Lowering Uric Acid May Improve Prognosis in Patients With Hyperuricemia and Heart Failure With Preserved Ejection Fraction

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BACKGROUND: An association between uric acid (UA) and cardiovascular diseases, including heart failure (HF), has been reported. However, whether UA is a causal risk factor for HF is controversial. In particular, the prognostic value of lowering UA in patients with HF with preserved ejection fraction (HFpEF) is unclear.

METHODS AND RESULTS: We enrolled patients with HFpEF from the PURSUIT-HFpEF (Prospective Multicenter Observational Study of Patients With Heart Failure With Preserved Ejection Fraction) registry. We investigated whether UA was correlated with the composite events, including all-cause mortality and HF rehospitalization, in patients with hyperuricemia and HFpEF (UA >7.0 mg/dL). Additionally, we evaluated whether lowering UA for 1 year (≥1.0 mg/dL) in them reduced mortality or HF rehospitalization. We finally analyzed 464 patients with hyperuricemia. In multivariable Cox regression analysis, UA was an independent determinant of composite death and rehospitalization (hazard ratio [HR], 1.15 [95% CI, 1.03–1.27], P=0.015). We divided them into groups with severe and mild hyperuricemia according to median estimated value of serum UA (8.3 mg/dL). Cox proportional hazards models revealed the incidence of all-cause mortality was significantly higher in the group with severe hyperuricemia than in the group with mild hyperuricemia (HR, 1.73 [95% CI, 1.19–2.25], P=0.004). The incidence of all-cause mortality was significantly decreased in the group with lowering UA compared with the group with nonlowering UA (HR, 1.71 [95% CI, 1.02–2.86], P=0.041). The incidence of urate-lowering therapy tended to be higher in the group with lowering UA than in the group with nonlowering UA (34.9% versus 24.6%, P=0.06).

CONCLUSIONS: UA is a predictor for the composite of all-cause death and HF rehospitalization in patients with hyperuricemia and HFpEF. In these patients, lowering UA, including the use of urate-lowering therapy, may improve prognosis.

Key Words: heart failure with preserved ejection fraction ■ hyperuricemia ■ prognosis ■ uric acid ■ uric acid lowering therapy

The prevalence of heart failure with preserved ejection fraction (HFpEF) is increasing, but mortality in these patients remains unchanged. Moreover, few treatments for this entity are available, besides possible but limited beneficial effects of mineralcorticoid receptor antagonists and the recently reported sodium-glucose cotransporter 2 inhibitors. Serum uric acid (UA) is the terminal product of purine nucleotide metabolism in the human body and several reports have revealed a correlation of elevated
serum UA level with cardiovascular disease and heart failure (HF).6,7 However, because a few recent studies demonstrated a negative impact of lowering UA on cardiovascular disease,6,9 it has not been established whether serum UA is a causal risk factor for cardiovascular disease or HF and a potential therapeutic target in clinical practice. In particular, the correlation between serum UA and HFpEF has not been well investigated. Moreover, because it has been reported that serum UA levels have U-shaped prognostic effects, which showed both high and low UA levels are associated with poor prognosis compared with normal UA levels,10 the impact of serum UA on the general population or on patients with HF and normal UA may be weak.

Accordingly, in this study, we evaluated the prognostic impact of serum UA, especially lowering UA, on patients with hyperuricemia and HFpEF.

 METHODS

Our study data will not be made available to other researchers for purposes of reproducing the results because of institutional review board restrictions.

 PURSUIT-HFpEF Registry

The PURSUIT-HFpEF (Prospective Multicenter Observational Study of Patients With Heart Failure With Preserved Ejection Fraction) study is a prospective, multicenter, observational study conducted at collaborating hospitals in the Osaka region of Japan (UMIN-CTR ID: UMIN000021831). The enrolled patients were hospitalized with acute decompensated HF based on the Framingham criteria11 and had a left ventricular ejection fraction ≥50% using transthoracic echocardiography. Brain natriuretic peptide was ≥100 ng/L or N-terminal pro-brain natriuretic peptide (NT-proBNP) ≥400 ng/L on admission. The exclusion criteria were (1) severe aortic stenosis, aortic regurgitation, mitral stenosis, or mitral regurgitation because of structural changes in the valve detected by transthoracic echocardiography; (2) age <20 years; (3) acute coronary syndrome on admission; (4) poor 6-month prognosis because of noncardiac diseases; and (5) post-heart transplantation status. Investigative cardiologists and trained research nurses recorded patient data, including medical history, comorbidities, examined data, therapeutic procedures, and clinical events from the medical records, and direct interview of the patients and family members during their hospital stay. They also obtained vital signs, echocardiographic data, laboratory data, and medications on admission and at discharge. After discharge, all patients were followed up by their treating hospital. Coordinators and investigators obtained clinical data including various medications (eg, urate lowering drug use) by direct contact in an outpatient setting, telephone interview with patient families, or by mail. In the present analysis, we analyzed all available clinical follow-up data up to June 2021. All patients gave informed consent to participate in this study, which was approved by the ethics committee in all participating facilities. This study was conducted according to the Helsinki Declaration, and the present study protocol was approved by the institutional review board of all participating facilities.

 Study Population

Our study patients were enrolled from the PURSUIT-HFpEF registry between June 2016 and June 2021.
this registry, we investigated patients with hyperuricemia and HFpEF and defined hyperuricemia as a serum UA level >7.0 mg/dL according to the Japanese guideline. In this study, composite end points (CE) were defined as a composite of all-cause death and HF rehospitalization. We evaluated the impact of serum UA and the other parameters between a CE group and a non-CE group by univariable and multivariable analysis. In addition, we evaluated the clinical impact of lowering UA on prognosis in patients with hyperuricemia and HFpEF. We enrolled consecutive patients who had both serum UA values at discharge and 1-year follow-up and compared the impact of a 1-mg/dL decrease in UA during the year on prognosis in patients with hyperuricemia and HFpEF. We adopted a 1-mg/dL decrease in UA because the definition of hyperuricemia is UA level >7.0 mg/dL and target to treat for hyperuricemia is 6.0 mg/dL of UA according to the Japanese guideline, indicating that a ≥1.0 mg/dL decrease in UA may have clinical importance.

### Laboratory Measurements at Discharge
Blood samples were collected at discharge. Laboratory measurements, including sodium, potassium, chloride, albumin, hemoglobin, creatinine, estimated glomerular filtration rate (eGFR), CRP (C-reactive protein), NT-proBNP, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, UA, and hemoglobin A1c, were performed by standard methods in the clinical laboratory of the participating hospital.

### Echocardiographic Data at Discharge
A comprehensive echocardiographic examination was performed at discharge by trained physicians at each institution. The left ventricular diastolic diameter, left ventricular systolic diameter, left atrial diameter at end-systole, and tricuspid annular plane excursion were measured as previously described. Left ventricular ejection fraction was measured by the modified Simpson method. Tricuspid annular plane systolic excursion (TAPSE) was acquired from the left apical 4-chamber view. This measurement was obtained from 2D cine loops by drawing a line from the lateral tricuspid valve annulus to the right ventricular apex at end-diastole. Moderate mitral regurgitation and tricuspid regurgitation were also evaluated.

### Medications at Discharge
We evaluated medications for HF at discharge to determine if the following medications were prescribed: angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, losartan, calcium channel blocker, β blockers, mineralocorticoid receptor antagonists, diuretics, thiazide, antiplatelet drugs, aspirin, statins, and fibrates. We evaluated losartan, thiazide, and aspirin separately from angiotensin II receptors, diuretics, and antiplatelet drugs because correlations between UA and losartan, thiazide, or aspirin have been reported. We also investigated urate-lowering therapy in detail by evaluating the incidence of urate-lowering therapy and category of urate-lowering agents. Urate-lowering agents can be divided into 2 main categories, namely those reducing UA production with xanthine oxidase (XO) inhibitors, including allopurinol and febuxostat; and those increasing UA excretion using uricosurics, including probenecid and benz bromarone.

### Follow-Up and End Points
In this study, end point events were defined as a composite of all-cause death and HF rehospitalization. All patients were followed up in each hospital after discharge. We evaluated the following parameters: age, sex, body mass index, history of alcohol, coronary artery disease, HF admission, incidence of hypertension, diabetes, dyslipidemia, stroke, chronic kidney disease, atrial fibrillation, and the aforementioned various laboratory, echocardiographic, and medications data. In addition, to evaluate the clinical impact of lowering UA in patients with hyperuricemia and HFpEF, we compared all-cause mortality and HF rehospitalization between the group with lowering UA who showed a ≥1.0 mg/dL decrease in UA for 1 year and a group with nonlowering UA who showed a <1.0 mg/dL decrease or increase in UA for 1 year. Following reports that diuretics are associated with serum UA levels via increasing UA reabsorption and decreasing UA secretion, we evaluated the incidence of diuretics use between discharge and at 1-year follow-up to exclude the effect of change in diuretics use.

### Statistical Analysis
Continuous variables are expressed as median [interquartile range] and compared using the Mann–Whitney U test. Categorical variables are expressed as counts (percentages) and compared with chi-square test or Fisher exact test. Multivariable Cox regression to evaluate the prognostic impact for CE was performed using covariates, which showed significant differences between the CE and non-CE groups, in addition to considering the collinearity of each parameter. If variance inflation factor between the factors that show the possible collinearity was <10, we adopted the most clinical important factor. Further, we evaluated the impact of UA on all-cause mortality by comparison between the group with severe hyperuricemia and the group with mild hyperuricemia according to median estimated value of serum UA using the Kaplan–Meier method. All-cause mortality between the groups with lowering UA and nonlowering UA were also estimated using...
the Kaplan–Meier method. In addition, we performed Gray’s test because death was treated as a competing risk for comparison of HF rehospitalization between the groups with severe hyperuricemia and with mild hyperuricemia and the groups with lowering UA and non-lowering UA, respectively. Cox proportional hazards models were used to evaluate all-cause mortality and Fine-Gray subdistribution hazard models were used to evaluate HF rehospitalization. Values of \( P < 0.05 \) were considered statistically significant. Statistical analysis was performed using JMP 14 statistical software (SAS Institute Inc., Cary, NC, USA).

RESULTS

Study Patients

The flow chart for this analysis is shown in Figure 1. Between June 2016 and June 2021, 1169 patients were enrolled from the PURSUIT-HFpEF registry. We excluded 19 patients who died during hospitalization and 31 patients who had a lack of UA data at discharge. In addition, because we focused on patients with hyperuricemia (UA >7.0 mg/dL) we also excluded 655 patients with a UA ≤7.0 mg/dL at discharge. Finally, we investigated 464 patients with hyperuricemia and HFpEF. Additionally, we examined the 291 patients with hyperuricemia who had both UA data at discharge and 1-year follow-up (Figure 1). During the follow-up, there was 1 lost follow-up patient, and we also excluded 172 patients who did not have UA data at 1 year after discharge. Following this, the group with lowering UA consisted of 169 patients and the group with non-lowering UA of 122 patients.

Characteristics of Study Patients

Study participants were largely older, with median age 83 (78, 89) years old. The percentage of women was 50.2%, body mass index was 25 (21, 28) kg/m², and the incidences of coronary artery disease and HF readmission were 18% and 28%, respectively. The systolic/diastolic blood pressure and heart rate were 118 (105, 130)/64 (58, 73) mm Hg and 68 (60, 78), respectively. The NT-proBNP concentration was 1130 (504, 2640) pg/mL, the UA concentration was 8.3 (7.6, 9.2) mg/dL, and left ventricular ejection fraction was 61 (58, 65)%. The rates of HF medications such as angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, β blocker, and mineralocorticoid receptor antagonists were 58%, 59%, and 43%, respectively.

![Flow chart of study patients](image-url)

**Figure 1.** Flow chart of study patients. PURSUIT-HFpEF indicates the Prospective Multicenter Observational Study of Patients With Heart Failure With Preserved Ejection Fraction; and UA, uric acid.
**Prognostic Factors for CE**

During a median follow-up of 693 days, the CE including all-cause death and HF rehospitalization occurred in 197 (110 patients died) of 464 study patients (42.5%). We used the covariates that showed significant differences between the CE and non-CE groups, excluding creatinine and chronic kidney disease because of the clinical collinearity of eGFR. The values of variance inflation factor of eGFR, creatinine, and chronic kidney disease were 1.80, 1.67, and 1.23, respectively. We selected eGFR owing to clinical importance. Multivariable analysis showed that UA, history of HF admission, and NT-proBNP (using log-transformed NT-proBNP) were significantly and independently correlated with CE (Table 1).

**Impact of UA on Prognosis**

Median value of UA in this study population was 8.3 mg/dL. We divided our patients into a group with severe hyperuricemia (UA ≥8.3 mg/dL, n=238) and a group with mild hyperuricemia (7.0<UA<8.3 mg/dL, n=226). As shown in Table 2, UA of the groups with mild and severe hyperuricemia was 7.5 mg/dL (7.3, 7.9) and 9.2 mg/dL (8.7, 10.2), which showed significant difference (P<0.001), respectively. In addition, heart rate (70 [63, 80] versus 68 [60, 76], P=0.003) and the incidence of diuretics (86.3% versus 92.4%, P=0.035) were significantly lower in the group with mild hyperuricemia than in the group with severe hyperuricemia. On the other hand, creatinine (1.25 mg/dL [0.9, 1.6] versus 1.4 mg/dL [1.1, 1.9], P<0.001) and eGFR (39.9 mL/min per 1.73 m² [29.0, 53.3] versus 34.5 mL/min per 1.73 m² [23.6, 44.6], P<0.001) were significantly higher in the group with mild hyperuricemia than in the group with severe hyperuricemia. No significant differences in other parameters were observed between these 2 groups.

The severe hyperuricemic group had significantly greater risk of all-cause death than the mild hyperuricemic group (P=0.004, Figure 2A). In contrast, regarding HF rehospitalization, no significant difference between the 2 groups was noted (Figure 2B).

**Clinical Impact of Lowering UA on Prognosis**

Median follow-up duration was 480 days in the 291 patients with hyperuricemia and HFpEF who had both UA data at discharge and 1-year follow-up in this study. Clinical characteristics between the group with lowering UA and the group with nonlowering UA are shown in Table 3. Although body mass index (26 kg/m² [23, 29] versus 24 kg/m² [21, 27], P=0.014), the incidence of diabetes (42.6% versus 28.7%, P=0.019), and serum UA (8.7 mg/dL [7.8, 9.8] versus 8.0 mg/dL [7.5, 8.5], P<0.001) were significantly higher in the group with lowering UA than in the group with nonlowering UA, there were no significant differences in the other parameters between the 2 groups. The group with lowering UA (n=169) had a significantly greater risk of all-cause death than the group with nonlowering UA (P=0.041, Figure 3A), but there was no significant difference in HF rehospitalization between the 2 groups (Figure 3B). We also showed the hazard ratio and 95% CI of body mass index, diabetes, and nonlowering UA for all-cause death and HF rehospitalization (Table 4).

Regarding urate-lowering therapy, the incidence of urate-lowering therapy (% of using urate-lowering therapy) tended to be higher, but not significantly higher, in the group with lowering UA compared with the group with nonlowering UA (34.9% versus 24.6%, P=0.06). The incidence of agents reducing UA production with XO inhibitors in the urate-lowering therapy was similar in the groups with lowering UA and nonlowering UA were also similar (89.3% and 93.4% at discharge and 85.8% and 93.4% at 1-year follow-up, respectively).

**DISCUSSION**

**Main Findings**

The main findings of this study are that in the patients with hyperuricemia (UA ≥7.0 mg/dL) with HFpEF, (1) UA was an important prognostic factor, in addition to a history of HF admission and NT-proBNP; (2) the group with severe hyperuricemia (UA ≥8.3 mg/dL) showed worse all-cause mortality, but similar HF rehospitalization, compared with the group with mild hyperuricemia; and (3) lowering UA for 1 year (≥1.0 mg/dL) was correlated with reduced all-cause mortality. These findings suggest that UA is a simple prognostic factor for patients with hyperuricemia and HFpEF, and that lowering UA, including the use of urate-lowering therapy, may have a beneficial effect on the prognosis of these patients.

**UA as a Prognostic Factor for HFpEF**

Relationships between UA and cardiovascular disease have been reported for many years, but whether UA is an independent risk factor for cardiovascular disease or events is still controversial. In addition, the mechanism explaining why hyperuricemia is correlated with cardiovascular disease is still unknown. It is known that UA is an antioxidant that induces inflammation in vascular endothelial and smooth muscle cells and intracellular oxidative stress, leading to endothelial dysfunction. Indeed, many clinical studies have revealed that elevated UA is associated with endothelial...
Table 1. Univariate and Multivariate Cox Regression Analysis for Prognostic Prediction

|                                | Univariate analysis | Multivariate analysis |
|--------------------------------|---------------------|-----------------------|
|                                | HR (95% CI)         | P value               | HR (95% CI)         | P value               |
| Age                            | 1.03 (1.01–1.05)    | 0.001                 | 1.01 (0.99–1.03)    | 0.376                 |
| Heart failure readmission      | 1.99 (1.48–2.65)    | <0.001                | 1.66 (1.15–2.37)    | 0.007                 |
| Hemoglobin                     | 0.87 (0.80–0.93)    | <0.001                | 0.94 (0.85–1.05)    | 0.329                 |
| Albumin                        | 0.57 (0.41–0.78)    | <0.001                | 0.92 (0.59–1.44)    | 0.717                 |
| Estimated glomerular filtration rate | 0.98 (0.97–0.99) | <0.001                | 1.00 (0.98–1.01)    | 0.491                 |
| Log N-terminal pro-brain natriuretic peptide | 1.46 (1.28–1.66) | <0.001                | 1.33 (1.13–1.56)    | 0.001                 |
| Low-density lipoprotein cholesterol | 0.99 (0.99–1.00) | 0.011                 | 1.00 (0.99–1.00)    | 0.364                 |
| Uric acid                      | 1.18 (1.07–1.28)    | <0.001                | 1.15 (1.03–1.27)    | 0.015                 |
| Left atrium dimension          | 1.02 (1.00–1.04)    | 0.020                 | 1.00 (0.98–1.02)    | 0.901                 |

HR indicates hazard ratio.

dysfunction, as assessed by flow-mediated dilation and intracoronary acetylcholine testing.23,24 We also previously demonstrated that UA was significantly correlated with vasospastic angina caused by coronary endothelial dysfunction using intracoronary acetylcholine testing.25 Accordingly, UA is correlated with vascular endothelial dysfunction, which may partially cause cardiovascular disease.28 However, the question of whether UA is a causal factor for cardiovascular disease in clinical settings remains controversial.

Regarding coronary artery disease (CAD), several epidemiologic studies reported that UA was correlated with risk of CAD.27,28 In addition, UA was also reported to be useful in predicting clinical events.29 Thus, it appears easy to consider that urate-lowering agents—especially agents reducing UA production with XO inhibitors—have possible beneficial effects on CAD. In addition, it has been reported that the effect of XO inhibition is significantly higher with febuxostat than allopurinol.30 Therefore, we speculate that febuxostat will have more favorable effects on CAD than allopurinol, because endothelial dysfunction is an important step in the progression of atherosclerosis.31 However, the CARES (Cardiovascular Safety of Febuxostat and Allopurinol in Patients With Gout and Cardiovascular Morbidities) study, a randomized clinical trial in 6190 patients with gout, revealed that all-cause (7.8% versus 6.4%, P=0.04) and cardiovascular mortality (4.3% versus 3.2%, P=0.03) were significantly higher in the febuxostat group than in the allopurinol group.6 Other large-scale clinical trials have also shown the nonbeneficial effects of XO inhibitors, especially febuxostat, on cardiovascular events.9,32 Therefore, the therapeutic significance of urate-lowering agents, especially XO inhibitors, on CAD was not anticipated and remains unknown. The reason urate-lowering agents are not useful for CAD is primarily because CAD results from epicardial coronary atherosclerosis—which is a feature of advanced atherosclerosis as severe as coronary artery stenosis—and is not already affected by endothelial dysfunction, which is a feature of early atherosclerosis. Therefore, traditional coronary risk factors, including dyslipidemia, hypertension, and diabetes, are more strongly correlated with epicardial coronary atherosclerosis than hyperuricemia, which can induce endothelial dysfunction, an early step of atherosclerosis.31

With regard to HF, several epidemiologic studies have also reported that elevated UA is common in patients with HF.33,34 Although the mechanisms by which UA influences HF development are incompletely understood, UA may directly contribute to HF worsening by impairing endothelial function,23,24 elevating blood pressure,20 and reducing renal function.35 Moreover, several recent reports demonstrated that elevated UA is associated with worsening of HfPEF.7,10 In addition, given the U-shaped association between UA and cardiovascular prognosis,7,10 we anticipate that the clinical impact of UA can be indicated not in a general population but in patients with hyperuricemia. Indeed, PARAGON-HF (Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] With ARB [Angiotensin Receptor Blockers] Global Outcomes in HF With Preserved Ejection Fraction) showed an increase in clinical events above a UA value of 6 mg/dL.7 The present study clearly demonstrated that UA is significantly and independently correlated with prognosis in patients with hyperuricemia and HfPEF. Because a systemic proinflammatory state induced by comorbidities, including hyperuricemia, could cause myocardial structural and functional alterations,36 UA may have more significant correlation with HfPEF than epicardial coronary atherosclerosis. Moreover, recent reports have revealed that coronary microvascular dysfunction has been linked to HfPEF.37,38 Because it has been reported that UA levels are significantly associated with the capillaroscopic patterns, reflecting a progressive microvascularopathy,39 UA may be therapeutic targets for HfPEF regarding microvascularopathy in HfPEF.
### Table 2. Baseline Patient Characteristics Between the Groups With Mild and Severe Hyperuricemia

|                          | Group with mild hyperuricemia (n=226) | Group with severe hyperuricemia (n=238) | P value |
|--------------------------|---------------------------------------|----------------------------------------|---------|
| **Clinical data**        |                                       |                                        |         |
| Age, y                   | 82 [75, 87]                           | 83 [77, 87]                            | 0.512   |
| Female sex, %            | 117 (51.8)                            | 116 (48.7)                             | 0.517   |
| Body mass index, kg/m²   | 25 [21, 28]                           | 24 [22, 28]                            | 0.893   |
| Alcohol, %               | 98 (43.8)                             | 92 (38.7)                              | 0.345   |
| Coronary artery disease, %| 38 (16.8)                           | 45 (18.9)                              | 0.628   |
| Heart failure readmission, %| 56 (29.8)                   | 74 (31.1)                              | 0.148   |
| **Comorbidities**        |                                       |                                        |         |
| Hypertension, %          | 195 (86.2)                            | 209 (89.8)                             | 0.679   |
| Diabetes, %              | 73 (32.3)                             | 82 (34.5)                              | 0.694   |
| Dyslipidemia, %          | 104 (46.0)                            | 119 (50.0)                             | 0.404   |
| Stroke, %                | 20 (8.8)                              | 32 (13.4)                              | 0.304   |
| Chronic kidney disease, %| 89 (39.4)                             | 116 (48.7)                             | 0.050   |
| Atrial fibrillation, %   | 103 (45.6)                            | 114 (47.9)                             | 0.643   |
| **General condition**    |                                       |                                        |         |
| Systolic BP, mmHg        | 119 [106, 132]                        | 116 [105, 130]                         | 0.204   |
| Diastolic BP, mmHg       | 84 [55, 75]                           | 634 [57, 72]                           | 0.376   |
| Heart rate               | 70 [63, 80]                           | 68 [60, 76]                            | 0.003   |
| **Laboratory examination**|                                      |                                        |         |
| Serum sodium, mEq/L      | 140 [137, 141]                        | 140 [138, 141]                         | 0.935   |
| Serum potassium, mmol/L  | 4.3 [4.0, 4.6]                        | 4.3 [3.9, 4.6]                         | 0.369   |
| Serum chloride, mmol/L   | 103 [99, 106]                         | 103 [100, 105]                         | 0.767   |
| Albumin, g/dL            | 3.5 [3.2, 3.7]                        | 3.4 [3.1, 3.8]                         | 0.767   |
| Hemoglobin, g/dL         | 11.4 [10.1, 13.0]                     | 11.2 [9.9, 12.6]                       | 0.208   |
| Creatinine, mg/dL        | 1.2 [0.9, 1.6]                        | 1.4 [1.1, 1.9]                         | 0.001   |
| Estimated glomerular filtration rate, mL/min per 1.73m² | 33.7 [23.6, 44.8] | 38.9 [28.9, 50.8]   | <0.001 |
| C-reactive protein, mg/dL| 0.30 [0.12, 0.92]                     | 0.32 [0.13, 1.10]                      | 0.914   |
| N-terminal pro-brain natriuretic peptide, pg/mL | 987 [528, 2658] | 1221 [499, 2621] | 0.526   |
| Low-density lipoprotein cholesterol, mg/dL | 93 [75, 113] | 92 [70, 110] | 0.364   |
| High-density lipoprotein cholesterol, mg/dL | 43 [36, 49] | 42 [34, 510] | 0.775   |
| Uric acid, mg/dL         | 7.5 [7.3, 7.9]                        | 9.2 [8.7, 10.2]                        | <0.001  |
| HbA1c, %                 | 6.0 [5.6, 6.4]                        | 6.0 [5.6, 6.6]                         | 0.401   |
| **Echocardiographic parameters** |                                      |                                        |         |
| LV end-diastolic diameter, mm | 46 [41, 51] | 47 [41, 51] | 0.736   |
| LV end-systolic diameter, mm | 30 [26, 33] | 30 [26, 34] | 0.742   |
| LV ejection fraction, %  | 60 [54, 65]                           | 61 [56, 66]                            | 0.270   |
| Left atrium diameter, mm | 44 [40, 49]                           | 45 [41, 51]                            | 0.001   |
| Tricuspid annular plane systolic excursion, mm | 17 [14, 20] | 17 [15, 20] | 0.083   |
| Mitral regurgitation (≥ moderate), % | 37 [16, 4]  | 45 [18.9]   | 0.543   |
| Tricuspid regurgitation (≥ moderate), % | 42 [18.6] | 50 [21.0]   | 0.561   |

(Continued)
Impact of UA and Lowering UA on All-Cause Mortality But Not HF Rehospitalization

The reason UA and lowering UA were correlated with all-cause mortality but not with HF rehospitalization is as follows: elevated UA induces a systemic inflammatory state, which can induce HfPEF and the other diseases, including various infections and/or malignancies; and these in turn are major causes of mortality in patients with HfPEF, especially elderly patients. Actually, compared with patients with HFrEF, patients with HfPEF are usually older, with higher rates of noncardiac comorbidities. Thus, noncardiac deaths, which may be correlated with comorbidities, including hyperuricemia, make up a higher proportion of deaths in our study (noncardiac death: 52.5%). On the other hand, because congestion is the main reason for HF rehospitalization in patients even in HfPEF, residual congestion at discharge (eg, high BNP levels at discharge) may be more closely correlated with HF rehospitalization than elevated UA. Therefore, UA and lowering UA were both correlated with all-cause mortality—including noncardiac death (Figure 2A and 3A)—mainly because of noncardiac comorbidities, including hyperuricemia, but were not correlated with HF.

![Figure 2. All-cause mortality and heart failure rehospitalization between mild and severe hyperuricemia groups.](image)

**Figure 2.** All-cause mortality and heart failure rehospitalization between mild and severe hyperuricemia groups. **A**, All-cause mortality. Kaplan–Meier curve showed the group with severe hyperuricemia had a significantly greater risk of all-cause mortality compared with the group with mild hyperuricemia ($P=0.004$). **B**, Heart failure rehospitalization. Gray test revealed that there was no significant difference in heart failure rehospitalization between the groups with mild and severe hyperuricemia ($P=0.895$). HF indicates heart failure; and HR, hazard ratio.
rehospitalization partially because of residual congestion at discharge (Figure 2B and 3B).

**Impact of Lowering UA on HFpEF**

It has been reported that management of comorbidities is useful in improving clinical outcomes, on the basis that comorbidities have the ability to induce a systemic inflammatory state, which can induce HFpEF. Thus, it can be considered that management of hyperuricemia, one such comorbidity, can cause the beneficial effects of HFpEF. However, whether lowering UA is effective in improving prognosis in patients with hyperuricemia and HFpEF is unclear. In the present study, we first demonstrated that lowering UA was useful for the prognosis of patients with hyperuricemia and HFpEF. Because the 1-year incidence of diuretics use was similar between the lowering UA and nonlowering UA groups (89.3% and 93.4% at discharge, and 85.8% and 93.4% at 1-year follow-up, respectively), our data are not affected by diuretic use. In addition, the incidence of urate-lowering therapy tended to be higher in the group with lowering UA than in the group with nonlowering UA (34.9% versus 24.6%, \( P = 0.06 \)). Therefore, urate-lowering therapy can partially contribute to the better clinical outcomes of the group with lowering UA group in patients with hyperuricemia and HFpEF.
Correlation of NT-proBNP and History of HF Admission to HFpEF

We previously reported that the NT-proBNP level at discharge is a useful predictor of HF rehospitalization. A high level of NT-proBNP may represent a sign of mild fluid overload at discharge, which is a reliable predictor of HF rehospitalization. Thus, the reason for the significant and independent correlation of NT-proBNP with clinical events in our study—including HF rehospitalization and all-cause mortality—may be the strong correlation between NT-proBNP and HF rehospitalization.

Regarding history of HF admission, this study demonstrated that a history of HF admission was a significant and independent factor associated with CE in patients with hyperuricemia and HFpEF. It has been reported that a history of HF admission is a strong risk factor for adverse cardiac outcomes for acute HF, and this may also be the case for patients with hyperuricemia and HFpEF.

Study Limitations

Several limitations of our study warrant mention. First, our sample size was limited and the observation period was relatively short. We evaluated only 1-year follow-up data of UA. Longer evaluation of UA may be favorable because UA is dynamic laboratory value and can be changed with medications, diet, and body weight change. However, our data showing the better prognostic impact of lowering UA for 1 year on patients with hyperuricemia and HFpEF provide valuable information in the management of patients with hyperuricemia and HFpEF. Second, we enrolled asymptomatic patients with hyperuricemia, as in recent randomized trials in Japan. Thus, these data may differ from those of studies performed in regions other than Japan and may not be applied to symptomatic hyperuricemia. Third, we could not clearly show the beneficial clinical impact of urate-lowering drug on the prognosis possible owing to the small number of the patients with urate-lowering drug use in this study. We only show the beneficial effect of lowering UA on the prognosis and tendency of better effect of urate-lowering drug use. In addition, we did not have accurate data regarding the timing of the urate lowering drug in this study. Majority of the study patients started to receive urate-lowering drug after the admission, but unfortunately, we did not have the accurate data in this study. To confirm whether urate-lowering drug can achieve the clinical benefit for the patients with hyperuricemia and HFpEF, further large-scaled trials should be performed. Fourth,
usually U-shaped prognostic effects of UA have been reported, but, many reports have shown UA ≈<4.0 mg/dL is correlated with adverse events.10,19 Because we focused on patients with hyperuricemia and HFpEF (UA >7.0 mg/dL) in this study, U-shaped prognostic effects of UA may not strongly affect our results. Finally, in this study, we did not evaluate the anti-inflammatory treatments including colchicine, NRLP3 inflammasome inhibitors, and interleukin-1 blockers, which are effective for HF according to recent reports.16,47

CONCLUSIONS
In conclusion, the PURSUIT-HFpEF prospective multicenter HFpEF registry has shown that, in patients with hyperuricemia and HFpEF, UA is a prognostic factor for composite all-cause death and HF rehospitalization. In addition, a higher UA level confers a greater risk of all-cause mortality and lowering UA, including the use of urate-lowering therapy, may improve the prognosis of patients with hyperuricemia and HFpEF.

APPENDIX
The OCVC-Heart Failure Investigators
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