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ORIGINAL ARTICLE

The combined impact of blood pressure category and glucose abnormality on the incidence of cardiovascular diseases in a Japanese urban cohort: the Suita Study

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Few prospective studies have examined the combined impact of blood pressure (BP) categories and glucose abnormalities on the incidence of cardiovascular disease (CVD) in the general Asian population. This study aimed to examine the effect of the combined risks of these factors on the incidence of CVD in a general Japanese population. We studied 5321 Japanese individuals (aged 30–79 years), without CVD at baseline, who received follow-up for an average of 11.7 years. Serum fasting glucose categories were defined according to the 2003 American Diabetes Association recommendations. BP categories were defined by the 2009 Japanese Society of Hypertension Guidelines for the Management of Hypertension. The Cox proportional hazard ratios (HRs) for CVD according to the serum glucose and BP categories were calculated. In 62 036 person-years of follow-up, we documented 364 CVD events (198 stroke and 166 coronary heart disease (CHD)). Compared with normoglycemic subjects, the multivariable HRs (95% confidence intervals (CIs)) for CVD, CHD and stroke were 1.25 (1.00–1.58), 1.46 (1.04–2.04) and 1.11 (0.81–1.52), respectively, in individuals with impaired fasting glucose (IFG), whereas these values were 2.13 (1.50–3.03), 2.28 (1.34–3.88) and 2.08 (1.29–3.35), respectively, in individuals with diabetes mellitus (DM). Compared with normoglycemic and optimal blood pressure (BP) subjects, increased risks of CVD were observed in the normoglycemic subjects with high-normal BP or hypertension, the IFG subjects with normal or higher BP, and the DM subjects regardless of BP category (*P*-value for interaction=0.046). In conclusion, the high-normal BP subjects in all glucose categories and the normal BP subjects with IFG showed increased risk of CVD in this Japanese population. Further investigation of larger cohorts of DM subjects should be conducted to better understand this phenomenon.
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Keywords: blood pressure category; cardiovascular disease; cohort study; diabetes mellitus; impaired fasting glucose

INTRODUCTION

Hypertension is one of the strongest risk factors for increased incidence of cardiovascular disease (CVD) worldwide.[1–3] Recently, high-normal blood pressure (BP)[1,2] and prehypertension[3] have also been recognized as risk factors for CVD.[4–6] Increased BP is the most likely precipitator of CVD and stroke.[5,7,8] Furthermore, the prevalence of glucose intolerance and obesity has increased greatly in recent years.[9,10] Diabetes mellitus (DM) has become a major public health problem[11,12] as well as a risk factor for all-cause mortality[11] and CVD.[10,13–15] Recently, prediabetic hyperglycemia has been recognized to confer an increased risk for CVD.[16] However, a few population studies[17] have reported a positive association between CVD and impaired fasting glucose (defined as blood glucose of 5.6–6.9 mmol l^{-1} according to the 2003 American Diabetes Association definition).[18]

Evaluation of the combined impact of these two major borderline risk factors is essential in preventing CVD because elevated BP is the highest population attributable fraction (PAF) of CVD incidence, and the incidence of hyperglycemia is increasing in Asian and Western countries. There have been a few population studies on the association between the occurrence of hypertension together with DM and the risk of stroke[19–21] and coronary heart disease (CHD).[22] However, few population cohort studies have evaluated the impact of the combination of BP categories (optimal BP, normal BP, high-normal BP (or prehypertension) and hypertension) and fasting glucose categories (normoglycemia, impaired fasting glucose (IFG) and DM) on the risk

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of CVD. Thus, the aim of this study was to examine the combined impact of BP categories and blood glucose abnormalities on the incidence of CVD in a general urban Japanese population.

METHODS

Study subjects

The Suita Study, a cohort study for CVD in urban residents, was established in 1989. The details of this study have been described elsewhere.[5,23–29] Briefly, 6485 individuals (aged 30 to 79 years) underwent regular health checkups between September 1989 and March 1994. Some cohort members were excluded for the following reasons: past or present history of CVD at baseline (n=208); missing data (n=170); nonfasting blood collections (n=173); or lost from follow-up (n=613). After applying these exclusions, a total of 5321 subjects (aged 30 to 79 years) participated in the baseline examination. Informed consent was obtained from all participants. This study was approved by the institutional review board of the National Cardiovascular Center.

Measurement of BP and fasting glucose

Measurement of BP has been described elsewhere.[5] In brief, well-trained physicians measured the BP of each individual three times in a seated position using a mercury column sphygmomanometer, an appropriately sized cuff and a standard protocol. Before the initial BP reading was obtained, participants were seated at rest for at least 5 min. Systolic (SBP) and diastolic (DBP) blood pressures were recorded as the average of the second and third measurements, which were taken more than 1 min apart.

At the time of the baseline examination, subjects were classified into one of the following BP categories based on the 2009 Japanese Society of Hypertension Guidelines for the Management of Hypertension:[2] optimal BP (SBP, <120 mm Hg and DBP, <80 mm Hg); normal BP (SBP, 120 to 129 mm Hg and DBP, 80 to 84 mm Hg); high-normal BP (SBP, 130 to 139 mm Hg and DBP, 85 to 89 mm Hg); and hypertension (SBP, ⩾140 mm Hg or DBP, ⩾90 mm Hg or antihypertensive drug use). If the SBP and DBP readings for a subject were in different categories, then the subject was categorized into the higher of the two categories.

We performed routine fasting blood collection and immediately measured serum glucose and total cholesterol levels using the same autoanalyzer (Toshiba TBA-80, Toshiba, Tokyo, Japan). Fasting serum glucose categories were defined as follows:[18] DM (fasting serum glucose ⩾7.0 mmol l^{-1} (126 mg per 100 ml) or medications for DM); IFG (fasting serum glucose levels 5.6 to 6.9 mmol l^{-1} (100 to 125 mg per 100 ml)); and normoglycemia (fasting serum glucose levels <5.6 mmol l^{-1} (<100 mg per 100 ml)). Hypercholesterolemia was defined as total serum cholesterol levels ⩾5.7 mmol l^{-1} (220 mg per 100 ml) or current use of antihyperlipidemic medications. Physicians or nurses administered questionnaires addressing personal habits and present illness at the baseline examination. Body mass index was calculated as weight (kg) divided by height (m) squared.

Confirmation of stroke and coronary heart disease and end point determination

Medical records were reviewed by registered hospital physicians or research physicians who were blinded to the baseline data. Strokes were defined according to the US National Survey of Stroke criteria.[30] For each stroke subtype (that is, cerebral infarction (thrombotic or embolic infarction), intracerebral hemorrhage and subarachnoid hemorrhage), a definite diagnosis was established based on examination of computed tomographic scans, magnetic resonance images or autopsies. Definite and probable myocardial infarctions were defined according to the criteria set out by the MONICA project.[31] The criteria for a diagnosis of CHD included first ever acute myocardial infarction, sudden cardiac death within 24 h after the onset of acute illness or coronary artery disease followed by coronary artery bypass surgery or angioplasty. In this study, CVD was defined as stroke or CHD.

To detect CHD and stroke occurrences, each participant's health status was checked during clinical visits to the National Cardiovascular Center every 2 years. Yearly questionnaires by mail or telephone were also completed by all participants. In addition, to complete our surveillance for fatal strokes and CHD, we conducted a systematic search for death certificates. All data were checked against medical records to confirm the incidence of CVD. When informed consent could not be obtained for a medical records survey (19.5%), we identified possible strokes or CHD using information from (1) questionnaires for present illness of stroke and CHD at the health examination and/or (2) death certificates bearing a diagnosis of probable stroke or CHD. The end point of the follow-up period for each participant was, whichever of the following options occurred first: (1) date of the first diagnosis of CHD or stroke event; (2) date of death; (3) date of leaving Suita; or (4) 31 December, 2005.

Statistical analysis

Analyses of variance and χ^2-tests were used to compare mean values and frequencies. The Cox proportional hazard ratios (HRs) and 95% confidence intervals (95% CIs) were fitted to each glucose category (normoglycemia, IFG and DM) after adjusting for sex and age in 5-year increments as stratified variables and other potential confounding factors at baseline, including BP category (optimal, normal, and high-normal BP and hypertension), hypercholesterolemia (positive or negative), body mass index (continuous variable), smoking status (never, ex-smoker and current smoker) and drinking status (never, ex-drinker and current drinker). Test for effect modification by glucose category was conducted with an interaction term generated by multiplying BP category by glucose category. We conducted tests for trend across the BP categories and tested the significance of this variable.

To express the combined impact of glucose and BP categories on the incidence of CVD in these participants, we estimated the PAF as follows:

$$PAF = Pe \times (HR - 1)/HR,$$

where Pe is the proportion of incident cases in the combination of glucose and BP categories, and HR is the multivariable-adjusted hazard ratio.[32] All statistical analyses were conducted using the SAS statistical software package (release version 8.2; SAS Institute, Cary, NC, USA).

RESULTS

The frequencies of IFG and DM increased with age in both men and women (Figure 1). Table 1 shows the distribution of CVD risk factors at baseline according to fasting glucose categories at baseline. Both men and women with DM were older and had a higher body mass index as well as a higher prevalence of hypertension, hypercholesterolemia and medication for hypertension than those without DM. Men with DM had a lower frequency of never drinking than men without DM.

In 62 036 person-years of follow-up (an average of 11.7 years of follow-up), we documented 364 CVD (198 strokes and 166 CHD) events. Table 2 shows the age- and sex-adjusted HRs and multivariable-adjusted HRs for incidence of CVD according to glucose categories in men and women. Compared with normoglycemic subjects, the multivariable HRs (95% CIs) for CVD, CHD and stroke were 1.25 (1.00–1.58), 1.46 (1.04–2.04) and 1.11 (0.81–1.52), respectively in IFG subjects, whereas these values were 2.13 (1.50–3.03), 2.28 (1.34–3.88) and 2.08 (1.29–3.35), respectively in DM subjects. Compared with normoglycemic subjects, IFG and DM were risk factors for CVD and CHD in women, and DM was a risk factor for CVD and stroke in men.

Figure 2 shows the multivariable HRs of CVD for the combined impact of the fasting glucose and BP categories. Compared with normoglycemic subjects with optimal BP, the following groups showed increased risk of CVD: the normoglycemic subjects with high-normal BP or hypertension (P-value for trend of BP category<0.001); the IFG subjects with normal or higher BP (P-value for trend of BP category=0.001); and the DM subjects in any BP category (P-value for trend of BP category=0.41). After excluding subjects taking diabetic medication, the P-value for the BP category trend was not statistically significant in the DM subjects.

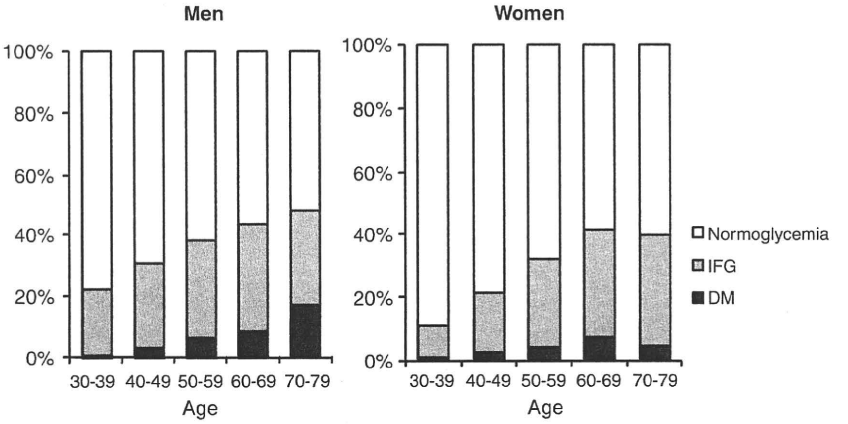

Figure 1 Frequency of type 2 diabetes mellitus according to sex and age.

Table 1 Baseline characteristics of study subjects according to fasting glucose categories at baseline

	Men				*Women*			
	Normoglycemia	*IFG*	*DM*	P-*value*	*Normoglycemia*	*IFG*	*DM*	P-*value*
Number of subjects, *n*	1458	874	154	—	2126	611	98	—
Age, in years	54±14	57±12	60±10	<0.001	52±13	59±11	60±10	<0.001
Body mass index, kg m^{-2}	22.5±2.8	23.3±2.9	23.3±3.2	<0.001	21.8±3.0	23.1±3.4	24.5±4.2	<0.001
Blood pressure category, %[a]				<0.001				<0.001
Optimal blood pressure	37	24	20		49	23	17	
Normal blood pressure	19	19	17		16	16	17	
High-normal blood pressure	16	19	14		13	18	15	
Hypertension	28	39	49		21	43	51	
Hypercholesterolemia, %[b]	26	33	36	<0.001	38	54	59	<0.001
Medication, %								
Hypertension	10	12	18	0.002	8	16	22	<0.001
Diabetes	—	—	36	—	—	—	38	—
Smoking status, %				0.156				0.325
Current	55	51	50		13	10	11	
Quit	25	29	32		3	3	4	
Never	19	20	18		84	87	85	
Drinking status, %				<0.001				0.330
Current	76	77	76		34	32	24	
Quit	2	2	9		1	1	2	
Never	22	20	15		65	67	74	

Abbreviations: DM, diabetes mellitus; DBP, diastolic blood pressure; IFG, impaired fasting glucose; SBP, systolic blood pressure.
Normoglycemia: fasting glucose levels <5.6 mmol l^{-1}; IFG: fasting glucose levels 5.6 to 6.9 mmol l^{-1}; DM: fasting glucose levels ⩾7.0 mmol l^{-1} or medication for diabetes.
[a]Blood pressure category was based on the ESH–ESC 2007 guidelines: optimal (SBP <120 mm Hg and DBP <80 mm Hg), normal blood pressure (SBP 120–129 mm Hg and DBP 80–84 mm Hg), high-normal blood pressure (SBP 130–139 mm Hg and DBP 85–89 mm Hg) and hypertension (SBP ⩾140 mm Hg or DBP ⩾90 mm Hg or antihypertensive drug use).
[b]Hypercholesterolemia: antilipidemic drug user or total cholesterol ⩾5.7 mmol l^{-1} ± values are the means±s.d.'s.

The significant interaction terms between fasting blood glucose and BP categories were observed in CVD (P=0.046); however, the interaction term was not significant after exclusion of DM subjects.

Using the HRs, we estimated the PAF for CVD to exposure to the combined impact of fasting glucose and BP categories at baseline (Figure 3). The population-attributable risk percentage for CVD incidence was estimated at 3.7% for subjects with normoglycemia and high-normal BP, 5.7% for subjects with IFG and normal or high-normal BP group and 8.2% for subjects with DM and any BP category group, when comparing these groups with the normoglycemic and optimal BP group.

DISCUSSION

In this population cohort study, we found that DM was a risk factor for CVD, stroke and CHD, whereas an IFG of 5.6 to 6.9 mmol l^{-1} was a risk factor for CVD and CHD only. A combined effect of IFG

Table 2 Age- and multivariable-adjusted hazard ratios (95% confidential intervals) for cardiovascular disease according to blood glucose category

	Blood glucose category			
	Normoglycemia	*IFG*	*Diabetes*	*P-value for trend*
Men and women, number	3584	1485	252	
Person-years, in years	42701	16741	2594	
Cardiovascular disease				
Case	184	139	41	
Age and sex-adjusted	1	1.34 (1.07–1.68)	2.45 (1.73–3.45)	<0.001
Multivariable-adjusted	1	1.25 (1.00–1.58)	2.13 (1.50–3.03)	<0.001
Coronary artery disease				
Case	78	70	18	
Age and sex-adjusted	1	1.54 (1.10–2.13)	2.53 (1.51–4.25)	<0.001
Multivariable-adjusted	1	1.46 (1.04–2.04)	2.28 (1.34–3.88)	0.001
Stroke				
Case	106	69	23	
Age and sex-adjusted	1	1.21 (0.89–1.65)	2.51 (1.58–3.96)	<0.001
Multivariable-adjusted	1	1.11 (0.81–1.52)	2.08 (1.29–3.35)	0.016
Men, number	1,458	874	154	
Person-years, years	16,901	9844	1560	
Cardiovascular disease				
Case	107	91	25	
Age-adjusted	1	1.19 (0.90–1.58)	1.93 (1.25–2.99)	0.007
Multivariable-adjusted	1	1.13 (0.85–1.51)	1.75 (1.12–2.73)	0.032
Coronary artery disease				
Case	50	50	11	
Age-adjusted	1	1.39 (0.93–2.06)	1.89 (0.98–3.64)	0.027
Multivariable-adjusted	1	1.31 (0.87–1.96)	1.69 (0.86–3.31)	0.077
Stroke				
Case	57	41	14	
Age-adjusted	1	1.01 (0.68–1.52)	2.00 (1.11–3.61)	0.103
Multivariable-adjusted	1	0.97 (0.64–1.46)	1.78 (1.00–3.12)	0.216
Women, number	2,126	611	98	
Person-years, in years	25,800	6897	1033	
Cardiovascular disease				
Case	77	48	16	
Age-adjusted	1	1.62 (1.12–2.33)	3.70 (2.14–6.40)	<0.001
Multivariable-adjusted	1	1.49 (1.02–2.16)	3.07 (1.73–5.45)	<0.001
Coronary artery disease				
Case	28	20	7	
Age-adjusted	1	1.86 (1.04–3.25)	4.62 (1.99–10.72)	<0.001
Multivariable-adjusted	1	1.83 (1.01–3.32)	4.32 (1.81–10.31)	<0.001
Stroke				
Case	49	28	9	
Age-adjusted	1	1.53 (0.96–2.45)	3.54 (1.71–7.29)	<0.001
Multivariable-adjusted	1	1.36 (0.84–2.19)	2.66 (1.22–5.80)	0.018

Abbreviations: DM, diabetes mellitus; IFG, impaired fasting glucose.
Multivariate analyses were adjusted for age, body mass index, hypertension, hyperlipidemia and smoking and drinking status.
Blood glucose categories: Normal, fasting glucose levels $<5.6\,mmol\,l^{-1}$; IFG, fasting glucose levels $5.6–6.9\,mmol\,l^{-1}$; DM, fasting glucose levels $\geq 7.0\,mmol\,l^{-1}$ or medication for diabetes.

and prehypertension on the incidence of CVD was observed. The high-normal BP subjects in any glucose category and the normal BP subjects with IFG in the Japanese population showed increased risks of CVD. To our knowledge, this study is the first on the combined impact of these borderline risk factors, IFG and prehypertension on the incidence of CVD in a general Asian population.

Previous cohort studies have shown that DM is a risk factor for CVD, stroke[14,15] and CHD.[13] The results of our study are also essentially compatible with the previous cohort studies in Japan. The Hisayama Study demonstrated that glucose intolerance for 2421 participants was a risk factor for increased incidence of stroke and CHD.[15] Iso *et al.*[20] reported that glucose abnormalities were a risk factor for ischemic stroke in a Japanese population by using nonfasting glucose levels. The NIPPON DATA 80 Study indicated that DM, defined by nonfasting blood glucose levels, was a risk factor for CVD mortality.[33] In the Funagata Diabetes Study, IFG was not a risk factor

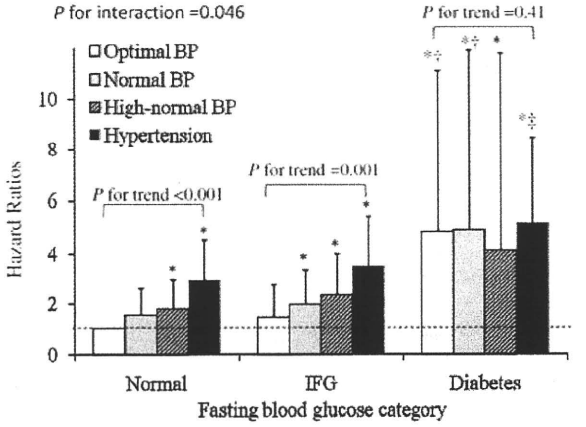

Figure 2 The influence of fasting glucose and BP categories on multivariable-adjusted hazard ratios and 95% confidence intervals for the incidence of cardiovascular disease. $^{*}P<0.05$, compared with normoglycemic subjects with optimal BP. $^{\dagger}P<0.05$, compared with normoglycemic subjects in the same BP category. $^{\ddagger}P<0.05$, compared with normoglycemic subjects with hypertension.

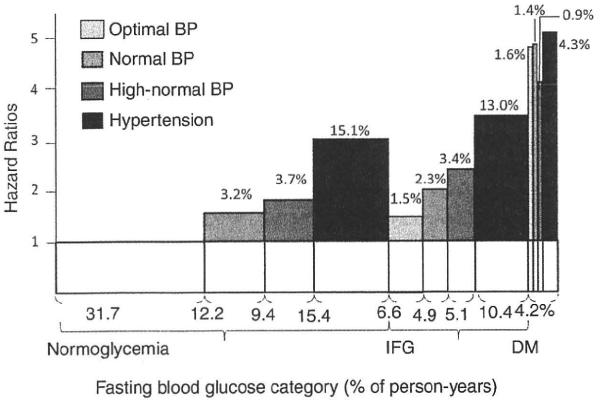

Figure 3 The hazard ratios and population attributable fractions for CVD to exposure to the combined impact of glucose (normoglycemia, impaired fasting glucose and diabetes) and blood pressure categories (optimal, normal, and high-normal blood pressures and hypertension) at baseline were estimated. The gray and black areas represent excessive incidence of CVD in the high blood glucose and high blood pressure categories compared with the subjects with normoglycemia and optimal blood pressure as a reference.

for CVD mortality, although impaired glucose tolerance was a risk factor for CVD.[34]

Compared with previous studies, our study has several methodological strengths. First, our cohort population was relatively large and was selected at random from an urban population in contrast to most other cohort populations in Asia, which were selected from rural populations.[15,20,34] Second, all of our cohort participants were examined at one place and measured using the same autoanalyzer at one laboratory. Finally, our study examined the risk of CVD incidence, not CVD mortality.

In our study, we used the definitions of IFG and CVD/CHD set forth by the 2003 American Diabetes Association recommendations. In the Framingham Heart Study, the 2003 IFG definition was predictive of CHD in women but not in men,[17] a finding which was similar to our results. However, fewer studies have examined the association of the 2003 IFG definitions for CHD and stroke. Kanaya *et al.*[35] showed that the 2003 defination for IFG was not associated with increased risk of CHD or stroke among postmenopausal women with coronary artery disease.Kim *et al.*[36] reported that one-third of the population has IFG according to the 2003 definition. However, many of these individuals do not have increased prevalence of CHD.

Hu *et al.*[19] reported that hypertension and DM increased stroke risk independently and that their combination additively increased stroke risk. In our study, the risks of CVD in the normoglycemic and IFG groups were linearly related to the BP category (*P*-value for trend <0.001). However, the risks of CVD in the DM group did not change with BP category (*P*-value for trend=0.4), which was compatible with a previous result for trends between glucose category and hypertension status.[20] Recently, the ACCORD BP Study has shown that targeting an SBP <120 mm Hg, as opposed to an SBP <140 mm Hg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events in patients with type 2 diabetes.[37] Although present studies suggest that decreasing BP may be an effective way to prevent CVD in normoglycemic or IFG subjects, further investigations are required to clarify the interaction between the BP categories of DM subjects at risk for CVD in other large cohorts.

The percentage of the PAF for CVD incidence in normoglycemic subjects with high-normal BP or IFG subjects with normal or high-normal BP (PAF=12.6%) was 1.5 times higher than that in the DM subjects in any BP category (PAF=8.2%). Also, the PAF suggested that 12.6% of CVD cases would be preventable if the borderline glucose and blood pressure levels were controlled to within normoglycemic and optimal BP ranges.

Our results showed that hyperglycemia conferred a slightly higher risk of CVD incidence in women than in men, although men had greater absolute event rates for CVD. Previous studies have shown that the impact of DM on the risk of CVD is significantly greater in women than in men.[13,17,38] Lee *et al.* reported that the HRs of coronary heart disease for DM were 2.6 for women and 1.9 for men. In the Framingham Heart Study, [17] IFG was associated with increased CHD risk only in women (HR=1.7; 95% CI, 1.0–3.0). The reason for these sex differences in the association between DM and CVD remains unclear.

Our study has several limitations. The primary limitation is the regression dilution bias; this study was based on a single day measurement of serum glucose and BP levels.[39] That is, the fasting serum glucose and BP levels might have been misclassified. Second, as we did not perform glucose tolerance tests, we may have missed subjects with impaired glucose tolerance. Finally, we did not examine the combined effect of BP categories and glucose abnormalities after stratification by CVD subtypes, such as stroke and CHD because of the small sample size.

In conclusion, DM is a risk factor for CVD, stroke, and CHD, whereas an IFG of 5.6 to 6.9 mmoll^{-1} is a risk factor for CVD and CHD in women. The risks of CVD in the normoglycemic and IFG groups were linearly related to the BP category. The high-normal BP subjects in any glucose categories and the normal BP subjects with IFG showed increased risks of CVD in this Japanese population. Further investigations of larger cohorts of DM subjects are needed.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Hyperuricemia predicts adverse outcomes in patients with heart failure

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ABSTRACT

Background: Hyperuricemia is associated with worse outcomes of patients with chronic heart failure (HF). However, it is unknown in an unselected HF patients encountered in routine clinical practice. We thus assessed the impact of hyperuricemia on long-term outcomes including mortality and rehospitalization among patients hospitalized with worsening HF.

Methods: The Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) studied prospectively the characteristics and treatments in a broad sample of hospitalized HF patients and the outcomes were followed for 2.1 years after discharge. Study cohorts ($n=1869$) were divided into 2 groups according to serum uric acid (UA) at discharge; ≥7.4 mg/dL ($n=908$) and <7.4 mg/dL ($n=961$).

Results: Of the total cohort of HF patients, 56% had hyperuricemia defined as UA≥7.0 mg/dl. Patients with UA≥7.4 mg/dL had higher rates of all-cause death, cardiac death, rehospitalization, and all-cause death or rehospitalization due to worsening HF. After multivariable adjustment, higher UA levels were a significant and independent predictor for all-cause death (adjusted hazard ratio [HR] 1.413, 95% confidence interval [CI] 1.094–1.824, $P=0.008$) and cardiac death (adjusted HR 1.399, 95% CI 1.020–1.920, $P=0.037$).

Conclusions: Hyperuricemia was common in patients with HF encountered in clinical practice and higher UA was independently associated with long-term adverse outcomes in these patients.

1. Introduction

High serum uric acid (UA) or hyperuricemia has been well demonstrated to be associated with morbidity and mortality in general population [1–3] as well as in patients with coronary artery disease [4,5]. It is also associated with poor outcomes in patients with mild to severe heart failure (HF) [6–9]. Hyperuricemia in HF may be due to the upregulation of the xanthine oxidase (XO), a key enzyme in the generation of oxygen free radicals. Therefore, it may induce proinflammatory activation [10], impaired oxidative metabolism [11], vascular endothelial dysfunction [12], and exercise intolerance [13,14] in HF. These conditions may well explain the association between hyperuricemia and poor outcome in chronic [6,8] as well as acute HF [9]. However, previous studies enrolled small numbers of HF patients ($n=100$–500) and were performed in a single center [6,8,9]. The impact of hyperuricemia on outcomes has not been assessed in a broad cohort of HF patients. Therefore, the purpose of this study was to examine the prevalence of hyperuricemia in HF patients encountered in routine clinical practice and to determine whether it is independently associated with the long-term outcomes. We analyzed the data from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD), a prospective database of the clinical characteristics, treatments, and outcomes in a broad sample of patients hospitalized with worsening HF in Japan [15–19].

2. Materials and methods

2.1. Study patients

The details of the JCARE-CARD have been described previously [15]. Briefly, eligible patients were those hospitalized due to worsening HF as the primary cause of admission. The patients with acute HF were excluded. For each patient, baseline data obtained at discharge included (1) demography; (2) causes of HF; (3) precipitating causes; (4) comorbidities; (5) complications; (6) clinical status; (7) electrocardiographic and echocardiographic findings; (8) plasma brain-type natriuretic peptide (BNP); and (9) treatments including discharge medications. Histories of hypertension, diabetes mellitus, hyperlipidemia, prior stroke, chronic obstructive pulmonary disease (COPD), smoking, prior myocardial infarction, and sustained ventricular tachycardia/fibrillation (VT/VF) were recorded if they were documented at the discharge of index hospitalization. The definition of each comorbidity was described in our previous report [15]. The diagnosis of atrial fibrillation (AF) was based on a 12-lead standard electrocardiogram performed during the hospitalization.

The JCARE-CARD enrolled a total of 2675 patients hospitalized for HF at 164 participating hospitals. Individual participating hospitals entered the data using a web-based electronic data capture (EDC) system licensed by the JACRE-CARD (www.jcare-

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card.jp). 806 patients were excluded with missing data of serum uric acid, resulting in 1869 patients included in this analysis. They were divided into 2 groups according to serum UA levels at discharge; ≥7.4 mg/dL ($n=908$) and <7.4 mg/dL ($n=961$).

2.2. Outcomes

The status of all patients was surveyed after discharge and the following information was obtained: (1) survival, (2) causes of death, and (3) the rehospitalization due to an exacerbation of HF that required more than continuation of their usual therapy on prior admission. Only patients who survived the initial hospitalization were included in the follow-up analysis. Out of 1869 patients, 104 patients (5.6%) who died during the hospitalization and 145 patients (7.7%) who were missed during the follow-up were excluded from the follow-up analysis. Follow-up data were obtained in 1620 out of 1869 patients (86.7%). Mean post-discharge follow-up was 777 ± 312 days (2.1 ± 0.9 years).

2.3. Statistical analysis

Patient characteristics and treatments were compared using Pearson chi-square test for categorical variables and Mann–Whitney U test for continuous variables. Multiple linear regression analysis was used to select those variables that were significantly associated with serum UA levels. The model was obtained by using a stepwise regression selection. Cumulative event-free rates during the follow-up were derived using the method of Kaplan and Meier. The relationship between the serum UA level at baseline and outcomes was evaluated among patients with multivariable adjustment. Baseline clinical variables, treatment factors, and the severity of HF at discharge were used in developing the post-discharge Cox proportional hazard models. A P value of <0.05 was used for criteria for variables to stay in the model. SPSS version 16.0 J for Windows was used for all statistical analyses.

3. Results

3.1. Patient characteristics

Fig. 1 shows the distribution of serum UA among 1869 patients. Mean serum UA level in the study subjects was 7.3 ± 2.4 mg/dL, ranging from 0.3 to 22.5 mg/dL. 1041 (55.7%) patients had hyperuricemia defined as serum UA≥7.0 mg/dL.

The mean age of the total cohort was 71.1 ± 12.9 years and 60.0% was men (Table 1). The causes of HF were ischemic in 32.5%, valvular in 28.5%, hypertensive in 25.9%, and dilated cardiomyopathy in 17.7%. The mean echocardiographic left ventricular ejection fraction (LVEF) was 44.6 ± 16.4%.

Patients with serum UA≥7.4 mg/dL were more often men and significantly higher body mass index (BMI) (Table 1). Causes of HF did not differ between groups. They were more likely to be smoker and have chronic atrial fibrillation and coronary artery bypass grafting (CABG). Serum creatinine and plasma BNP levels were significantly higher and estimated glomerular filtration rate (eGFR) was lower in patients with serum UA≥7.4 mg/dL. They had greater LV end-diastolic and end-systolic diameters and lower LVEF. The implantations of ICD, CRT, and CRT-D were not significantly different between 2 groups.

Patients with serum UA≥7.4 mg/dL were prescribed more by diuretics, especially loop diuretics, and digitalis at discharge (Table 2). However, the use of other medications such as angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), and β-blocker did not differ between groups.

3.2. Variables associated with serum UA levels

In a multiple linear regression analysis, younger age [standardized partial regression coefficients (β) 0.183, $P<0.001$], male gender (β 0.092, $P=0.013$), lower eGFR (β 0.405, $P<0.001$), higher hemoglobin concentration (β 0.120, $P=0.004$), and diuretics use (β 0.103, $P=0.003$) were significantly associated with serum UA levels. Low eGFR was the most important factor in this model. However, the multiple correlation coefficient (R^2) of the model entered these five variables was 0.190, indicating that the contribution of these variables to serum UA levels would be minor.

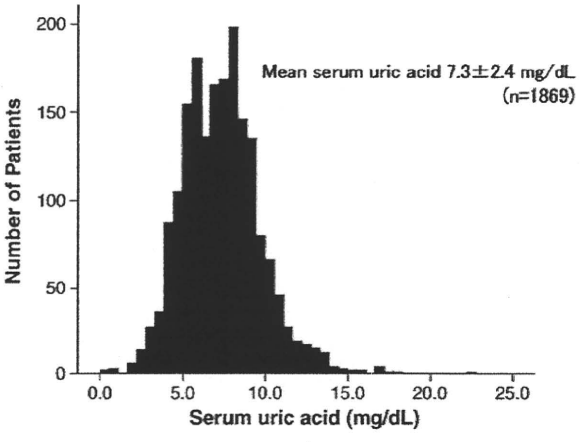

Fig. 1. The distribution of serum UA (mg/dL) at baseline among 1869 patients.

Table 1
Baseline patient characteristics.

Characteristics	Total ($n=1869$)	UA≥7.4 mg/dL ($n=908$)	UA<7.4 mg/dL ($n=961$)	P value
Demographics				
Age, yrs (mean ± SD)	71.1 ± 12.9	70.4 ± 14.0	71.8 ± 11.8	0.243
Male, %	60.0	67.4	53.0	<0.001
BMI, kg/m^2	22.3 ± 4.1	22.5 ± 4.1	22.1 ± 4.1	0.013
Causes of heart failure, %				
Ischemic	32.5	33.0	32.0	0.648
Valvular heart disease	28.5	28.7	28.3	0.833
Hypertensive	25.9	24.9	27.0	0.310
Dilated cardiomyopathy	17.7	18.5	17.0	0.383
Hypertrophic cardiomyopathy	1.9	2.1	1.7	0.496
Medical history, %				
Hypertension	53.4	54.4	52.4	0.395
Diabetes mellitus	31.5	32.0	31.1	0.702
Hyperlipidemia	25.0	25.8	24.2	0.436
Prior stroke	16.1	16.7	15.5	0.500
COPD	6.7	7.2	6.2	0.408
Smoking	38.2	43.7	32.9	<0.001
Prior myocardial infarction	27.5	28.2	26.8	0.502
Atrial fibrillation	35.5	38.1	33.0	0.022
Sustained VT/VF	6.5	6.5	6.5	0.968
Previous procedures, %				
PCI	18.5	18.0	19.0	0.590
CABG	9.1	10.6	7.7	0.030
Valvular surgery	7.0	7.1	6.9	0.906
ICD	2.2	2.2	2.2	0.972
CRT	1.6	1.7	1.5	0.830
CRT-D	0.2	0.1	0.2	0.611
Vital signs at discharge				
NYHA functional class	1.8 ± 0.7	1.8 ± 0.7	1.7 ± 0.7	0.006
NYHA classes 3 and 4, %	10.2	11.1	9.3	0.192
Heart rate, bpm	70.6 ± 12.3	70.2 ± 12.4	71.0 ± 12.1	0.156
SBP, mmHg	117.7 ± 19.2	117.1 ± 18.9	118.2 ± 19.4	0.260
DBP, mmHg	66.2 ± 11.9	66.1 ± 12.4	66.3 ± 11.4	0.938
Laboratory data at discharge				
Serum creatinine, mg/dl	1.4 ± 1.2	1.6 ± 1.3	1.2 ± 1.1	<0.001
eGFR, ml/min/1.73 m^2	51.1 ± 25.2	42.4 ± 20.9	58.5 ± 26.1	<0.001
Hemoglobin, g/dL	12.1 ± 2.6	12.0 ± 2.7	12.1 ± 2.6	0.289
Plasma BNP, pg/ml	403 ± 539	485 ± 643	327 ± 405	<0.001
Echocardiographic data at discharge				
LV EDD, mm	55.7 ± 10.3	57.1 ± 10.9	54.4 ± 9.5	<0.001
LV ESD, mm	43.0 ± 12.3	44.8 ± 12.8	41.4 ± 11.6	<0.001
LVEF, %	44.6 ± 16.4	42.8 ± 16.4	46.1 ± 16.3	0.002

BMI, body mass index; COPD, chronic obstructive pulmonary disease; VT/VF, ventricular tachycardia/fibrillation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy device with defibrillator; NYHA, New York Heart Association; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; BNP, brain-type natriuretic peptide; LV, left ventricular; EDD, end-diastolic diameter; ESD, end-systolic diameter; EF, ejection fraction. Values are percent or means ± SD.

3.3. Outcomes

During the follow-up of 2.1 years after hospital discharge, the rates of adverse outcomes were as follows; all-cause death 21.0%, cardiac death 13.5%, rehospitalization due to the worsening HF 36.5%, and all-cause death or rehospitalization 43.9% (Fig. 2). These event rates were significantly higher in patients with serum UA≥7.4 mg/dL.

On multivariate analysis with patients with serum UA<7.4 mg/dL as the reference, patients with serum UA≥7.4 mg/dL had adverse risk for all-cause death (adjusted hazard ratio [HR] 1.413, 95% confidence interval [CI] 1.094–1.824, $P=0.008$) and cardiac death (adjusted HR 1.399, 95% CI 1.020–1.920, $P=0.037$) (Table 3). Therefore, serum UA levels were significantly associated with long-term adverse outcomes including all-cause death and cardiac death even after adjustment for all other covariates including eGFR and the use of diuretics. They were also associated with

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Table 2
Medication use at hospital discharge.

	Total ($n=1869$)	UA≥7.4 mg/dL ($n=908$)	UA<7.4 mg/dL ($n=961$)	*P* value
ACE inhibitor, %	36.9	36.1	37.6	0.527
ARB, %	45.8	45.2	46.4	0.617
β blocker, %	48.3	47.9	48.6	0.785
Diuretics, %	88.6	91.4	85.9	<0.001
Loop diuretics, %	80.1	84.4	76.0	<0.001
Thiazide diuretics, %	3.6	4.1	3.2	0.275
Potassium sparing diuretics, %	41.6	41.2	42.0	0.719
Digitalis, %	31.5	34.0	29.2	0.030
Ca channel blocker, %	25.8	27.3	24.4	0.168
Nitrates, %	24.4	24.0	24.8	0.671
Antiarrhythmics, %	16.4	16.9	15.9	0.579
Aspirin, %	47.1	47.9	46.3	0.491
Warfarin, %	40.8	41.8	40.0	0.438
Statin, %	19.8	19.0	20.6	0.406

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.

rehospitalization due to worsening HF (unadjusted HR 1.248, $P=0.040$) and all-cause death or rehospitalization (unadjusted HR 1.322, $P=0.013$), which, however, did not reach statistical significance after multivariable adjustment (adjusted HR 1.025, $P=0.801$ and adjusted HR 1.089, $P=0.304$) (Table 3). CABG was not significantly associated with any endpoints including all-cause death, cardiac death, rehospitalization, and all-cause death or rehospitalization. ICD implantation was significantly associated with rehospitalization (adjusted HR 2.094, 95% CI 1.340–3.273, $P=0.001$) and all-cause death or rehospitalization (adjusted HR 1.844, 95% CI 1.186–2.868, $P=0.007$). CRT implantation was associated with cardiac death (adjusted HR 2.668, 95% CI 1.164–6.114, $P=0.020$), rehospitalization (adjusted HR 2.248, 95% CI 1.327–3.809, $P=0.003$), and all-cause death or rehospitalization (adjusted HR 2.009, 95% CI 1.192–3.386, $P=0.009$). In contrast, valvular surgery was associated with lower rates of all-cause death (adjusted HR 0.466, 95% CI 0.238–0.910, $P=0.025$) and cardiac death (adjusted HR 0.419, 95% CI 0.184–0.951, $P=0.038$). However, the inclusion of these procedures as covariates in the Cox regression model did not change our original results shown in Table 3.

The independent predictors associated with all-cause death among those entered into the Cox proportional hazard analysis were serum UA, BMI, eGFR, plasma BNP, age, and NYHA functional class (Table 4). There was 6.8% increase in all-cause death for each 1 mg/dL increase in serum UA level ($P=0.017$).

4. Discussion

The present study demonstrated that hyperuricemia was seen in 56% of the patients hospitalized with HF. They had higher serum creatinine, higher plasma BNP, and lower LVEF and were prescribed more by loop diuretics and digitalis. Importantly, the risk of adjusted long-term adverse outcomes including all-cause death and cardiac death were significantly higher in patients with UA≥7.4 mg/dl.

Even though the association between UA and cardiovascular diseases, including HF, has remained controversial [20,21], previous studies have demonstrated that UA is an independent risk factor for cardiovascular diseases [2,22,23]. Furthermore, experimental studies have identified mechanisms by which UA induces cardiovascular diseases [24,25]. The present results were consistent with these previous reports [6–9,26,27] and extended their prognostic value to a

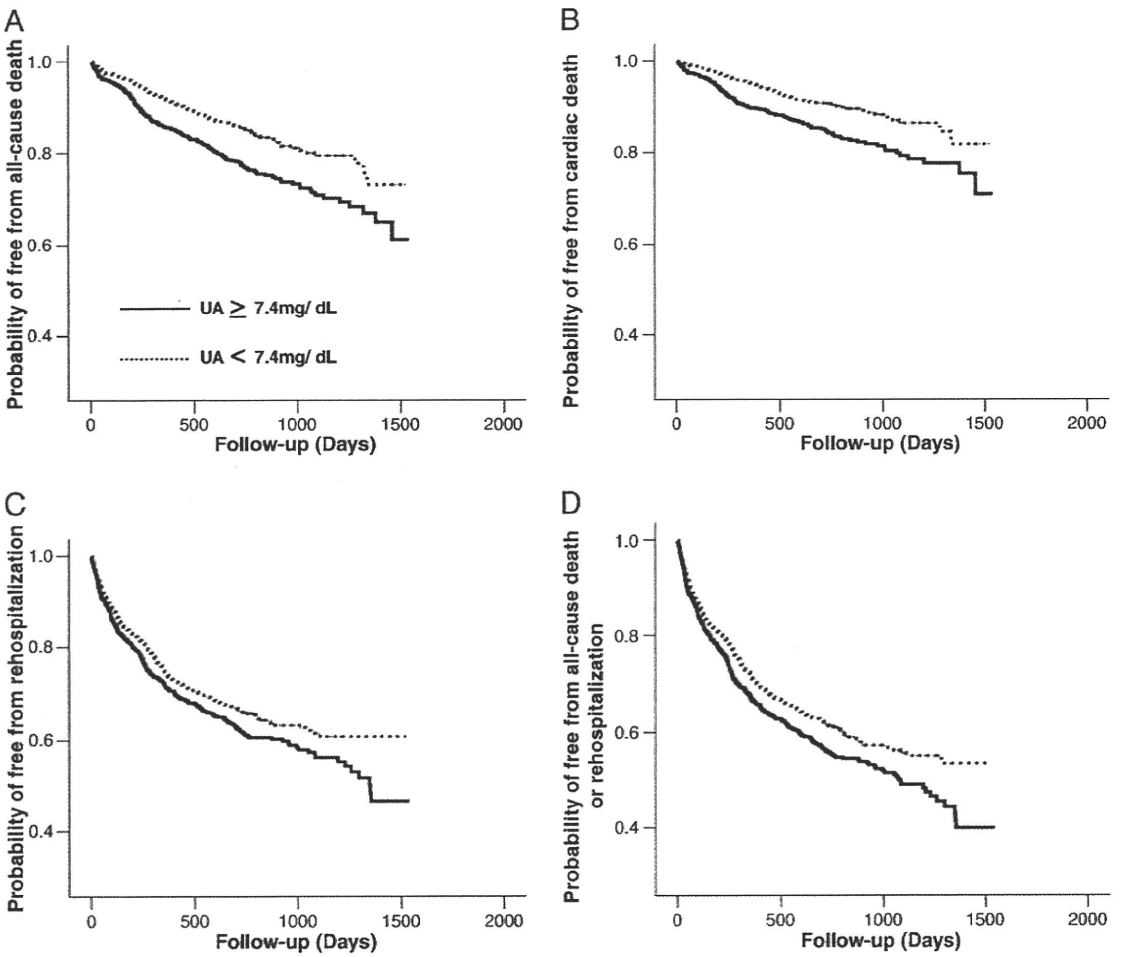

Fig. 2. Kaplan–Meier event-free curves free from all-cause death (A), cardiac death (B), rehospitalization due to worsening HF (C), and all-cause death or rehospitalization (D) comparing patients with serum UA≥7.4 mg/dL (solid lines) and those with serum UA<7.4 mg/dL (dashed lines).

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Table 3
Cox analysis for hazard ratios of outcomes associated with the UA level.

Outcomes	Number (%)					
	UA ≥ 7.4 mg/dl (n = 776)	UA < 7.4 mg/dl (n = 844)	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
All-cause death	199 (25.6)	141 (16.7)	1.772 (1.388–2.261)	<0.001	1.413 (1.094–1.824)	0.008
Cardiac death	132 (17.0)	87 (10.3)	1.738 (1.285–2.350)	<0.001	1.399 (1.020–1.920)	0.037
Rehospitalization	303 (39.0)	289 (34.2)	1.248 (1.043–1.494)	0.040	1.025 (0.848–1.239)	0.801
All-cause death or rehospitalization	367 (47.3)	344 (40.8)	1.322 (1.120–1.560)	0.013	1.089 (0.914–1.298)	0.340

The Cox regression model used in the analysis was adjusted for the following covariates: demographics (age, sex, and BMI), medical history (smoking and chronic atrial fibrillation), CABG, NYHA functional class, eGFR, BNP, LVEF, and medication use (diuretics and digitalis). BNP and LVEF at discharge were entered into the model as the categorical variables; i.e. BNP at discharge ≥ 240 pg/ml or <240 pg/ml or unknown and LVEF at discharge < 40% or ≥ 40% or unknown. HR, hazard ratio; CI, confidence interval.

large, non-selected HF population encountered in routine clinical practice and, more importantly, during the long-term follow-up up to 2.1 years by analyzing the large registry data of hospitalized HF patients.

It should be noted that our results were adjusted with all covariates known to have prognostic value in HF and hyperuricemia was demonstrated to be associated with adverse clinical outcomes independent of renal function and diuretic use (Table 3). In the present study, patients with higher UA had more severe renal dysfunction (Table 1). Renal dysfunction causes hyperuricemia via decreased excretion of UA. Moreover, an elevation of UA level itself can lead to renal dysfunction [25,28–32]. In the present study, the multiple linear regression analysis demonstrated that renal function was the most important factor determining UA level. However, the contribution rate of renal function to serum UA levels was low and serum UA levels were independently associated with the adverse outcomes in HF (Tables 3 and 4). These findings have been also reported by other previous studies [10,11,33]. Therefore, even though serum UA levels can be affected by various factors such as age, gender, renal function, and diuretic use, the present study and other previous studies confirmed that hyperuricemia was independently associated with the adverse clinical outcomes in HF.

The normal UA values are usually higher in men than women. The patients with higher UA levels were more often men in the present study (Table 1). Therefore, the association between UA levels and adverse outcomes might be affected by their gender differences. However, the significant impact of serum UA levels on outcomes was consistently observed even after adjustment with gender (Tables 3 and 4). In addition, to exclude the contribution of gender differences of UA levels, we further analyzed by using the different definition of hyperuricemia based on the genders; >7 mg/dL for men and >6 mg/dL for women. Based on this definition, 1112 (59.5%) patients had hyperuricemia. The prevalence of male was the same between hyperuricemia and no hyperuricemia groups (60.3 vs 59.6%, P = 0.770). However, even with the use of different definition of hyperuricemia according to the genders, the relationship between UA and outcomes was consistent with that in our original submission with the UA cut-off values of 7.4 mg/dL.

Table 4
Multivariate predictors of all-cause death by Cox proportional hazard models.

Variables	HR	95% CI	P value
BMI (per 1 kg/m^2 increase)	0.958	0.924–0.993	0.019
eGFR (per 1 ml/min/1.73 m^2 decrease)	1.016	1.010–1.023	<0.001
Serum uric acid (per 1 mg/dL increase)	1.068	1.012–1.127	0.017
Age (per 10 years increase)	1.368	1.214–1.542	<0.001
BNP at discharge ≥ 240 pg/ml	1.579	1.090–2.287	0.016
NYHA classes 3 and 4 at discharge	1.699	1.165–2.476	0.006

The Cox regression model used in the analysis was adjusted for the following covariates: demographics (age, sex, and BMI), medical history (smoking and chronic atrial fibrillation), CABG, NYHA functional class, eGFR, BNP, LVEF, and medication use (diuretics and digitalis). BNP, LVEF, and NYHA functional class at discharge were entered into the model as the categorical variables; i.e. BNP at discharge ≥ 240 pg/ml or <240 pg/ml or unknown, LVEF at discharge <40% or ≥40% or unknown, and NYHA classes 1 and 2 or 3 and 4. HR, hazard ratio; CI, confidence interval.

There are several mechanisms of hyperuricemia responsible for the increased mortality risk in HF. Serum UA levels may reflect the degree of XO activation in HF [34,35]. XO is one of the major sources of oxygen free radical production and its excess has been shown to be involved in the pathogenesis of HF [36–39]. XO is also shown to impair the regulation of vascular tone [12,33] and reduced vasodilator capacity could lead to exercise intolerance [13,40]. In addition, XO can induce the upregulation of inflammatory cytokines [10]. Hyperuricemia can also reflect an impairment of oxidative metabolism [11]. An inverse relationship between the anaerobic threshold and serum UA concentration has been shown to be present in HF [14]. Finally, hyperuricemia can be a result of renal dysfunction, which may decrease the clearance of UA. However, in the present study as well as other previous studies [11,33], the significant effect of hyperuricemia on outcomes was observed even after the adjustment for risk factors including renal dysfunction.

Several limitations inherent in the design of the registry should be considered. First, the documentation of serum UA levels at hospital discharge might not accurately reflect those after discharge or their changes over time. Second, the information regarding the use of hypouricemiant drugs was not collected in the present study. Similar to the previous studies which also did not collect such information [4–9,27], the critical analysis based on the subgroups with and without the use of hypouricemiant drugs could not be performed. Third, the present study is not a prospective randomized trial and, despite covariate adjustment, other measured and unmeasured factors might have influenced outcomes. For example, serum UA levels have been shown to be higher in patients with postmenopausal state, insulin resistance, elevated leptin level, obstructive sleep apnea, peripheral vascular disease, and movement from rural to urban communities [20]. These factors might be associated with adverse cardiovascular outcomes. Moreover, hyperuricemia is related to inflammation, free radicals and oxidative stress, including XO. However, this study did not collect these data. In addition, the data regarding an indication for surgical treatment were also not collected. However, in the subgroup of prior CABG or valvular surgery higher UA levels were not a significant risk of adverse outcomes either before or after multivariable adjustment. Forth, Cox proportional hazard model has proven to be a useful approach for identifying the relationships of risk factors. However, such approaches must be interpreted with extreme caution when used to determine the covariates. The other hand, the Cox proportional hazard model for survival analysis has gained widespread use from medical researchers. This is mainly due to the fact that this model is quite well suited for the analysis of epidemiological cohort studies and clinical

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trials [41]. In fact, this has been used in the previous studies which assessed the relationship between variables including hyperuricemia and survival [8,27]. Fifth, although the present study demonstrated that low BMI values were significant predictors of all-cause death (Table 4), their values themselves were as low as 22 kg/m^2 compared to those in patients from Europe and United States. However, according to the International Study of Macro-Micro nutrients and Blood Pressure (INTERMAP) study [42], the mean BMI values of Japanese middle-aged men and women were 23.7 and 23.2 kg/m^2, respectively, which were much lower than those of 29.1 and 28.7 kg/m^2 in US population, indicating that the low BMI values in our study patients are a population issue of Japanese. Finally, data were dependent on the accuracy of documentation and abstraction by individual medical centers that participated in this study. However, it was not the objective of this study to restrict enrollment to the narrowly defined population of HF usually included in clinical trials but rather to include a broad range of patients reflecting the current reality of clinical practice. Even though we made an extensive effort to better address and focus the limitation of this study, some major limitation may be still present.

In conclusion, the present study demonstrated that hyperuricemia was common in patients hospitalized with worsening HF and independently associated with long-term adverse outcomes in these patients. Further studies are definitely needed to establish the role of serum UA levels as a potential biomarker for the future risk stratification and a therapeutic target for HF.

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Images in Cardiovascular CT

64-Slice MDCT imaging of endocardial cushion defect associated with other cardiac and extracardiac abnormalities

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KEYWORDS:
Congenital heart disease;
Endocardial cushion defect;
Heterotaxy syndrome;
Multidetector computed tomography;
Volume-rendering view

Abstract. Electrocardiographic-gated 64-slice multidetector computed tomography (MDCT) was performed on a 30-year-old man who presented with a complete endocardial cushion defect (ECD) and severe pulmonary hypertension diagnosed when he was 3 years old. Multiplanar reconstruction image showed the common atrium without an atrial septum, a large ventricular septum defect, and a small right ventricle due to a complete atrioventricular canal defect. Three-dimensional CT volume-rending imaging showed a patent ductus arteriosus, dilation of the ascending aorta, and an anomalous-origin right coronary artery. This patient also had heterotaxy syndrome with polysplenia and azygos continuation. MDCT proved to be a good noninvasive imaging method for the evaluation of ECD associated with cardiac as well as extracardiac abnormalities.

A 30-year-old man presented with heart failure and bradycardia (40–45 beats/min). He had been diagnosed with a complete endocardial cushion defect when he was 3 years old. Before permanent pacemaker insertion, a contrast-enhanced electrocardiographic-gated 64-slice multidetector computed tomography (MDCT) was performed to define the cardiac anatomy. Multiplanar reformats showed the common atrium without atrial septum, large ventricular septal defect, and small right ventricle because of complete atrioventricular canal defect (Fig. 1A and B). A volume-rendered image also showed the patent ductus arteriosus, dilatation of the ascending aorta (Fig. 2A), and the anomalous interarterial course of the right coronary artery between the ascending aorta and pulmonary artery (Fig. 2B). This patient also had heterotaxy syndrome with polysplenia and azygos continuation. (Fig. 3A and B).

Conflict of interest: The authors report no conflicts of interest.
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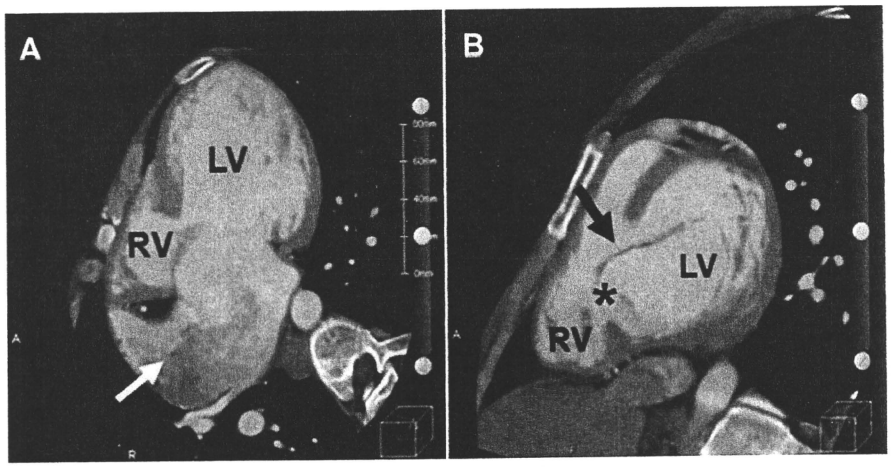

Figure 1 (**A**) Multiplanar reformat showing the common atrium (*white arrow*) and small right ventricle. A movie clip is available in the supplementary material. (**B**) Short-axis multiplanar reformat showing atrioventricular valve leaflets (*black arrow*) straddling the ventricular septum and a large ventricular septal defect (*asterisk*). RV, right ventricle; LV, left ventricle.

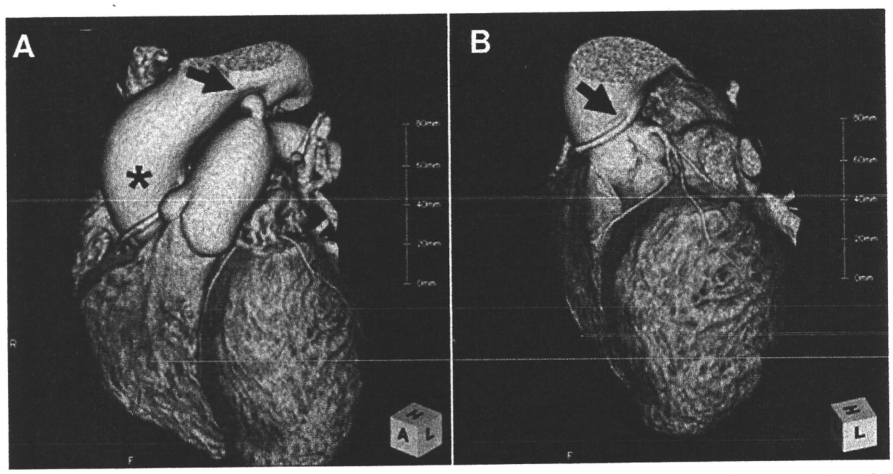

Figure 2 (**A**) Volume-rendered image (left anterior view) showing the patent ductus arteriosus (*black arrow*) and dilated ascending aorta (*asterisk*); (**B**) volume-rendered image without pulmonary artery showing the anomalous origin of the right coronary artery (*black arrow*).

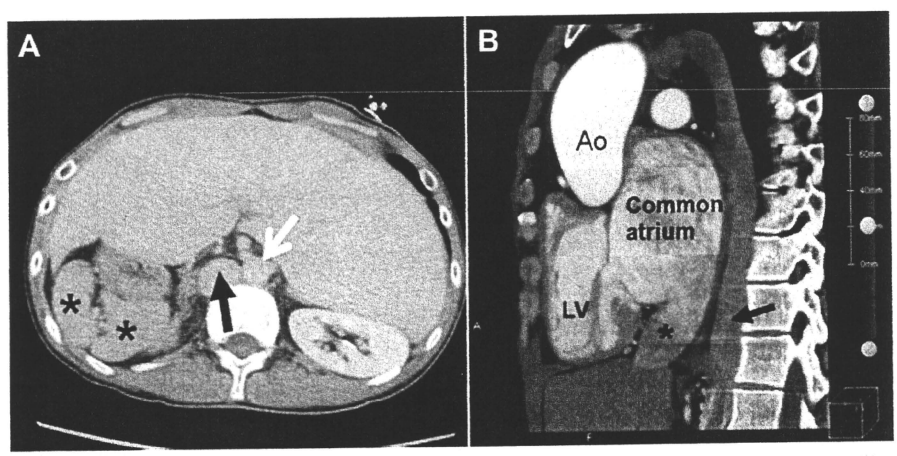

Figure 3 (**A**) Axial contrast-enhanced image showing heterotaxy syndrome with polysplenia (*asterisks*). A dilated azygos vein (*black arrow*) runs beside the descending aorta (*white arrow*). (**B**) Sagittal multiplanar reformat showing the azygos continuation (*black arrow*) and inferior vena cava (*asterisk*). Ao, ascending aorta; LV, left ventricle.

Endocardial cushion defects arise from the abnormal or inadequate fusion of the superior and inferior endocardial cushion, which normally occurs during the fifth week of gestation. They are characterized by a spectrum of cardiac defects involving the atrial septum, ventricular septum, and atrioventricular valves[1] for which MDCT provides a method of comprehensive assessment.[2]

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ORIGINAL ARTICLE

Combination of conventional biomarkers for risk stratification in chronic heart failure

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KEYWORDS
Chronic heart failure;
Biomarkers;
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Summary
Background: Although there is substantial interest in the use of newer biomarkers to identify patients with chronic heart failure (CHF), recently few investigations have evaluated the incremental usefulness of multiple conventional biomarkers. Combination of several biomarkers simultaneously could enhance risk stratification in CHF.
Methods and results: We analyzed 7 biomarkers (brain natriuretic peptide, uric acid, sodium, hemoglobin, creatinine, creatinine clearance, high-sensitivity C-reactive protein), which were known as established prognostic markers for CHF, in 154 consecutive CHF patients, and patients were prospectively followed with endpoints of cardiac death or re-hospitalization. When there was an abnormal value, we scored it for one point to calculate multimarker score. Patients were categorized into 3 strata according to multimarker score. There were 83 cardiac events during the follow-up period. A Cox proportional hazard model showed that patients in the high stratum were associated with the highest risk of cardiac events among the 3 strata. Kaplan–Meier analysis revealed that patients in the high stratum had a significantly higher cardiac event rate compared with lower strata.
Conclusion: The combination of conventional biomarkers could potentially improve the risk stratification of CHF patients for the prediction of cardiac events with low cost and wide availability.

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Introduction

Chronic heart failure (CHF) still represents the major cause of death and hospitalization and has a poor prognosis despite the significant reduction in mortality achieved in clinical trials [1–3]. The prognostic evaluation of CHF patients involves a complex assessment of multiple interacting variables. There is currently no simple clinical criterion or score for predicting early outcome and identifying patients who require such caution. New York Heart Association (NYHA) functional classification and several tests including chest X-ray, echocardiography, radionuclide ventriculography, cardiopulmonary exercise test, and hemodynamic measurements, while helping to estimate the degree of CHF, are subject to interobserver variations in interpretation. Therefore, the ability to identify CHF patients at higher risk for adverse outcomes has led to optimize therapeutic interventions and improve the ominous prognosis [4].

Although there has been substantial interest in the use of newer biomarkers for identification of CHF patients, risk assessment, and prevention of cardiac events recently, few investigations have evaluated the incremental usefulness of multiple conventional biomarkers. Measurement of several biomarkers simultaneously could enhance risk stratification. Previous studies demonstrated that elevated levels of brain natriuretic peptide (BNP) [5], uric acid [6], and high-sensitivity C-reactive protein (hs-CRP) [7], and decreased levels of sodium [8] and hemoglobin [9], and renal insufficiency [10] were associated independently with increased risk of cardiac events in patients with CHF. Importantly, each of these markers assesses different pathophysiological mechanisms. We hypothesized that simultaneous assessment of these biomarkers will provide complimentary information and enable clinicians to stratify risk more effectively among CHF patients. We therefore evaluated the combination of 7 biomarkers (BNP, uric acid, hs-CRP, sodium, hemoglobin, creatinine, creatinine clearance) for predicting cardiac events in 154 consecutive patients hospitalized for CHF from various etiologies during a mean follow-up period of 526±313 days.

Methods

Study population

Between November 2001 and September 2007, we prospectively studied 154 consecutive CHF patients (62 men and 92 women, mean age 71±12 years, range 37–93 years) who had been admitted to the Yamagata University Hospital for the treatment of worsening CHF. The diagnosis of CHF was made by two senior cardiologists using the generally accepted Framingham criteria. Baseline characteristics of the population are shown in Table 1. Exclusion criteria in this study were patients with clinical or electrocardiographic evidence suggestive of acute coronary syndrome within 3 months prior to admission, those with renal insufficiency characterized by a serum creatinine concentration >1.5 mg/dl, and those with active hepatic dis-

Table 1 Clinical and laboratory characteristics of 154 patients with chronic heart failure.

	All chronic heart failure patients (n=154)
Age (years)	71±12
Gender (male/female)	62/92
NYHA functional class (III/IV)	113/41
Hypertension	87 (56%)
Diabetes mellitus	40 (26%)
Hyperlipidemia	28 (18%)
Smoking	28 (18%)
Etiology of chronic heart failure	
Dilated cardiomyopathy	52 (34%)
Ischemic heart disease	34 (22%)
Valvular heart disease	33 (21%)
Hypertensive heart disease	20 (13%)
Others	15 (10%)
Laboratory markers	
Creatinine (mg/dl)	1.15±0.86
Hemoglobin (g/dl)	12.0±2.2
Sodium (mmol/L)	139.2±3.8
Uric acid (mg/dl)	6.9±2.4
BNP (pg/ml)	1019±1140
hs-CRP (mg/dl)	0.46±0.35
Creatinine clearance (ml/min)	44.5±30.8
Multimarker score	4.27±1.44
Echocardiography	
LVEDD (mm)	56±11
LVEF (%)	42±19
Medications at discharge	
ACE inhibitors and/or ARBs	108 (70%)
β-Blockers	48 (31%)
Calcium channel blockers	26 (17%)
Spironolactone	51 (33%)
Loop diuretics	119 (77%)
Digoxin	55 (36%)
Statins	17 (11%)

NYHA, New York Heart Association; BNP, brain natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein; LVEDD, left ventricular dimension at end-diastole; LVEF, left ventricular ejection fraction; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

ease, active pulmonary disease, and degenerative disease of the muscles. Patients who underwent percutaneous coronary intervention or coronary artery bypass graft within 3 months prior to admission were also excluded. 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.

Blood samples were obtained at admission from all patients. The optimal cut-off values for 7 biomarkers were determined as those with the largest sum of sensitivity plus specificity on each of the receiver operating characteristic (ROC) curves. When there was an abnormal value, we scored it for one point to calculate multimarker score. Patients were categorized into 3 strata according to multimarker score. Transthoracic echocardiography was performed by experienced echocardiologists without knowledge of the biochemical data using an ultrasound instrument (Hewlett Packard SONOS 5500 and 7500) equipped with a sector transducer (carrier frequency of 2.5 or 3.75 MHz) within 1 week of admission. Demographics and clinical data, including age, sex, and NYHA functional class at admission, were collected from hospital medical records and patient interviews. Physicians were kept blind to the results of the biochemical markers, and optimal medical therapy was administered independently based on improvement in symptoms, physical examination findings, and pulmonary congestion on chest X-ray [11]. Diuretics were given in flexible dosages on the basis of body weight and daily diuresis. Spironolactone was administered as 25 or 50 mg/day. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and β-blockers were gradually increased to the maximum dosage possible. The discharge was decided by two senior cardiologists using clinical examination, electrocardiogram, and chest X-ray film. The etiologies of CHF were dilated cardiomyopathy in 52 patients, ischemic heart disease in 34 patients, valvular heart disease in 33 patients, and hypertensive heart disease in 20 patients. The diagnosis of dilated cardiomyopathy was based on the definition of the WHO/ISFC task force [12]. The diagnoses of hypertension, diabetes, and hyperlipidemia were obtained from medical records or patient history of currently or previously received medical therapy.

Endpoints and follow-up

Patients were prospectively followed-up and no patients were lost to follow-up (mean follow-up 526 ± 313 days) after discharge from the Yamagata University Hospital. The endpoints were (1) cardiac death, defined as death from worsening CHF or sudden cardiac death, and (2) worsening CHF requiring readmission. Sudden cardiac death was defined as death without definite premonitory symptoms or signs and was established by the attending physician. A review of medical records and follow-up telephone interviews were conducted by senior cardiologists to survey cardiac events, who were blinded to blood examination data. Cardiac events were adjudicated using electrocardiograms, chest X-ray reports, autopsy reports, death certificates, and witness statements.

Statistical analysis

Results are presented as mean ± standard deviation (S.D.) for continuous variables and as the percentage of total patients for categorical variables. The independent samples *t*-test or Mann–Whitney test and chi-square test were used for comparisons of continuous and categorical variables, respectively. A Cox proportional hazard analysis was performed to evaluate the associations between cardiac events and blood measurements. The cardiac event-free curve was computed according to the Kaplan–Meier method and compared by the log-rank test. All *p*-values reported are two-sided, and a p-value < 0.05 was considered significant. Statistical analysis was performed with a standard statistical program package (StatView, version 5.0, SAS Institute Inc, Cary, NC, USA).

Results

The mean age of study subjects was 71 ± 12 years old. As shown in Table 1, 62 patients were men, 41 were in NYHA functional class IV, and 34 had ischemic heart disease. Mean multimarker score was 4.27 ± 1.44.

Associations with subsequent clinical outcomes

There were 9 noncardiac deaths (3 cerebral infarction, 2 pneumonia, 2 lung cancer, 1 septic shock, and 1 suicide) and 83 cardiac events, including 43 cardiac deaths (5 in-hospital deaths) and 40 readmissions for worsening heart failure during the follow-up period. The causes of cardiac death were worsening CHF in 34 patients, fatal acute myocardial infarction in 3 patients, and sudden cardiac death in 6 patients.

As shown in Table 2, patients with cardiac events were older, and had a higher multimarker score

Table 2 Comparisons of clinical characteristics between patients with and without cardiac events.

	Event free ($n=71$)	Cardiac events ($n=83$)	p-Value
Age (years)	68±15	74±10	0.0100
Gender (male/female)	29/42	33/50	0.8911
NYHA functional class (III/IV)	54/17	59/24	0.4856
Hypertension	43 (61%)	44 (53%)	0.3456
Diabetes mellitus	21 (30%)	19 (23%)	0.3461
Hyperlipidemia	10 (14%)	18 (22%)	0.2193
Current smoking	12 (17%)	16 (19%)	0.6270
Etiology of chronic heart failure			
Dilated cardiomyopathy	27 (38%)	25 (30%)	
Ischemic heart disease	13 (18%)	21 (25%)	
Valvular heart disease	18 (25%)	15 (18%)	
Hypertensive heart disease	6 (9%)	14 (17%)	
Others	7 (10%)	8 (10%)	0.2951
Laboratory markers			
Creatinine (mg/dl)	1.04±0.64	1.25±1.01	0.0436
Hemoglobin (g/dl)	12.9±2.4	11.9±2.2	0.0328
Sodium (mmol/L)	140.7±2.6	138.2±4.4	0.0008
Uric acid (mg/dl)	6.4±1.9	7.2±2.7	0.0254
BNP (pg/ml)	604±1156	1032±1134	<0.0001
hs-CRP (mg/dl)	0.33±0.30	0.57±0.34	0.0094
Creatinine clearance (ml/min)	56.8±38.5	35.2±19.3	0.0031
Multimarker score	3.85±1.32	4.63±1.45	0.0007
Echocardiography			
LVEDD (mm)	55±9	56±11	0.6403
LVEF (%)	39±18	43±18	0.2741

Abbreviations as in Table 1.

compared with those without cardiac events. Furthermore, as reported in previous studies [5–10], patients with cardiac events showed renal dysfunction, anemia, hyponatremia, hyperuricemia, and higher levels of BNP and hs-CRP compared with those without cardiac events. Other parameters including gender, NYHA functional class, and numbers of patients with hypertension, diabetes mellitus, hyperlipidemia, or currently smoking were not significantly different between patients with and without cardiac events. In addition, there was no difference in etiology of heart failure, left ventricular end-diastolic diameter (LVEDD), and left ventricular ejection fraction (LVEF).

Strata of multimarker score in CHF patients

The optimal cut-off values for 7 biomarkers were determined as those with the largest sum of sensitivity plus specificity on each of the ROC curves, respectively (Fig. 1). When there was an abnormal value, we scored it for one point to calculate multimarker score. Patients were categorized into 3 strata according to multimarker score: low stratum (multimarker score 0–3, $n=48$), intermediate stratum (multimarker score 4, $n=40$), and high stratum (multimarker score 5–7, $n=66$). Table 3 summarizes the comparisons of the clinical characteristics of the 3 strata. Patients in the high stratum were older, had more severe NYHA functional class, and higher rate of use of loop diuretics compared with lower strata. Furthermore, patients in the high stratum had significantly higher rates of re-hospitalization and cardiac deaths than those in the lower strata (Fig. 2). Average periods of follow-up days for the 3 strata were 817±632 (low stratum), 696±586 (intermediate stratum), and 444±492 (high stratum) days. The period was significantly shorter in the high stratum compared with lower strata ($p<0.01$). Whereas, other parameters including gender, etiology of heart failure, LVEDD, and LVEF were not significantly different among the 3 strata. In addition, there was no difference in the numbers of patients who had hypertension, diabetes mellitus, hyperlipidemia, or were currently smoking, and rate of use of ACE inhibitors, ARBs, and β-blockers at discharge among the 3 strata.

Risk stratification by the stratum analysis

Prognostic results by the univariate Cox proportional hazard analysis to predict cardiac events are

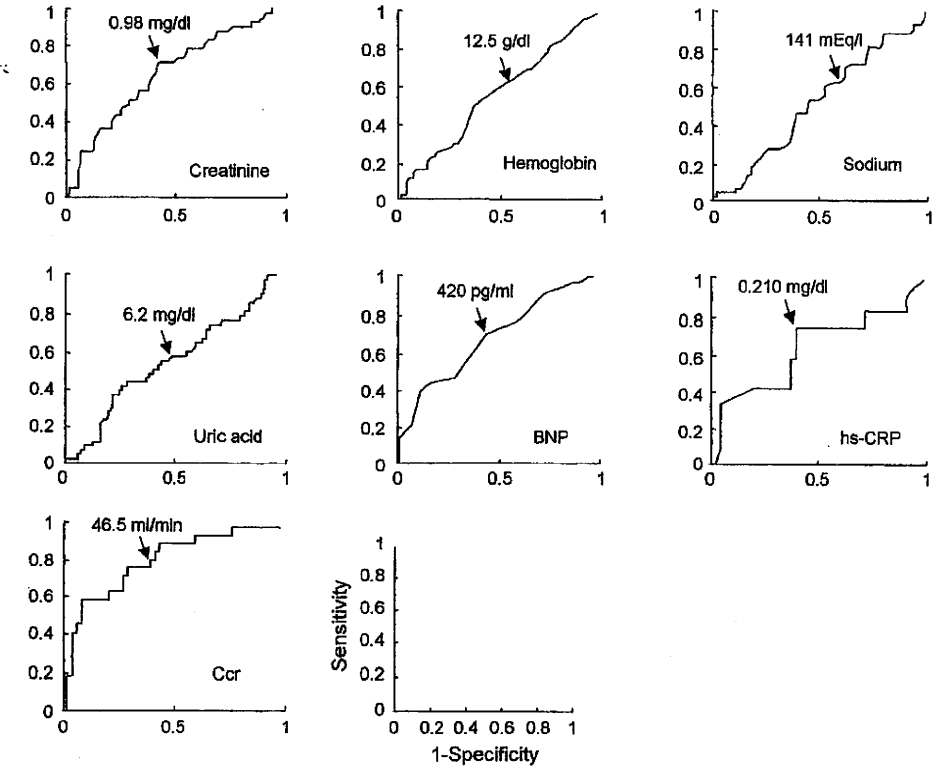

Figure 1 Receiver operating characteristic (ROC) curve analysis of 7 biomarkers. BNP, brain natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein; and Ccr, creatinine clearance.

shown in Fig. 3. The univariate Cox proportional hazard analysis showed that risk of total cardiac events (Fig. 3A) and cardiac deaths (Fig. 3B) were significantly higher in patients in the high stratum compared with low stratum patients. In addition, patients in the high stratum were at higher risk of total cardiac events (hazard ratio 1.934, $p=0.0144$) and cardiac death (hazard ratio 1.393, $p=0.0313$) compared with intermediate-stratum patients. The hazard ratios of total cardiac events (Fig. 4A) and cardiac deaths (Fig. 4B) adjusted for age and sex were significantly higher in patients in the high stratum compared with low stratum patients.

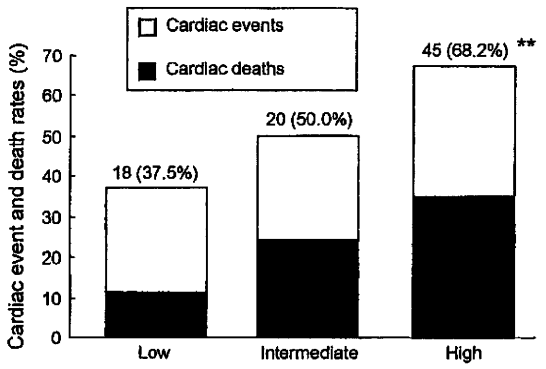

Figure 2 Cardiac mortality and cardiac events among the 3 strata. Patients in the high stratum had higher rates of re-hospitalization and cardiac deaths compared with lower strata. **$p<0.001$ by chi-square test.

We performed univariate and multivariate Cox proportional hazard regression analyses of predicting cardiac events among multimarker score, age, NYHA functional class, and LVEF (Table 4). In the univariate Cox proportional hazard regression analysis, multimarker score and age were significantly associated with cardiac events. Furthermore, only multimarker score was an independent predictor of cardiac events among these variables by the multivariate Cox proportional hazard regression analysis.

Kaplan–Meier analysis demonstrated that patients in the high stratum had a significantly higher total cardiac events rate (Fig. 5A) and cardiac death rate (Fig. 5B) compared with lower strata. One- and 2-year total cardiac event rates were 14.6% and 29.2% in low stratum, 27.5% and 37.5% in intermediate stratum, and 51.5% and

Table 3 Comparisons of clinical characteristics among the 3 strata in chronic heart failure patients.

	Low stratum ($n=48$)	Intermediate stratum ($n=40$)	High stratum ($n=66$)
Age (years)	68±14	70±12	74±10$^{**\#\#}$
Gender (male/female)	23/25	14/26	25/41
NYHA functional class (III/IV)	39/9	28/12	46/20$^{\$\$}$
Hypertension	26 (54%)	24 (60%)	37 (56%)
Diabetes mellitus	18 (38%)	9 (23%)	13 (20%)
Hyperlipidemia	8 (17%)	6 (15%)	14 (21%)
Current smoking	9 (19%)	8 (20%)	11 (17%)
Etiology of chronic heart failure			
Dilated cardiomyopathy	17 (35%)	12 (30%)	23 (35%)
Ischemic heart disease	13 (27%)	8 (20%)	13 (20%)
Valvular heart disease	4 (8%)	12 (30%)	17 (26%)
Hypertensive heart disease	6 (13%)	4 (10%)	10 (15%)
Others	8 (17%)	4 (10%)	3 (4%)
Laboratory markers			
Creatinine (mg/dl)	0.76±0.23	1.08±0.67*	1.48±1.10$^{*\#\#}$
Hemoglobin (g/dl)	12.7±2.1	12.8±2.0*	10.9±2.0$^{**\#\#}$
Sodium (mmol/L)	141.1±2.6	139.6±3.9*	138.5±4.1$^{**\#}$
Uric acid (mg/dl)	5.3±1.8	6.9±2.3**	7.9±2.3$^{**\#}$
BNP (pg/ml)	566±587	962±844**	1380±1447$^{**\#}$
hs-CRP (mg/dl)	0.34±0.30	0.49±0.40*	0.55±0.32$^{*\#}$
Creatinine clearance (ml/min)	77.9±44.2	50.3±28.3**	32.4±15.8$^{**\#\#}$
Multimarker score	2.60±0.64	4.00±0.00**	5.66±0.73$^{**\#\#}$
Echocardiography			
LVEDD (mm)	56±10	55±10	56±11
LVEF (%)	39±18	42±18	42±19
Medications at discharge			
ACE inhibitors and/or ARBs	33 (69%)	30 (75%)	45 (68%)
β-Blockers	12 (25%)	14 (35%)	22 (33%)
Calcium channel blockers	10 (21%)	4 (10%)	12 (18%)
Spironolactone	12 (25%)	19 (48%)	20 (30%)
Loop diuretics	31 (65%)	35 (88%)	53 (80%)$^{\#}$
Digoxin	16 (33%)	15 (38%)	24 (36%)
Statins	5 (10%)	4 (10%)	8 (12%)

$^{*}p<0.05$ and $^{**}p<0.01$ vs low, and $^{\#}p<0.05$ and $^{\#\#}p<0.01$ vs intermediate. $^{\$}p<0.05$ and $^{\$\$}p<0.01$ by chi-square test. Abbreviations as in Table 1.

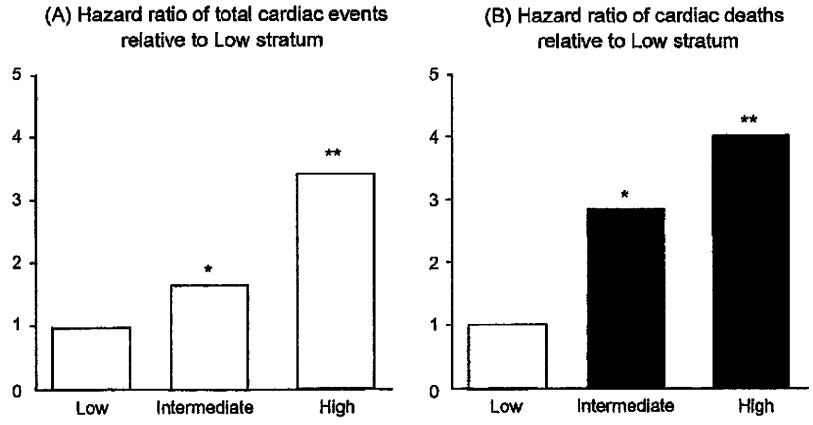

Figure 3 Hazard ratios to predict cardiac events among the 3 strata. The univariate Cox proportional hazard analysis demonstrated that the high stratum was associated with the highest risk for total cardiac events (A) and cardiac deaths (B) among the 3 strata. $^{**}p<0.001$ vs low stratum patients.