# 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 $451 \pm 235$ days mean $\pm$ 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.

*J Cardiol 2006 May ; 47 5 : 219 228*

## 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[1 5]. CHF is accompanied by various pathophysiological changes which trigger disease progression, and deterioration of ventricular function is still common in elderly patients with CHF[6,7]. Although the current therapy for CHF such as angiotensin-converting enzyme inhibitors and -blockers can relieve symptoms and prolong life, the incidence, readmission rate and mortality are still increasing beacause of the aging of the population[8 12]. 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[13 17]. 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[18,19]. In addition, hyperuricemia is related to impaired oxidative metabolism and vascular dysfunction in CHF[20, 21].

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    70 years 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[22,23].

### End-points and follow-up

No patients were lost to follow-up  mean follow-up $451 \pm 235$ 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[24,25]. The end-points, 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 $\pm$ 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.

**Table 1  Clinical characteristics of 247 patients with chronic heart failure**

|  | ≥70 years old n＝123 | <70 years old n＝124 |
|---|---|---|
| Age yr | 77± 5 | 57± 11 |
| Sex male/female | 59/64 | 84/40 |
| NYHA functional class Ⅰ/Ⅱ/Ⅲ/Ⅳ | 17/50/41/15 | 43/49/29/3 |
| Hypertension | 67 54 | 53 43 |
| Diabetes mellitus | 24 20 | 33 27 |
| Hyperlipidemia | 20 16 | 29 23 |
| Current smoking | 17 14 | 39 31 |
| Etiology of chronic heart failure |  |  |
| Dilated cardiomyopathy | 44 36 | 46 37 |
| Ischemic heart disease | 29 24 | 33 27 |
| Valvular heart disease | 26 21 | 22 18 |
| Hypertensive heart disease | 18 14 | 10 8 |
| Tachycardia-induced cardiomyopathy | 6 5 | 13 10 |
| Blood examination at admission |  |  |
| Uric acid mg/dl | 6.35± 2.26 | 5.89± 1.87 |
| Creatinine mg/dl | 0.91± 0.31 | 0.88± 0.30 |
| Hemoglobin g/dl | 12.6± 1.98 | 13.7± 2.12 |
| Na mEq/l | 140± 3.5 | 141± 2.7 |
| Echocardiography at admission |  |  |
| LVEDD mm | 52± 9.8 | 54± 9.8 |
| LVEF % | 49± 19 | 47± 19 |
| Cardiac events |  |  |
| Cardiac deaths | 18 15 | 6 5 |
| Re-hospitalizations | 29 24 | 19 15 |
| Total events | 47 38 | 25 20 |
| Medical treatment |  |  |
| ACE inhibitors and/or ARBs | 88 72 | 73 59 |
| Beta-blockers | 38 31 | 36 29 |
| Ca channel blockers | 31 25 | 30 24 |
| Spironolactone | 31 25 | 26 21 |
| Loop diuretics | 79 64 | 54 44 |
| Digoxin | 46 37 | 27 22 |
| Statins | 15 12 | 18 15 |
| Allopurinol | 17 14 | 15 12 |

（ ）: %. $p < 0.05$ vs ＜70 years old group.
NYHA＝New York Heart Association; LVEDD＝left ventricular dimension at end-diastole; LVEF＝left ventricular ejection fraction; ACE＝angiotensin-converting enzyme; ARB＝angiotensin Ⅱ receptor blocker.

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 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**

|  | Event-free n 76 | Cardiac event n 47 | p value |
|---|---|---|---|
| Age  yr | 78± 5 | 77± 5 | 0.5273 |
| Sex  male/female | 32/44 | 27/20 | 0.2988 |
| NYHA functional class    / / / | 14/36/21/5 | 3/14/20/10 | 0.0039 |
| Hypertension | 47 62 | 20 43 | 0.0369 |
| Diabetes mellitus | 15 20 | 9 19 | 0.9363 |
| Hyperlipidemia | 10 13 | 10 21 | 0.2358 |
| Current smoking | 8 11 | 9 19 | 0.1782 |
| Etiology of chronic heart failure |  |  |  |
| Ischemic heart disease | 19 25 | 10 21 |  |
| Non-ischemic heart disease | 57 75 | 37 79 | 0.1492 |
| Blood examination at admission |  |  |  |
| Uric acid  mg/dl | 5.9± 2.0 | 6.8± 2.6 | 0.0082 |
| Creatinine  mg/dl | 0.84± 0.24 | 0.97± 0.37 | 0.0063 |
| Hemoglobin  g/dl | 12.7± 1.96 | 12.8± 2.05 | 0.6322 |
| Na  mEq/l | 141± 2.5 | 140± 4.5 | 0.2980 |
| Echocardiography at admission |  |  |  |
| LVEDD  mm | 51± 9 | 53± 11 | 0.3261 |
| LVEF  % | 51± 18 | 46± 21 | 0.1913 |

: %.
Abbreviations as in Table 1.
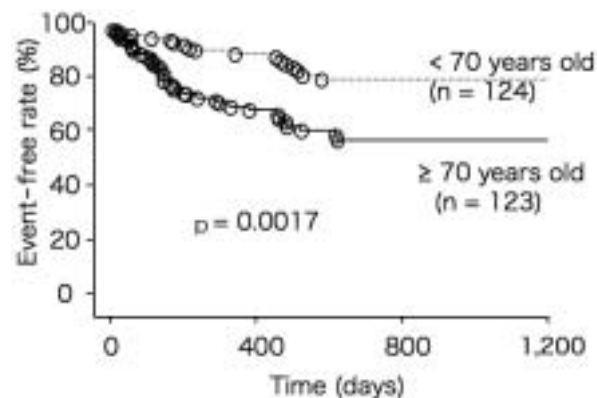


**Fig. 1   Kaplan-Meier analysis of cardiac event-free rates in patients with chronic heart failure**

betes mellitus, hyperlipidemia, etiologies of heart failure, serum creatinine levels, Na levels, hemoglobin levels, or echocardiographic findings. Elderly CHF patients aged  70 years were given angiotensin-converting enzyme inhibitors/angiotensin  receptor blockers, loop diuretics and digoxin more frequently than those aged  70 years.

The 247 CHF patients had 72 cardiac events dur-ing a mean follow-up period of 451± 235 days, and 47 of these 72 events 65% 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** .

**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 47 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 within 12 months after admission 3 in-hospital cardiac deaths, 11 cardiac deaths, and 16 readmissions for worsening heart failure . The cause of cardiac death was worsening chronic heart failure in 11 patients, fatal acute myocardial infarction in 3 patients and sudden death in 4 patients. The 3 in-hospital cardiac deaths

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

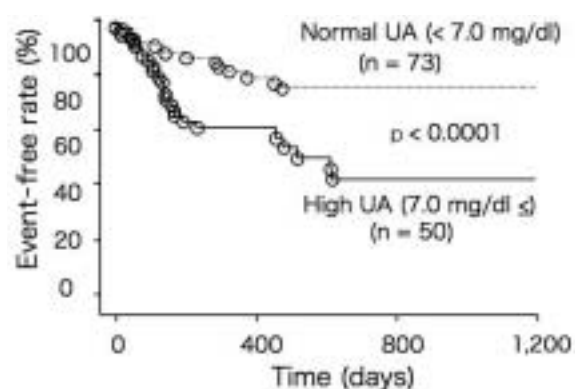| Variable | Hazard ratio | 95% confidence interval | | *p* value |
|---|---|---|---|---|
| Univariate analysis | | | | |
| Uric acid | 1.803 | 1.199 | 2.337 | 0.0001 |
| Creatinine | 2.431 | 1.833 | 6.743 | 0.0107 |
| NYHA functional class | 1.935 | 1.227 | 2.587 | 0.0332 |
| | | | | |
| Multivariate analysis | | | | |
| Uric acid | 1.544 | 1.215 | 2.582 | 0.0001 |
| Creatinine | 1.846 | 0.952 | 4.434 | 0.1110 |
| NYHA functional class | 1.250 | 0.873 | 3.772 | 0.3502 |

Abbreviation as in Table 1.



**Fig. 2 Kaplan-Meier analysis of cardiac event-free rates in elderly patients with chronic heart failure**
UA uric acid.

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* 0.0039 , 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 recep-tor blockers, statins, Ca channel blockers, -blockers, and allopurinol at discharge were also similar in the two groups.

High uric acid levels 7.0 mg/d*l* were observed in 2 of 17 patients 11.8% with NYHA functional class , in 19 of 50 patients 38.0% with class , in 20 of 41 patients 48.8% with class , and in 9 of 15 patients 60.0% with class *p* 0.0236 . Uric acid levels were not different between patients with ischemic and non-ischemic etilogies 5.9± 2.5 vs 6.4± 2.3 mg/d*l*, *p* 0.2662 . In patients with NYHA functional class / , use of loop diuretics was more frequent compared to patients with NYHA class / 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 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 hazard ratio 1.544, 95% confidence interval CI 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 7.0 mg/d*l* had significantly lower cardiac event-
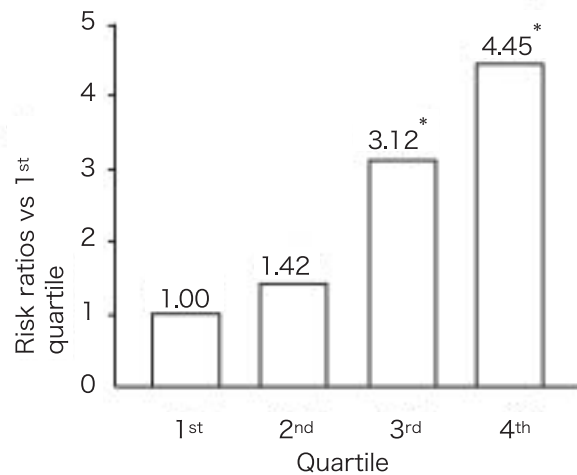
Fig. 3　Association between concentrations of serum uric acid and cardiac events in 123 elderly patients with chronic heart failure

Patients were divided into four groups based on the uric acid levels:1st quartile 5.0 mg/d*l*, *n* 30 , 2nd quartile 5.1 6.4 mg/d*l*, *n* 30 , 3rd quartile 6.5 8.6 mg/d*l*, *n* 31 , and 4th quartile 8.7 mg/d*l* , *n* 32 . Hazard ratios relative to 1st quartile are shown.

*p* 0.05 vs 1st quartile patients.



Fig. 4　Kaplan-Meier analysis of elderly patients with chronic heart failure

Patients divided into four groups as in Fig. 3.

free rates than those with normal uric acid levels 7.0 mg/d*l* . 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 5.0 mg/d*l*, *n* 30 , 2nd quartile 5.1 6.4 mg/d*l*, *n* 30 , 3rd quartile 6.5 8.6 mg/d*l*, *n* 31 , and 4th quartile 8.7 mg/d*l* , *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 4.453 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 .
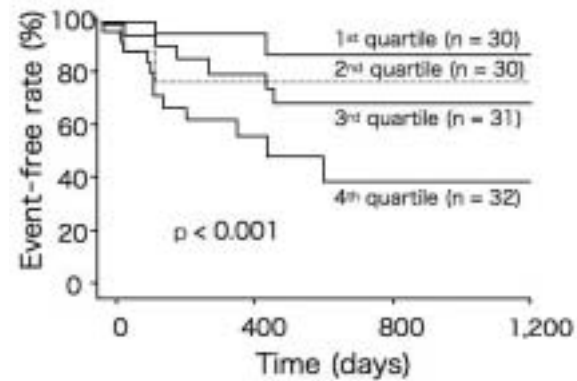
## DISCUSSION

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 aid 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

**Table 4   Comparisons of clinical characteristics in elderly chronic heart failure patients between quartiles of uric acid levels**

|  | 1st quartile<br>*n* 30 | 2nd quartile<br>*n* 30 | 3rd quartile<br>*n* 31 | 4th quartile<br>*n* 32 |
|---|---|---|---|---|
| Uric acid range mg/dl | 5.0 | 5.1 6.4 | 6.5 8.6 | 8.7 |
| Age yr | 77± 6 | 77± 5 | 77± 6 | 79± 5[#] |
| Sex male/female | 16/14 | 14/16 | 12/19 | 17/15 |
| NYHA functional class | 2.0± 0.7 | 2.2± 0.9 | 2.4± 0.7 | 2.9± 0.6 [#] |
| Hypertension | 22 73 | 15 50 | 17 55 | 13 41 |
| Diabetes mellitus | 8 27 | 4 13 | 5 16 | 7 22 |
| Hyperlipidemia | 7 23 | 5 17 | 5 16 | 3 9 |
| Current smoking | 6 20 | 3 10 | 4 13 | 4 13 |
| Etiology of chronic heart failure |  |  |  |  |
| Dilated cardiomyopathy | 7 23 | 14 47 | 11 35 | 12 38 |
| Ischemic heart disease | 8 27 | 5 17 | 8 26 | 8 25 |
| Valvular heart disease | 5 17 | 7 23 | 6 19 | 8 25 |
| Hypertensive heart disease | 8 27 | 1 3 | 5 16 | 4 13 |
| Tachycardia-induced |  |  |  |  |
| Cardiomyopathy | 2 7 | 3 10 | 1 3 | 0 |
| Blood examination |  |  |  |  |
| Uric acid mg/dl | 4.0± 0.8 | 5.7± 0.4 | 7.6± 0.7 [##] | 9.4± 2.1 [##] |
| Creatinine mg/dl | 0.78± 0.24 | 0.88± 0.20 | 0.98± 0.29 | 1.03± 0.39 |
| Hemoglobin g/dl | 12.2± 2.1 | 13.1± 1.9 | 12.6± 1.8 | 12.3± 2.1 |
| Na mEq/l | 141± 4.4 | 141± 2.4 | 141± 3.5 | 140± 3.4 |
| Echocardiography |  |  |  |  |
| LVEDD mm | 49± 10 | 53± 9 | 52± 10 | 53± 11 |
| LVEF % | 60± 19 | 51± 14 | 48± 21 | 40± 18 [#] |
| Cardiac events |  |  |  |  |
| Cardiac deaths | 5 17 | 4 13 | 3 10 | 6 19 |
| Re-hospitalizations | 1 3 | 6 20 | 10 32 | 12 38 † |
| Total events | 6 20 | 10 33 | 13 42 | 18 56 † |
| Treatment before admission |  |  |  |  |
| ACE inhibitors and/or ARBs | 22 73 | 17 57 | 27 87 | 22 69 |
| Beta-blockers | 5 17 | 9 30 | 12 39 | 12 38 |
| Ca channel blockers | 12 40 | 7 23 | 9 29 | 3 9 |
| Spironolactone | 5 17 | 10 33 | 7 23 | 9 28 |
| Loop diuretics | 13 43 | 20 67 | 21 68 | 25 78 † |
| Digoxin | 6 20 | 15 50 | 10 32 | 15 47 |
| Statins | 4 13 | 5 17 | 3 10 | 3 9 |
| Allopurinol | 3 10 | 5 17 | 2 6 | 7 22 |

: %. *p* 0.05 vs 1st quartile, [#]*p* 0.05 vs 2nd quartile, and *p* 0.05 vs 3rd quartile. *p* 0.01 vs 1st quartile, [##]*p* 0.01 vs 2nd quartile, and *p* 0.01 vs 3rd quartile. † *p* 0.05 by chi-square test.

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[1 5]. Increasing age has been reported to increase the mortality of CHF patients[8 12]. 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[8][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[6,7]. In the present study, we examined the clinical characteristics and the potential prognostic value of uric aid in elderly CHF patients aged 70 years, because the prevalence of CHF increases[1] and these patients have higher rate of readmission and mortality[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.

## References

1　Senni M, Tribouilloy CM, Rodeheffer RJ, Jacobsen SJ, Evans JM, Bailey KR, Redfield MM: Congestive heart failure in the community: A study of all incident cases in Olmsted County, Minnesota, in 1991. Circulation 1998; **98**: 2282 2289

2　Mosterd A, Hoes AW, de Bruyne MC, Deckers JW, Linker DT, Hofman A, Grobbee DE: Prevalence of heart failure and left ventricular dysfunction in the general population: The Rotterdam Study. Eur Heart J 1999; **20**: 447 455

3　Senni M, Tribouilloy CM, Rodeheffer RJ, Jacobsen SJ, Evans JM, Bailey KR, Redfield MM: Congestive heart failure in the community: Trends in incidence and survival in a 10-year period. Arch Intern Med 1999; **159**: 29 34

4　Cohen-Solal A, Desnos M, Delahaye F, Emeriau JP, Hanania G: A national survey of heart failure in French hospitals: The Myocardiopathy and Heart Failure Working Group of the French Society of Cardiology, the National College of General Hospital Cardiologists and the French Geriatrics Society. Eur Heart J 2000; **21**: 763 769

5　Davies MK, Hobbs FDR, Davis RC, Kenkre JE, Roalfe AK, Hare R, Wosornu D, Lancashire RJ: Prevalence of left-ventricular systolic dysfunction and heart failure in the Echocardiographic Heart of England Screening study: A population based study. Lancet 2001; **358**: 439 444

6　Rich MW: Management of heart failure in the elderly. Heart Fail Rev 2002; **7**: 89 97

7　Sharma R, Coats AJS, Anker SD: The role of inflammatory mediators in chronic heart failure: Cytokines, nitric oxide, and endothelin-1. Int J Cardiol 2000; **72**: 175 186

8　Schocken DD, Arrieta MI, Leaverton PE, Ross EA: Prevalence and mortality rate of congestive heart failure in the United States. J Am Coll Cardiol 1992; **20**: 301 306

9　Bourassa MG, Gurne O, Bangdiwala SI, Ghali JK, Young JB, Rousseau M, Johnstone DE, Yusuf S: Natural history and patterns of current practice in heart failure: The Studies of Left Ventricular Dysfunction SOLVD Investigators. J Am Coll Cardiol 1993; **22** Suppl A : 14A 19A

10　McDermott MM, Feinglass J, Lee PI, Mehta S, Schmitt B, Lefevre F, Gheorghiade M: Systolic function, readmission rates, and survival among consecutively hospitalized patients with congestive heart failure. Am Heart J 1997; **134**: 728 736

11　MacIntyre K, Capewell S, Stewart S, Chalmers JW, Boyd J, Finlayson A, Redpath A, Pell JP, McMurray JJ: Evidence of improving prognosis in heart failure: Trends in case fatality in 66547 patients hospitalized between 1986 and 1995. Circulation 2000; **102**: 1126 1131

12　Cowie MR, Wood DA, Coats AJ, Thompson SG, Suresh V, Poole-Wilson PA, Sutton GC: Survival of patients with a new diagnosis of heart failure: A population based study. Heart 2000; **83**: 505 510

13　Bettencourt P, Ferreira A, Dias P, Pimenta J, Frioes F, Martins L, Cerqueria-Gomes M: Predictors of prognosis in patients with stable mild to moderate heart failure. J Card Fail 2000; **6**: 306 313

14　Maeda K, Tsutamoto T, Wada A, Mabuchi N, Hayashi M, Tsutsui T, Ohnishi M, Sawaki M, Fujii M, Matsumoto T, Kinoshita M: High levels of plasma brain natriuretic peptide and interleukin-6 after optimized treatment for heart failure are independent risk factors for morbidity and mortality in patients with congestive heart failure. J Am Coll Cardiol 2000; **36**: 1587 1593

15　Setsuta K, Seino Y, Ogawa T, Arao M, Miyatake Y, Takano T: Use of cytosolic and myofibril markers in the detection of ongoing myocardial damage in patients with chronic heart failure. Am J Med 2002; **113**: 717 722

16　Goto T, Takase H, Toriyama T, Sugiura T, Sato K, Ueda R, Dohi Y: Circulating concentrations of cardiac proteins indicate the severity of congestive heart failure. Heart 2003; **89**: 1303 1307

17　Brophy JM, Dagenais GR, McSherry F, Williford W, Yusuf S: A multivariate model for predicting mortality in patients with heart failure and systolic dysfunction. Am J Med 2004; **116**: 300 304

18　Leyva F, Anker SD, Godsland IF, Teixeira M, Hellewell G, Kox WJ, Poole-Wilson PA, Coats AJ: Uric acid in chronic heart failure: A marker of chronic inflammation. Eur Heart J 1998; **19**: 1814 1822

19　Anker SD, Doehner W, Rauchhaus M, Sharma R, Francis D, Knosalla C, Davos CH, Cicoira M, Shamim W, Kemp M, Segal R, Osterziel KJ, Leyva F, Hetzer R, Ponikowski P, Coats AJ: Uric acid and survival in chronic heart failure : Validation and application in metabolic, functional, and hemodynamic staging. Circulation 2003; **107**: 1991 1997

20　Hoeper MM, Hohlfeld JM, Fabel H: Hyperuricaemia in patients with right or left heart failure. Eur Respir J 1999; **13**: 682 685

21　Alderman MH: Uric acid and cardiovascular risk. Curr Opin Pharmacol 2002; **2**: 126 130

22　Committee on Evaluation and Management of Heart Failure: Guidelines for the evaluation and management of heart failure : Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 1995; **92**: 2764 2784

23　Arimoto T, Takeishi Y, Shiga R, Fukui A, Tachibana H, Nozaki N, Hirono O, Nitobe J, Miyamoto T, Hoit BD, Kubota I: Prognostic value of elevated circulating heart-type fatty acid binding protein in patients with congestive heart failure. J Card Fail 2005; **11**: 56 60

24　Packer M, O'Connor CM, Ghali JK, Pressler ML, Carson PE, Belkin RN, Miller AB, Neuberg GW, Frid D, Wertheimer JH, Cropp AB, DeMets DL, for the Prospevtive Randomized Amlodipine Survial Evaluation Study Group: Effect of amlodipine on morbidity and mortality in severe chronic heart failure. N Engl J Med 1996; **335**: 1107 1114

25　O'Connor CM, Carson PE, Miller AB, Pressler ML, Belkin RN, Neuberg GW, Frid DJ, Cropp AB, Anderson S, Wertheimer JH, DeMets DL: Effect of amlodipine on mode of death among patients with advanced heart failure in the PRAISE trial: Prospective Randomized Amlodipine Survival Evaluation. Am J Cardiol 1998; **82**: 881 887

26　Bettencourt P, Ferreira A, Dias P, Pimenta J, Frioes F, Martins L, Cerqueria-Gomes M: Predictors of prognosis in patients with stable mild to moderate heart failure. J Card Fail 2000; **6**: 306 313

27　Rich MW, Freedland KE: Effect of DRGs on three-month readmission rate of geriatric patients with congestive heart

failure. Am J Public Health 1988; **78**: 680  682

28  Vinson JM, Rich MW, Sperry JC, Shah AS, McNamara T:
Early readmission of elderly patients with congestive heart failure. J Am Geriatr Soc 1990; **38**: 1290  1295