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Association of serum uric acid change with mortality, renal function and diuretic dose administered in treatment of acute heart failure

H.-B. Zhou [a,1], T.-Y. Xu [b,c,1], S.-R. Liu [a], Y.-J. Bai [a], X.-F. Huang [a], Q. Zhan [a], Q.-C. Zeng [a], D.-L. Xu [a,*]

[a] State Key Laboratory of Organ Failure Research, Department of Cardiology, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China
[b] State Key Laboratory of Cardiovascular Disease, Heart Failure Center, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, 167 Beilishi Road, Beijing 100037, China
[c] First School of Clinical Medicine, Southern Medical University, Guangzhou 510515, China

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Abstract *Background and aims:* Hyperuricemia is reportedly associated with poor outcome in acute heart failure (AHF). The association between changes in Uric acid (UA) levels with renal function change, diuretic doses, and mortality in patients with AHF were studied.
Methods and results: Consecutive patients hospitalized with AHF were reviewed (n = 535). UA levels were measured at admission and either at discharge or on approximately the seventh day of admission. Patients with an UA change in the top tertile were defined as having an increase (UA-increase) and were compared to those outside the top tertile (non-UA-increase). The endpoint was all-cause mortality, with a mean follow-up duration of 22.2 months. Patients in the UA-increase group presented with greater creatine increase ($P < 0.001$), and were administered a higher average daily dose of loop diuretic ($P = 0.016$) compared with the non-UA-increase group. In-hospital UA-increase was associated with higher risk of mortality even after adjusting for confounding variables including creatine change and diuretic dosage [harzard ratio (HR) 1.53, 95% confidence interval (CI) 1.02–2.30, $P = 0.042$]. In patients with hyperuricemia on admission, UA-increase was associated with increased mortality (adjusted HR 2.21, 95% CI 1.38–3.52, $P = 0.001$). Whereas, in those without admission hyperuricemia, UA-increase had no significant association with mortality.
Conclusions: An increase in UA during in-hospital treatment is associated with an increase in creatine levels and daily diuretic dose. Mortality associated with increased UA is restricted to patients who already have hyperuricemia at admission. A combination of UA levels at admission and UA changes on serial assessment during hospitalization may be additional value in the risk stratification of AHF patients.

Introduction

Uric acid (UA), the final product of purine metabolism by xanthine oxidase (XO), is produced primarily in the liver and excreted predominantly by the proximal tubules [1]. UA has been recognized as a marker of diverse activities, among

* Corresponding author. Department of Cardiology, Nanfang Hospital, Southern Medical University, 1838 Northern Guangzhou Avenue, Guangzhou 510515, China. Fax: +86 020 61360416.
E-mail address: dinglixu@fimmu.com (D.-L. Xu).
[1] These authors contributed equally to this work.

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which are impaired oxidative metabolism, inflammatory cytokine activation, endothelial dysfunction and insulin resistance [2–5]. In particular, elevated UA level is a risk factor for diabetes, chronic kidney disease (CKD), and several cardiovascular diseases, including hypertension, coronary and cerebrovascular diseases and heart failure (HF) [6].

Hyperuricemia, defined as UA level greater than 7.0 mg/dl for men and 6.0 mg/dl for women, is a common condition affecting approximately half of HF admissions [7–9]. The elevation in serum UA levels is usually attributed to both increased production, caused by increased XO activity, and impaired excretion, caused by impaired renal function or diuretic treatment. Epidemiological studies have explored the role of hyperuricemia in both chronic and acute heart failure (AHF) and consistently indicate that in patients hospitalized for HF, the presence of hyperuricemia is a significant independent predictor of poor outcome [8–11]. More recently, Mantovani et al. grouped chronic heart failure (CHF) patients into tertiles of UA, and found those in the top UA tertile to have poor long-term survival and increased risk of hospitalization [12].

Accumulating evidence suggests that increased XO activity rather than UA itself is involved in the pathophysiology of HF and contributes to poorer outcome [11,13,14].

However, previous studies on hyperuricemia merely focused on UA levels at a single timepoint, either at the time of admission or discharge, when general clinical status is likely to be either poor or improved. Nothing is known about the effects of short-term changes in UA concentration during the treatment of AHF on survival and its association with concomitant changes in renal function and loop diuretic use. Therefore, we sought to determine whether an increase in serum UA was associated with a higher risk of all-cause mortality. In addition, considering the influence of renal function and diuretic therapy on UA levels, we further aimed to determine the relationship between UA-increase with renal function change, and diuretic usage in patients with hospitalization for AHF.

Methods

Study population

Records of consecutively admitted patients between April 2011 and July 2015 to Nanfang hospital, Southern Medical University with a primary discharge diagnosis of AHF and documented left ventricular ejection fraction (LVEF) at the time of admission were reviewed. AHF was defined according to the Chinese Society of Cardiology guidelines on heart failure HF as a rapid onset of symptoms and signs secondary to abnormal cardiac function requiring urgent treatment [15,16]. Demography, physical examination, laboratory tests, echocardiography, medical history, prescriptions and medication related data were collected retrospectively from hospital clinical database for analysis. The assessment of LVEF by echocardiography was standardized. Guideline-recommended medical therapy was administered to all the patients. Inclusion criteria included a baseline (within 24 h) N-terminal pro-brain natriuretic peptide (NT-proBNP) level >300 pg/ml along with a length of stay ≥3 days. We excluded patients who were taking antihyperuricemic agents, and who were <18 years of age. Those with acute myocardial infarction, primary pulmonary arterial hypertension, malignant hematological diseases, severe anemia (hemoglobin <6 g/dl), end stage kidney disease (requiring renal replacement therapy) and malignancy were excluded. Patients who died during hospitalization and those without follow-up data were also excluded. For those with multiple hospitalizations, only data from the first hospitalization were included for analysis. The study was approved by the institutional review board of Nanfang Hospital. No patient consent was required because the data in this study was anonymized.

Definition of covariates

Venous blood samples for measurements of UA were taken within 24 h of admission (baseline) and either at discharge or on approximately the seventh day postadmission (whichever came first, second timepoint). For the second timepoint, UA values obtained outside the 3–10 day postadmission window were excluded. Furthermore, patients with incomplete baseline/second timepoint pairs of UA levels were excluded. The patient population was dichotomized based on the baseline to second timepoint change in UA. Patients with an UA change in the top tertile (in-hospital UA change >30 μmol/L) were defined as having an increase (UA-increase). Hyperuricaemia was defined as a baseline UA level of >7 mg/dl for men and >6 mg/dl for women [8]. To assess the joint effect of baseline UA levels and in-hospital changes of UA levels on survival, the patient population was stratified into four subgroups based on baseline hyperuricemia status and the presence of UA-increase during hospitalization.

Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation [17]. Worsening renal function (WRF) was defined as an increase in serum creatine of ≥0.3 mg/dl (≥26.4 umol/L) from baseline to the second timepoint [18]. Loop diuretic doses were converted to furosemide equivalents (1 mg bumetanide = 20 mg torsemide = 80 mg furosemide for oral diuretics, and 1 mg bumetanide = 20 mg torsemide = 40 mg furosemide for intravenous diuretics). Average daily loop diuretic doses from admission to the second timepoint were calculated.

Follow-up

Information regarding survival was obtained by telephone contact, or from the medical records up to April 1, 2016. The primary endpoint was death from any cause after discharge.

Statistical analysis

Normally distributed continuous variables were presented as mean ± SD, while non-normal data was presented as median and interquartile range (IQR). Categorical variables

were presented as percentages. Differences between groups were tested by the Chi-sqaure test for categorical data and the independent Student' t-test, Mann-Whitney-*U* test, Analysis of Variance, or the Kruskal–Wallis test for continuous data, as appropriate. Kaplan–Meier curves were used to evaluate survival and differences in survival between groups were tested using the log-rank test. Cox proportional hazards models were used to identify predictors of mortality. Cox models fulfilled the proportional-hazards assumption (using R software version 3.2.2). Variables with >10% missing values were not included in the univariate analysis. Variables with a P-value <0.1 at univariate analysis were entered into multivariate models. Variables that had a $p > 0.1$ but were clinically relevant were also included in the models. Among variables that showed multicollinearity, only one was included in multivariate analysis. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated.

A P value < 0.05 was considered statistically significant. All tests were two-sided. All analyses were performed using SPSS version 20.0 (IBM SPSS Statistics, IBM Corporation, Armonk, New York).

Result

Clinical characteristics of the population

The mean admission UA concentration was 8.3 ± 2.7 mg/dl. Hyperuricemia at baseline was present in 72.7% (389) of the patients (Table 1). The mean change in UA among patients in the top tertile was 1.7 ± 1.1 mg/dl (102.9 ± 66.6 umol/L).

Characteristics of patients with and without UA-increase are shown in Table 1. Patients who developed UA-increase were more likely to be older, diabetic, to have a higher systolic blood pressure, lower baseline UA, lower hemoglobin levels and were less likely to suffer from hyperuricemia at baseline (all $p < 0.01$) compared to those who did not. Disease severity indicators such as New York Heart Association (NYHA class IV, LVEF, NT-proBNP) level and administered medical therapy did not demonstrate a statistically significant difference between the two groups. The in-hospital or discharge use of angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs), beta-blockers and aldosterone antagonists were not significantly different between groups.

Table 2 shows characteristics of the four patient subgroups based on their baseline hyperuricemia status and in-hospital UA change. Among patients with hyperuricemia on admission, baseline indicators of HF disease severity were similar regardless of changes in UA level.

Relationship of UA-increase with renal function and loop diuretic use

There were no significant between-group differences in baseline renal function measured as eGFR between the two groups (Table 1). CKD was equally common on admission among grous. However, in-hospital change in creatinine levels were significantly greater in patients with increased UA compared to those without (0.12 ± 0.40 vs. −0.11 ± 0.46 mg/dl; $P < 0.001$). WRF was seen in 11.6% of the patients and was significantly more common in patients experiencing UA-increase. The percentage of patients that received loop diuretics over the hospitalization or at discharge was similar between groups. However, patients in the UA-increase group were more likely than those in the non-increased UA group to be treated with significantly higher daily doses of loop diuretic during hospitalization.

On subgroup analysis (Table 2), in patients with hyperuricemia, UA-increase was associated with impaired renal function on admission and WRF during hospitalization, and were administered a higher average daily dose of diuretic in comparison with non-UA-increase patients.

Associations with mortality

A total of 116 (21.7%) deaths occurred over a mean follow-up period of 22.2 ± 13.8 months. Kaplan–Meier curves revealed that baseline hyperuricemia and UA-increase were both associated with significantly higher mortality (Fig. 1A, B, respectively). Consistent with findings from previous studies, baseline hyperuricemia was associated with higher risk of all-cause mortality before (HR 1.86, 95% CI 1.16–2.99, P = 0.010) and after (HR 1.86, 95% CI 1.09–3.16, P = 0.023) adjustment for age, diastolic blood pressure, NYHA class IV, sodium, eGFR, NTpro-BNP (log), hemoglobin, albumin, diabetes mellitus, WRF, in-hospital ACE inhibitors/ARBs and betablocker use as well as creatinine change and daily loop diuretic doses (Table 3). UA-increase was associated with a significantly higher risk of mortality compared with non-UA-increase (HR 1.47, 95% CI 1.02–2.13, P = 0.039). This association persisted after adjusting for the aforementioned confounders (HR 1.53, 95% CI 1.02–2.30, P = 0.042).

Figure 2 displays survival curves according to hyperuricemia and UA-increase. On subgroup analysis stratified by baseline hyperuricemia status, in patients with hyperuricemia at admission UA-increase was associated with a higher risk of mortality (HR 1.93, 95% CI 1.28–2.90, P = 0.002). This pattern remained after multivariable adjustment for the aforementioned confounding variables (HR 2.21, 95% CI 1.38–3.52, P = 0.001). In those not experiencing hyperuricemia at admission, UA-increase lost its predictive power both before (HR 1.04, 95% CI 0.44–2.45, P = 0.930) and after adjustment for mortality-associated variables.

Discussion

This study demonstrates that among patients hospitalized with AHF, patients showing a more prominent increase in UA levels during hospitalization also present with greater increase in creatine and are administered a higher average daily dose of loop diuretic. In addition, an in-hospital increase in UA levels is associated with increased risk of death independent of creatine change and diuretic dosage.

Table 1 Characteristics of Patients grouped by Hyperuricemia on Admission or In-hospital UA-increase respectively.

Variables	Total	Hyperuricemia			UA-increase		
		Yes	No	P-value	Yes	No	P-value
	(n = 535)	(n = 389)	(n = 146)		(n = 179)	(n = 356)	
Demographics							
Age, years	65.4 ± 14.2	64.7 ± 14.5	67.2 ± 13.1	0.065	67.6 ± 13.5	64.3 ± 14.4	0.010
Female	200 (37.4)	150 (38.6)	50 (34.2)	0.358	57 (31.8)	143 (40.2)	0.060
Admission physical examination							
Systolic BP, mm Hg	132.3 ± 25.0	131.3 ± 24.9	134.9 ± 25.0	0.135	136.9 ± 26.0	130.0 ± 24.1	0.002
Diastolic BP, mm Hg	78.7 ± 15.5	78.7 ± 15.8	78.8 ± 14.7	0.975	79.7 ± 14.6	78.2 ± 15.9	0.289
Heart rate, beats/min	89.1 ± 24.5	89.0 ± 23.6	89.2 ± 26.8	0.929	86.8 ± 22.9	90.2 ± 25.2	0.129
BMI, kg/m^2	23.1 ± 3.9	23.3 ± 4.1	22.5 ± 3.3	0.030	23.4 ± 3.6	22.9 ± 4.1	0.260
NYHA class IV	158 (29.5)	134 (34.4)	24 (16.4)	<0.001	52 (29.1)	106 (29.8)	0.862
Echocardiography data							
LVEF, %	47.6 ± 12.7	46.5 ± 12.8	50.6 ± 11.6	0.001	47.9 ± 12.0	47.5 ± 13.0	0.727
HFrEF	150 (28.0)	124 (31.9)	26 (17.8)	0.001	47 (26.3)	103 (28.9)	0.516
LVEDD, mm	53.4 ± 10.5	54.5 ± 10.8	50.2 ± 9.0	<0.001	53.4 ± 10.1	53.3 ± 10.6	0.972
Laboratory values							
Sodium, mEq/L (baseline)	139.5 ± 4.2	139.3 ± 4.2	140.0 ± 4.1	0.116	139.9 ± 4.3	139.3 ± 4.1	0.167
Sodium, mEq/L (2nd timepoint)	139.4 ± 4.7	139.5 ± 4.5	139.1 ± 5.3	0.395	139.4 ± 4.8	139.4 ± 4.7	0.952
Absolute sodium change, mEq/L[a]	−0.04 ± 5.0	0.3 ± 4.6	−0.8 ± 5.8	0.031	−0.4 ± 5.1	0.1 ± 4.9	0.286
Uric acid, mg/dl (baseline)	8.3 ± 2.7	9.4 ± 2.3	5.4 ± 1.0	<0.001	7.4 ± 2.3	8.8 ± 2.8	<0.001
Uric acid, mg/dl (2nd timepoint)	7.8 ± 2.7	8.6 ± 2.5	5.8 ± 1.9	<0.001	9.1 ± 2.6	7.2 ± 2.5	<0.001
Absolute uric acid change, mg/dl	−0.5 ± 2.2	−0.8 ± 2.2	0.4 ± 1.7	<0.001	1.7 ± 1.1	−1.6 ± 1.7	<0.001
eGFR, ml/min/1.73m^2	59.0 ± 28.8	54.4 ± 27.9	71.5 ± 27.5	<0.001	57.2 ± 30.0	59.9 ± 28.1	0.303
Creatinine, mg/dl (baseline)	1.42 ± 0.83	1.53 ± 0.87	1.12 ± 0.60	<0.001	1.53 ± 0.95	1.36 ± 0.75	0.044
Creatinine, mg/dl (2nd timepoint)	1.38 ± 0.92	1.47 ± 0.96	1.16 ± 0.74	<0.001	1.65 ± 1.12	1.25 ± 0.77	<0.001
Absolute creatinine change, mg/dl	−0.04 ± 0.45	−0.06 ± 0.47	0.04 ± 0.41	0.021	0.12 ± 0.40	−0.11 ± 0.46	<0.001
NT-proBNP, pg/mL	3858.0 (1541.0–8265.0)	4576.0 (1663.5–9281.5)	2538.5 (1252.0–6129.3)	<0.001	4257.0 (1750.0–7706.0)	3754.0 (1445.5–8412.8)	0.393
Hemoglobin, g/dL	12.6 ± 2.4	12.7 ± 2.5	12.4 ± 2.2	0.139	12.2 ± 2.3	12.8 ± 2.5	0.009
Albumin, g/dL	3.6 ± 0.5	3.7 ± 0.5	3.6 ± 0.6	0.041	3.6 ± 0.5	3.7 ± 0.5	0.247
Medical history							
Hypertensive etiology	136 (25.4)	97 (24.9)	39 (26.7)	0.674	48 (26.8)	88 (24.7)	0.599
Ischemic heart disease	204 (38.1)	131 (33.7)	73 (50.0)	0.001	65 (36.3)	139 (39.0)	0.539
Dilated cardiomyopathy	114 (21.3)	101 (26.0)	13 (8.9)	<0.001	39 (21.8)	75 (21.1)	0.848
Diabetes mellitus	150 (28.0)	106 (27.2)	44 (30.1)	0.508	65 (36.3)	85 (23.9)	0.003
Stroke	55 (10.3)	34 (8.7)	21 (14.4)	0.056	21 (11.7)	34 (9.6)	0.433
CKD	294 (55.0)	242 (62.2)	52 (35.6)	<0.001	107 (59.8)	187 (52.5)	0.112
WRF	61 (11.6)	44 (11.6)	17 (11.6)	0.999	34 (19.3)	27 (7.8)	<0.001
Atrial fibrillation	168 (31.4)	127 (32.6)	41 (28.1)	0.311	49 (27.4)	119 (33.4)	0.155
Medications after admission							
Daily IV loop diuretic, mg[b]	20.0 (8.6–33.3)	21.7 (10.0–36.0)	10.9 (3.6–26.7)	<0.001	22.5 (10.0–36.0)	20.0 (8.0–31.0)	0.031
Loop diuretic	468 (87.6)	348 (89.7)	120 (82.2)	0.019	161 (89.9)	307 (86.5)	0.251
ACE inhibitor/ARB	392 (73.3)	278 (71.5)	114 (78.1)	0.123	135 (75.4)	257 (72.2)	0.426
Beta-blocker	351 (65.6)	251 (64.5)	100 (68.5)	0.389	123 (68.7)	228 (64.0)	0.283
Aldosterone antagonist	432 (80.7)	316 (81.2)	116 (79.5)	0.641	150 (83.8)	282 (79.2)	0.204
Medications at discharge							

Loop diuretic	386 (76.0)	292 (79.3)	94 (67.1)	0.004	136 (80.5)	250 (73.7)	0.094
ACE inhibitor/ARB	331 (65.2)	240 (65.2)	91 (65.0)	0.963	108 (63.9)	223 (65.8)	0.676
Beta-blocker	287 (56.5)	206 (56.0)	81 (57.9)	0.703	95 (56.2)	192 (56.6)	0.928
Aldosterone antagonist	365 (71.9)	271 (73.6)	94 (67.1)	0.146	118 (69.8)	247 (72.9)	0.473

Values are mean ± SD, n (%), or median (interquartile range).
BP, blood pressure; BMI, body mass index; NYHA, New York Heart Association; LVEF, left ventricle ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEDD, left ventricular end-diastolic diameter; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; CKD, chronic kidney disease; WRF, worsening renal function; ACE inhibitor/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.
[a] 4.1% (22 of 535 cases) of values for Serum sodium at the second time point were missing.
[b] Average daily dose of intravenous loop diuretics (in furosemide dose equivalents).

Most importantly, UA-increase is an adverse prognostic sign only in patients with hyperuricemia at baseline and is not a risk factor in those with normal baseline UA levels. These findings suggest that, in routine clinical practice, the use of a combination of UA levels at admission and serial measurements of UA levels during hospitalization may be more accurate in identification of high-risk patients than baseline UA alone.

In this study we observed a high prevelance of hyperuricemia. While most studies on chronic heart failure have reported lower mean UA values than observed herein [12,19], mean UA values comparable to those reported herein have been reported in multiple studies investigating acute heart failure [20,21]. Furthermore, it must be noted that due to dietary habits and economic development, the prevelance of hyperuricemia in the general population is known to be higher in south China [22]. This study found that the presence of hyperuricemia can independently predict all-cause mortality, therefore corroborating the findings obtained in previous studies [8−11]. Pascual-Figal et al. found an association between hyperuricemia measured prior to discharge and increased risk for death, new HF readmission and the combined event over a median 20.4-month period of follow-up in patients with AHF and reduced ejection fraction [8]. In a retrospective analysis from the Loop Diuretics Administration and Acute Heart Failure (Diur-HF) trial, Palazzuoli et al. found hyperuricemia was independently predictive of HF hospitalization and death at 6 months [10]. Of interest, the study conducted in decompensated servere HF patients by Ochiai et al. yielded inconsistent results, having found renal dysfunction, but not hyperuricemia, was associated with mortality [23]. Our study extends these results by showing for the first time, to the best of our knowledge, that an in-hospital increase in UA is associated with increased risk of death, and this association is confined to patients already experiencing hyperuricemia at admission.

Although hyperuricemia portends negative outcomes in heart failure, the exact mechanisms linking hyperuricaemia and HF have not been completely established. Whether the predominant driver for hyperuricemia-associated mortality is UA itself or whether an elevated UA level is a mere marker of increased XO activity, which actually carries negative prognostic effects, is not clearly established. However, an increasing amount of data supports that XO activity may indeed be a pathophysiological contributor to heart failure disease progression, rather than the serum UA itself. This is supported by the following. First, XO activity are increased in CHF patients compared to controls [24]. Second, in a previous study comparing the prognostic significance of hyperuricaemia in systolic HF, among patients with CKD versus those without, hyperuricaemia predicted dismal prognosis only in those without CKD, suggesting that unfavorable survival may be due principally to increased XO activity rather than reduced renal excretion of serum UA [11]. Third, in an interventional study involving patients with mild to moderate systolic CHF, XO inhibitor therapy with

Table 2 Characteristics of patients subgrouped based on both Hyperuricemia on Admission and In-hospital UA-increase.

Variables	Hyperuricemia		Non-hyperuricemia		P-value
	UA-increase	Non-UA-increase	UA-increase	Non-UA-increase	
	(n = 105)	(n = 284)	(n = 74)	(n = 72)	
Demographics					
Age, years	68.3 ± 13.7	63.4 ± 14.6	66.6 ± 13.3	67.7 ± 13.0	0.006
Female	34 (32.4)	116 (40.8)	23 (31.1)	27 (37.5)	0.280
Admission physical examination					
Systolic BP, mm Hg	136.4 ± 24.6	129.4 ± 24.8	137.5 ± 28.0	132.2 ± 21.4	0.018
Diastolic BP, mm Hg	80.5 ± 15.0	78.1 ± 16.1	78.6 ± 14.2	78.9 ± 15.3	0.585
Heart rate, beats/min	86.3 ± 21.8	90.0 ± 24.2	87.5 ± 24.5	91.0 ± 29.1	0.476
BMI, kg/m^2	23.9 ± 3.8	23.1 ± 4.2	22.6 ± 3.0	22.4 ± 3.6	0.073
NYHA class IV	36 (34.3)	98 (34.5)	16 (21.6)	8 (11.1)	<0.001
Echocardiography data					
LVEF, %	47.2 ± 12.2	46.2 ± 13.1	48.8 ± 11.9	52.6 ± 11.1	0.001
HFrEF	31 (29.5)	93 (32.7)	16 (21.6)	10 (13.9)	0.008
LVEDD, mm	54.2 ± 10.5	54.6 ± 10.9	52.2 ± 9.5	48.2 ± 7.9	<0.001
Laboratory values					
Sodium, mEq/L (baseline)	139.7 ± 4.1	139.2 ± 4.2	140.1 ± 4.5	139.9 ± 3.8	0.289
Sodium, mEq/L (2nd timepoint)	139.3 ± 5.6	139.5 ± 4.0	139.4 ± 3.4	138.7 ± 6.7	0.637
Absolute sodium change, mEq/L[a]	−0.3 ± 5.3	0.5 ± 4.3	−0.4 ± 4.9	−1.2 ± 6.6	0.057
Uric acid, mg/dl (baseline)	8.8 ± 1.8	9.7 ± 2.4	5.3 ± 1.1	5.5 ± 0.9	<0.001
Uric acid, mg/dl (2nd timepoint)	10.5 ± 2.1	7.9 ± 2.2	7.0 ± 1.7	4.6 ± 1.2	<0.001
Absolute uric acid change, mg/dl	1.7 ± 1.1	−1.8 ± 1.8	1.7 ± 1.2	−0.9 ± 0.9	<0.001
eGFR, ml/min/1.73 m^2	48.0 ± 26.0	56.7 ± 28.2	70.3 ± 30.7	72.6 ± 23.9	<0.001
Creatinine, mg/dl (baseline)	1.76 ± 1.02	1.44 ± 0.79	1.20 ± 0.72	1.04 ± 0.44	<0.001
Creatinine, mg/dl (2nd timepoint)	1.90 ± 1.22	1.30 ± 0.80	1.30 ± 0.86	1.02 ± 0.58	<0.001
Absolute creatinine change, mg/dl	0.14 ± 0.38	−0.14 ± 0.47	0.10 ± 0.41	−0.02 ± 0.41	<0.001
NT-proBNP, pg/mL	4536.0 (2093.5–8924.5)	4697.0 (1559.3–9285.8)	3606.5 (1546.0–7177.5)	1936.5 (960.0–4217.5)	<0.001
Hemoglobin, g/dL	12.4 ± 2.3	12.8 ± 2.5	12.0 ± 2.2	12.8 ± 2.2	0.038
Albumin, g/dL	3.7 ± 0.5	3.7 ± 0.5	3.5 ± 0.6	3.7 ± 0.5	0.016
Medical history					
Hypertensive etiology	27 (25.7)	70 (24.6)	21 (28.4)	18 (25.0)	0.931
Ischemic heart disease	33 (31.4)	98 (34.5)	32 (43.2)	41 (56.9)	0.002
Dilated cardiomyopathy	31 (29.5)	70 (24.6)	8 (10.8)	5 (6.9)	<0.001
Diabetes mellitus	37 (35.2)	69 (24.3)	28 (37.8)	16 (22.2)	0.024
Stroke	9 (8.6)	25 (8.8)	12 (16.2)	9 (12.5)	0.239
CKD	76 (72.4)	166 (58.5)	31 (41.9)	21 (29.2)	<0.001
WRF	23 (22.5)	21 (7.6)	11 (14.9)	6 (8.3)	0.001
Atrial fibrillation	33 (31.4)	94 (33.1)	16 (21.6)	25 (34.7)	0.258
Medications after admission					
Daily loop diuretic dose, mg[b]	25.0 (13.4–38.0)	20.0 (10.0–34.0)	16.0 (7.9–32.1)	8.5 (0.5–20.0)	<0.001
Loop diuretic	95 (90.5)	253 (89.4)	66 (89.2)	54 (75.0)	0.006
ACE inhibitor/ARB	77 (73.3)	201 (70.8)	58 (78.4)	56 (77.8)	0.451
Beta-blocker	69 (65.7)	182 (64.1)	54 (73.0)	46 (63.9)	0.539
Aldosterone antagonist	85 (81.0)	231 (81.3)	65 (87.8)	51 (70.8)	0.072
Medications at discharge					
Loop diuretic	82 (82.8)	210 (78.1)	54 (77.1)	40 (57.1)	0.001
ACE inhibitor/ARB	66 (66.7)	174 (64.7)	42 (60.0)	49 (70.0)	0.644
Beta-blocker	55 (55.6)	151 (56.1)	40 (57.1)	41 (58.6)	0.980
Aldosterone antagonist	69 (69.7)	202 (75.1)	49 (70.0)	45 (64.3)	0.293

Values are mean ± SD, n (%), or median (interquartile range).
BP, blood pressure; BMI, body mass index; NYHA, New York Heart Association; LVEF, left ventricle ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEDD, left ventricular end-diastolic diameter; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; CKD, chronic kidney disease; WRF, worsening renal function; ACE inhibitor/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.
[a] 4.1% (22 of 535 cases) of values for Serum sodium at the second time point were missing.
[b] Average daily dose of intravenous loop diuretics (in furosemide dose equivalents).

allopurinol was associated with an improvement in endothelial function, while uricosuric treatment without XO inhibition wasn't despite equivalent UA lowering [13]. Similarly, in a study by Ogino et al., uricosuric agent benzbromarone was not superior to placebo in improving plasma NT-proBNP levels and cardiac performance [14].

HF is characterized by tissue hypoxia resulting in increased XO activity, which may induce oxygen free radical accumulation, culminating in a wide range of

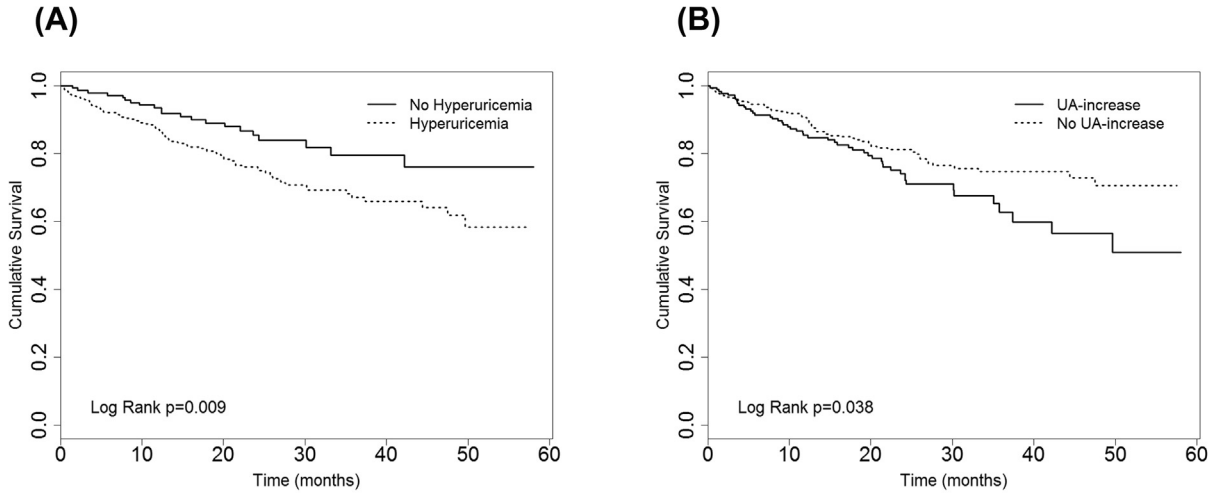

Figure 1 Kaplan–Meier survival curve stratified by hyperuricemia status at admission (A) and presence or absence of in-hospital UA-increase (B).

deleterious effects in HF pathophysiology [2,9,25]. Oxygen free radicals contribute to decreased cardiac function and an increased risk of cardiovascular events through multiple mechanisms including myocyte damage, endothelial dysfunction, overexpression of inflammatory cytokines and myocardial fibrosis [3,10,14]. Patients with decompensated heart failure receive optimized and aggressive treatment during hospitalization. An acute increase in UA despite optimal treatment may reflect further activation of XO, and may thereby be related to increased adverse outcomes. Our study therefore raises the question of whether an increased XO activity causes increased UA levels during hospitalization for AHF, and how this relates to subsequent survival.

The efficacy of XO inhibitor in HF remains controversial. Some clinical and experimental studies have shown that XO inhibition therapy with allopurinol has favorably improved endothelial function, myocardial energetics, myocardial perfusion as well as cardiac remodeling [13,26,27]. However, some studies also report contradictory findings [28–30]. Randomized, double-blind, placebo-controlled clinical trials investigating XO inhibitor therapy failed to demonstrate significant improvement in clinical outcomes despite lowering of UA [31,32]. The Efficacy and Safety Study of Oxypurinol Added to Standard Therapy in Patients With New York Heart Association Class III-IV Congestive Heart Failure (OPT-CHF) study did not reveal a particularly pronounced improvement in outcome with XO inhibitor treatment [31]. Recently, in The Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients (EXACT-HF) study involving patients with heart failure and a reduced ejection fraction, the inhibition of XO with allopurinol also did not show any difference in the risk of death or hospitalization at 24 weeks [32]. Further studies are warranted to determine whether the subset of patients with both admission hyperuricemia and an in-hospital UA-increase may benefit from urate lowering treatment.

The kidney is a prominent regulator of circulating uric acid levels. Approximately two-thirds of the UA is excreted by the kidney, with the remaining eliminated by gastrointestinal tract [33]. Serum UA exists primarily in the form of monosodium urate which is freely filtered through the

Table 3 Univariate and multivariable predictors of all-cause mortality.

Group		Cases/Deaths	Univariate		Multivariable	
			HR (95% CI)	P value	HR (95% CI)	P value
Baseline hyperuricemia[a]		389/95	1.86 (1.16–2.99)	0.010	1.86 (1.09–3.16)	0.023
UA-increase[a]		179/49	1.47 (1.02–2.13)	0.039	1.53 (1.02–2.30)	0.042
Yes baseline hyperuricemia	No UA-increase	284/57	1 (referent)		1 (referent)	
Yes baseline hyperuricemia	Yes UA-increase	105/38	1.93 (1.28–2.90)	0.002	2.21 (1.38–3.52)	0.001
No baseline hyperuricemia	No UA-increase	72/10	1 (referent)		1 (referent)	
No baseline hyperuricemia	Yes UA-increase	74/11	1.04 (0.44–2.45)	0.930	N/A	

HR, hazard ratio; CI, confidence interval; BP, blood pressure; BMI, body mass index; NYHA, New York Heart Association; LVEF, left ventricle ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEDD, left ventricular end-diastolic diameter; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; CKD, chronic kidney disease; WRF, worsening renal function; ACE inhibitor/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.

[a] No as referent group. Adjusted for age, diastolic blood pressure, NYHA class IV, sodium, eGFR, NT-proBNP (log), hemoglobin, albumin, diabetes mellitus, WRF, in-hospital ACE inhibitors/ARBs, beta-blocker use, creatinine change, daily loop diuretic doses.

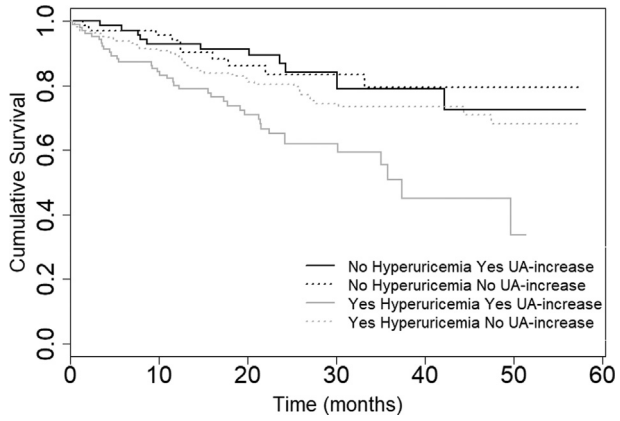

Figure 2 Kaplan–Meier survival curve for patients with combinations of hyperuricemia and UA-increase.

glomerulus, with about 90% being reabsorbed at proximal tubule [34]. Renal insufficiency and hyperuricemia are common and often coexistenting conditions and interact to worsen prognosis. A few studies have shown that patients who exhibit higher serum UA levels have worse renal function [9,21]. At the same time, Gerasimos et al. reported that hyperuricaemia was associated with adverse outcomes only in those without CKD [11]. Subsequently, data from the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trail showed that baseline UA was associated with a poorer prognosis in patients whose eGFR $\geq$30 ml/min/1.73 m^2 rather than in those whose eGFR $<$30 ml/min/1.73 m^2 [21]. A transient increase in serum creatinine levels secondary to overdiuresis, hypotension or initiation of ACE inhibitors/ARBs therapy during AHF therapy, constituting WRF, is a common condition but does not appear to affect post-discharge outcomes [35,36]. A decline in renal function occurring after hospitalization treatment may result in an impaired renal excretion of UA, thereby causing serum UA to increase. It should be noted that in the current analysis, change in creatinine levels were greater and WRF was more common in patients who developed UA-increase during AHF hospitalization. Increased UA levels may in large part be influenced by deteriorated renal function. However, in-hospital increase in UA was independently predictive of adverse outcome even after controlling for creatine change.

The majority of patients hospitalized with AHF have volume overload [37]. Diuretics are the cornerstone of therapy allowing removal of excessive volume and relieving the congestive signs and symptoms of AHF. Diuretics potentially increase serum UA level by stimulating UA reabsorption in the proximal tubule, and diuretic-induced elevations in serum UA are known to be dose-dependent [38,39]. In our patient population, we observed that patients experiencing UA-increase received higher daily loop diuretic doses. The change in UA levels might be a consequence of treatment because diuretics may potentially increase serum UA levels by stimulating UA reabsorption in the proximal tubule. Nevertheless, UA-increase was prognostically important independent of traditional risk factors including diuretic dosage.

Limitations

Our study had several limitations. First, the study was a retrospective design and data were generated from a single center. Second, due to the observational design of this study, it is impossible to prove causality and findings in our study are hypothesis generating. Third, we did not have serial measurements of NT-proBNP levels, echocardiographic parameters and serial assessments of NYHA class and volume status. Therefore, we were unable to describe the relation between these changes and UA-increase. In addition, data on rehospitalizations was not available in the present analysis.

Conclusion

This study found that an increase in uric acid during AHF therapy is associated with increased risk of mortality independent of creatine change and diuretic dosage. However, adverse outcomes were restricted to patients who were hyperuricemic on admission. The results suggest that combining both baseline UA levels and UA change during an AHF hospitalization might provide additive value in identifying patients at higher risk of death, and could even potentially serve as a new target for therapeutic intervention. Further investigation is necessary better understand the role of uric acid changes in patients with AHF.

Conflicts of interest

The authors declare no conflict of interest.

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