Clinical Investigation

Does Serum Uric Acid to Creatinine Ratio Predict Mortality Risk in Patients With Heart Failure?

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Abstract

Background: Previous studies have established a positive correlation between serum uric acid to creatinine (SUA/Cr) ratio and cardiovascular disease, but the relationship between SUA/Cr ratio and the prognosis of heart failure (HF) remains unknown. This study investigated the potential of SUA/Cr ratio as a prognostic predictor for patients with HF.

Methods: This single-center prospective cohort study enrolled 2,122 patients with HF between March 2013 and June 2017. All patients were divided into 3 groups according to SUA/Cr ratio tertiles and were followed up with until December 31, 2022. The association between SUA/Cr ratio and the prognosis of HF was assessed using the Cox proportional hazards model.

Results: The mean (SD) age and mean (SD) SUA/Cr ratio of the study cohort (66% male) were 59.3 (14.7) years and 4.71 (2.09), respectively. During a median follow-up period of 15 months (range, 11-26 months), 390 end-point events were observed. Prognosis analysis revealed that a high SUA/Cr ratio was associated with an increased mortality risk of HF (hazard ratio, 1.62 [95% CI, 1.26-2.09]; $P < .001$) compared with the SUA/Cr ratio in the lowest tertile. After adjusting for covariates, the hazard ratio for mortality risk of HF was 1.71 (95% CI, 1.23-2.37; $P = .001$). Subgroup analysis showed that mortality risk increased in direct proportion with the SUA/Cr ratio in female patients, patients with a history of hypertension and β-blocker use, and patients with UA levels below 428 μmol/L and creatinine levels less than 97 mg/dL. Stratification by age; by history of diabetes, hyperlipidemia, and smoking; and by level of fasting plasma glucose, however, had no obvious effect on the association between SUA/Cr ratio and HF prognosis. Patients with higher SUA/Cr ratios had reduced left ventricular ejection fraction and increased left ventricular end-diastolic diameter.

Conclusion: A high SUA/Cr ratio was an independent risk factor for the mortality risk of HF.

Keywords: Heart failure; prognosis; uric acid; creatinine

Introduction

Heart failure (HF) is a complex clinical syndrome with high morbidity and mortality rates.[1] Because of factors such as an increase in the prevalence of the aging population and poorly controlled risk factors, the medical costs associated with HF lead to large financial burdens.[2] Despite notable advancements in chronic HF treatment, the prognosis for HF remains pessimistic.[3]

Uric acid (UA) is an end product of purine nucleotide catabolism arising from endogenous and exogenous sources. Numerous studies have demonstrated the correlation between serum UA levels and many diseases, such as liver disease morbidity and mortality[4] and risk of diabetic kidney disease progression in individuals with type 2 diabetes.[5] In recent years, the role of UA in cardiovascular disease (CVD) has gained much attention. Wu et al[6] conducted a cohort study involving 2,749 participants and identified asymptomatic hyperuricemia as a valuable biomarker

for predicting the development of chronic HF in patients 65 years of age or older without comorbidities. In a retrospective study with 861 patients with chronic HF, Yılmaz Öztekin et al[7] found that hyperuricemia was an independent predictor of all-cause mortality.

Conflicting data exist, however, regarding the predictive value of serum UA (SUA) in CVD. An observational study with 1,268 participants diagnosed with type 2 diabetes found that SUA levels were not an independent predictor of CVD or all-cause mortality.[8] Similarly, Palmer et al[9] found no association between UA levels and ischemic heart disease or blood pressure in 58,072 participants. These inconsistent conclusions may be attributed to the fact that the level of endogenous UA depends primarily on kidney clearance function. Kidney dysfunction often contributes to increased UA levels, so kidney function to normalized UA (the SUA to creatinine [SUA/Cr] ratio) has emerged as a new biomarker; it is considered a superior indicator of net UA production. Several studies have revealed that the SUA/Cr ratio is associated with metabolic disorders and CVD,[10-12] but the association between SUA/Cr ratio and the prognosis of HF has not been reported. This clinical investigation aimed to examine the relationship between SUA/Cr ratios and the prognosis of HF in the Chinese population.

Patients and Methods

Study Population

This prospective cohort study was conducted at the First Affiliated Hospital of Shihezi University. A total of 2,531 patients with HF were consecutively recruited from February 2013 to July 2017. The diagnosis of HF was confirmed by physical examination, laboratory tests, and echocardiography, according to the American College of Cardiology/American Heart Association guidelines.[13] The exclusion criteria were as follows: (1) severe valvular heart disease as the primary etiology of HF; (2) life-threatening complications, such as severe liver dysfunction, kidney dysfunction (defined as serum creatinine levels >265 µmol/L), or a history of malignancy and life expectancy less than 1 year; (3) second-degree or third-degree atrioventricular block, unless a pacemaker was present; (4) acute myocardial infarction or unstable angina within 1 month before admission; and (5) refusal to participate in the follow-up process. Finally, 2,122 patients were included in the association analysis. The flowchart of the selection process is pro-

Key Points

- A high SUA/Cr ratio was associated with an increased risk of mortality in HF (HR, 1.62 [95% CI, 1.26-2.09]; $P < .001$).
- Stratification by age; by history of diabetes, hyperlipidemia, and smoking; and by FPG level had no obvious effect on the association between SUA/Cr ratio and HF prognosis.
- Patients with a higher SUA/Cr ratio had reduced left ventricular ejection fraction and increased left ventricular end-diastolic diameter.

Abbreviations and Acronyms

CVD	cardiovascular disease
FPG	fasting plasma glucose
HF	heart failure
HR	hazard ratio
SUA/Cr	serum uric acid to creatinine [ratio]

vided in Figure 1. This study was approved by Review Board of the First Affiliated Hospital of Shihezi University, and written informed consent was obtained from all participants. The investigation conformed to the principles of the Declaration of Helsinki.

Clinical Follow-Up and Data Collection

In this study, follow-up was conducted every 3 months through outpatient interview or by telephone. The primary end points were defined as cardiovascular deaths or heart transplantation. Baseline demographic data included patient age; sex; and history of hypertension, diabetes, hyperlipidemia, and smoking, which were obtained from the patients' records at the time of enrollment. All patients underwent fasting blood sampling and laboratory tests in the early morning after admission to the study. Hypertension was characterized by a systolic blood pressure higher than 140 mm Hg, a diastolic blood pressure higher than 90 mm Hg, or current treatment with an antihypertensive drug. Diabetes was identified based on a fasting plasma glucose (FPG) level greater than 7.8 mmol/L or a glucose level greater than 11.1 mmol/L at 2 hours after an oral glucose tolerance test. Hyperlipidemia was defined as a total plasma cholesterol level greater than 5.72 mmol/L or plasma triglyceride levels greater than 1.70 mmol/L. A history of smoking of more than 2 pack-years or smoking within the preceding year was defined as smoking. The use of β-blockers as an eligibility criterion was at the discretion of the treating physician and was defined as being used for more than 6 months.
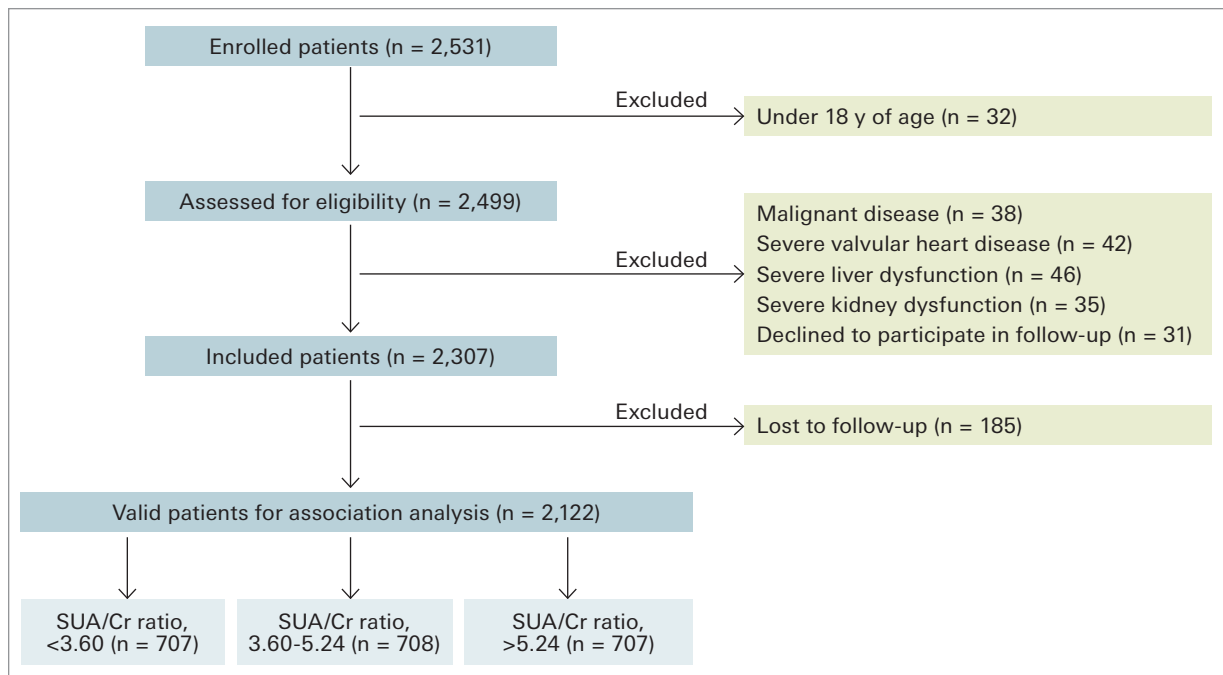
Fig. 1 The flowchart shows patient selection for this cohort study.

SUA/Cr, serum uric acid to creatinine [ratio].

Statistical Analysis

Statistical analyses were conducted using SPSS, version 15 (IBM Corp) for Windows (Microsoft Corporation). Normally distributed quantitative data were presented as mean (SD), while abnormally distributed quantitative data were presented as median (IQR). Categorical variables were presented as numbers (percentages). The SUA/Cr ratio was calculated by dividing the SUA levels by the serum creatinine levels. Participants were allocated to the following 3 groups according to SUA/Cr ratio tertile: tertile 1, SUA/Cr ratio less than 3.60; tertile 2, SUA/Cr ratio between 3.60 and 5.24; and tertile 3, SUA/Cr ratio greater than 5.24. Differences among the groups were examined using χ^2 tests, 1-way analysis of variance, 2-tailed t tests, and Kruskal-Wallis tests, where appropriate. Logistic regression analysis was performed to identify risk factors for a high SUA/Cr ratio. Variables with significant effect ($P < .1$) in the univariate model were entered into the multivariate model.

The sample size was calculated using SPSS, version 15, software. The results indicated that this study could achieve a power of 90% at a significance level of .05 when the populations in tertiles 1, 2, and 3 were 502 individuals each. In reality, the sample sizes were 707 in tertile 1, 708 in tertile 2, and 707 in tertile 3, so the sample sizes were deemed sufficient to attain the desired power of the test. Before Cox proportional hazards regression, the Schoenfeld test was conducted, demonstrating that the Pearson correlation coefficient was 0.588 between Schoenfeld residuals and failure time rank. This finding indicates that the Cox proportional hazards regression model satisfied the proportional hazard assumption.

Cox proportional hazards regression models were used to calculate the hazard ratios (HRs) and 95% CIs for the associations between SUA/Cr ratio and the prognosis of HF with and without adjustment for covariates. Covariates with $P<.1$ in univariate models or with clinical importance were selected for multivariate Cox proportional hazard regression modeling. Uric acid and creatinine were not included in the multivariate Cox proportional hazard regression model to avoid collinearity and potential spurious results because the SUA/Cr ratio was calculated from these variables. Forest plots were constructed to identify whether the HRs of increased SUA/Cr ratio differed among the subgroups based on baseline characteristics, FPG levels, UA, creatinine, or β-blocker use. Statistical significance was defined as a $P<.05$ using 2-tailed tests.

Results

Patient Characteristics

A total of 2,122 patients with HF were included in the final analysis (Fig. 1). Among these patients, 66% were male, and the mean (SD) age was 59.3 (14.7) years. A total of 88.9% of patients had hypertension, 32.1% had diabetes, 24.9% had hyperlipidemia, 38.4% were currently smoking, and 84.1% used β-blockers. The mean (SD) SUA/Cr ratio was 4.71 (2.09). The median (IQR) SUA level was 370 (306-439) μmol/L, and the median (IQR) creatinine level was 83 (67-103) mg/dL. Table I shows the baseline demographic and clinical charac-

teristics of patients according to SUA/Cr ratio tertiles. Patients with higher SUA/Cr ratios were older; more likely to have a history of diabetes; and had higher levels of low-density lipoprotein cholesterol and UA but a lower percentage of β-blocker use, lower heart rates, and lower levels of creatinine ($P<.05$). No differences were observed among the groups in terms of sex ($P<.22$); the presence of hypertension ($P<.94$) and hyperlipidemia ($P<.60$); smoking status ($P<.35$); systolic blood pressure ($P<.22$) and diastolic blood pressure ($P<.74$); and levels of total cholesterol ($P<.67$), triglycerides ($P<.93$), high-density lipoprotein cholesterol ($P<.05$), and FPG ($P>.29$). Multivariate logistic analysis showed that older age (odds ratio, 1.02 [95% CI, 1.01-1.03];

TABLE I. Patient Demographics[a]

		SUA/Cr ratio			
Characteristic	Total (N = 2,122)	Tertile 1 (<3.60) (n = 707)	Tertile 2 (3.60-5.24) (n = 708)	Tertile 3 (>5.24) (n = 707)	P value
Age, mean (SD), y	59.3 (14.7)	57.0 (14.9)	58.8 (14.2)	59.3 (14.7)	<.001
Male sex, No. (%)	1400 (66.0)	472 (66.8)	479 (67.7)	449 (63.5)	.22
Hypertension, No. (%)	1886 (88.9)	629 (89.0)	631 (89.1)	626 (88.5)	.94
Diabetes, No. (%)	681 (32.1)	201 (28.4)	226 (31.9)	254 (35.9)	.01
Hyperlipidemia, No. (%)	528 (24.9)	167 (23.6)	178 (25.1)	183 (25.9)	.60
Smoking, No. (%)	815 (38.4)	260 (36.8)	269 (38.0)	286 (40.5)	.35
β-blocker use, No. (%)	1784 (84.1)	647 (91.5)	573 (80.9)	564 (79.8)	<.001
Systolic blood pressure, mean (SD), mm Hg	131.3 (25.5)	133.7 (28.0)	129.7 (24.4)	130.3 (23.7)	.22
Diastolic blood pressure, mean (SD), mm Hg	80.4 (16.2)	80.9 (17.8)	80.3 (15.3)	80.1 (15.2)	.74
Heart rate, mean (SD), beats/min	84 (20)	85 (21)	83 (21)	82 (20)	.004
Total cholesterol, mean (SD), mg/dL	3.92 (1.12)	3.89 (1.22)	3.93 (1.06)	3.94 (1.07)	.67
Triglycerides, median (IQR), mg/dL	1.1 (0.8-1.62)	1.09 (0.79-1.60)	1.07 (0.8-1.66)	1.13 (0.80-1.60)	.93
High-density lipoprotein cholesterol, mean (SD), mg/dL	1.0 (0.54)	0.97 (0.48)	0.99 (0.45)	1.04 (0.66)	.05
Low-density lipoprotein cholesterol, mean (SD), mg/dL	2.37 (0.89)	2.29 (0.89)	2.42 (0.93)	2.40 (0.84)	.03
FPG, mean (SD), mmol/L	6.65 (3.33)	6.78 (3.47)	6.69 (3.71)	6.49 (2.75)	.29
Creatinine, median (IQR), mg/dL	83 (67-103)	109 (93-142)	83 (72-94)	65 (56-75)	<.001
Uric acid, median (IQR), μmol/L	370 (306-439)	307 (260-358)	360 (311-412)	445 (387-513)	<.001
Serum uric acid to creatinine ratio, mean (SD)	4.71 (2.09)	2.71 (0.66)	4.38 (0.47)	7.05 (1.70)	<.001

FPG, fasting plasma glucose.

SI conversion factors: To convert mm Hg to kPa, multiply by 0.133. To convert mg/dL for cholesterol to mmol/L, multiply by 0.0259. To convert mg/dL for triglycerides to mmol/L, multiply by 0.0113. To convert mg/dL for creatinine to μmol/L, multiply by 88.4.

$P < .05$ was considered statistically significant.

$P < .001$), no β-blocker use (odds ratio, 0.68 [95% CI, 0.53-0.89]; $P = .004$), and a lower heart rate (odds ratio, 0.99 [95% CI, 0.99-1.00] $P=.008$) were associated with a higher SUA/Cr ratio (Supplemental Table I).

SUA/Cr Ratio and the Prognosis of HF

The median (IQR) follow-up time in this study was 15 (11-26) months. During the follow-up period, patients were excluded for a variety of reasons: 390 (18.4%) patients with HF died; 32 were younger than 18 years of age; 38 were diagnosed with malignant disease; and 42 patients had severe liver dysfunction, while 35 patients had severe kidney dysfunction. Patients with severe kidney dysfunction may require hemodialysis, which can affect the SUA/Cr ratio. These patients often experience numerous complications that can influence the prognosis of HF and potentially affect study findings. A total of 31 patients declined to participate in follow-up procedures, and 185 patients were lost to follow-up. The number of deaths in the lowest tertile was 100 (14.1%), in the middle tertile was 135 (19.1%), and in the highest tertile was 155 (21.9%).

Univariate Cox proportional hazard regression model analysis was conducted to evaluate the predictive value of all variables for the prognosis of HF. Table II shows that several variables were associated with the prognosis of HF, including age (HR, 1.03 [95% CI, 1.03-1.04]; $P<.001$), diabetes (HR, 0.62 [95% CI, 0.51-0.76]; $P<.001$), smoking (HR, 0.83 [95% CI, 0.70-0.99]; $P = .043$), β-blocker use (HR, 7.18 [95% CI, 5.46-9.44]; $P<.001$), total cholesterol (HR, 0.98 [95% CI, 0.97-0.98]; $P<.001$), triglycerides (HR, 0.68 [95% CI, 0.59-0.78]; $P<.001$), high-density lipoprotein cholesterol (HR, 0.61 [95% CI, 0.45-0.82]; $P=.001$), and low-density lipoprotein cholesterol (HR, 0.82 [95% CI, 0.73-0.92]; $P=.001$). Next, variables with $P<.1$ and variables of clinical importance (hypertension and hyperlipidemia) in the univariate model were selected for multivariate Cox proportional hazard regression modeling. To evaluate the effects of different co-variables on the association between SUA/Cr ratio and teh prognosis of HF, we created 4 adjusted models. As demonstrated in Table III, SUA/Cr ratio was associated with HF prognosis in the univariate Cox proportional hazard regression model. The highest SUA/Cr ratio was identified as

TABLE II. Univariate Analyses of the Prognostic Factors of Patients With HF

Variable	HR	95% CI	*P* value
Age	1.03	1.03-1.04	<.001
Sex	1.19	0.99-1.44	.07
Hypertension	1.06	0.89-1.27	.52
Diabetes	0.62	0.51-0.76	<.001
Hyperlipidemia	1.420	0.92-2.17	.11
Smoking	0.83	0.70-0.99	.04
β-blocker use	7.18	5.46-9.44	<.001
Systolic blood pressure	1.00	1.00-1.01	.999
Diastolic blood pressure	1.00	1.00-1.00	.23
Heart rate	1.00	1.00-1.01	.09
Total cholesterol	0.98	0.97-0.98	<.001
Triglycerides	0.68	0.59-0.78	<.001
High-density lipoprotein cholesterol	0.61	0.45-0.82	.001
Low-density lipoprotein cholesterol	0.82	0.73-0.92	.001
FPG	1.00	1.00-1.01	.999

FPG, fasting plasma glucose; HF, heart failure; HR, hazard ratio.

$P < .05$ was considered statistically significant.

TABLE III. Association of Serum Uric Acid to Creatinine Ratio With Mortality Risk of HF in the Study Cohort

Mortality	Serum uric acid to creatine ratio tertile		
	1	2	3
Event rate, %	14.1	19.1	21.9
Events/total	100/707	135/708	155/707
Model, HR (95% CI); *P* value			
Unadjusted	1 [Reference]	1.40 (1.08-1.82); .011	1.62 (1.26-2.09); <.001
1[a]	1 [Reference]	1.39 (1.07-1.81); .014	1.61 (1.23-2.11); .001
2[b]	1 [Reference]	1.43 (1.10-1.86); .008	1.61 (1.23-2.10); .001
3[c]	1 [Reference]	1.48 (1.07-2.04); .018	1.77 (1.28-2.44); .001
4[d]	1 [Reference]	1.41 (1.02-1.95); .038	1.71 (1.23-2.37); .001

HF, heart failure; HR, hazard ratio.

[a] Model 1 was adjusted for age and sex.

[b] Model 2 was adjusted for model 1 covariates and hypertension, diabetes, hyperlipidemia, and smoking.

[c] Model 3 was adjusted for model 2 covariates and heart rate, total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol.

[d] Model 4 was adjusted for model 3 covariates and β-blocker use.

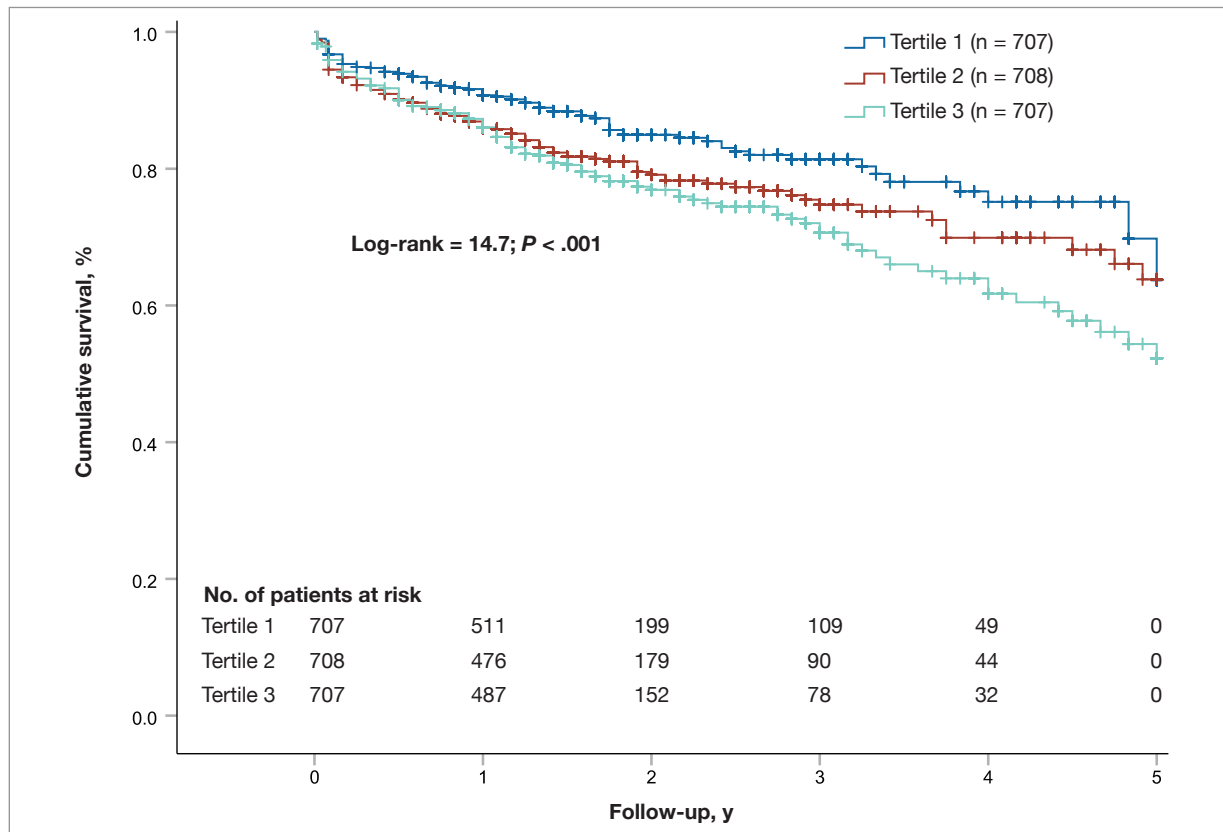*P* < .05 was considered statistically significant.

Fig. 2 Kaplan-Meier curves are shown for patients with heart failure with different serum uric acid to creatinine ratios.

Tertile 1 had a ratio <3.60; tertile 2 had a ratio between 3.60 and 5.24; and tertile 3 had a ratio above 5.24. *P* < .05 was considered statistically significant. Tick marks indicate censoring.

an independent predictor of mortality risk in HF (HR, 1.62 [95% CI, 1.26-2.09]; *P* < .001). The statistical significance remained (HR, 1.71 [95% CI, 1.23-2.37]; *P* = .001), even after adjusting for various covariates (model 4; see Table III).

The cumulative survival rates were analyzed using the Kaplan-Meier survival curve. At the end of 1, 2, 3, 4, and 5 years, these rates were 90.7%, 84.9%, 81.4%, 75.1%, and 63.7% in tertile 1; 86%, 79.1%, 74.7%, 69.9%, and 63.8% in tertile 2; and 86%, 76.9%, 70.6%, 61.7%, and 52.3% in tertile 3 (Fig. 2). The survival rate was lower in those individuals with the highest SUA/Cr ratio than in those individuals with the lower ratio (log-rank, 14.7; *P* < .001).

Subgroup analyses were conducted to further assess the associations between SUA/Cr ratio and the prognosis of HF in different clinically relevant subgroups. The mortality risk of HF increased with higher SUA/Cr ratios in female patients, patients with a history of hypertension and β-blocker use, and patients with SUA levels less than 428 μmol/L and creatinine levels less than 97 mg/dL (Fig. 3). Stratification by age; by history of diabetes, hyperlipidemia, and smoking; and by FPG level, however, had no obvious effect on the association between SUA/Cr ratio and the prognosis of HF.

Correlation Between SUA/Cr Ratio and Clinical Characteristics

Stratified analysis was also conducted to detect the association between SUA/Cr ratio and clinical characteristics. As illustrated in Figure 4A and Figure 4B, patients in tertiles 2 and 3 exhibited reduced left ventricular ejection fraction and increased left ventricular end-diastolic diameter compared with patients in tertile 1 (*P* < .001). No significant differences were observed, though, in interventricular septal thickness at diastole or in left ventricular posterior wall diastolic thickness among the different groups (Fig. 4C and Fig. 4D).

Discussion

This prospective cohort study investigated the association between SUA/Cr ratio and the prognosis of HF in the Chinese population. The study revealed that patients with a higher SUA/Cr ratio exhibited an increased mortality risk of HF compared with those with a lower SUA/Cr ratio, even after adjusting for multiple risk fac-

tors. Subgroup analysis indicated a strong association between an elevated SUA/Cr ratio and higher mortality in female patients, patients with a history of hypertension and β-blocker use, and patients with SUA levels less than 428 μmol/L and creatinine levels less than 97 mg/dL. Stratification by age; by history of diabetes, hyperlipidemia, and smoking; and by FPG levels had no obvious effect on the association between SUA/Cr ratio and the prognosis of HF. Notably, patients with a higher SUA/Cr ratio exhibited decreased left ventricular ejection fraction and increased left ventricular end-diastolic diameter. To the best of the reporting authors' knowledge, this study was the first to investigate the relationship between SUA/Cr ratio and the prognosis of HF.

The role of SUA in CVD has been a topic of debate for a long time. A prospective observational study that included 210 patients with HF with preserved ejection fraction indicated that elevated SUA levels are associated with readmission rates related to HF.[14] Rebora et al[15] found a significant positive association between SUA levels and acute HF, cardiogenic shock, and left ventricular ejection fraction in a cohort of 1,269 patients with acute coronary syndrome.[15] Some epidemiologic studies, such as the Apolipoprotein MOrtality RISk (AMORIS) study and the Rotterdam study, have also supported a positive association between SUA levels and CVD.[16,17] Other observational studies, however, such as the Fremantle Diabetes Study and the results of a Mendelian randomization analysis, failed to demonstrate a significant association between SUA levels and CVD.[8,9] This discrepancy may be attributed to several factors: SUA levels were primarily determined by kidney clearance function, individuals with lower estimated glomerular filtration rates are more likely to have higher SUA levels, and kidney dysfunction may be a major confounder in studies on the association between SUA levels and CVD.[18-20] If SUA level is a risk factor for CVD, the ratio of baseline kidney function to normalized SUA, which may reflect net SUA production, could therefore serve as a more precise predictor of incident CVD.

Previous studies have reported that SUA/Cr ratio is associated with many diseases, such as metabolic syndrome in postmenopausal women,[21] diabetic kidney disease in patients with type 2 diabetes,[22] and nonalcoholic fatty liver disease in Chinese people without obesity with normal low-density lipoprotein cholesterol values.[23] All these conditions are known to be risk factors for CVD.[24-27] The positive correlation between SUA/Cr ratio and

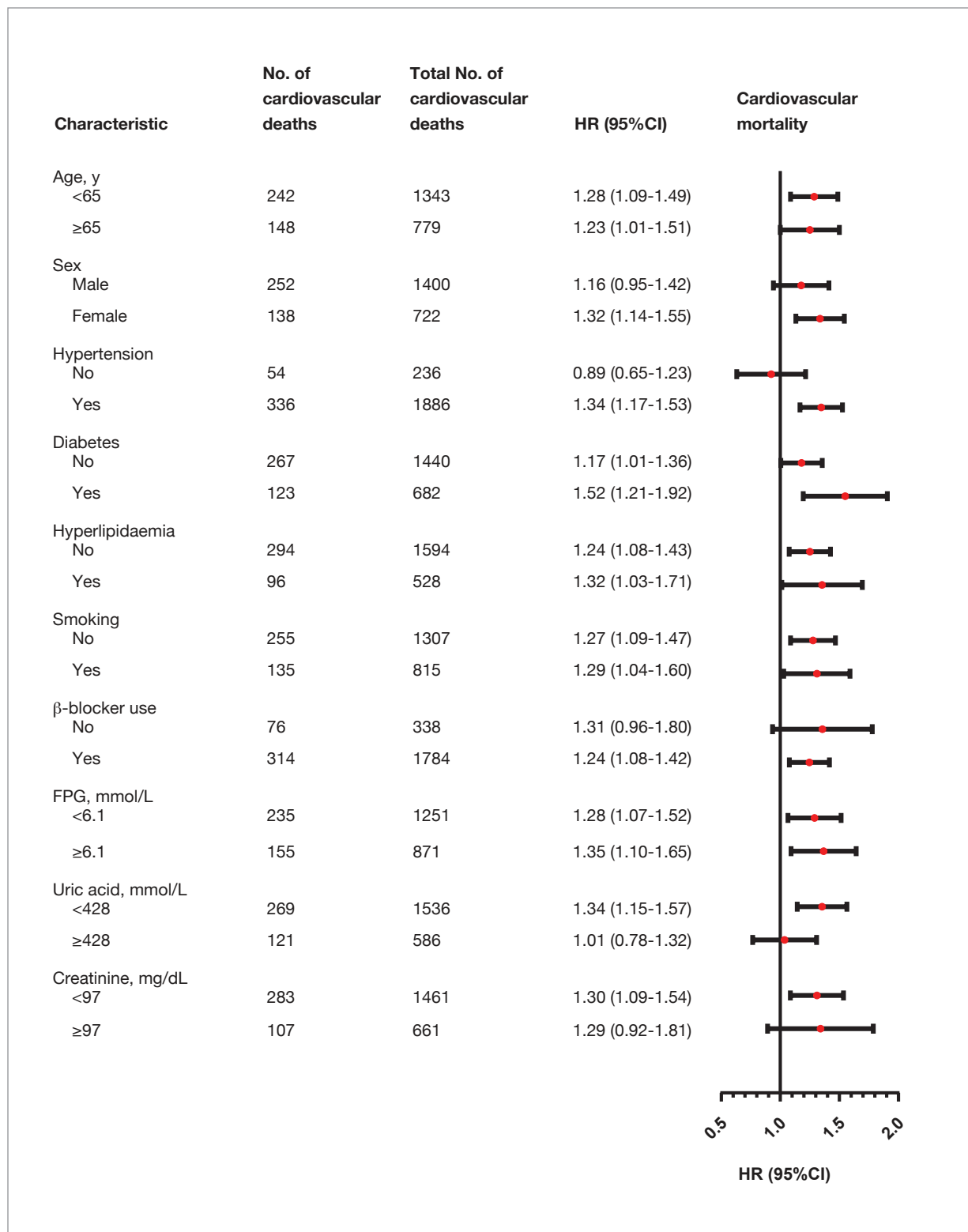| Characteristic	No. of cardiovascular deaths	Total No. of cardiovascular deaths	HR (95%CI)	Cardiovascular mortality
Age, y				
<65	242	1343	1.28 (1.09-1.49)	
≥65	148	779	1.23 (1.01-1.51)	
Sex				
Male	252	1400	1.16 (0.95-1.42)	
Female	138	722	1.32 (1.14-1.55)	
Hypertension				
No	54	236	0.89 (0.65-1.23)	
Yes	336	1886	1.34 (1.17-1.53)	
Diabetes				
No	267	1440	1.17 (1.01-1.36)	
Yes	123	682	1.52 (1.21-1.92)	
Hyperlipidaemia				
No	294	1594	1.24 (1.08-1.43)	
Yes	96	528	1.32 (1.03-1.71)	
Smoking				
No	255	1307	1.27 (1.09-1.47)	
Yes	135	815	1.29 (1.04-1.60)	
β-blocker use				
No	76	338	1.31 (0.96-1.80)	
Yes	314	1784	1.24 (1.08-1.42)	
FPG, mmol/L				
<6.1	235	1251	1.28 (1.07-1.52)	
≥6.1	155	871	1.35 (1.10-1.65)	
Uric acid, mmol/L				
<428	269	1536	1.34 (1.15-1.57)	
≥428	121	586	1.01 (0.78-1.32)	
Creatinine, mg/dL				
<97	283	1461	1.30 (1.09-1.54)	
≥97	107	661	1.29 (0.92-1.81)	

0.5   1.0   1.5   2.0

HR (95%CI)

Fig. 3 Forest plots are shown for subgroup analysis of the association between serum uric acid to creatinine ratio and the mortality risk of heart failure.

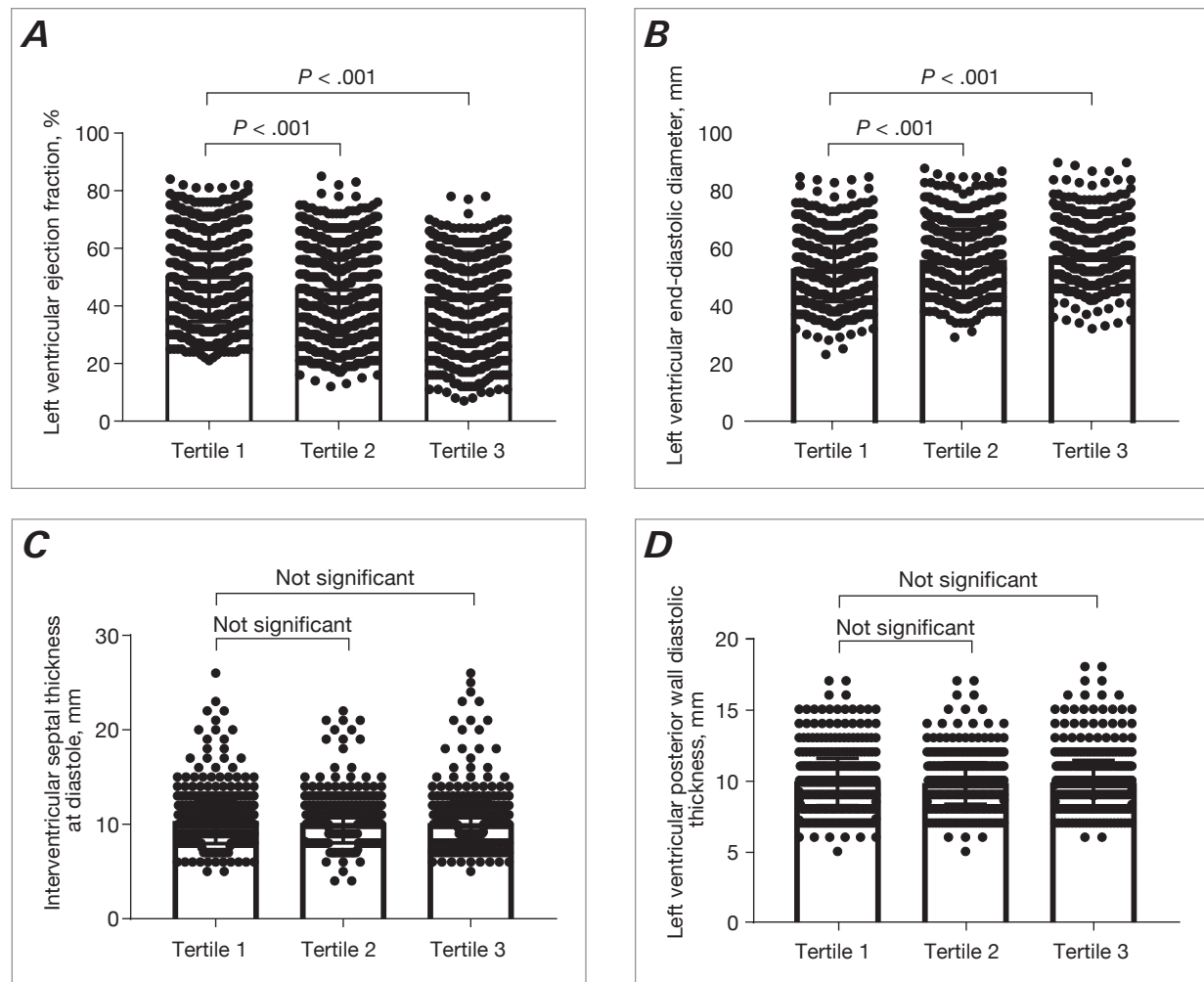FPG, fasting plasma glucose; HR, hazard ratio.

Fig. 4 Histogram plots compare clinical characteristics, including **(A)** left ventricular ejection fraction, **(B)** left ventricular end-diastolic diameter, **(C)** interventricular septal thickness at diastole, and **(D)** left ventricular posterior wall diastolic thickness, among patients with different serum uric acid to creatinine ratios.

$P < .05$ was considered statistically significant.

CVD was also identified in 2 prospective studies with 96,378 participants[11] and 20,724 participants,[10] respectively. To the best of the reporting authors' knowledge, the association between SUA/Cr ratio and the prognosis of HF has not been fully characterized. The results of the present study show that a higher SUA/Cr ratio is associated with a poorer prognosis of HF.

In fact, SUA exhibits proinflammatory properties through various mechanisms. In particular, it activates the mitogen-activated protein kinase pathway and the phosphatidylinositol-3 kinase-AKT pathway[28,29] while suppressing the adenosine monophosphate–activated protein kinase pathway.[30] It is also capable of inducing the aging and death of human endothelial cells through local activation of oxidative stress and the renin-angiotensin system.[31] Inflammation and oxidative stress are risk factors for cardiovascular events.[32,33] High levels of proinflammatory and inflammatory indices were associated with adverse outcomes in patients with HF.[34,35] In summary, inflammation and oxidative stress may serve as biological mechanisms linking SUA/Cr ratio to the mortality risk of HF. Specifically, a high SUA/Cr ratio indicates increased inflammation and oxidative stress, contributing to poor HF prognosis. The SUA/Cr ratio is also associated with many cardiometabolic factors,[12,36] which may provide a mediating pathway for the association between SUA/Cr ratio and HF.

Study Limitations

The study had some limitations. First, the sample size was limited, so a larger cohort study should be conducted in the future. Second, this was a single-center study, and the conclusions deserve verification in other centers. Third, some unmeasured or residual confounding effects may have been present in this observational study. Fourth, this study only focused on baseline SUA and creatinine levels, disregarding any dynamic changes in SUA/Cr ratio that could have provided more valuable information for understanding the underlying mechanism. Fifth, caution should be exercised when extrapolating the findings of this study to other populations as all patients included were from China. To confirm and expand these findings, further prospective studies involving diverse populations will be required. Finally, the exact mechanism by which SUA/Cr ratio affects the prognosis of HF remains unknown.

Conclusion

This study found that a higher SUA/Cr ratio is associated with an increased mortality risk of HF compared with a lower SUA/Cr ratio, suggesting that SUA/Cr ratio could be used as a preferred predictor of mortality risk in clinical practice.

Article Information

Author Contributions: All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Xiaoqing Xi, Jinfeng Cai, Chen Zhang, and Xuefei Wang. The first draft of the manuscript was written by Xiaoqing Xi, and all authors commented on subsequent versions of the manuscript. All authors read and approved the final manuscript.

Conflict of Interest/Disclosure: The authors have no conflicts of interest to declare.

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