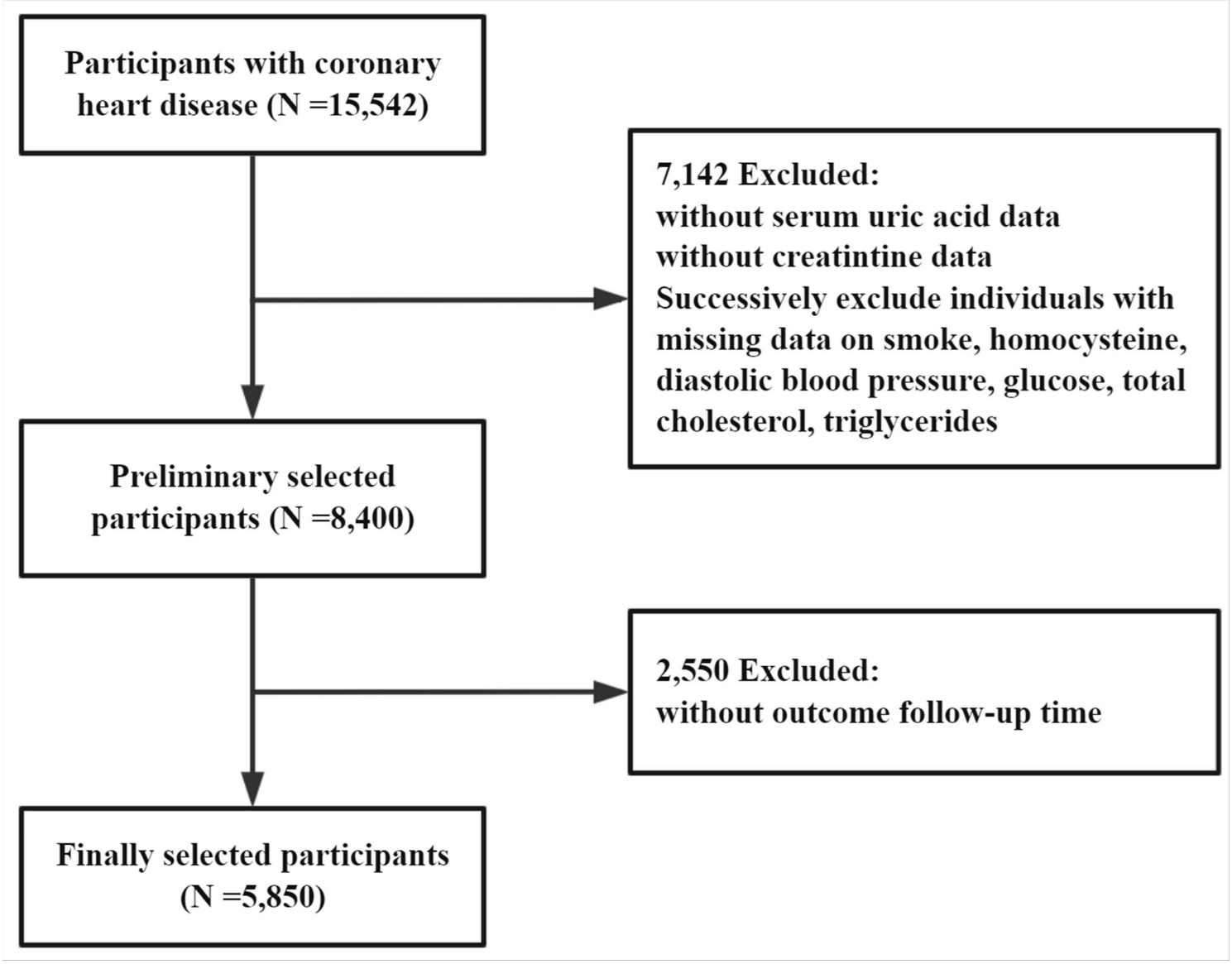


Figure 1

The flow chart of participant selection

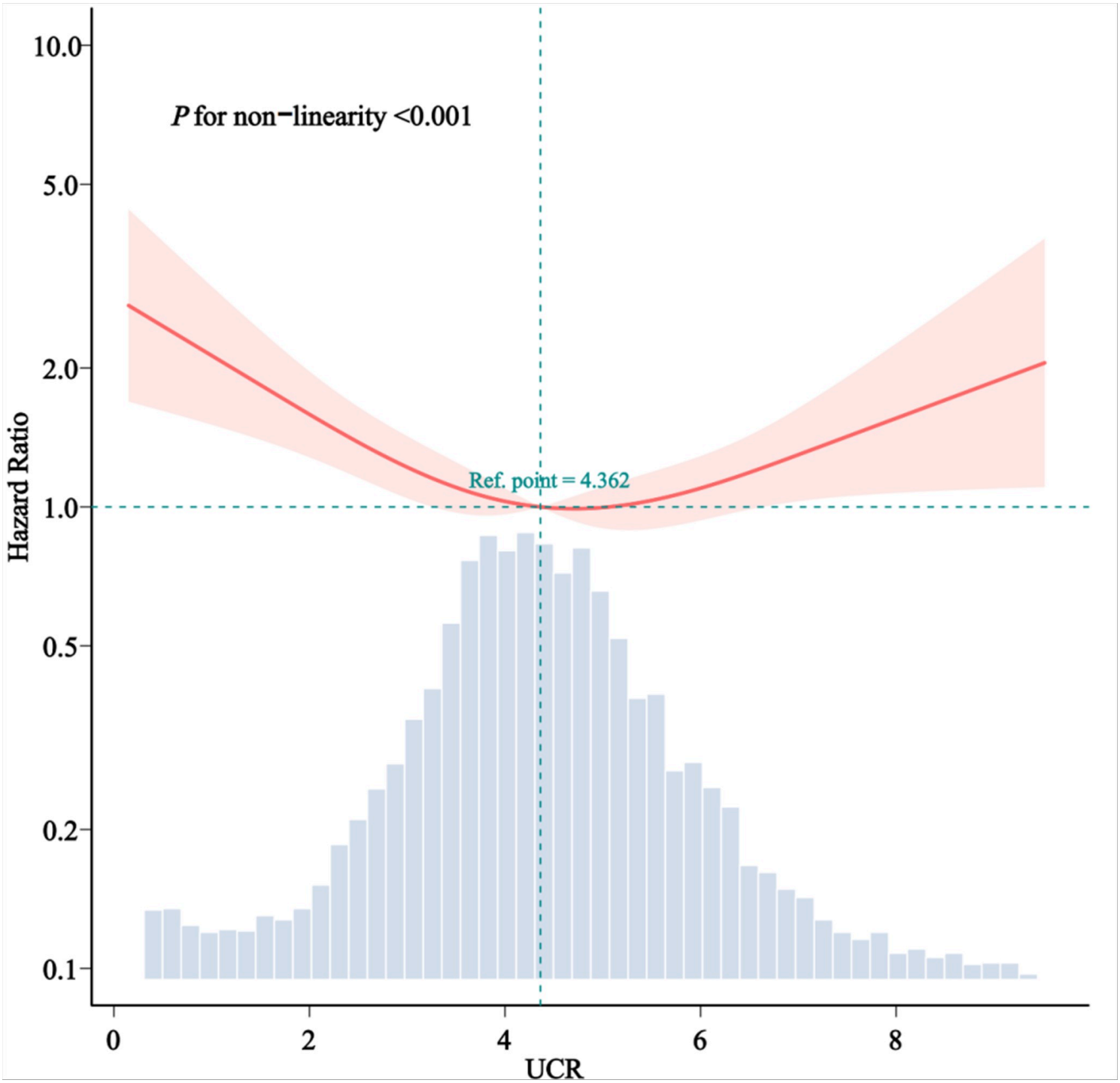


Figure 2

Association between UCR and all-cause mortality risk using a RCS regression model and histogram. The model was adjusted for age, sex, smoking status, diastolic blood pressure, homocysteine, blood urea nitrogen, total cholesterol, triglyceride, HDL-C, AST, ALT, total protein, albumin, globulin, alkaline phosphatase, hypertension, diabetes, ischemic stroke, left heart failure, renal dysfunction, α-blockers, β-blockers, calcium channel blockers, statins, antiplatelet agents, ACEI, and diuretics. ACEI, angiotensin-converting enzyme inhibitors; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL-C, high-density lipoprotein cholesterol; UCR, uric acid-to-creatinine ratio.

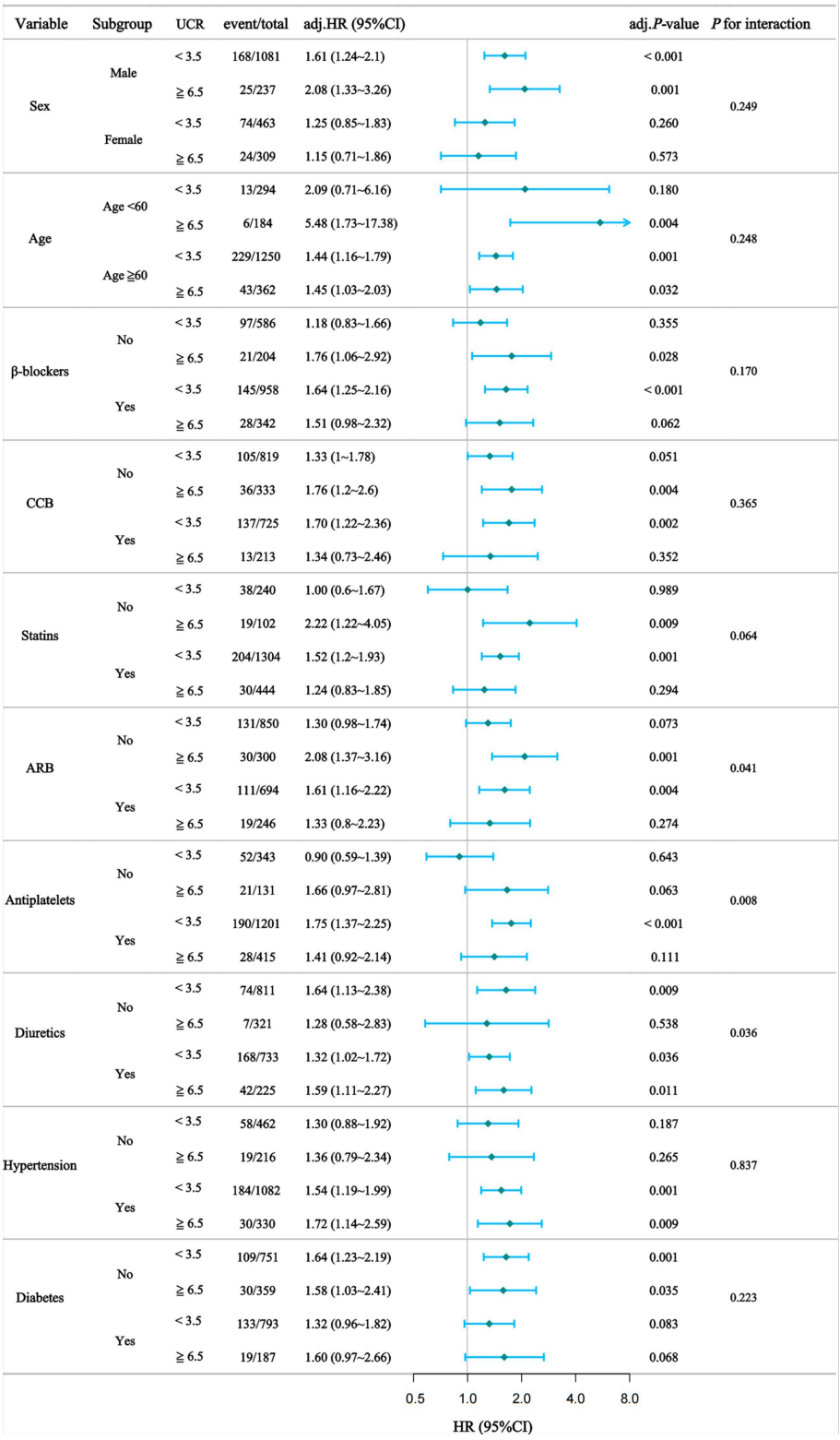


Figure 3

Forest plot of hazard ratios for all-cause mortality in different subgroups. ARB, angiotensin receptor blockers; CCB calcium channel blockers.