Hyperuricemia Associated With High Cardiac Event Rates in the Elderly With Chronic Heart Failure

Takeshi NIIZEKI, MD
Yasuchika TAKEISHI, MD, FJCC
Takanori ARIMOTO, MD
Hidenobu OKUYAMA, MD
Naoki NOZAKI, MD
Osamu HIRONO, MD
Yuichi TSUNODA, MD
Tetsu WATANABE, MD
Joji NITOBE, MD
Takehiko MIYASHITA, MD
Hiroki TAKAHASHI, MD
Yo KOYAMA, MD
Isao KUBOTA, MD, FJCC

Abstract

Objectives. Congestive heart failure (CHF) is the major cause of death and hospitalization in the elderly population. Simple markers that can be measured anywhere at low cost are necessary to identify patients at high risk. Recent studies have reported that hyperuricemia is a prognostic marker for CHF. However, it is not yet known whether serum levels of uric acid may provide prognostic information in the elderly population. Therefore, this study tried to identify the clinical characteristics of elderly CHF patients (≥ 70 years) in our institution and to evaluate whether uric acid levels can effectively estimate the prognosis for elderly CHF patients.

Methods and Results. Uric acid levels were analyzed in 247 CHF patients, and patients were followed up for 451 ± 235 days (mean ± SD). Elderly CHF patients aged ≥ 70 years (123 patients) had higher rate of hypertension, lower current smoking rate and higher uric acid levels than those aged < 70 years (124 patients). There were 72 cardiac events including cardiac deaths and readmissions for worsening CHF. Multivariate analysis with the Cox proportional hazard model showed that uric acid was the only independent predictor of cardiac events (hazard ratio 1.544, 95% confidence interval 1.215 - 2.582, p < 0.0001) in the elderly with CHF. The highest quartile of uric acid level was associated with the highest risk of cardiac events (a 4.45-fold compared to the lowest quartile). Kaplan-Meier analysis revealed that uric acid levels effectively risk stratified elderly CHF patients for cardiac events.

Conclusions. These findings suggest that measurement of uric acid levels in elderly CHF patients may add valuable prognostic information to predict cardiac events.

Key Words
- Heart failure (uric acid)
- Prognosis
- Elderly
INTRODUCTION

Chronic heart failure (CHF) is the leading cause of death and hospitalization among elderly patients, and the incidence of CHF increases with advancing age. CHF is accompanied by various pathophysiological changes which trigger disease progression, and deterioration of ventricular function is still common in elderly patients with CHF. Although the current therapy for CHF such as angiotensin-converting enzyme inhibitors and ß-blockers can relieve symptoms and prolong life, the incidence, readmission rate and mortality are still increasing because of the aging of the population. The frequent coexistence of co-morbid illness and psychosocial issues in older patients often makes diagnosis and management difficult, and prognostic parameters of elderly patients with CHF have not been definitely identified. Therefore, objective parameters are needed to diagnose and assess the severity of CHF in elderly patients.

A number of parameters are useful to predict prognosis of patients with CHF. However, many modern markers are used only for research purposes and are not widely available in routine clinical practice. Several studies have recently shown that serum level of uric acid is a promising marker for prognosis in CHF patients. In addition, hyperuricemia is related to impaired oxidative metabolism and vascular dysfunction in CHF.

The present study tried to clarify the clinical characteristics and prognosis of elderly CHF patients in our institution, and to assess whether uric acid levels can effectively estimate prognosis in elderly CHF patients. Serum uric acid levels were measured at admission and the association with subsequent cardiac events was assessed in 247 consecutive patients hospitalized for chronic heart failure.

SUBJECTS AND METHODS

Study design

We prospectively studied 247 consecutive patients who had been admitted for the treatment of worsening chronic heart failure, or for diagnosis and pathophysiological investigations, or therapeutic evaluations of heart failure from April 1996 to February 2005. Informed consent was obtained from all patients before participation in this study, and the protocol was approved by the Human Investigations Committee of our institution.

The diagnosis of heart failure was based on a history of dyspnea and symptomatic exercise intolerance with signs of pulmonary congestion or peripheral edema, or documentation of left ventricular enlargement or dysfunction by chest radiography, echocardiography, or radionuclide ventriculography. Baseline characteristics of the patients are presented in Table 1. Definite hypertension was defined as self-reported hypertension and systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg, or patients received antihypertensive treatment. A diagnosis of diabetes and hyperlipidemia were obtained from medical records or patient history.

Venous blood samples were obtained at admission, and two-dimensional echocardiography was performed by experts unaware of patient characteristics within 1 week after admission. Attending physicians were kept unaware of the results of the biochemical markers, and optimal medical therapy was performed independently based on measurements such as improvement in symptoms, physical examination findings, and pulmonary congestion on chest radiography.

End-points and follow-up

No patients were lost to follow-up. Mean follow-up was 451 ± 235 days, range 5 to 1,080 days, after admission to Yamagata University Hospital. Events were adjudicated using medical records, electrocardiograms, chest radiographs, autopsy reports, death certificates, and witness statements. The endpoints, which were judged independently by researchers, were cardiac death, defined as death from worsening heart failure or sudden cardiac death, and worsening heart failure requiring readmission. Sudden cardiac death was defined as death without definite premonitory symptoms or signs and was established by the attending physician.

Statistical analysis

Results are presented as the mean ± SD value for continuous variables and as the percentage of total patients for categorical variables. The independent samples t-test and chi-square test or linear regression analysis were used for comparison of continuous and categorical variables, respectively. p values < 0.05 were considered statistically significant. Cox proportional hazard analyses were performed to determine the independent predictor of cardiac events for the entire population.
Independent predictors selected by univariate analysis were entered into multivariate analysis. We determined the multivariate-adjusted risk for quartiles 2 through 4 compared with quartile 1. Cardiac event-free curve was computed according to the Kaplan-Meier method and analyzed by a log-rank test. All analyses were performed using a standard statistical program package (StatView, version 5.0, SAS Institute Inc).

RESULTS

Clinical characteristics of elderly CHF patients

Comparison of the clinical characteristics between CHF patients aged ≥ 70 and < 70 years is presented in Table 1. Elderly CHF patients ≥ 70 years old had higher rate of hypertension, lower current smoking rate and higher uric acid levels than those aged < 70 years. There were no differences in dia-
Table 2  Comparisons of clinical characteristics of 123 elderly patients with chronic heart failure between event-free and cardiac event groups

<table>
<thead>
<tr>
<th></th>
<th>Event-free</th>
<th>Cardiac event</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 78)</td>
<td>(n = 47)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>78 ± 9</td>
<td>77 ± 9</td>
<td>0.5273</td>
</tr>
<tr>
<td>Gender</td>
<td>male 53%</td>
<td>male 49%</td>
<td>0.2988</td>
</tr>
<tr>
<td>diabetes mellitus</td>
<td>90%</td>
<td>96%</td>
<td>0.3956</td>
</tr>
<tr>
<td>hyperlipidemia</td>
<td>85%</td>
<td>85%</td>
<td>0.8707</td>
</tr>
<tr>
<td>Etiologies of heart failure</td>
<td>85%</td>
<td>85%</td>
<td>0.7899</td>
</tr>
<tr>
<td>Serum creatinine levels</td>
<td>78 ± 25</td>
<td>79 ± 25</td>
<td>0.0039</td>
</tr>
<tr>
<td>Na levels</td>
<td>135 ± 10</td>
<td>134 ± 10</td>
<td>0.4356</td>
</tr>
<tr>
<td>Hemoglobin levels</td>
<td>13 ± 1.5</td>
<td>13 ± 1.5</td>
<td>0.2358</td>
</tr>
<tr>
<td>Echocardiographic findings</td>
<td>85%</td>
<td>85%</td>
<td>0.1782</td>
</tr>
</tbody>
</table>

Clinical outcomes in elderly CHF patients

In 123 elderly patients with CHF, there were 12 non-cardiac deaths (3 cerebral hemorrhage, 3 colon cancer, 2 ileus, 2 pneumonia, and 2 suicides) and total cardiac events (38%) including 18 cardiac deaths (3 in-hospital deaths) and 29 readmissions for worsening heart failure. Thirty of the 47 cardiac events (64%) occurred in those aged ≥ 70 years. Rates of cardiac death (15% vs 5%), re-hospitalization (23% vs 15%), and total cardiac events (38% vs 20%) were significantly higher in patients aged ≥ 70 years (Table 1). Kaplan-Meier analysis also showed that elderly CHF patients aged ≥ 70 years had significantly lower cardiac event-free rates (p = 0.0017; Fig. 1).

The 247 CHF patients had 72 cardiac events during a mean follow-up period of 451 ± 235 days, and 47 of these 72 events (65%) occurred in those aged ≥ 70 years.
were caused by worsening chronic heart failure.

Clinical characteristics in the 123 elderly patients with CHF were compared between patients with and without cardiac events (Table 2). Patients with cardiac events had more severe New York Heart Association (NYHA) functional class \( p < 0.0001 \), higher levels of uric acid \( p = 0.0082 \), higher levels of creatinine \( p = 0.0063 \), and lower rate of hypertension \( p = 0.0369 \) compared to those without cardiac events. Other parameters including age, sex, numbers of patients with ischemic heart disease, levels of hemoglobin and Na, and echocardiographic data were not significantly different. Medical treatments such as digitalis, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins, Ca channel blockers, \( \beta \)-blockers, and allopurinol at discharge were also similar in the two groups.

Table 3  Univariate and multivariate analyses of predictors of cardiac events in elderly chronic heart failure patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95% confidence interval</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uric acid</td>
<td>1.803</td>
<td>1.199 - 2.337</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Creatinine</td>
<td>2.431</td>
<td>1.833 - 6.743</td>
<td>0.0107</td>
</tr>
<tr>
<td>NYHA class ( \geq 3 )</td>
<td>1.935</td>
<td>1.227 - 2.587</td>
<td>0.0332</td>
</tr>
<tr>
<td>Uric acid</td>
<td>1.544</td>
<td>1.215 - 2.582</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.846</td>
<td>0.952 - 4.434</td>
<td>0.1110</td>
</tr>
<tr>
<td>NYHA class ( \geq 3 )</td>
<td>1.250</td>
<td>0.873 - 3.772</td>
<td>0.3502</td>
</tr>
</tbody>
</table>

Abbreviation as in Table 1.

High uric acid levels \( \geq 7.0 \text{mg/dl} \) were observed in 2 of 17 patients \( 11.8\% \) with NYHA functional class \( \geq 3 \), in 19 of 50 patients \( 38.0\% \) with class \( \geq 3 \), in 20 of 41 patients \( 48.8\% \) with class \( \geq 3 \), and in 9 of 15 patients \( 60.0\% \) with class \( \geq 3 \) \( p = 0.0236 \). Uric acid levels were not different between patients with ischemic and non-ischemic etiologies \( 5.9 \pm 2.5 \text{vs} 6.4 \pm 2.3 \text{mg/dl} \), \( p = 0.2662 \). In patients with NYHA functional class \( \geq 3 \) / 4, use of loop diuretics was more frequent compared to patients with NYHA class \( \geq 3 \) / 4 \( 44/56 \) \( 78.6\% \) vs \( 35/67 \) \( 52.2\% \) \( p = 0.0097 \).

Comparison of uric acid levels and cardiac event rates between patients with preserved left ventricular systolic function \( \geq 50\% \) and those with reduced left ventricular systolic function \( < 50\% \) showed no significant difference.

Independent predictors of cardiac events in elderly CHF patients

Prognostic variables to predict cardiac events in elderly CHF patients were examined by univariate and multivariate Cox proportional hazard analyses (Table 3). Univariate analysis related uric acid, creatinine, and NYHA functional class to subsequent cardiac events. Thus, these three parameters were entered into multivariate analysis. Multivariate analysis showed uric acid was the only independent predictor of cardiac events in elderly patients with CHF \( \text{hazard ratio} 1.544, 95\% \text{confidence interval} 1.215 - 2.582, p < 0.0001 \).

Kaplan-Meier curves were constructed for patients with normal and high levels of uric acid (Fig. 2). Patients with high uric acid levels \( \geq 7.0 \text{mg/dl} \) had significantly lower cardiac event-
free rates than those with normal uric acid levels \(( < 7.0 \text{ mg/dl} )\) Serum uric acid levels could reliably risk stratify elderly patients with CHF for future cardiac events.

**Graded relationships between uric acid levels and cardiac events**

Patients were divided into four groups based on the uric acid levels: 1st quartile \(( \leq 5.0 \text{ mg/dl}, n = 30 \) \), 2nd quartile \(( 5.1 - 6.4 \text{ mg/dl}, n = 30 \) \), 3rd quartile \(( 6.5 - 8.6 \text{ mg/dl}, n = 31 \) \), and 4th quartile \(( 8.7 \text{ mg/dl} \geq, n = 32 \) \). In the highest quartile, NYHA functional class was more severe, creatinine level was higher, and left ventricular ejection fraction was lower than in the lower three quartiles ( *Table 4* ). The highest quartile of uric acid was associated with the highest risk of cardiac events (4.45-fold compared to the lowest quartile) as shown in *Fig. 3*. Hazard ratios were 1.000, 1.424 (95% CI 0.479 - 2.254), 3.118 (CI 1.011 - 6.181), and 4.45 (CI 1.201 - 8.889) for quartiles 1 through 4. Cumulative event-free curves were constructed by the Kaplan-Meier method ( *Fig. 4* ). Patients in the highest quartile had a significantly lower cardiac event-free rate than the other three quartiles \(( p < 0.001 \) ).

**DISCUSSION**

Our results demonstrated that serum uric acid level was associated with a high risk of cardiac events in elderly patients with CHF. Uric acid level could potentially improve the risk stratification of elderly with CHF.

It is important to accurately define prognostic factors in patients with heart failure to identify high-risk individuals who require closer follow-up and more intensive intervention. A number of parameters can predict the prognosis of patients with CHF\(^ {13,17} \). Brain natriuretic peptide is released from the ventricles as ventricular function deteriorates, and is a well-established prognostic indicator in CHF patients\(^ {14,26} \). However, many modern parameters are used only for research purposes and are not widely available. Therefore, simple markers that can be measured anywhere at low cost are necessary. High serum uric acid levels are a strong, independent marker of impaired prognosis in patients with moderate and severe heart failure\(^ {18,19} \). Hyperuricemia is a marker of impaired oxidative metabolism, hyperinsulinemia, inflammatory cytokine activation, and vascular dysfunction\(^ {20,21} \).

In the present study, we examined the potential prognostic value of uric acid in elderly persons with CHF. Univariate and multivariate Cox proportional hazard analyses demonstrated that uric acid level was an independent predictor of future cardiac events ( *Table 3* ). We also showed that the risk of cardiac events increased with increasing uric acid level. The highest quartile of uric acid level was associated with a 4.45-fold event risk ( *Fig. 3* ).

In the present study, elderly CHF patients
aged ≥ 70 years had higher uric acid levels than those aged < 70 years, suggesting decreases in renal function with aging. In addition, elderly CHF patients aged ≥ 70 years were given loop diuretics more frequently than those aged < 70 years, and this might affect the higher uric acid levels in the elderly.

The incidence and prevalence of CHF increase dramatically with advancing age. Increasing age has been reported to increase the mortality of CHF patients. However, prognostic assessment of elderly patients with CHF is far from clearly estab-
lished. Epidemiologic data indicate that CHF represents a crucial problem in the elderly population in terms of social, economic, and health burden\textsuperscript{6,12}. Despite their importance in the worsening of CHF and prevention of the progression of this syndrome, the risks of re-hospitalization and the causes of exacerbation have not been systematically evaluated. In addition, the detailed mechanisms behind the increased mortality in older CHF patients are still unclear\textsuperscript{6,7}. In the present study, we examined the clinical characteristics and the potential prognostic value of uric acid in elderly CHF patients aged \textgtr 70 years, because the prevalence of CHF increases\textsuperscript{13} and these patients have higher rate of readmission and mortality\textsuperscript{27,28}. Ageing is associated with important structural and functional changes in the vascular system and the heart, but little is known about how ageing interacts with the pathophysiology underlying the process of developing heart failure. Further research needs to elucidate more effective treatment strategies for prevention of CHF and to decrease the morbidity and mortality of CHF in the elderly.

**CONCLUSIONS**

These data suggest that high serum uric acid level is a reliable marker for prognosis in the elderly patients with chronic heart failure. We suggest that measurement of uric acid levels should be considered as a routine measurement in the assessment and follow-up for elderly patients with chronic heart failure with low cost and wide availability.

**Acknowledgments**

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