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Hyperuricemia complicated with acute kidney injury is associated with adverse outcomes in patients with severely decompensated acute heart failure☆

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ABSTRACT

Background: The relationship between the serum level of uric acid (UA) and the acute kidney injury on admission in patients with acute heart failure (AHF) remain unclear.
Methods and results: A total of 1326 AHF patients were screened, and data for 1047 patients who were admitted to the intensive-care unit were analyzed. The patients were assigned to a low-UA group (UA ≤ 7.0 mg/dl, $n = 569$) or a high-UA group (UA > 7.0 mg/dl, $n = 478$) according to their UA level at admission. Acute kidney injury (AKI) at admission was defined based on the ratio of the serum creatinine value recorded on admission to the baseline creatinine value: no-AKI ($n = 736$) or AKI ($n = 311$). The patients were therefore assigned to four groups: low-UA/no-AKI ($n = 428$), high-UA/no-AKI ($n = 308$), low-UA/AKI ($n = 141$) and high-UA/AKI ($n = 170$). The high-UA patients were significantly more frequent in the AKI group than in the non-AKI group among all patients and the non-chronic kidney injury (CKD) cohort. A Kaplan-Meier curve showed a significantly lower 365-day survival rate in the high-UA/AKI group than in the other groups. The multivariate Cox regression model identified only high-UA/AKI as an independent predictor of 365-day mortality (hazard ratio [HR]: 2.511, 95% confidence interval [CI] 1.671–3.772 in all AHF patients, HR: 1.884, 95% CI 1.022–3.473 in non-CKD patients and HR: 3.546, 95% CI 2.136–5.884 in CKD patients).
Conclusion: An elevated serum UA level complicated with AKI was an independent predictor of mortality in patients with severely decompensated AHF.

1. Introduction

An elevated level of serum uric acid (UA) had been recognized as a long-term prognostic predictor in patients with acute heart failure (AHF) [1–3]. Furthermore, hyperuricemia, which leads to adverse outcomes, has been reported to be closely associated with chronic kidney disease (CKD) in AHF [1,2]. For patients visiting an outpatient clinic, the mechanisms through which the serum UA levels are elevated has been considered to be the excessive intake of high-purine foods (productivity factors). However, some critically ill patients have shown elevated serum UA levels due to serious conditions, such as failed excretion by the kidney (excretory factors). In our previous report, although hyperuricemia itself was an independent predictor of the long-term prognosis in patients with AHF [1], the prognostic value of hyperuricemia was not associated with atherosclerotic risk factors, which were associated with the excessive intake of high-purine foods [4]. Thus, an elevated UA level not due to the excessive intake of purine-containing food might be associated with a poor outcome in AHF patients.

As a productivity factor in AHF patients, xanthine oxidoreductase (XOR), which is the generic term for xanthine oxidase (XO) and xanthine dehydrogenase (XDH), was newly suggested to be involved in the mechanism underlying the elevation in the serum UA level of AHF patients [5]. As an excretory factor, we focused on acute kidney injury (AKI) in the present study. The risk, injury, failure, loss, and end-stage (RIFLE) criteria have been established as the standard criteria for AKI in intensive-care patients, especially those with AHF [6,7]. We previously reported that 33.2% of AHF patients already have AKI at admission to the intensive-care unit (ICU) [7], and these patients exhibit a worse long-term prognosis than no-AKI patients among subjects with AHF

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[8]. We therefore hypothesized that AKI at admission is a factor inducing hyperuricemia in AHF patients, and elevated serum UA levels in patients complicated with AKI at admission might lead to adverse outcomes in cases of severely decompensated AHF. In the present study, we investigated the clinical data of AHF patients receiving emergency care to test this hypothesis.

2. Methods

2.1. Subjects

A total of 1326 patients with AHF admitted to the ICU of Nippon Medical School, Chiba Hokusoh Hospital, between January 2000 and July 2017 were enrolled in this study. One-hundred and seventy patients who did not undergo the measurement of serum UA were excluded from the study. In addition, 39 patients who had undergone renal replacement therapy before admission were excluded (there were no exclusion criteria regarding the creatinine value on admission). Furthermore, only the first admission was considered for patients who were readmitted to the ICU during the 1-year period after their discharge, so a further 70 patients were also excluded. A total of 1047 AHF patients who were admitted to the ICU were ultimately enrolled in this study.

AHF was defined as either new-onset HF or decompensation of chronic HF with symptoms sufficient to warrant hospitalization. The 2016 ESC Guidelines provide the level of evidence for the diagnosis of AHF. Based on this recommended evidence level, we diagnosed AHF by the measurement of plasma natriuretic peptide (i.e. a b-type natriuretic peptide [BNP] level of ≥100 pg/ml) (Class I, level A), a 12 lead electrocardiogram (Class I, level C), laboratory measurements (i.e. troponins, blood urea nitrogen [BUN], creatinine, sodium, potassium, glucose, liver function and complete blood count) (Class I, level C) and echocardiography (Class I, level C) [9]. Furthermore, all of the included patients were administered diuretics or vasodilators for the treatment of AHF. The treating physician in the emergency department diagnosed AHF based on these criteria within 30 min of admission and included the patient in the present study by filling out a form. All of the patients had a New York Heart Association (NYHA) functional class of either III or IV.

The patients who met any of the following criteria were admitted to the ICU: 1) patients who required high-flow oxygen inhalation (>6 L oxygen by mask) or mechanical support to treat orthopnea; 2) patients who required inotrope or mechanical support due to low blood pressure; and 3) patients who required various types of diuretics to improve general or lung edema. Patients with HF caused by acute coronary syndrome were excluded from the study. The treatment strategy was chosen by each physician.

2.2. Serum UA measurement

Serum samples were obtained from all 1047 patients on the day of admission, within 30 min of admission from 548 patients who were admitted from May 2011 to December 2014, and within 24 h of admission from 499 patients who were admitted from January 2000 to April 2011. The blood samples were collected into tubes within 15 min of admission and centrifuged within 30 min of admission. If it was difficult to examine the blood samples on the day of sampling, they were cooled to 2–10 °C. The samples of patients who were admitted between 9:00 AM and 5:00 PM (daytime) were usually examined immediately, while those of patients who were admitted between 5:00 PM and 9:00 PM (nighttime) were examined after being cooled to 2–10 °C. The timing of the examination did not affect the data. An absorptiometry kit (Sekisui Medical Company, Tokyo, Japan) was used to measure the UA level based on the hydrogen peroxide produced in the chemical reaction that occurs when UA is combined with uricase. In the present study, a UA level of >7.0 mg/dl was defined as high, according to the Japanese guidelines [10].

2.3. Evaluation of AKI on admission

Because we evaluated the presence of AKI at admission, urine criteria were not included in the evaluation of AKI. We therefore evaluated the presence of AKI using only the creatinine criteria of the RIFLE classification [7]. As this approach did not completely satisfy the RIFLE criteria, we defined these criteria as the "modified RIFLE" criteria in the present study. AKI upon admission was defined based on the ratio of the serum creatinine value recorded on admission to the baseline creatinine value. Patients were classified as having either no AKI or Class R (risk), Class I (injury) or Class F (failure) AKI. 'No AKI' was diagnosed as an increase in the serum creatinine level < 1.5-fold baseline, Class R as an increase in the serum creatinine level ≥ 1.5-fold baseline, Class I as an increase in the serum creatinine level ≥ 2.0-fold baseline and Class F as an increase in the serum creatinine level ≥ 3.0-fold baseline. Patients who were receiving continuous renal replacement therapy (CRRT) within 24 h were defined as Class F. With regard to the baseline level of creatinine, in CKD patients, the baseline level was defined as the lowest value recorded during admission. In patients without CKD (non-CKD) patients, the lower of either the lowest creatinine value during hospitalization or the Modification of Diet in Renal Disease (MDRD) creatinine level was used as the baseline creatinine value. The MDRD creatinine levels were calculated using the MDRD equation, as recommended by the Acute Dialysis Quality Initiative. The MDRD equation for serum creatinine was calculated by assuming a glomerular filtration rate (GFR) of 75 mL/min/1.73 m^2 [11]. CKD was diagnosed based on the creatinine value observed within one year. Furthermore, among patients in whom the creatinine value had not been measured within one year before admission, those who had been previously diagnosed with CKD at some point in the past were considered to have CKD. CKD was defined as a syndrome comprising a >3-month history of a low GFR (<60 mL/min/1.73 m^2) [12]. Patients who did not have medical records at Chiba Hokusoh Hospital for the three months before admission were diagnosed with CKD using the previous three months' data from another institution. Kidney damage, as identified by abnormal findings in the urine and imaging tests, was used to diagnose CKD in some patients in the present study; therefore, CKD was diagnosed only by a >3-month history of a low GFR. In the present study, 510 of 1047 patients (48.7%) were diagnosed with CKD.

2.4. Procedures

No AKI occurred in 736 patients (no-AKI) on admission. AKI was therefore present upon admission in 311 patients. The 1047 AHF patients were additionally divided into the following groups according to their serum UA level on admission: the low-UA group (UA ≤ 7.0 mg/dl; n = 569) and the high-UA group (UA > 7.0 mg/dl; n = 478). Therefore, the patients were ultimately assigned to 4 categories based on the serum UA level and AKI on admission: UA ≤ 7.0 mg/dl with no-AKI (low-UA/no-AKI; n = 428), UA > 7.0 mg/dl with no-AKI (high-UA/no-AKI; n = 308), UA ≤ 7.0 mg/dl with AKI (low-UA/AKI; n = 141) and UA > 7.0 mg/dl with AKI (high-UA/AKI; n = 170).

We compared the patients' characteristics between the low- and high-UA groups in each no-AKI or AKI category, including their age, gender, presence of de novo or recurrent HF, etiology of HF, risk factors for atherosclerosis (diabetes mellitus, hypertension and dyslipidemia), vital signs on admission (systolic blood pressure [SBP] and heart rate), left ventricular ejection fraction (LVEF) on echocardiography on admission, presence of orthopnea, presence of CKD, arterial blood gas data on admission, laboratory data on admission (BUN, total bilirubin, hemoglobin, BNP, C-reactive protein [CRP] and other variables) and medications administered during ICU admission. The LVEF was calculated using the Teicholz method or Sympson's method on admission (Sonos 5500, Hewlett Packard, Palo Alto, CA, USA; or Vivid I, GE Yokogawa Medical, Tokyo, Japan).

2.5. AKI, serum UA and the prognosis

The short-term prognosis was evaluated as the length of the ICU stay and the length of total hospitalization. Furthermore, the long-term prognosis was also evaluated as any-cause death. The patients were clinically followed up at a routine outpatient clinic. For the patients followed up at another institute, their prognoses were determined by telephoning the other institutes. All variables on admission, including the SBP, heart rate, creatinine, sodium, potassium, hemoglobin, LVEF and low- or high-UA/no-AKI or AKI category, were selected for inclusion in the multivariate logistic regression model. The continuous variables were evaluated by every 0.1-, 1- or 10-unit increase based on the meaning of each category. The prognostic value for the one-year mortality was evaluated using the Cox regression hazard model and Kaplan-Meier curve.

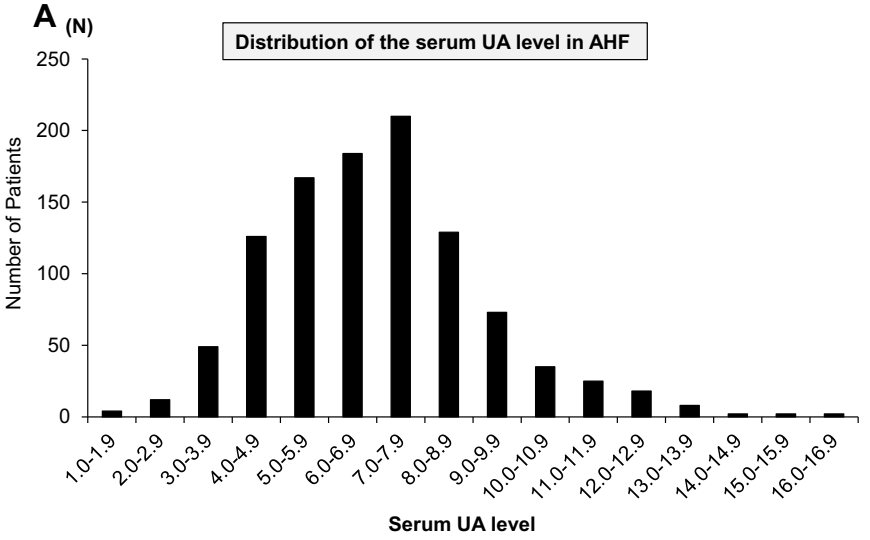
2.6. Statistical analyses

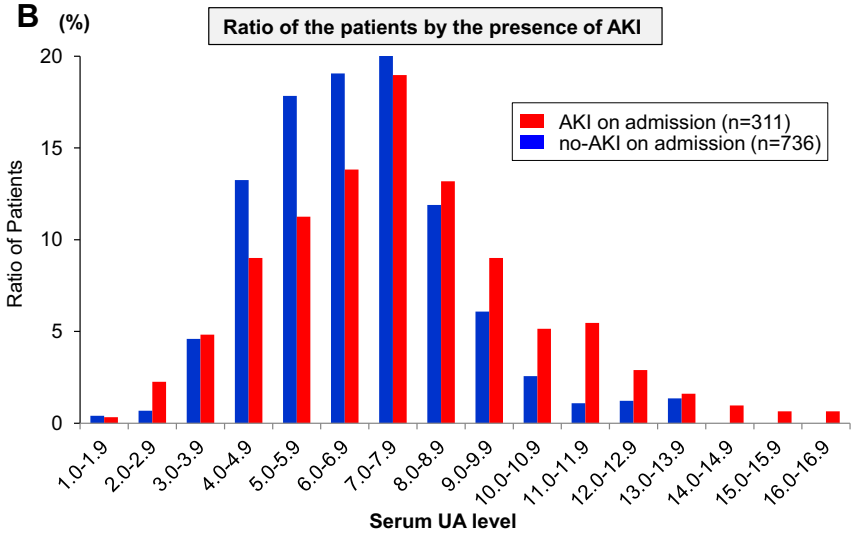
All of the data were statistically analyzed using the SPSS 22.0 software program (SPSS Japan Institute, Tokyo, Japan). All of the numerical data were expressed as the median and range or interquartile range. The Mann-Whitney *U* test was used for comparisons between two groups. The chi-squared test was used to compare proportions. *p* values of <0.05 were considered to indicate statistical significance.

The prognostic value of the serum UA level and AKI status vs. a reference group of normal patients (low-UA/no-AKI) was assessed using a multivariate Cox proportional hazards regression model. A multivariate Cox regression analysis was performed to determine the hazard ratio (HR) for the one-year mortality. The cumulative survival rates in each of the four groups were analyzed using Kaplan-Meier curves. A log-rank test was used to calculate the statistical significance of the differences by Kaplan-Meier curves.

2.7. Ethics review board

The research ethics committee of Nippon Medical School, Chiba Hokusoh Hospital approved the study protocol. Regarding informed consent, we presented the content of the present study on a poster displayed at our institute as well as on our homepage where it could be seen easily by everyone in accordance with the advice of the ethics committee.





	no-AKI (n=736)	AKI (n=311)	P value
UA ≥ 7.0 mg/dl (yes, %)	208 (41.8%)	170 (54.7%)	<0.001

Fig. 1. (A) The distribution of the serum UA levels. Among all 1047 AHF patients, the median value was 6.8 mg/dl. The serum UA levels were < 4 mg/dl in 65 patients (6.2%) and ≥ 10.0 mg/dl in 93 patients (8.9%). (B) The distribution of the ratio of the patients by the presence of AKI. The patients whose serum UA levels were ≥ 7.0 mg/dl were significantly more frequent in the AKI group ($n = 170$, 54.7%) than in the no-AKI group ($n = 208$, 41.8%). UA, uric acid; AHF, acute heart failure; AKI, acute kidney injury.

3. Results

3.1. Serum UA levels and AKI on admission in all AHF cohort

The distribution of the serum UA levels in the AHF patients is described in Fig. 1-**A**. Of the 1047 patients admitted to receive cardiovascular intensive care, a majority ($n = 889$, 84.9%) had serum UA levels of 4–9 mg/dl. The serum UA levels were <4 mg/dl in 65 patients (6.2%) and ≥10.0 mg/dl in 93 patients (8.9%). Forty-six patients had a serum UA level ≥ 10.0 mg/dl among 736 no-AKI patients (6.3%), while 54 patients had a serum UA level ≥ 10.0 mg/dl among 311 AKI patients (17.3%) (Fig. 1-**B**). The patients whose serum UA level was ≥7.0 mg/dl (high-UA patients) were significantly more frequent in the AKI group ($n = 170$, 54.7%) than in the no-AKI group ($n = 208$, 41.8%) (Fig. 1-**B**).

The study population included 698 (66.7%) men with a median age of 74 years, and 308 (29.4%) patients had been re-admitted for HF. A total of 434 (41.5%) patients had ischemic heart disease, and 613 (58.5%) had non-ischemic heart disease, including cardiomyopathy ($n = 121$), hypertensive heart disease ($n = 174$), valvular disease ($n = 233$) and other heart diseases ($n = 85$). Most patients were NYHA class IV ($n = 825$, 78.8%), and the median LVEF on admission was 36.0%.

Among the no-AKI patients, the high-UA group was significantly younger with significantly higher serum levels of BUN, creatinine, CRP and BNP than the low-UA group (Table 1). Among the AKI patients, the serum levels of BUN, creatinine, CRP and BNP were also significantly higher in the high-UA group than in the low-UA group.

The Kaplan-Meier survival curves, including all-cause death within 365 days, for the low- or high-UA levels and the presence or no-AKI groups are shown in Fig. 2. One-hundred and eighty-seven patients (17.8%) died within 365 days, and 165 patients (15.8%) went missing during follow-up. The survival rates were similar between the low-UA/no-AKI and high-UA/no-AKI groups ($p = 0.637$) and were significantly lower in the low-UA/AKI group than in the low-UA/no-AKI ($p \leq 0.001$) and high-UA/no-AKI groups ($p = 0.003$), and in the high-UA/AKI group than in the low-UA/no-AKI ($p \leq 0.001$), high-UA/no-AKI ($p \leq 0.001$) and low-UA/AKI groups ($p = 0.007$). A multivariate Cox regression model

Table 1
Characteristics of the patients by the difference in the serum UA levels and AKI.

	no AKI		*p* value	AKI		*p* value
	UA ≤ 7.0 mg/dl (low-UA, n = 428)	UA ≥ 7.1 mg/dl (high-UA, n = 308)		UA ≤ 7.0 mg/dl (low-UA, n = 141)	UA ≥ 7.1 mg/dl (high-UA, n = 170)	
Status and vital signs						
Age (years old)	75 (66–81)	72 (62–80)	0.002	75 (68–80)	73 (63–80)	0.093
Type (readmission, %)	116 (27.1%)	103 (33.4%)	0.072	42 (29.8%)	47 (27.6%)	0.707
LVEF (%)	38 (28–50)	33 (25–45)	<0.001	38 (28–52)	33 (21–50)	0.084
NYHA (IV, %)	335 (78.3%)	235 (76.3%)	0.533	114 (80.9%)	141 (82.9%)	0.659
Systolic blood pressure (mm Hg)	164 (141–192)	168 (142–192)	0.694	140 (108–172)	130 (105–166)	0.221
Pulse (beats/min)	113 (96–130)	112 (96–130)	0.734	105 (83–128)	107 (87–128)	0.653
Etiology						
Ischemia (yes, %)	187 (43.7%)	125 (40.5%)	0.407	62 (43.7%)	60 (35.3%)	0.130
Past medical history						
Hypertension (yes, %)	311 (72.7%)	248 (80.5%)	0.014	97 (68.8%)	113 (66.5%)	0.716
Diabetes mellitus (yes, %)	194 (45.3%)	133 (43.2%)	0.599	61 (43.3%)	71 (41.7%)	0.818
Dyslipidemia (yes, %)	206 (48.1%)	156 (50.6%)	0.502	67 (47.5%)	66 (38.8%)	0.135
Arterial blood gas						
pH	7.33 (7.23–7.42)	7.32 (7.20–7.43)	0.705	7.33 (7.21–7.43)	7.35 (7.21–7.44)	0.227
PCO2 (mm Hg)	44.5 (35.3–57.0)	41.3 (34.1–55.7)	0.109	39.6 (30.9–55.2)	38.1 (29.5–52.0)	0.280
PO2 (mm Hg)	91.9 (68.2–137.5)	92.1 (68.1–134.5)	0.748	86.3 (63.7–129.0)	84.4 (65.9–133.0)	0.827
HCO3– (mmol/l)	22.6 (20.7–24.8)	21.4 (19.1–23.9)	<0.001	20.8 (17.0–23.8)	20.2 (16.7–23.7)	0.755
SaO2 (%)	96 (91–98)	96 (92–98)	0.555	96 (91–98)	96 (91–98)	0.533
Lactate (mmol/l)	1.4 (1.0–2.7)	1.8 (1.2–3.9)	0.021	2.8 (1.3–5.7)	2.4 (1.6–5.0)	0.968
Laboratory data						
Total bilirubin (mg/dl)	0.5 (0.4–0.7)	0.6 (0.4–0.9)	0.004	0.6 (0.4–1.0)	0.8 (0.5–1.4)	0.007
Sodium (mmol/l)	140 (138–142)	140 (138–142)	0.761	139 (135–141)	139 (136–142)	0.459
Potassium (mmol/l)	4.1 (3.8–4.5)	4.2 (3.9–4.7)	0.021	4.5 (3.9–4.9)	4.5 (4.0–5.2)	0.273
Hemoglobin (g/dl)	12.5 (10.8–14.1)	12.8 (10.9–15.1)	0.061	11.6 (10.1–13.5)	12.7 (10.5–14.4)	0.024
BUN (mmol/l)	19.9 (16.1–26.8)	25.0 (19.0–36.0)	<0.001	29.1 (19.1–43.5)	33.3 (24.1–54.3)	0.006
Creatinine (g/dl)	0.94 (0.72–1.30)	1.27 (1.01–1.78)	<0.001	1.24 (0.96–2.04)	1.50 (1.08–2.11)	0.049
CRP (mg/dl)	0.50 (0.16–1.63)	0.60 (0.21–1.80)	0.274	1.04 (0.30–4.38)	1.54 (0.37–5.93)	0.173
BNP (pg/ml)	647 (358–1100)	866 (411–1504)	<0.001	762 (503–1418)	1141 (593–2081)	0.001
Medication (cases) during ICU						
Furosemide (yes, %)	398 (93.0%)	294 (95.5%)	0.207	127 (90.1%)	160 (94.1%)	0.235
Nitroglycerin (yes, %)	281 (65.7%)	201 (65.3%)	0.937	70 (49.6%)	63 (37.1%)	0.029
Nicorandil (yes, %)	82 (19.2%)	43 (14.0%)	0.073	20 (14.2%)	22 (12.9%)	0.868
Carperitide (yes, %)	204 (47.7%)	169 (54.9%)	0.062	52 (36.9%)	72 (42.4%)	0.353
Dopamine (yes, %)	65 (15.2%)	41 (13.3%)	0.524	46 (32.6%)	53 (31.2%)	0.808
Dobutamine (yes, %)	56 (13.1%)	52 (16.9%)	0.170	52 (36.9%)	77 (45.3%)	0.165
ACE-I/ARB (yes, %)	176 (41.1%)	145 (47.1%)	0.114	40 (28.4%)	34 (20.0%)	0.108
β-blocker (yes, %)	109 (25.5%)	94 (30.5%)	0.133	26 (18.4%)	36 (21.2%)	0.571
Spironolactone (yes, %)	176 (41.1%)	126 (40.9%)	1.000	38 (27.0%)	62 (36.5%)	0.088
Outcome						
ICU hospitalization (days)	4 (3–6)	4 (3–6)	0.011	6 (3–9)	6 (4–11)	0.351
Total hospitalization (days)	24 (16–38)	25 (17–41)	0.406	38 (22–60)	35 (20–61)	0.386
In-hospital mortality (yes, %)	13 (3.0%)	19 (6.2%)	0.045	20 (14.2%)	47 (27.6%)	0.005

AKI, acute kidney injury; UA, uric acid; LVEF, left ventricular ejection fraction measured by echocardiography; NYHA, New York Heart Association.
BUN, blood urea nitrogen; CRP, C-reactive protein; BNP, brain natriuretic peptide;
PNI, prognostic nutritional index; CONUT, controlling nutritional status.
ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ICU, intensive-care unit.
The *p* values between the low-UA and the high-UA groups were determined using the Mann-Whitney U test or the $\chi 2$ test.
All numerical data are expressed as the median (25%–75% interquartile range).

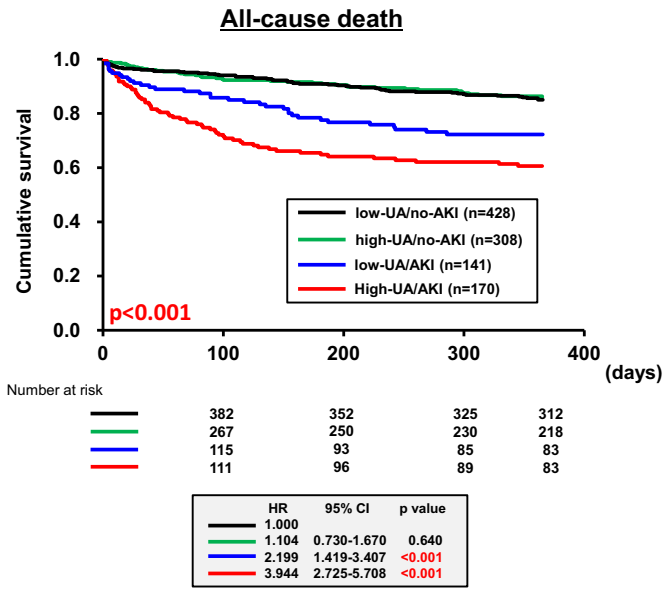


Fig. 2. The Kaplan-Meier survival curves showed that the rate of all-cause death within 365 days in the high-UA/AKI group (n = 170) was significantly higher than that in the low-UA/no-AKI (n = 428), high-UA/no-AKI (n = 308) and low-UA/AKI (n = 141) groups. UA, uric acid; AKI, acute kidney injury.

showed that only high-UA/AKI was an independent predictor of the 365-day mortality in patients with AHF (HR 2.511, 95% confidence interval [CI] 1.671–3.772) (Table 2).

3.2. Serum UA levels and AKI on admission in each non-CKD or CKD category

The distribution of the serum UA levels in each non-CKD and CKD category is noted in Fig. 3. The patients with hyperuricemia (UA level ≥ 7.0 mg/dl) were significantly more frequent in the AKI group (n = 93, 51.9%) than in the no-AKI group (n = 105, 29.3%) in non-CKD category (Fig. 3-**A**), while there was no significant difference in the AKI group (n = 77, 58.3%) and the no-AKI group (n = 203, 53.7%) in CKD category (Fig. 3-**B**). The survival rates of the high-UA/AKI group tended to be lower than in the low-UA/AKI groups (p = 0.084) and were significantly lower than in the low-UA/no-AKI ($p \leq 0.001$) and high-UA/no-AKI ($p \leq 0.001$) in non-CKD patients (Fig. 4-**A**) The survival rates of the high-UA/AKI group were significantly lower than in the low-UA/no-AKI ($p \leq 0.001$), high-UA/no-AKI ($p \leq 0.001$), and low-UA/AKI groups (p = 0.049) in CKD patients (Fig. 4-**B**). A multivariate Cox regression model showed that only high-UA/AKI was an independent predictor of the 1-year mortality in both non-CKD (HR 1.884, 95% CI 1.022–3.473, p = 0.042) and CKD (HR 3.546, 95% CI 2.136–5.884, p < 0.001) patients (Table 3).

4. Discussion

Patients with elevated UA levels complicated with AKI on admission showed the worst outcome of the four UA/AKI combination groups. Of note, serum UA elevation without AKI on admission was not associated with an adverse outcome compared to serum UA elevation with AKI. Furthermore, patients with elevated UA levels complicated with AKI and CKD showed the worst outcome in the total AHF cohort. These findings suggest that additional evaluations of the renal function are essential to predict a poor outcome in patients with severely decompensated AHF who are complicated with hyperuricemia.

4.1. Mechanisms of AKI induced by hyperuricemia

Hyperuricemia was suggested to be a predictor of AKI following surgery or contrast media exposure [13,14]; furthermore, several studies have attempted to prevent AKI by reducing the serum urate concentration. The uric lowering medications can decrease concentrations of the kidney tubular injury marker and can prevent the development of AKI (defined as the worsening of the serum creatinine by 25%) [15,16]. These results suggest that hyperuricemia itself might induce AKI. Although the mechanisms by which the elevated UA level induces AKI remains unclear, several mechanisms by which UA contributes to AKI have been reported [17]. These mechanisms were based on the some effect of the hyperuricemia [18,19]. A high level of UA can activate the RAAS, which can lead to strong constriction of blood vessels and further diminish the renal blood flow as well as increase renal vascular resistance [18]. Furthermore, an elevated UA level is also associated with an increased production of many inflammatory factors (i.e. interleukin-6 and C-reactive protein), which also induce renal dysfunction [19]. These factors, such as the activation of RAAS and inflammation, might directly induce AHF. Furthermore, urate crystals occur in renal stone, which might also induce microscopic tubule damage and lead to kidney injury [20]. As mentioned above, hyperuricemia has been reported to cause AKI in various diseases [13,14]. However, no data are available regarding AKI on admission and hyperuricemia in patients with AHF.

Table 2
Multivariate Cox analyses of the associations between 365-day cardiovascular death and the clinical findings.

All patients cohort	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
AKA and serum UA status						
Low-UA/no-AKI	1.000			1.000		
High-UA/no AKI	1.104	0.730–1.67	0.640	1.082	0.712–1.644	0.712
Low-UA/AKI	2.199	1.419–3.407	<0.001	1.343	0.848–2.125	0.209
High-UA/AKI	3.944	2.725–5.708	<0.001	2.511	1.671–3.772	<0.001
Laboratory data						
SBP (per 10-mm Hg increase)	0.863	0.834–0.893	<0.001	0.891	0.859–0.925	<0.001
Heart rate (per 1-bpm increase)	0.992	0.987–0.997	0.001			
Creatinine (per 0.1-mg/dl increase)	1.019	1.011–1.027	<0.001	1.011	1.000–1.021	0.040
Total bilirubin (per 1-mg/dl increase)	1.125	1.036–1.221	0.005			
Sodium (per 1.0-mmol/L increase)	0.944	0.920–0.968	<0.001			
Hemoglobin (per 1.0-mg/dl increase)	0.841	0.795–0.889	<0.001	0.877	0.826–0.932	<0.001
LVEF (per 1% increase)	1.000	0.991–1.008	0.911			

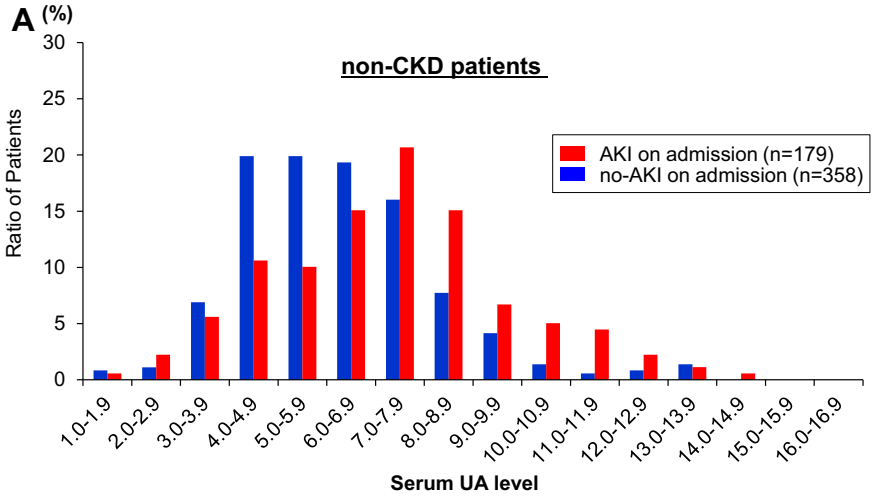
HR, hazard ratio; CI, confidence interval; UA, uric acid; AKI, acute kidney injury.
low-UA, UA ≤ 7.0 mg/dl; high-UA, UA ≥ 7.1 mg/dl.
SBP, systolic blood pressure; LVEF, left ventricular ejection fraction measured by echocardiography.

4.2. Differences in the prognostic utility of serum UA based on the renal function

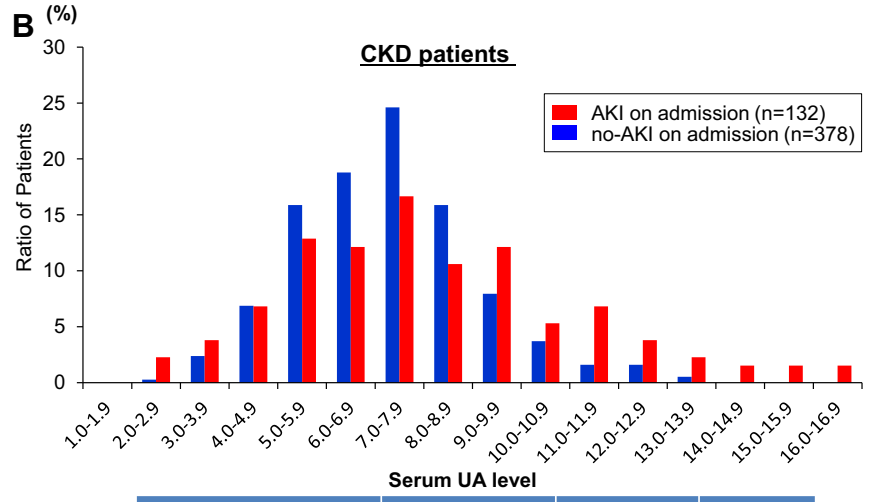
Various findings have already been reported in this field, and some results from previous studies may differ from those obtained in the present study. The sub-analysis of the data from a multicenter study (The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan [21] and the Beta-Blocker Evaluation of Survival Trial) suggested the relationship between the renal function and hyperuricemia in patients with chronic or hospitalized worsening HF [21,22]. The baseline serum UA level was reported to be associated with worse clinical endpoints in patients with an estimated glomerular filtration rate (eGFR) ≥30 ml/min/1.73 m^2 at the time of enrollment than in those with eGFR <30 ml/min/1.73 m^2 in the EVEREST trial. Although the details were not mentioned, a baseline eGFR <30 ml/min/1.73 m^2 might indicate both AKI and/or CKD. The Beta-Blocker Evaluation of Survival Trial also showed that hyperuricemia was associated with the all-cause mortality and HF hospitalization only in patients with chronic HF without CKD, not in those with CKD. These results suggest that an elevated serum UA level may be associated with adverse outcomes when it is the result of increased production rather than decreased clearance alone. However, the present study showed that serum UA elevation without AKI on admission was not associated with an adverse outcome compared to serum UA elevation with AKI. This result seems to emphasize that both an increased production and decreased clearance are essential for predicting the prognosis in patients with AHF complicated with hyperuricemia.

Mechanisms underlying the increased production and decreased excretion of serum UA in the AHF setting.

Two theories have been established regarding the increased production of serum UA. First, hyperuricemia would usually be caused by the excessive intake of high-purine foods, which has been associated with metabolic syndrome or atherosclerotic risk factors. Alternatively, enhanced XOR activity was recently suggested to be a key factor involved in the development of hyperuricemia in patients with cardiovascular disease [5]. We also reported that the XOR activity was extremely high



	no-AKI (n=358)	AKI (n=179)	P value
UA ≥ 7.0 mg/dl (yes, %)	105 (29.3%)	93 (51.9%)	<0.001



	no-AKI (n=379)	AKI (n=132)	P value
UA ≥ 7.0 mg/dl (yes, %)	203 (53.7%)	77 (58.3%)	0.363

Fig. 3. (A) The distribution of the ratio of the patients by the presence of AKI in the non-CKD category. The patients whose serum UA levels were ≥ 7.0 mg/dl were significantly more frequent in the AKI group ($n = 93$, 51.9%) than in the no-AKI group ($n = 105$, 29.3%). (B) The distribution of the ratio of patients by the presence of AKI in the non-CKD category. The patients whose serum UA levels were ≥ 7.0 mg/dl were not markedly different between the AKI group ($n = 77$, 58.3%) and no-AKI group ($n = 203$, 53.7%). CKD, chronic kidney disease; UA, uric acid; AKI, acute kidney injury.

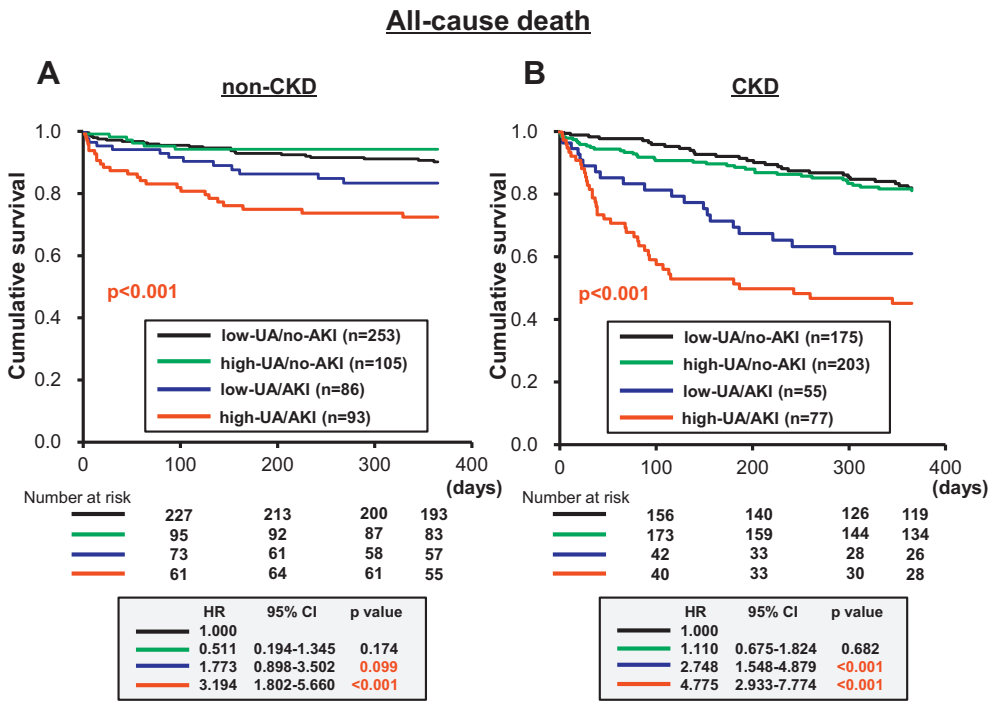


Fig. 4. (A) The Kaplan-Meier survival curves of non-CKD patients showed that the prognosis (including all-cause death within 365 days) was significantly poorer in the high-UA patients who had AKI than in those who had non-AKI as well as the low-UA patients regardless of the presence of AKI. (B) The Kaplan-Meier survival curves of CKD patients showed that the prognosis (including all-cause death within 365 days) was significantly poorer in the high-UA patients who had AKI than in those without AKI as well as in the low-UA patients regardless of the presence of AKI. CKD, chronic kidney disease; UA, uric acid; AKI, acute kidney injury.

in patients with severely decompensated AHF. XO and XDH are the most important enzymes in this metabolic system [23,24]. Although XO and XDH are both enzymes that catalyze UA production, their electron acceptors are different. XO and XDH both exist in human blood with different electron acceptors (oxygen and NAD^+, respectively) [23]. XOR is the generic term for XO and XDH. Some acute

Table 3
The multivariate analyses of the associations between 365-day cardiovascular death and the clinical findings in each category.

	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Non-CKD patient cohort						
AKI and serum UA status						
Low-UA/no-AKI	1.000			1.000		
High-UA/no-AKI	0.511	0.194–1.345	0.174	0.623	0.477–1.993	0.945
Low-UA/AKI	1.773	0.898–3.502	0.099	0.975	0.236–1.649	0.341
High-UA/AKI	3.194	1.802–5.660	<0.001	1.884	1.022–3.473	0.042
Laboratory data						
SBP (per 10-mm Hg increase)	0.863	0.834–0.893	<0.001	0.854	0.801–0.911	<0.001
Heart rate (per 1-bpm increase)	0.992	0.987–0.997	0.001			
Creatinine (per 0.1-mg/dl increase)	1.019	1.011–1.027	<0.001			
Total bilirubin (per 1-mg/dl increase)	1.125	1.036–1.221	0.005			
Sodium (per 1.0-mmol/L increase)	0.944	0.920–0.968	<0.001			
Hemoglobin (per 1.0-mg/dl increase)	0.841	0.795–0.889	<0.001	0.859	0.781–0.945	0.002
LVEF (per 1% increase)	1.000	0.991–1.008	0.911			
CKD patient cohort						
AKA and serum UA status						
Low-UA/no-AKI	1.000			1.000		
High-UA/no-AKI	1.110	0.675–1.824	0.682	1.069	0.646–1.769	0.795
Low-UA/AKI	2.748	1.548–4.879	0.001	1.974	1.095–3.557	0.024
High-UA/AKI	4.775	2.933–7.774	<0.001	3.546	2.136–5.884	<0.001
Laboratory data						
SBP (per 10-mm Hg increase)	0.879	0.844–0.916	<0.001	0.914	0.874–0.955	<0.001
Heart rate (per 1-bpm increase)	0.994	0.987–1.000	0.049			
Creatinine (per 0.1-mg/dl increase)	1.008	0.997–1.019	0.150			
Total bilirubin (per 1-mg/dl increase)	1.134	1.049–1.225	0.002	1.160	1.051–1.280	0.003
Sodium (per 1.0-mmol/L increase)	0.935	0.910–0.961	<0.001			
Hemoglobin (per 1.0-mg/dl increase)	0.901	0.838–0.968	0.004	0.906	0.840–0.978	0.011
LVEF (per 10% increase)	1.002	0.991–1.013	0.716			

HR, hazard ratio; CI, confidence interval; CKD, chronic kidney disease; UA, uric acid; AKI, acute kidney injury low-UA, UA ≤ 7.0 mg/dl; high-UA, UA ≥ 7.1 mg/dl.
SBP, systolic blood pressure; LVEF, left ventricular ejection fraction measured by echocardiography.

stressors (e.g. the increased production of lactate, or tissue hypoxia) that are exacerbated at the acute phase of AHF directly induce the mobilization of XDH to the blood. The exchange to XO then leads to the enhancement of XOR activity, which subsequently increases the serum UA level. Systemic hypoxia due to pulmonary congestion and peripheral circulatory insufficiency caused by the central shift of the blood flow as a consequence of low cardiac output has been suggested as one of the pathophysiological mechanisms that can lead to the development of AHF. These situations then result in the production of lactate and the subsequent elevation of serum lactate levels. Thus, the serum lactate level is an indicator of tissue hypoxia in patients with severely decompensated AHF, and a high lactate level might be associated with the XOR activity in AHF patients.

The decreased excretion of UA also indicated the presence of a renal or gut disorder. According to the current guidelines, hyperuricemia caused by excretory failure accounts for approximately 60% of all cases of hyperuricemia [10]. We also found that UA elevation, which is associated with poor long-term outcomes, was common among patients complicated with CKD or with severely decompensated AHF who had been treated with loop-diuretics before admission [1]. Excretory trouble induced by AHF might therefore be an important factor in the mechanism of UA elevation [1]. Urate is freely filtered at the glomerulus and thereafter reabsorbed and secreted in the proximal tubule. Reabsorption is dominant, and the fractional excretion of uric acid is below 10% [25]. Furthermore, urate is also transported to the gut, where as much as one-third is degraded by uricolytic bacteria. Although the mechanisms underlying urate transport to the gut are unknown, AHF patients sometimes develop intestinal edema that leads to absorption disorder. This might be an excretory factor inducing hyperuricemia in patients with AHF.

4.3. Prognostic importance of the evaluation of the renal function in patients with AHF complicated with hyperuricemia

Our results suggest the importance of both production and excretion factors in the evaluation of the prognostic impact of AHF. Hyperuricemia was associated with the all-cause mortality only in patients with AHF with AKI and not in those with non-AKI. So far, numerous studies have been published regarding the association between AKI and prognosis in patients with AHF [7,8,26,27]. AKI at admission can be detected using cardiac markers but not renal tubular injury markers [27]. This means that AKI is sometimes induced by acute cardiac stress, as with cardio-renal syndrome [28]. The serum UA levels are subsequently increased by excretion disorder. The Serum UA has been shown to be an index of an impaired renal function in patients with congestive HF [29]. The evaluation of not only the production factors, but also the presence of excretion disorders, especially regarding the renal function (AKI and/or CKD), is therefore important for predicting an adverse prognosis in AHF patients complicated with hyperuricemia.

4.4. Study limitations

Several limitations associated with the present study warrant mention. First, as it was a single-center study, some patient-related biases might have been included. Second, we assessed the presence of AKI using only the creatinine criteria of the RIFLE classification because we assessed the presence of AKI upon admission. As this approach did not completely satisfy the RIFLE criteria, we had to use "modified RIFLE" criteria in the present study. Third, our study population was limited to those who were admitted to the ICU; therefore, AHF patients who were admitted to general wards were excluded from this study. The patients were treated in a "closed ICU" at our institute, and all of the physicians in our "closed ICU" are cardiologists. The majority of severely decompensated AHF patients were therefore admitted to the ICU. Fourth, blood samples could not be obtained within 30 min of admission in some patients. The serum levels of UA on admission might be unstable and easily affected by certain factors, such as recovery of the respiratory status or the therapeutic procedure. Therefore, sampling before such procedures is important. To resolve this issue, we performed the same analysis in a subset of 548 patients who were admitted after May 2011 and whose samples could be confirmed to have been obtained within 30 min of admission. The results of this analysis showed almost no differences in the key findings from the data in the present manuscript (data not shown). However, we still maintain that differences in sampling timing are a major limitation of this study. Fifth, we were unable to evaluate the serum UA level for all study participants in the compensated phase. This might be important for clarifying the differences in mechanisms of hyperuricemia and AKI. Finally, the influence of high UA levels on the risk of adverse outcomes seems to be far less relevant than that of AKI. Although our findings did not confirm the causal dependence between the high UA and AKI in the present study, the influence of high UA levels and AKI on the risk of adverse outcomes might depend on the causal dependence. Further prospective studies will be required regarding this issue.

5. Conclusion

A high serum UA level complicated with AKI on admission was an independent predictor of 365-day mortality in AHF patients who were emergently hospitalized in the cardiovascular ICU. Their critical status and AKI during the acute phase of AHF might induce elevation of the serum UA level and lead to an adverse outcome in patients with severely decompensated AHF.

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Conflict of interest

The authors declare no conflicts of interest in association with the present study.

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