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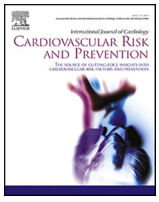

Hyperuricemia and adverse outcomes in patients with cardiorenal syndrome: A nationwide prospective cohort study in China

Zhanyuan Chen [a,1], Yaoyao Wang [a,1], Lili Liu [a], Xuejiao Liu [a], Rui Zhu [a], Yu Wei [a], Lihua Zhang [b], Jianfang Cai [a,*]

[a] Department of Nephrology, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, 100037, Beijing, China

[b] National Clinical Center for Cardiovascular Diseases, NHC Key Laboratory of Clinical Research for Cardiovascular Medications, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, 100037, Beijing, China

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ABSTRACT

Background: Serum uric acid (UA) has been associated with adverse outcomes in patients with heart failure. However, it remains inconclusive whether such association persists in patients with cardiorenal syndrome (CRS).
Methods: In a nationwide prospective cohort from China, 4907 adults hospitalized for heart failure were enrolled. Of them, 1284 had an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 at admission were included in this study. The Cox regression model was employed to evaluate the relationship between UA levels and mortality, major cardiovascular events (MACE), and hospitalization for heart failure (HHF). Additionally, Harrell's concordance index was utilized to assess the incremental value of UA levels in predicting mortality.
Results: During a median follow-up of 3.28 years, hyperuricemia was associated with a 27 % increased risk of all-cause mortality (HR 1.27, 95 % confidence interval [CI] 1.08–1.49) and a 36 % increased risk of cardiovascular mortality (HR 1.36, 95 % CI 1.11–1.65), regardless of patients' eGFR levels. This relationship remained consistent throughout the whole follow-up period. Hyperuricemia increased the risk of 3-month MACE by 39 % (HR 1.39, 95 % CI 1.03–1.88), 3-month HHF by 47 % (HR 1.47, 95 % CI 1.11–1.95), and 1-year MACE by 26 % (HR 1.26, 95 % CI 1.02–1.57). The additive effect of uric acid levels in predicting mortality was also confirmed.
Conclusions: Serum UA levels possess significant value in prognosis of mortality, MACE, and HHF among patients with CRS. These findings underscore the importance of monitoring serum UA in the management of patients with CRS, as UA may provide valuable insights into risk stratification.

1. Introduction

Heart failure (HF) represents the terminal phase of a spectrum of cardiovascular diseases, with an escalating prevalence of 1 %–2 % among adults [1]. It is linked to an elevated risk of comorbidities, mortality, and rehospitalization, imposing a substantial strain on the global healthcare system [2]. HF frequently coexists with kidney disease, forming a complex bi-directional relationship known as cardiorenal syndrome (CRS). Approximately 50 % of HF patients also have chronic kidney disease (CKD), and conversely, 30 % of CKD patients will experience acute decompensated heart failure (ADHF) [3–5]. The intricate interplay between HF and CKD accelerates deterioration of both organs and increases the risk of mortality and other complications [6]. Hyperuricemia may serve as a pivotal link in the interplay between HF and CKD.

Hyperuricemia is prevalent among individuals suffering from either HF or CKD. A large body of evidence has accumulated, demonstrating elevated uric acid (UA) levels are correlated with increased risk of mortality and cardiovascular events in HF patients and in other various populations, as well as with the development and progression of both HF and CKD [7–10]. However, in patients with CRS, the metabolism of UA is influenced by several additional factors. Firstly, renal dysfunction

* Corresponding author. Department of Nephrology, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 167 Beilishi Rd, Xicheng District, Beijing, 100037, China.
E-mail address: caijfbj@126.com (J. Cai).
[1] These authors contributed equally.

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reduces the renal elimination of UA, resulting in its accumulation. Secondly, HF can strikingly trigger xanthine oxidase activity, thereby increasing UA production [11]. Thirdly, diuretics, commonly prescribed to patients with CRS, can both promote the reabsorption and attenuate the excretion of UA. These factors may complicate and obscure the association between uric acid and adverse outcomes. Consequently, epidemiological studies are essential to elucidate the association between UA levels and adverse health outcomes, including death, in patients with CRS. Unfortunately, such studies are scarce. Moreover, the findings from these studies are inconsistent. Two studies did not find any significant relationship between UA levels and mortality in CRS patients [12,13], while another two indicated that such association was present only in HF patients with an estimated glomerular filtration rate (eGFR) $>$ 60 mL/min/1.73 m^2 [14] or $>$ 30 mL/min/1.73 m^2 [15]. Additionally, there is a lack of evidence regarding the relationship between UA and major adverse cardiovascular events (MACE) in CRS patients.

Therefore, in the present study, we sought to investigate the association of UA with mortality, MACE, and Hospitalization for HF (HHF) among patients with CRS in a large nationwide prospective HF cohort.

2. Materials and method

2.1. Study design and participants

Our current study is based on the China Patient-Centered Evaluative Assessment of Cardiac Events Prospective Heart Failure (China PEACE 5p-HF) cohort, a nationwide multicenter prospective study. The protocol of the China PEACE 5p-HF study has been previously described elsewhere [16]. In brief, 4907 patients aged 18 years or older, hospitalized primarily due to new-onset HF or decompensation of chronic HF, were consecutively enrolled from 52 hospitals throughout 20 provinces in China between August 2016 and May 2018. HF was diagnosed by local physicians in accordance with the Chinese guidelines of HF, which is consistent with those of the European Society of Cardiology, the American College of Cardiology, and the American Heart Association. All participants provided informed consent and were followed up at 1st, 6th, and 12th months post-discharge and annually thereafter until death, lost to follow-up, or the censoring date. If patients were unable to attend the scheduled in-person interview, the trained staff at the national coordinating center would conduct telephone interviews. The China PEACE 5p-HF Study was approved by the Ethics Committees of Fuwai Hospital and all collaborating hospitals, and was registered on www.clinicaltrials.gov (NCT02878811).

In the current study, we excluded patients with missing eGFR (n = 3) or missing serum UA (n = 533). Subsequently, we further omitted patients with eGFR $\geq$60 mL/min/1.73 m^2 (n = 3076) or who died during index hospitalization (n = 14), leaving 1284 participants for the final analyses. Among these, 133 (10.4 %) patients had missing body mass index (BMI), 88 (6.9 %) had missing left ventricular ejection fraction (LVEF), 1 (<0.1 %) had missing New York Heart Association (NYHA) functional classification, 18 (1.4 %) had missing hemoglobin (Hb), 36 (2.8 %) had missing N-terminal pro-B type natriuretic peptide (NT-proBNP), 3 (0.2 %) had missing triglyceride (TG), and 22 (1.7 %) had missing albumin. To optimize statistical power and reduce bias from excluding patients with missing data we employed multiple imputation by chained equations (MICE) in the R software to impute the missing values.

2.2. Data collection and definitions

During the index hospitalization, data on sociodemographic characteristics, such as age, sex, and smoking status, were collected by physicians via a standardized questionnaire in face-to-face interviews. Information on comorbidities, clinical characteristics at admission including height and weight, NYHA functional class, medical histories encompassing stroke, ischemic heart disease (IHD), HF, hypertension, diabetes, and dialysis, local laboratory tests, and current medication were extracted from the medical records of the index hospitalization. BMI was calculated by dividing weight in kilograms by the square of height in meters. LVEF was measured in accordance with standard echocardiography protocols. Fasting blood samples were taken within 48 h of admission and assayed for serum creatinine (Scr), glycosylated hemoglobin A1c, NT-proBNP, and serum TG at the central laboratory. Hb and serum albumin levels were derived from local laboratory tests on admission. EGFR was calculated using the modification of diet in renal disease formula for Chinese (cMDRD)s: eGFR $= 175 \times (\mathrm{Scr})^{-1.234} \times (\mathrm{age})^{-0.179} \times 0.742$ [if female] $\times$ 0.790.

Serum uric acid levels were measured by the Uricase-Peroxidase method on automated biochemical analyzers, with the following reference intervals: (1) Males: 2.5–7.0 mg/dL; (2) Females: 1.5–6.0 mg/dL. Hyperuricemia was defined as a serum UA >7 mg/dL. Serum UA levels were also categorized into three groups: >9 mg/dL, 7–9 mg/dL, and <7 mg/dL, or alternately by their tertiles (<6.94 mg/dL, 6.94–9.21 mg/dL, and>9.2 mg/dL). NT-proBNP levels were divided into three groups based on their tertiles (<1533 ng/L,1533–4713 ng/L, and >4713 ng/L). Hypertriglyceridemia was defined as a serum TG $\geq$ 2.3 mmol/L. Hypoalbuminemia was defined as a serum albumin <35 g/L. LVEF was categorized as $\leq$ 40 %, 41–49 %, and $\geq$50 %. EGFR was classified as Stage 3a (45–59 mL/min/1.73 m^2), Stage 3b (30–44 mL/min/1.73 m^2), and Stage 4 or 5 (<30 mL/min/1.73 m^2) according to the 2024 Kidney Disease: Improving Global Outcomes clinical practice guideline. Anemia was defined as a Hb < 130 g/L in men or <120 g/L in women. Stroke, IHD, history of HF, hypertension, diabetes, and dialysis were defined according to the medical history, discharge diagnosis, or positive laboratory test results. Finally, CRS was defined as HF with an eGFR <60 mL/min/1.73 m^2.

2.3. Assessment of outcomes

The primary outcomes of this study were all-cause mortality (ACM) and cardiovascular mortality (CVM) over the entire follow-up period. The secondary outcomes included ACM and CVM in 1-year, 2-year, 3-year, and 4-year follow-up periods, as well as MACE and HHF in 1-month, 3-month, 6-month, 9-month and 1-year follow-up periods. CVM comprised sudden cardiac death and death from HF, acute myocardial infarction (AMI), stroke, and other cardiovascular causes. MACE was defined as a composite of CVM, non-fatal AMI, and non-fatal stroke. Information on death events was obtained via interviews with patients' relatives, death certificates, and the national database of death causes. All data were centrally adjudicated by trained clinicians at the National Center for Cardiovascular Diseases.

2.4. Statistical analysis

In this study, categorical variables were expressed as numbers (percentages) and compared with the Mantel-Haenszel Chi-square test. Continuous variables were presented as mean $\pm$ standard deviation or median (interquartile range, IQR) as appropriate and compared with analysis of variance tests.

Multivariate cox proportional hazard regression model was employed to calculate the hazard ratios (HRs) and their 95 % confidence intervals (CIs) for the adverse outcomes associated with serum UA levels, adjusted for age (continuous), gender (male or female), BMI (continuous), smoking status (never, former, or current smokers), stroke (yes or no), IHD (yes or no), hypertension (yes or no), diabetes (yes or no), anemia (yes or no), history of HF (yes or no), eGFR stages (stage 3a, 3b, and 4 or 5), LVEF($\leq$40 %, 41–49 %, and $\geq$50 %), NYHA functional class (stage II, III, and IV), NT-proBNP (<1533 ng/L,1533–4713 ng/L, and >4713 ng/L), hypoalbuminemia (yes or no), hypertriglyceridemia (yes or no), and use of diuretics (yes or no). The Schoenfeld residual method was utilized to assess the proportional hazards assumption of the Cox model.

We subsequently examined the linearity of the association of serum UA levels with mortality by applying restricted cubic splines within Cox regression models. We employed four knots for the restricted cubic splines regression to achieve optimal fit.

We introduced a multiplicative interaction term between serum UA levels on continuous scale and each covariate into the multivariate Cox model to explore the potential effect modification. Subgroup analyses were performed to estimate the effects of UA on mortality across different populations stratified by these covariates.

We assessed the predictive performance of serum UA levels for predicting mortality by using a receiver-operating characteristic (ROC) curve analysis and further preformed time-dependent ROC analysis to evaluate the accuracy of the serum UA levels at different time points in predicting mortality.

To test the robustness of the findings, we conducted a series of sensitivity analyses by considering the association between sex-based diagnosis of hyperuricemia and prognosis, confining analyses to non-dialytic CRS patients, reclassifying serum UA levels into three categories based on their tertiles or specific values of 7 and 9 mg/dL, re-selecting CRS patients according to eGFR calculated using the 2012 and 2021 CKD-EPI equations, and employing the Fine-Gray competing risk model to compute the HRs for adverse outcomes other than ACM, respectively.

All statistical analyses were performed with R software version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). Two-sided $p < 0.05$ was considered statistically significant.

3. Results

3.1. Patients' characteristics

The mean age of the study participants was 69 ± 12 years; 743 (58 %) were male, and 844 (66 %) had hyperuricemia. Compared to those without hyperuricemia, patients with hyperuricemia tended to be younger, male, tobacco users, and had higher use of diuretics, and exhibited higher BMI and NT-proBNP levels, as well as lower LVEF and eGFR values. But they were less likely to have comorbidities such as stroke, IHD, diabetes, and anemia. Nevertheless, no significant differences were observed between the two groups regarding serum albumin, serum TG, NYHA functional classification, hypertension, history of dialysis, history of HF, or prescriptions of renin-angiotensin system inhibitors (RASI), beta blockers, and mineralocorticoid antagonists (MRA) (Table 1).

3.2. Association between serum UA levels and mortality

During a median follow-up of 3.28 (1.10–4.49) years, 769 (60 %) all-cause deaths and 541 (42 %) cardiovascular deaths were documented.

Throughout the entire follow-up, hyperuricemia was found to be associated a 27 % increased risk of ACM (HR 1.27, 95 % CI 1.08–1.49, $p = 0.004$) and a 36 % increased risk of CVM (HR 1.36, 95 % CI 1.11–1.65, $p = 0.002$) after fully adjustment (Table 2). We also explored the association within different follow-up durations and observed that the association attenuated slightly with the extension of follow-up duration, but constantly stayed significant (Fig. 3).

The restricted cubic splines analysis revealed a positive linear graded association between serum UA levels and both all-cause and cardiovascular mortality, as depicted in Fig. 1. In the fully adjusted model, each 1 mg/dL increase in serum UA was associated with a 7 % rise in the risk of ACM (HR 1.07, 95 % CI 1.04–1.10, $p < 0.001$) and 8 % increase in the risk of CVM (HR 1.08, 95 % CI 1.04–1.11, $p < 0.001$) during the entire follow-up period (Table 2) (Fig. 3).

Serum albumin modified the relationship between UA and both all-cause and cardiovascular mortality. However, the history of HF and hypertension only influenced the association between UA and ACM. Specifically, hypoalbuminemia attenuated the risk for ACM associated with elevated serum UA levels (HR [1.04, 95 % CI 1.01–1.08] vs [1.13, 95 % CI 1.09–1.17], p for interaction = 0.003), as well as that for CVM (HR [1.06, 95 % CI 1.02–1.10] vs. [1.15, 95 % CI 1.09–1.20], p for interaction = 0.01). So did hypertension (HR [1.06, 95 % CI 1.03–1.09] vs. [1.11, 95 % CI 1.07–1.16], p for interaction = 0.04) with the risk of ACM. Conversely, history of HF enhanced the risk of ACM (HR [1.10, 95 % CI 1.07–1.13] vs. [1.01, 95 % CI 0.94–1.07], p for interaction = 0.02). No significant interaction effects were observed UA and other covariates in relation to mortality risk, including LVEF, cardiac function, and use of

Table 1
Baseline characteristics of the study population by serum uric acid levels.

Variables	Non-hyperuricemia (N = 440)	Hyperuricemia (N = 844)	*P* Value
Demographic factors			
Age (yr), mean (SD)	72 (11)	68 (13)	<0.001
Gender, n (%)			<0.001
Male	198 (45)	545 (65)	
Female	242 (55)	299 (35)	
Body mass index, mean (SD)	23.7 (4.0)	24.5 (4.2)	0.002
Smoking status, n (%)			0.007
Never smoker	315 (72)	518 (61)	
Former smoker	76 (17)	177 (21)	
Current smoker	49 (11)	149 (18)	
Comorbidities			
Stroke, n (%)	146 (33)	201 (24)	0.003
Ischemic heart diseases, n (%)	321 (73)	530 (63)	0.003
Hypertension, n (%)	330 (75)	605 (72)	0.204
Diabetes, n (%)	191 (43)	316 (37)	0.038
History of heart failure, n (%)	322 (73)	651 (77)	0.117
Anemia, n (%)	242 (55)	390 (46)	0.003
History of dialysis, n (%)	26 (6)	31 (4)	0.065
Clinical factors			
LVEF, n (%)			<0.001
≥50 %	223 (50)	315 (35)	
41–49 %	108 (25)	210 (22)	
≤40 %	109 (25)	396 (43)	
NYHA functional class, n (%)			0.320
II	54 (12)	88 (10)	
III	198 (45)	361 (43)	
IV	188 (43)	395 (47)	
eGFR (ml/min/1.73m^2), median (IQR)	50 (39–56)	45 (33–54)	<0.001
eGFR stages (ml/min/1.73m^2), n (%)			0.001
45-59	268 (61)	425 (50)	
30-44	109 (25)	251 (30)	
<30	63 (14)	168 (20)	
NT-proBNP (ng/L), median (IQR)	2061 (805–5089)	3119 (1320–7636)	<0.001
NT-proBNP tertiles, n (%)			0.001
T1 (<1533 ng/L)	179 (41)	249 (30)	
T2 (1533–4713 ng/L)	141 (32)	287 (34)	
T3 (>4713 ng/L)	120 (27)	308 (36)	
Uric acid (mg/dL), median (IQR)	5.9 (5.1–6.4)	9.3 (8.0–10.9)	<0.001
Triglyceride (mg/dL), median (IQR)	97 (71–133)	97 (71–142)	0.444
Hypertriglyceridemia, n (%)	34 (8)	80 (10)	0.295
Albumin (g/L), median (IQR)	38.3 (34.9–41.0)	38 (34.8–41.3)	0.894
Hypoalbuminemia, n (%)	235 (53)	425 (50)	0.299
Medication status			
RASi and/or MRA, n (%)	319 (73)	609 (72)	0.331
Beta blockers, n (%)	253 (58)	496 (59)	0.662
Diuretics, n (%)	273 (62)	571 (68)	0.045

SD: Standard deviation; IQR: interquartile range; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association; eGFR: estimated glomerular filtration rate; RASi: renin-angiotensin system inhibitors; MRA: mineralocorticoid antagonists.

Table 2
Associations between serum uric acid levels and mortality in patients with cardiorenal syndrome during the entire follow-up period.

	All-cause mortality		Cardiovascular mortality	
	HR (95 % CI)	*P* Value	HR (95 % CI)	*P* Value
Hyperuricemia				
Unadjusted	1.35 (1.15–1.57)	<0.001	1.46 (1.21–1.75)	<0.001
Age- and sex-adjusted	1.40 (1.19–1.64)	<0.001	1.52 (1.25–1.83)	<0.001
Fully-adjusted[a]	1.27 (1.08–1.49)	0.004	1.36 (1.11–1.65)	0.002
Per 1 mg/dL increase in uric acid				
Unadjusted	1.08 (1.06–1.11)	<0.001	1.10 (1.07–1.13)	<0.001
Age- and sex-adjusted	1.10 (1.07–1.13)	<0.001	1.11 (1.08–1.15)	<0.001
Fully-adjusted[a]	1.07 (1.04–1.10)	<0.001	1.08 (1.04–1.11)	<0.001

HR, hazard ratio; CI, confidence interval; UA, uric acid.
[a] Adjusted for age, gender, body mass index, smoking status, stroke, ischemic heart diseases, hypertension, diabetes, anemia, history of heart failure, LVEF, NYHA functional classification, NT-proBNP levels, eGFR stages, hypoalbuminemia, hypertriglyceridemia, and use of diuretics.

diuretics (Fig. 2).

3.3. Serum UA levels in predicting mortality

Upon incorporating UA into a fundamental multivariate Cox regression model that included age, gender, BMI, smoking status, NT-proBNP, NYHA functional classification, LVEF, eGFR stage, presence of comorbidities, laboratory indexes and use of diuretics, the Harrell's concordance index (C-index) increased significantly for ACM from 0.680 to 0.685 (p = 0.013) and for CVM from 0.697 to 0.706 (p = 0.001). Further time-dependent C-index revealed similar improvements in the model's predictive capabilities for 2-year, 3-year, and 4-year CVM when UA was added to the primary full models (Table S1).

3.4. Association between serum UA levels and MACE and HHF

During the first year of follow-up after index discharge, 434 (34 %) MACE, and 532 (41 %) HHF were observed. Hyperuricemia was associated with a 26 % increased risk of MACE at 1 year (HR 1.26, 95 % CI 1.02–1.57, p = 0.034) as well as a 47 % increased risk of HHF in 3 months (HR 1.47, 95 % CI 1.11–1.95, p = 0.008). However, the association between hyperuricemia and risk of HHF diminished abruptly after 3 months post-discharge and did not reach significance at 6 months or at 1 year (Fig. 3).

Table 3
Associations between serum uric acid levels and MACE and HHF in patients with cardiorenal syndrome.

	Major adverse cardiovascular events				Hospitalization for heart failure			
	1-month		1-year		1-month		1-year	
	HR (95 % CI)	P Value	HR (95 % CI)	*P* Value	HR (95 % CI)	*P* Value	HR (95 % CI)	*P* Value
Hyperuricemia								
Unadjusted	1.26 (0.86–1.85)	0.240	1.36 (1.10–1.67)	0.004	1.53 (1.05–2.24)	0.030	1.15 (0.96–1.38)	0.130
Sex-and age-adjusted	1.31 (0.88–1.93)	0.180	1.39 (1.12–1.71)	0.002	1.54 (1.05–2.27)	0.030	1.20 (1.00–1.45)	0.050
Fully-adjusted[a]	1.24 (0.83–1.85)	0.294	1.26 (1.02–1.57)	0.034	1.46 (0.98–2.17)	0.061	1.14 (0.94–1.38)	0.187
Per 1 mg/dL increase in uric acid								
Unadjusted	1.08 (1.02–1.15)	0.009	1.09 (1.05–1.12)	<0.001	1.13 (1.07–1.19)	<0.001	1.06 (1.02–1.09)	<0.001
Sex-and age-adjusted	1.10 (1.03–1.17)	0.003	1.10 (1.06–1.14)	<0.001	1.14 (1.07–1.21)	<0.001	1.07 (1.04–1.11)	<0.001
Fully-adjusted[a]	1.08 (1.01–1.16)	0.019	1.07 (1.03–1.11)	<0.001	1.12 (1.05–1.19)	<0.001	1.05 (1.02–1.09)	0.002

HR, hazard ratio; CI, confidence interval; UA, uric acid; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events.
[a] Adjusted for age, gender, body mass index, smoking status, stroke, ischemic heart diseases, hypertension, diabetes, anemia, history of heart failure, LVEF, NYHA functional classification, NT-proBNP levels, eGFR stages, hypoalbuminemia, hypertriglyceridemia, and use of diuretics.

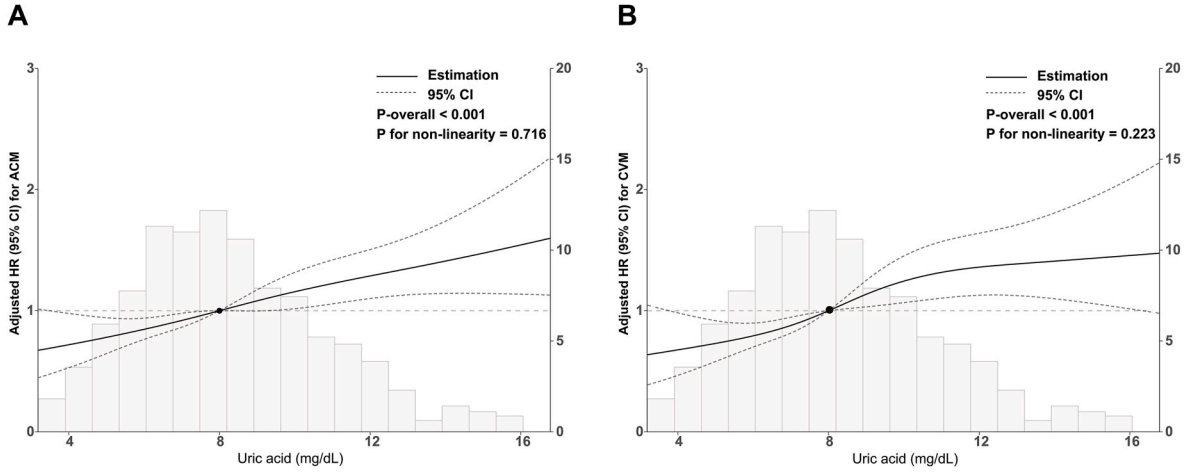

Fig. 1. Dose-response relationship between serum uric acid levels and mortality. (A) All-cause mortality within the entire follow-up duration, (B) Cardiovascular mortality within the entire follow-up duration. The black solid lines are fitted based on Cox-proportional hazard models. The black dotted areas show 95 % confidential intervals (CIs).
Adjusted for age, gender, body mass index, smoking status, stroke, ischemic heart diseases, hypertension, diabetes, anemia, history of heart failure, LVEF, NYHA functional classification, NT-proBNP levels, eGFR stages, hypoalbuminemia, hypertriglyceridemia, and use of diuretics.

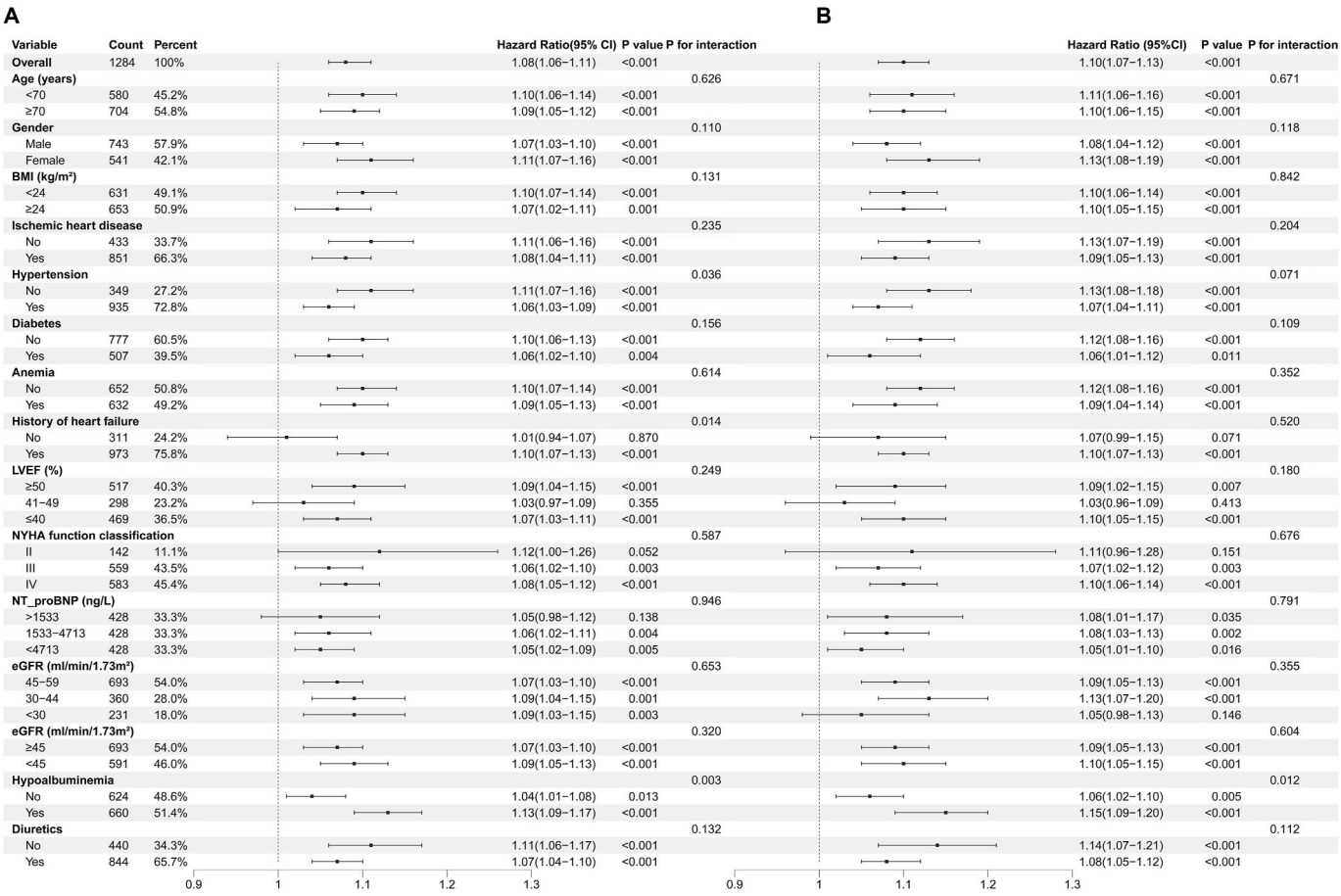

Fig. 2. Subgroup analyses on the association between serum uric acid levels and (A) All-cause mortality and (B) Cardiovascular mortality during the entire follow-up duration.
Adjusted for age, gender, body mass index, smoking status, stroke, ischemic heart diseases, hypertension, diabetes, anemia, history of heart failure, LVEF, NYHA functional classification, NT-proBNP levels, eGFR stages, hypoalbuminemia, hypertriglyceridemia, and use of diuretics.

3.5. Sensitivity analyses

Upon re-diagnosing hyperuricemia by the criteria of UA>7 mg/dL in male and >6 mg/dL in female, restricting analyses to non-dialytic CRS patients, reclassifying serum UA levels into three categories based on their tertiles or specific cutoffs of 7 and 9 mg/dL, re-selecting CRS patients per eGFR derived from the 2012 and the 2021 CKD-EPI equations, or employing the Fine-Gray competing risk model to compute the HRs for adverse outcomes other than ACM, similar findings were obtained (Tables S2–S6).

4. Discussion

In this prospective cohort study, we observed a graded positive relationship between serum UA levels and risks of all-cause and cardiovascular mortality in patients with CRS, irrespective of eGFR levels. The association remained stable for all-cause and cardiovascular mortality along the entire follow-up duration. Nevertheless, hyperuricemia solely increased the short-term risk of MACE and HHF.

Our finding has extended our understanding of the correlation between elevated serum UA levels and increased risk of mortality, MACE, and HHF to HF patients with concurrent reduced renal function, a population characterized by strikingly high rates of morbidity and mortality. Previous meta-analysis and research had associated UA with mortality in patients with either acute or chronic HF [17,18]. Nonetheless, in the context of CRS, such relationship remains obscure because of limited evidence and inconsistent findings [12–15]. A randomized controlled study (RCT) [12] involving 2645 patients with advanced chronic systolic HF, along with a prospective multicenter registry cohort [13] of 4652 chronic HF patients from Japan, revealed that elevated serum UA levels were associated with an increased risk of mortality exclusively in HF patients with eGFR ≥60 mL/min/1.73 m^2. In contrast, another RCT [15] involving 4133 patients hospitalized for worsening advanced chronic HF indicated such association was significant only in subgroup with eGFR ≥30 mL/min/1.73 m^2. However, a single-center retrospective cohort involving 9647 chronic HF patients from China, discovered a significant association between elevated serum UA levels and mortality irrespective of eGFR grades [14]. To our knowledge, our study is the first to demonstrate a positive correlation between serum UA levels and both all-cause and cardiovascular mortality in patients with CRS based on a prospective nationwide cohort. Our finding was also supported by those from general CKD populations, where elevated uric acid levels have been linked to increased risk of all-cause and cardiovascular mortality in patients with CKD [19–21].

These inconsistent findings may be attributed to differences in the study populations, sample size, follow-up period, and baseline characteristics. Furthermore, the distinct impacts of metabolic and renal hyperuricemia may also contribute to the situation. In patients with CRS, elevated UA stems from at least two processes: overproduction facilitated by the augmented activity of xanthine oxidase and inadequate renal excretion due to renal dysfunction and/or administration of diuretics [22]. Metabolic hyperuricemia may potentially be more harmful than renal hyperuricemia, considering the excessive production of reactive oxygen species (ROS) during the metabolism of purines into UA.

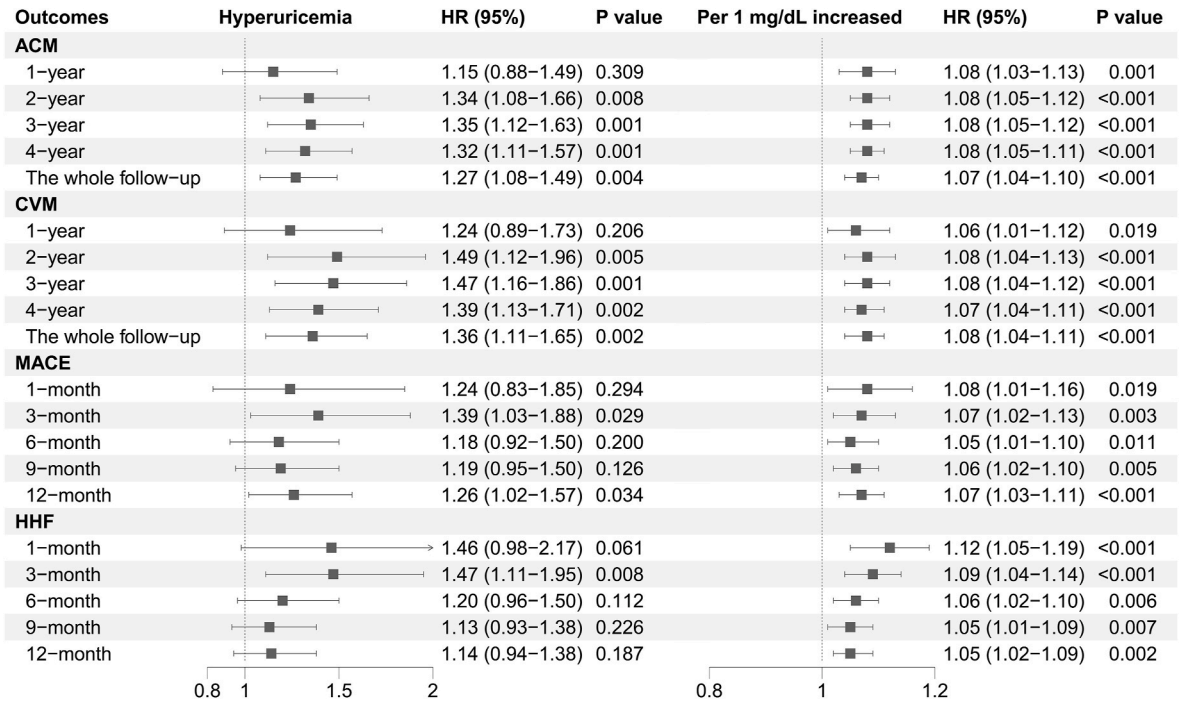

Fig. 3. Associations between serum uric acid levels and outcomes within various follow-up durations in patients with cardiorenal syndrome.
Adjusted for age, gender, body mass index, smoking status, stroke, ischemic heart diseases, hypertension, diabetes, anemia, history of heart failure, LVEF, NYHA functional classification, NT-proBNP levels, eGFR stages, hypoalbuminemia, hypertriglyceridemia, and use of diuretics.

Any hyperuricemia could be regarded as a blend of both metabolic and renal hyperuricemia, with the proportion of these two components varying among individuals and determining the final harmful effects of hyperuricemia. Additionally, UA's dual nature as both an antioxidant and a pro-oxidant, contingent upon specific conditions, could also partly explain the observed inconsistency in these findings.

It is important to highlight that within our study, the correlation between hyperuricemia and mortality remained significant even as the observation period was extended. Furthermore, UA proved additional prognostic value in predicting long-term mortality among patients with CRS. The findings, coupled with the easy accessibility and affordability of UA testing, suggest that it could serve as a reliable and stable biomarker for stratifying mortality risk. Consequently, UA should be routinely screened for and even regularly monitored in patients with CRS. But it remains debating whether UA could be a modifiable risk factor to be targeted to improve prognosis. Traditional urate-lowering medications, such as xanthine oxidase inhibitors and uricosuric agents, failed to confer any benefits to HF patients [23], whereas the newly developed urate-lowering drugs, namely sodium-glucose cotransporter 2 inhibiter (SGLT2i) and angiotensin receptor-neprilysin inhibitor (ARNI), have exhibited promising efficacy [24]. In fact, patients with a high xanthine oxidase (XO) activity should be the ideal target for urate-lowering therapies (ULT) while it could be unsuccessful, or potentially harmful, in patients with a low XO activity. In HF or CRS patients, multiple factors contribute to elevated UA levels, including renal dysfunction, intensive usage of diuretics, and neurohumoral activation-mediated pathways such as oxidative stress and inflammatory cascades. Traditional ULT that enhance UA excretion represent a downstream therapeutic approach and have not demonstrated prognostic benefits in HF. In contrast, novel agents like SGLT2i and ARNI primarily reduce UA production by targeting the underlying pathophysiology of HF and improve prognosis, constituting an upstream therapeutic strategy. However, the extent to which this prognostic improvement stems directly from UA reduction remains unclear. Considering UA's dual function as both an antioxidant and a pro-oxidant, as well as the potential risks associated with both hyperuricemia and hypouricemia [25], further clinical trials are needed to establish the threshold values for starting urate-lowering treatment and the optimal target levels to minimize the mortality risk in patients with HF.

Many factors can influence UA levels and potentially modify the association between elevated UA levels with adverse outcomes. Therefore, we elaborated detailed subgroup analyses. We found the association between UA and mortality were notably more pronounced in CRS patients with exacerbated chronic HF, as well as in those without hypertension or hypoalbuminemia, as compared with their respective counterparts. The diminished association in patients with hypoalbuminemia may be ascribed to malnutrition. Malnutrition is closely related with hypoalbuminemia and leads to decreased serum UA levels [26]. Hypouricemia can also increase the risk of mortality [27] partly due to insufficient UA to counteract ROS within the body. When evaluating the impact of hyperuricemia, patients with hypouricemia naturally are categorized in the control group, which can attenuate the observed association with hyperuricemia in the subgroup with hypoalbuminemia. In CRS patients with hypertension, the underlying common links between hypertension and hyperuricemia and the potent effect of hypertension may mask the effect of hyperuricemia on mortality [28].

Our findings may have significant clinical relevance and public health implications. HF is the final stage of various cardiovascular diseases, with an escalating prevalence. Kidney disease affects more than 50 % of HF patients and markedly increased risk of a variety of morbidities and mortality. Hyperuricemia is prevalent both in HF patients and CKD patients. In this context, our findings, by shedding confirmative lights on the impact of UA on mortality in patients with CRS, may be helpful for optimizing their management and improving their survival.

The mechanism underlying the link between hyperuricemia and adverse outcomes is believed to be multifaceted, although it has not been fully clarified. During the metabolism of purines into UA, ROS is naturally generated. Normally, UA functions as a potent antioxidant in extracellular environments. However, at elevated intracellular concentrations, it acts as a pro-oxidant. In conjunction with ROS produced

during purine metabolism, it enhances oxidative stress [29]. Additionally, hyperuricemia can exacerbate inflammation, activate the renin-angiotensin-aldosterone system, cause endothelial cell dysfunction, affect cellular activities such as cell proliferation, and interact with the immune system. These detrimental effects, along with their facilitation of the development and progression of various diseases—including kidney disease, HF and other cardiovascular diseases, type 2 diabetes, hypertension, dyslipidemia, and metabolic syndrome, collectively contribute to an increased risk of morbidity and mortality [30].

Our study has several strengths, including a nationally representative sample, a substantial large sample size, comprehensive statistical methods involving numerous sensitivity analyses, and multiple covariates that allow for rigorous confounding control. However, there are still limitations to be noted. Firstly, we only examined the baseline serum UA and eGFR and did not observe the change of those parameters in the whole follow-up. Secondly, we did not record the using of urate lowering drugs in this study. Thirdly, our study could not distinguish between acute and chronic renal impairment, nor determine the temporal sequence of heart failure and renal dysfunction. Consequently, our study population may include patients with both Type 1 and Type 3 cardiorenal syndrome. Fourthly, the extended duration of follow-up in this study overlapped with the COVID-19 pandemic [31], the absence of specific follow-up data related to pandemic-related disruptions limited our ability to account for potential confounding effects of COVID-19 infections on outcomes. Finally, as an observational study, there may be residual confounding and reverse causality which may bias the association between uric acid and adverse outcomes in the present study.

5. Conclusion

Hyperuricemia increases the risk of short-term and long-term adverse outcomes especially all-cause and cardiovascular mortality in patients with CRS. These findings indicated the importance of the management of serum UA in CRS patients and UA may represent a useful measure in prognostic stratification of this specific population.

CRediT authorship contribution statement

Zhanyuan Chen: Writing – original draft, Visualization, Software, Formal analysis, Conceptualization. **Yaoyao Wang:** Project administration, Methodology, Data curation. **Lili Liu:** Supervision, Resources, Investigation. **Xuejiao Liu:** Supervision, Resources, Investigation. **Rui Zhu:** Validation. **Yu Wei:** Validation. **Lihua Zhang:** Methodology, Investigation. **Jianfang Cai:** Writing – review & editing, Supervision, Project administration, Funding acquisition.

Data availability statement

The data underlying this article are sensitive health data and cannot be shared publicly due to privacy reasons. The data will be shared on reasonable request to the corresponding author.

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Declaration of Competing interest

All the authors declared no competing interest.

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Appendix A. Supplementary data

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