Relationship of hyperuricemia with mortality in heart failure patients with preserved ejection fraction

Takeshi Shimizu,1 Akiami Yoshihisa,1,2 Yuki Kanno,1 Mai Takiguchi,1 Akihiko Sato,1 Yuichi Nakamura,1 Hiroyuki Yamauchi,1 Takashi Owada,1 Satoshi Abe,1 Takamasu Sato,1 Satoshi Suzuki,1,2 Masayoshi Oikawa,1 Takayoshi Yamaki,1 Koichi Sugimoto,1 Hiroyuki Kunii,1 Kazuhiko Nakazato,2 Hitoshi Suzuki,1 Shuichi Saitoh,1 and Yasuchika Takeishi1,2

1Department of Cardiology and Hematology, Fukushima Medical University, Fukushima, Japan; and 2Department of Advanced Cardiac Therapeutics, Fukushima Medical University, Fukushima, Japan

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Shimizu T, Yoshiiha A, Kanno Y, Takiguchi M, Sato A, Miura S, Nakamura Y, Yamauchi H, Owada T, Abe S, Sato T, Suzuki S, Oikawa M, Yamaki T, Sugimoto K, Kunii H, Nakazato K, Suzuki H, Saitoh SI, Takeishi Y. Relationship of hyperuricemia with mortality in heart failure patients with preserved ejection fraction. Am J Physiol Heart Circ Physiol 309: H1123–H1129, 2015. First published August 21, 2015; doi:10.1152/ajpheart.00533.2015.—Serum uric acid is a predictor of cardiovascular mortality in heart failure with reduced ejection fraction. However, the impact of uric acid on heart failure with preserved ejection fraction (HFpEF) remains unclear. Here, we investigated the association between hyperuricemia and mortality in HFpEF patients. Consecutive 424 patients, who were admitted to our hospital for decompensated heart failure and diagnosed as having HFpEF, were divided into two groups based on presence of hyperuricemia (serum uric acid ≥7 mg/dl or taking antihyperuricemic agents). We compared patient characteristics, echocardiographic data, cardio-ankle vascular index, and cardiopulmonary exercise test findings between the two groups and prospectively followed cardiac and all-cause mortality. Compared with the non-hyperuricemia group (n = 170), the hyperuricemia group (n = 254) had a higher prevalence of hypertension (P = 0.013), diabetes mellitus (P = 0.01), dyslipidemia (P = 0.038), atrial fibrillation (P = 0.001), and use of diuretics (P < 0.001). Cardio-ankle vascular index (8.7 vs. 7.5, P < 0.001) and V̇V̇cO2 slope (34.9 vs. 31.9, P = 0.004) were also higher. In addition, peak V̇O2 (14.9 vs. 17.9 ml·kg⁻¹·min⁻¹, P < 0.001) was lower. In the follow-up period (mean 897 days), cardiac and all-cause mortalities were significantly higher in those with hyperuricemia (P = 0.006 and P = 0.004, respectively). In the multivariable Cox proportional hazard analyses after adjustment for several confounding factors including chronic kidney disease and use of diuretics, hyperuricemia was an independent predictor of all-cause mortality (hazard ratio 1.98, 95% confidence interval 1.036–3.793, P = 0.039). Hyperuricemia is associated with arterial stiffness, impaired exercise capacity, and high mortality in HFpEF.

diastolic dysfunction; heart failure; uric acid; exercise capacity; arterial stiffness

NEW & NOTEWORTHY

We elucidated that the presence of hyperuricemia indicates progressed arterial stiffness, impaired exercise capacity, and higher mortality in HFpEF patients. Further study is required to determine whether controlling hyperuricemia improves the prognosis in HFpEF patients.

HEART FAILURE (HF) IS A MAJOR cause of death among the elderly in many countries and has become a significant public health problem (3). Heart failure with preserved ejection fraction (HFpEF), which constitutes approximately half of all HF patients, has a poor prognosis similar to heart failure with reduced ejection fraction (HFrEF), but the pathogenesis of HFpEF has not yet been clearly defined (16). HFpEF patients tend to have multiple noncardiac comorbidities, and several pathophysiological factors contribute to the pathogenesis of HFpEF (15, 17, 35), which substantially differs from that of HFrEF (4, 26). Several biomarkers have been identified to estimate the prognosis and select the appropriate therapy for chronic HF patients (34). Serum uric acid (UA), produced in the terminal step of purine nucleotide metabolism by xanthine oxidase (XO), is a predictor of mortality in HFrEF, independent of chronic kidney disease (11, 30). However, the impact of serum UA on mortality in patients with HFpEF remains unclear.

Therefore, the aims of the present study were to investigate clinical features, cardiac function, arterial stiffness, exercise capacity, and cardiac and all-cause mortalities in HFpEF patients with or without hyperuricemia.

METHODS

Subjects and study protocol. This was a prospective observational study that enrolled consecutive symptomatic HFpEF patients that were hospitalized for treatment of decompensated HF and discharged from Fukushima Medical University between 2009 and 2013. Patients included in this study were those with symptomatic HF, which was previously defined based on the Framingham criteria (20) and New York Heart Association (NYHA) Class ≥II at enrollment, and left ventricular EF (LVEF) ≥50%. Patients with acute coronary syndrome and/or undergoing dialysis therapy were excluded. The patients were divided into two groups according to the presence of hyperuricemia, which was defined as the usual usage of antihyperuricemic agents or serum UA levels >7 mg/dl (30). We compared the clinical features and results from several examinations of each group, such as laboratory tests, echocardiography, cardio-ankle vascular index (CAVI), and cardiopulmonary exercise tests performed at the time of discharge. Hypertension was defined as the recent use of antihypertensive drugs, or systolic blood pressure ≥140 mmHg, and/or diastolic blood pressure ≥90 mmHg. Diabetes was defined as the recent use of insulin or antidiabetic drugs, a fasting blood glucose value of ≥126 mg/dl,
and/or a hemoglobin $A_{\text{c}}$ value of $\geq 6.5\%$. Dyslipidemia was defined as the recent use of cholesterol-lowering drugs, a triglyceride value of $\geq 150$ mg/dl, a low-density lipoprotein cholesterol value of $\geq 140$ mg/dl, and/or a high-density lipoprotein cholesterol value of $< 40$ mg/dl. The estimated glomerular filtration rate (GFR) was measured by the Modification of Diet in Renal Disease formula (18). Chronic kidney disease was defined as an estimated GFR $< 60$ ml·min$^{-1}$·1.73 m$^{-2}$ (18). Anemia was defined as hemoglobin of $< 12.0$ g/dl in females and $< 13.0$ g/dl in males (21). The primary outcome of our study was mortality. The patients were followed up for cardiac death and all-cause mortality. Cardiac death was adjudicated by independent experienced cardiologists including worsening HF, which met the Framingham criteria (20), and ventricular fibrillation documented by electrocardiogram or implantable devices. Noncardiac death included death due to respiratory failure, renal failure, infection, sepsis, stroke, or digestive hemorrhage, etc. Status and dates of deaths were obtained from the patients’ medical records. If these data were unavailable, status was ascertained by a telephone call to the patient’s referring hospital cardiologist. Survival time was calculated from the date of hospitalization until the date of death or last follow-up. These data were performed blindly to the analyses of this study. Written informed consent was obtained from all study subjects. The study protocol was approved by the Ethical Committee of Fukushima Medical University.

The investigation conforms to the principles outlined in the Declaration of Helsinki. Reporting of the study conforms to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) along with references to STROBE and the broader Enhancing the Quality and Transparency of Health Research (EQUATOR) guidelines (33).

Echocardiography. Echocardiography was performed blindly by an experienced echocardiographer using the standard techniques. Echocardiographic parameters included interventricular septum thickness, left ventricular dimension, posterior wall thickness, LVEF, left atrial volume, the ratio of early transmitial flow velocity to mitral annular velocity (mitral valve E/ε), inferior vena cava diameter, and right ventricular fractional area change (28). The LVEF was calculated using a Simpson’s method. Mitral valve E/E’ was calculated by transmitial Doppler flow and tissue Doppler imaging. Tissue Doppler imaging was obtained from the average of septal and lateral annulus velocities. The right ventricular fractional area change, defined as (end diastolic area-end systolic area)/end diastolic area × 100, is a measure of right ventricular systolic function (28). All recordings were performed on ultrasound systems (ACUSON Sequoia; Siemens Medical Solutions, Mountain View, CA).

Cardio-ankle vascular index. CAVI as an index of arterial stiffness was measured blindly using a Vasera VS-1000 device (Fukuda Denshi, Tokyo, Japan) as previously reported (29) while the subjects were awake between 8:00 AM and 12:00 PM. CAVI reflects the stiffness of the aorta, femoral arteries, and tibial arteries as a whole (29).

Cardiopulmonary exercise testing. All subjects underwent incremental symptom-limited exercise testing using an upright cycle ergometer with a ramp protocol (Strength Ergo 8; Fukuda Denshi). Breath-by-breath oxygen consumption (V$\text{O}_2$), carbon dioxide production (V$\text{CO}_2$), and minute ventilation (V$\text{E}$) were measured during exercise using an AE-300S respiratory monitor (Minato Medical Science, Osaka, Japan) (1, 24). Peak V$\text{O}_2$ was measured as an average of the last 30 s of exercise. Ventilatory response to exercise (expressed as a V$\text{E}$/V$\text{CO}_2$ slope) was calculated as the regression slope relating V$\text{E}$ to CO$_2$ from the start of exercise until the respiratory compensation point (the time at which ventilation is stimulated by CO$_2$ output and end-tidal CO$_2$ tension begins to decrease) (27). Ventilatory anaerobic threshold was calculated with the V-slope method.

Statistical analysis. Normally distributed data are presented as means ± SD, and nonnormally distributed data are presented as median (interquartile range). Categorical variables are expressed as numbers and percentages. The $\chi^2$-test was used for comparisons of categorical variables. Data of the two groups were compared using the independent Student’s t-test for normally distributed data and the Mann-Whitney U test for nonnormally distributed data. Correlations among CAVI, peak V$\text{O}_2$, and V$\text{E}$/V$\text{CO}_2$ slope and UA were assessed using Pearson correlation analysis. The Kaplan-Meier method was used for presenting the event-free rate, and the log-rank test was used for initial comparisons. Univariable and multivariable Cox proportional hazard analyses were used to analyze predictors of cardiac and all-cause mortalities with adjusting confounding factors. To prepare for potential confounding, we considered the following clinical factors, which are generally known to affect the risk of cardiac events in HF patients: age, gender, systolic blood pressure, LVEF, B-type natriuretic peptide, presence of ischemic etiology, diabetes, atrial fibrillation, chronic kidney disease, anemia, hyperuricemia, and usage of $\beta$-blockers, renin-angiotensin-aldosterone system inhibitors, and diuretics. Among these factors, those that were independent for predicting cardiac events with a value of $P < 0.10$ were selected in the final adjusted model. The proportional hazard assumption for the model was checked by examining log-minus-log transformed Kaplan-Meier estimates of the survival curves for the two groups plotted against time to follow-up period. These curves help in identifying nonproportionality patterns in hazard function such as convergence (difference in risk between the two groups decreases with time), divergence, or crossing of the curves. The Schoenfeld test for the violation of proportional hazards, which assesses the correlation between scaled residuals and time, was also conducted. As the proportional-hazard assumptions were violated in the above-mentioned diagnostic test, the extended Cox hazard model was used for time-varying exposure of the adjusting variable. There was no significant multicollinearity between hyperuricemia and other confounding factors. To assess potential heterogeneity of associations between hyperuricemia and all-cause mortality, we conducted subgroup analyses. Interactions between hyperuricemia and clinically relevant variables, including age, gender, presence of NYHA III or IV class, ischemic etiology, hypertension, diabetes, dyslipidemia, atrial fibrillation, chronic kidney disease, and all-cause mortality, were assessed using the adjusted Cox hazard model (33).

Table 1. Comparisons of clinical features between hyperuricemia group and non-hyperuricemia group

<table>
<thead>
<tr>
<th></th>
<th>Hyperuricemia (n = 254)</th>
<th>Non-hyperuricemia (n = 170)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>69.4 ± 13.5</td>
<td>66.8 ± 16.6</td>
<td>0.075</td>
</tr>
<tr>
<td>Male gender, %</td>
<td>141 (55.5)</td>
<td>71 (41.7)</td>
<td>0.005</td>
</tr>
<tr>
<td>Body mass index, kg/cm$^2$</td>
<td>23.4 ± 4.2</td>
<td>23.0 ± 3.8</td>
<td>0.268</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>121.8 ± 20.4</td>
<td>124.3 ± 19.3</td>
<td>0.215</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>67.2 ± 14.4</td>
<td>70.0 ± 13.1</td>
<td>0.038</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>75.2 ± 17.0</td>
<td>74.2 ± 17.2</td>
<td>0.554</td>
</tr>
<tr>
<td>NYHA class III or IV, %</td>
<td>14 (5.5)</td>
<td>6 (3.5)</td>
<td>0.345</td>
</tr>
<tr>
<td>Smoker, %</td>
<td>115 (48.3)</td>
<td>69 (45.0)</td>
<td>0.533</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td>0.870</td>
</tr>
<tr>
<td>Ischemic, %</td>
<td>33 (12.9)</td>
<td>25 (14.7)</td>
<td></td>
</tr>
<tr>
<td>Valvular, %</td>
<td>117 (46.0)</td>
<td>71 (41.7)</td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy, %</td>
<td>54 (21.2)</td>
<td>37 (21.7)</td>
<td></td>
</tr>
<tr>
<td>Others, %</td>
<td>50 (19.6)</td>
<td>37 (21.7)</td>
<td></td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>203 (79.9)</td>
<td>118 (69.4)</td>
<td>0.013</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>98 (38.5)</td>
<td>45 (26.4)</td>
<td>0.010</td>
</tr>
<tr>
<td>Dyslipidemia, %</td>
<td>203 (79.9)</td>
<td>121 (71.1)</td>
<td>0.038</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>123 (48.4)</td>
<td>54 (31.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>CKD, %</td>
<td>171 (67.3)</td>
<td>45 (26.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Anemia, %</td>
<td>169 (66.5)</td>
<td>82 (48.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAS inhibitors, %</td>
<td>195 (76.7)</td>
<td>109 (64.0)</td>
<td>0.005</td>
</tr>
<tr>
<td>$\beta$-Blockers, %</td>
<td>174 (68.5)</td>
<td>99 (58.2)</td>
<td>0.030</td>
</tr>
<tr>
<td>Diuretics, %</td>
<td>184 (72.4)</td>
<td>71 (41.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Statin, %</td>
<td>88 (34.6)</td>
<td>55 (32.3)</td>
<td>0.625</td>
</tr>
</tbody>
</table>

Values are means ± SD; $n$ in parenthesis = number of patients; $n = 424$ total patients. BP, blood pressure; NYHA, New York Heart Association; CKD, chronic kidney disease; RAS, renin-angiotensin-aldosterone system.
HYPERURICEMIA PREDICTS HIGHER MORTALITY OF HFpEF

H1125

disease, anemia, and use of diuretics were estimated by a Cox
proportional hazards regression model, and are shown in a Forest
plot. A value of $P < 0.05$ was considered significant for all comparisons.
These analyses were performed using a statistical software package
(SPSS ver. 21.0; IBM, Armonk, NY).

RESULTS

The clinical features of the present study’s subjects are
summarized in Table 1. Of all 424 HFpEF patients, 254
(59.9%) were classified as hyperuricemia group. Compared
with the non-hyperuricemia group, the hyperuricemia group
had a higher prevalence of male gender, more comorbidities,
including hypertension, diabetes, dyslipidemia, atrial fibrilla-
tion, chronic kidney disease, and anemia, and a higher usage of
renin-angiotensin-aldosterone system inhibitors, β-blockers,
and diuretics. Comparisons of laboratory data between the two
groups are shown in Table 2. The hyperuricemia group had
higher levels of serum UA and B-type natriuretic peptide,
lower levels of hemoglobin and estimated GFR, and higher
density lipoprotein than the non-hyperuricemia group. In con-
trast, C-reactive protein, albumin, and sodium did not differ
between the two groups. Parameters of echocardiography,
CAVI, and cardiopulmonary exercise tests are summarized in
Table 3. CAVI was significantly higher in the hyperuricemia
group than in the non-hyperuricemia group. Although left and
right ventricular systolic function by echocardiography did not
differ between the two groups, peak Vo2, end-tidal CO2 at
respiratory compensation point, and anaerobic threshold were
significantly lower, and the Ve/VCO2 slope was higher in the
hyperuricemia group than in the non-hyperuricemia group.
Moreover, there was a weak positive correlation between
serum UA and CAVI ($R = 0.167, P = 0.029$), and no
correlation among peak Vo2, Ve/VCO2 slope, and serum UA,
respectively.

During the follow-up period (median 897 days), there were
30 cardiac deaths including 23 due to worsening HF and 7 with
ventricular fibrillation (25 in the hyperuricemia group and 5 in
the non-hyperuricemia group, the hyperuricemia group
had a higher prevalence of male gender, more comorbidities,
including hypertension, diabetes, dyslipidemia, atrial fibrilla-
tion, chronic kidney disease, and anemia, and a higher usage of
renin-angiotensin-aldosterone system inhibitors, β-blockers,
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respectively.

During the follow-up period (median 897 days), there were
30 cardiac deaths including 23 due to worsening HF and 7 with
ventricular fibrillation (25 in the hyperuricemia group and 5 in
the non-hyperuricemia group, and 5). We checked that the Cox models support the assump-
tion of proportional hazards. There were no interactions
with other important variables, especially including presence of chronic kidney disease and usage of diuretics.

DISCUSSION

This study demonstrated that, compared with HFpEF pa-
tients without hyperuricemia, those with hyperuricemia had
more comorbidities, lower renal function, higher prevalence of diuretic therapy, higher arterial stiffness, lower exercise capacity, and higher event rate of cardiac and all-cause death. The present study also demonstrated that hyperuricemia was a predictor of all-cause mortality in HFpEF patients independent of other risk factors, including chronic kidney disease and use of diuretics.

Although hyperuricemia is an independent predictor of mortality in HFrEF, it remains controversial whether UA itself contributes to the pathophysiology of HF or it functions merely as a marker of status in HF patients. While UA is produced in the terminal step of purine nucleotide metabolism by the enzyme XO, XO is one of the major sources of reactive oxygen species generation. In HF patients, increased UA production occurs owing to the hypoxia on the microvasculature and impaired oxidative metabolism with increased amount and activity of XO in capillary endothelial cells (2). Increased oxidative stress induces impaired contractile function, endothelial dysfunction, and skeletal muscle impairment, thereby contributing to disease progression in HF (31, 35). Accordingly, several studies have elucidated the beneficial effects of UA-lowering therapy with the XO inhibitor allopurinol for physiological endpoints such as endothelial dysfunction (10), peripheral blood flow (9), and energetic inefficiency of myocardium (6). However, UA-lowering therapy with probenecid or benz bromarone, which is not involved in XO activity, showed no efficacy in HF patients (12, 25). This evidence indicates the detrimental role of oxidative stress generated by XO, but not of UA itself, for the pathogenesis of HF. As oxidative stress also contributes to the pathogenesis of HFpEF (26), the results of the present study may be explained by the adverse effects of oxidative stress generated by XO, which is indicated by high levels of serum UA.

On the other hand, the present study showed that HFpEF patients with hyperuricemia had a higher CAVI value (as a diagnostic parameter of arterial stiffness) than those without hyperuricemia. As recently reported, serum UA has independent positive correlation with CAVI (23), which is concordant with our data, and arterial stiffness is associated with cardiac diastolic dysfunction determined by echocardiographic parameters (7). HFpEF patients have abnormal ventriculo-arterial coupling (14, 32). Systolic-ventricular and arterial stiffening influence diastole by elevating systolic load to prolong relaxation, compromising filling, and raising end-diastolic pressure (14). Aortic stiffness (8) and endothelial dysfunction (5) are evident in patients with HFpEF. Central aortic stiffness may accelerate HF development in vulnerable patients by increasing systolic load and worsening ventricular-vascular coupling. El-

Table 4. Cox proportional hazard model of cardiac death in HFpEF

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Univariable</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age</td>
<td>1.014</td>
<td>0.988–1.041</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.320</td>
<td>0.641–2.719</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>0.981</td>
<td>0.963–0.999</td>
</tr>
<tr>
<td>Ischemic etiology</td>
<td>0.209</td>
<td>0.028–1.352</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.908</td>
<td>0.425–1.940</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2.162</td>
<td>1.041–4.492</td>
</tr>
<tr>
<td>CKD</td>
<td>3.565</td>
<td>1.527–8.327</td>
</tr>
<tr>
<td>Anemia</td>
<td>3.759</td>
<td>1.437–9.829</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>3.533</td>
<td>1.352–9.232</td>
</tr>
<tr>
<td>BNP</td>
<td>1.003</td>
<td>1.002–1.004</td>
</tr>
<tr>
<td>LVEF</td>
<td>1.016</td>
<td>0.975–1.059</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>0.936</td>
<td>0.445–1.969</td>
</tr>
<tr>
<td>RAS inhibitors</td>
<td>0.375</td>
<td>0.182–0.769</td>
</tr>
<tr>
<td>Diuretics</td>
<td>3.533</td>
<td>1.352–9.232</td>
</tr>
</tbody>
</table>

HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; CI, confidence interval; LVEF, left ventricular ejection fraction.
evolved arterial stiffness is in fact a risk factor for readmission or cardiac death of HF patients (22). These findings indicate the arterial stiffness, which is in part affected by serum UA, as a potential causative or exacerbating factor of HFpEF.

Many patients with HFpEF have symptoms of exertional intolerance in the absence of apparent volume overload. In HFpEF patients, similar to HFrEF, peak VO₂ was reduced in comparison with healthy controls (13). HFpEF patients have abnormalities in skeletal muscle, characterized by a shift in muscle fiber type distribution with reduced type I oxidative muscle fibers and may be associated with exercise intolerance (15). Regarding the relationship between UA and exercise intolerance, Leyva et al. (19) reported that the serum UA level was higher in HFpEF patients compared with healthy controls (13). HFpEF patients have lower peak VO₂ and higher V̇E/V̇CO₂ slope, probably reflecting the metabolic effects of hypoxia in the peripheral circulation.

Study limitations. Several limitations remain in the present study. First, the present study, conducted as a prospective observational study in a single institution with relatively small numbers of subjects, might be underpowered to accurately estimate the association between hyperuricemia and outcomes in HFpEF. Although we assessed associations between hyperuricemia and mortality using the multivariable Cox proportional hazard regression analyses and subgroup analyses under considerations of multiple confounding factors, the effects of differences in comorbidities between the two groups might not be completely adjusted, and the present results should be viewed as preliminary. Second, the present study was performed at a single hospital site with a homogenous racial mix and conformed by the guideline from the Japanese Circulation Society on a condition that still had many variations of therapeutic approaches, thereby potentially limiting the generalizability of the findings. Therefore, further studies with a larger population are needed. Third, our study did not elucidate whether increased UA has a causal role in the adverse outcome.

### Table 5. Cox proportional hazard model of all-cause death in HFpEF

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Univariable</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age</td>
<td>1.059</td>
<td>1.036–1.083</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.990</td>
<td>0.637–1.538</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>1.009</td>
<td>0.998–1.020</td>
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<td>Ischemic etiology</td>
<td>0.979</td>
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<td>Diabetes</td>
<td>1.354</td>
<td>0.867–2.114</td>
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<tr>
<td>Atrial fibrillation</td>
<td>2.115</td>
<td>1.349–3.316</td>
</tr>
<tr>
<td>CKD</td>
<td>2.182</td>
<td>1.364–2.182</td>
</tr>
<tr>
<td>Anemia</td>
<td>3.756</td>
<td>2.072–6.811</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>2.083</td>
<td>1.254–3.459</td>
</tr>
<tr>
<td>BNP</td>
<td>1.003</td>
<td>1.002–1.003</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.991</td>
<td>0.967–1.016</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>0.789</td>
<td>0.503–1.357</td>
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<td>RAS inhibitors</td>
<td>0.629</td>
<td>0.395–1.003</td>
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<tr>
<td>Diuretics</td>
<td>2.224</td>
<td>1.327–3.727</td>
</tr>
</tbody>
</table>

### Fig. 2. Forest plot of hazard ratios by patients’ subgroups.

The subgroup analysis describes associations between hyperuricemia and all-cause mortality in subgroups after adjustment for interactions between hyperuricemia and prespecified clinically important variables. There was a significant interaction with atrial fibrillation (P = 0.049); hazard ratio (HR) of 1.091 [95% confidence interval (CI), 0.565–2.107, P = 0.796] with atrial fibrillation and HR of 3.135 (95% CI, 1.407–6.984, P = 0.005) without atrial fibrillation. However, there was no interaction with other important variables, especially including presence of chronic kidney disease (CKD) and usage of diuretics.
or the mechanisms underlying the association. Our data suggest that increased UA is a potential biomarker that may be helpful in risk-stratification of patients with HFpEF and future studies to determine causal relationship and the impact of UA reduction treatment strategies in reducing mortality in HFpEF are required.

Conclusions and perspectives. Hyperuricemia was an independent predictor of all-cause mortality in HFpEF patients. Our study showed that the presence of hyperuricemia indicates progressed arterial stiffness and impaired exercise capacity in HFpEF patients. Appropriate management to control hyperuricemia may improve the prognosis of patients with HFpEF. Further study is required to determine whether controlling UA improves the prognosis in HFpEF patients.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES


