# Distinct Prognostic Factors in Patients With Chronic Heart Failure and Chronic Kidney Disease

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## SUMMARY

Impaired renal function is a strong predictor of mortality in chronic heart failure (CHF). However, the impact of chronic kidney disease (CKD) on prognostic factors has not been rigorously examined in CHF. The purpose of this study was to compare prognostic factors between CHF patients with and without CKD. Consecutive 505 patients with CHF, who performed cardiopulmonary exercise testing before discharge, were enrolled. Patients were divided into two groups: CKD group (eGFR < 60 mL/minute/1.73m$^2$, $n$ = 213) and non-CKD group (eGFR ≥ 60 mL/minute/1.73m$^2$, $n$ = 292). The patients were followed up to register cardiac events including cardiac death and re-hospitalization due to worsening heart failure. There were 115 events during the follow-up period (746 ± 238 days), and the cardiac event rate was higher in the CKD group than in the non-CKD group (34% versus 14%, $P < 0.001$). Multivariate Cox hazard analysis demonstrated that body mass index ($P < 0.001$), log BNP ($P < 0.001$), peak $VO_2$ ($P < 0.05$), and left atrial dimension ($P < 0.05$) were independent parameters to predict cardiac events after discharge in the non-CKD group. In contrast, peak $VO_2$ ($P < 0.01$), log BNP ($P < 0.01$), and the concentrations of hemoglobin ($P < 0.05$) and uric acid ($P < 0.05$) were independent prognostic factors in the CKD group. Prognostic factors were different between CHF patients with and without CKD, and this should be considered when managing CHF patients with CKD. (Int Heart J 2013; 54: 311-317)

**Key words:** Clinical outcome, BNP, Cardio-renal syndrome, Exercise capacity

Improvement in the treatment of heart failure results in progressive effects on outcome at the population level. However, prognosis still remains poor in heart failure.[1)] Many factors including cardiac functional parameters, exercise capacity, pulmonary function, biomarkers from bloods samples, and other clinical characteristics have determined the prognosis of patients with chronic heart failure (CHF).[2)]

Recent studies have demonstrated that chronic kidney disease (CKD) increases the risk of cardiovascular events.[3)] In CHF, a high incidence of renal dysfunction has been reported, and impaired renal function is a strong predictor of mortality and other clinical outcomes.[4)]

The impact of CKD on prognostic factors of CHF, however, has not been rigorously examined. Therefore, the purpose of this study was to compare prognostic factors between CHF patients with and without CKD.

## METHODS

**Study subjects and study protocol:** We examined consecutive 553 patients admitted to Fukushima Medical University Hospital for treatment of worsening CHF between 2007 and 2010. Written informed consent was obtained from all study subjects. The study complied with the Declaration of Helsinki, and the study protocol was approved by the ethical committee of Fukushima Medical University. We diagnosed CHF based on the Framingham criteria, including symptoms, physical examinations, chest x-rays, and echocardiographic findings. All patients received optimal medications and were in stable condition before discharge. They underwent echocardiography and cardiopulmonary exercise (CPX) testing on the same day when in stable condition within 3 to 5 days prior to discharge. Blood samples were obtained just prior to CPX testing. In the present study, patients with decompensated heart failure after treatment, end-stage renal disease (estimated glomerular filtration rate (eGFR) < 15 mL/minute/1.73m$^2$), malignant diseases, acute coronary syndrome, active infection diseases, and those who were unable to undergo CPX testing ($n$ = 48) were excluded. Thus, a total of 505 patients (408 males and 97 females, mean age 60.4 ± 13.8 year) were analyzed. Out of these 505 patients, 126 were in New York Heart Association (NYHA) functional class IIm, 275 in NYHA III, and 104 in NYHA IV at admission. There were 71 patients in NYHA class I, 199 patients in IIs, 174 patients in IIm, and 63 patients in III at CPX testing. The baseline clinical characteristics of the study patients are shown in Table I.

Patients were followed up after discharge to register car-

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**Table I.** Clinical Characteristics of Study Subjects

| | Total $n = 505$ | CKD (-) $n = 292$ | CKD (+) $n = 213$ | *P* |
|---|---|---|---|---|
| Age (years) | 60.4 ± 13.8 | 56.0 ± 14.3 | 66.4 ± 10.7 | < 0.001 |
| Male, *n* (%) | 408 (80.8%) | 226 (77.4%) | 182 (85.4%) | < 0.05 |
| BMI (kg/m$^2$) | 23.4 ± 4.2 | 23.6 ± 4.1 | 23.1 ± 4.3 | NS |
| Ischemic etiology, *n* (%) | 202 (40.0%) | 109 (37.3%) | 93 (43.7%) | NS |
| AF, *n* (%) | 130 (24.0%) | 42 (14.2%) | 81 (38.0%) | < 0.001 |
| NYHA class (I/IIs/IIm/III) | (71/199/174/63) | (61/123/83/25) | (8/76/91/38) | |
| *Laboratory data* | | | | |
| Hb (g/dL) | 12.9 ± 1.9 | 13.3 ± 1.6 | 12.4 ± 2.1 | < 0.001 |
| BUN (mg/dL) | 19.7 ± 9.7 | 15.2 ± 4.6 | 26.0 ± 11.2 | < 0.001 |
| Creatinine (mg/dL) | 1.00 ± 0.37 | 0.78 ± 0.13 | 1.31 ± 1.37 | < 0.001 |
| eGFR (mL/minute/1.73m$^2$) | 64.7 ± 21.9 | 79.1 ± 15.8 | 44.9 ± 10.8 | < 0.001 |
| Na (mEq/L) | 139.6 ± 3.0 | 139.7 ± 2.8 | 139.2 ± 3.0 | NS |
| Uric acid (mg/dL) | 6.47 ± 1.85 | 6.01 ± 1.51 | 7.16 ± 1.93 | < 0.001 |
| T.Bil (mg/dL) | 0.83 ± 0.46 | 0.84 ± 0.48 | 0.81 ± 0.43 | NS |
| BNP (pg/mL) | 146.5 (51.6-314.5) | 112.0 (30.5-249.5) | 205.0 (94.5-368.0) | < 0.001 |
| Log BNP | 4.82 ± 1.28 | 4.51 ± 1.34 | 5.23 ± 1.07 | < 0.001 |
| *Echocardiographic parameters* | | | | |
| LVEF (%) | 45.1 ± 15.6 | 47.3 ± 16.0 | 42.6 ± 111.1 | < 0.01 |
| LVEDV (mL) | 121.9 ± 59.0 | 120.1 ± 61.7 | 123.3 ± 55.4 | NS |
| LVESV (mL) | 72.8 ± 53.2 | 69.6 ± 56.2 | 77.3 ± 48.7 | NS |
| LAD (mm) | 43.8 ± 10.7 | 42.6 ± 11.1 | 45.4 ± 9.8 | < 0.05 |
| DcT (msec) | 202.9 ± 69.6 | 200.4 ± 61.3 | 206.2 ± 79.3 | NS |
| E/E' | 12.3 ± 6.5 | 11.4 ± 5.9 | 13.5 ± 7.1 | < 0.001 |
| *CPX parameters* | | | | |
| Peak $VO_2$ (mL/kg/minute) | 15.6 ± 4.8 | 16.9 ± 4.9 | 13.8 ± 4.1 | < 0.001 |
| Peak HR (bpm) | 119.0 ± 28.6 | 125.6 ± 28.1 | 110.0 ± 26.9 | < 0.001 |
| $VE/VCO_2$ slope | 33.1 ± 7.3 | 32.0 ± 7.0 | 34.6 ± 7.5 | < 0.001 |
| *Pharmacotherapy* | | | | |
| Digitalis, *n* (%) | 55 (10.9%) | 29 (9.9%) | 26 (12.2%) | NS |
| ACE inhibitor or ARB, *n* (%) | 427 (84.6%) | 239 (81.8%) | 188 (88.3%) | NS |
| *β*-blocker, *n* (%) | 409 (81.0%) | 224 (76.7%) | 185 (86.9%) | < 0.05 |
| CCB, *n* (%) | 97 (19.2%) | 60 (20.5%) | 37 (17.4%) | NS |
| Statin, *n* (%) | 244 (48.3%) | 134 (45.9%) | 110 (51.6%) | NS |
| Aldosterone antagonist, *n* (%) | 278 (55.0%) | 155 (53.1%) | 123 (57.7%) | NS |
| Diuretics, *n* (%) | 304 (60.2%) | 148 (50.7%) | 156 (73.2%) | < 0.001 |

BMI indicates body mass index; AF, atrial fibrillation; NYHA, New York Heart Association, Hb, hemoglobin; BUN, blood nitrogen urea; eGFR, estimated glomerular filtration rate; Na, sodium; T.Bil, total bilirubin; BNP, B-type natriuretic peptide ; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LAD, left atrial dimension; DcT, deceleration time; E/E', ratio of mitral peak velocity of early filling (E) to early diastolic annular mitral velocity (E'); Peak $VO_2$, peak oxygen uptake; peak HR, peak heart rate; $VE/VCO_2$ slope, rate of increase in ventilation per unit increase in carbon dioxide production; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; CCB, calcium channel blocker; and NS, not significant.

diac events. The endpoints were cardiac death and re-hospitalization due to worsening heart failure. The follow-up period was 746 ± 238 days (mean ± SD) and was completed for all patients. Follow-up and events were adjudicated using medical records, death certificates, and a questionnaire method for home doctors and patient themselves.

We compared blood sampling data, exercise capacity, systolic and diastolic function, and prognosis between patients with and without CKD. CKD was defined as an estimated glomerular filtration rate (eGFR) < 60 mL/minute/1.73 m$^2$ from the Modification of Diet in Renal Disease (MDRD) equation in Japan (recommendation of Japanese Society of Nephrology).

**Cardiopulmonary exercise testing:** All subjects underwent incremental symptom limited exercise testing using an upright cycle ergometer with a ramp protocol (Strength Ergo 8, Fukuda Denshi Co. Ltd., Tokyo). Breath by breath oxygen consumption ($VO_2$), carbon dioxide production ($VCO_2$), and minute ventilation (VE) were measured during exercise using an AE-300S respiratory monitor (Minato Medical Science, Osaka, Japan). Peak $VO_2$ was measured as an average of the last 30 seconds of exercise. Ventilatory response to exercise (expressed as a $VE/VCO_2$ slope) was calculated as the regression slope relating VE to $CO_2$ from the start of exercise until the respiratory compensation (RC) point (the time at which ventilation is stimulated by $CO_2$ output and end-tidal $CO_2$ tension begins to decrease).[5,6]

**Echocardiography:** Left ventricular end-diastolic and end-systolic volumes (LVEDV and LVESV) and left ventricular ejection fraction (LVEF) were measured by the modified Simpson's method. Standard measurements of left atrial diameter (LAD) were also obtained in the parasternal long axis view.[7] Pulsed-wave Doppler recordings of the mitral flow velocity at the tip of mitral leaflets were obtained from the apical 4 chamber view during quiet respiration. From the Doppler profile, the peak velocities of the early (E) wave and late (A)

**Table II.** Cardiac Events After Discharge of Study Subjects

| | Total $n = 505$ | CKD (-) $n = 292$ | CKD (+) $n = 213$ | $P$ |
|---|---|---|---|---|
| Cardiac deaths, $n$ (%) | 22 (4.4%) | 5 (1.7%) | 17 (8.0%) | < 0.01 |
| Re-hospitalization, $n$ (%) | 93 (18.4%) | 37 (8.9%) | 56 (18.6%) | < 0.001 |
| Total cardiac events, $n$ (%) | 115 (22.8%) | 42 (14.4%) | 73 (34.3%) | < 0.001 |

wave were calculated, together with the deceleration time of the E wave (DcT), taken as the time interval between the peak E wave and the zero intercept of the slope of the deceleration profile.[8] From the tissue-Doppler imaging, the mitral annulus velocity (E') was measured and the ratio of peak E wave velocity to E' wave velocity (E/E') was accepted for analysis.

**Statistical analysis:** Results are presented as the mean ± SD for continuous variables and as numbers and percentages for categorical variables. Student's *t*-test was used to compare continuous variables. If data were not distributed normally, the Mann-Whitney *U* test was used. The chi-square test was used to compare categorical variables. A $P$ value < 0.05 was considered statistically significant. The Cox proportional hazard regression models determined which variables were associated with a cardiac event. We examined 11 variables known to related to the prognosis of CHF (body mass index, uric acid, hemoglobin, eGFR, sodium, log B-type natriuretic peptide (BNP), LVEF, LAD, DcT, peak $VO_2$, and diuretic use) adjusted for age and gender in each group. Significant variables selected in the univariate analysis were entered into the multivariable analysis. The cardiac event-free rates were calculated using the Kaplan-Meier analysis, and the log-rank test was used to compare the results. The receiver operating characteristic (ROC) curve was constructed to evaluate the cut-off values. All statistical analyses were performed using SPSS statistics version 17.0 (SPSS Inc, Chicago, IL).

## Results

**Clinical characteristics, laboratory, echocardiographic and CPX data:** Out of the 505 CHF patients, 213 patients (42.2%) had CKD (defined as eGFR < 60 mL/minute/1.73 $m^2$). Comparisons of clinical characteristics, laboratory data, and echocardiographic and CPX findings between the study subjects with and without CKD are shown in Table I. Patients with CKD were older than those without CKD. Higher frequencies of male and atrial fibrillation were associated with patients with CKD. Patients with CKD had lower hemoglobin concentrations, higher concentrations of blood urea nitrogen (BUN), creatinine and uric acid, lower eGFR, and higher plasma BNP levels than those without CKD. In echocardiography, patients with CKD had a lower LVEF, larger LAD, and higher ratio of E/E' compared to those without CKD. The results of CPX revealed that patients with CKD had lower peak $VO_2$, lower peak HR, and higher $VE/VCO_2$ slope than those without CKD. Patients in the CKD group were more frequently given $\beta$-blockers and diuretics (Table I).

**Cardiac events in study subjects:** A total of 115 cardiac events were registered, including 22 cardiac deaths and 93 re-hospitalizations due to worsening heart failure, during the follow-up period (746 ± 238 days) as shown in Table II. Patients with CKD had higher rates of cardiac death and re-hospitalization due to worsening heart failure than those without CKD (Table II). This was also clearly demonstrated by Kaplan-Meier analysis (Figure 1).

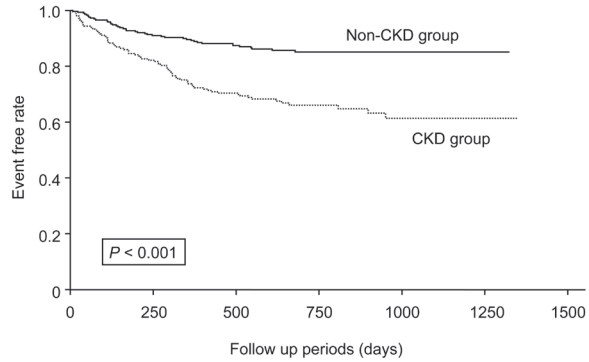


**Figure 1.** Kaplan-Meier survival analysis between patients with and without CKD. Event free rate was significantly lower in the CKD group ($P$ < 0.001 by a log-rank test).

**Prognostic factors for cardiac events in the non-CKD group:** The ability of variables including data for blood examination, echocardiography, and CPX to predict cardiac events in the non-CKD group was examined by univariate and multivariate Cox proportional hazard analyses (Table III). Univariate analysis revealed significant associations between body mass index, uric acid, hemoglobin, sodium, log BNP, LVEF, LAD, DcT, peak $VO_2$ and diuretic use with cardiac events. These variables with a $P$ value less than 0.05 by univariate analysis were entered into the multivariate Cox proportional hazard regression model. As presented in Table III, body mass index, log BNP, LAD, and peak $VO_2$ were independent prognostic factors to predict future cardiac events in the non-CKD group.

**Prognostic factors for cardiac events in the CKD group:** Similarly, the ability of variables to predict cardiac events in the CKD group was examined by univariate and multivariate Cox proportional hazard analyses (Table IV). Univariate analysis revealed significant associations between hemoglobin, eGFR, uric acid, sodium, log BNP, LVEF, LAD, DcT, peak $VO_2$, and diuretic use with cardiac events. These variables with a $P$ value less than 0.05 by univariate analysis were entered into the multivariate Cox proportional hazard regression model. As presented in Table IV, hemoglobin, uric acid, log BNP, and peak $VO_2$ were independent prognostic factors to predict future cardiac events in the CKD group.

**Risk stratification of CHF patients in the non-CKD group:** In the non-CKD group, patients with CHF were risk-stratified by independent prognostic factors, body mass index, log BNP, LAD, and peak $VO_2$, obtained by the multivariate Cox proportional hazard analysis. Cut-off values for each factor were determined by receiver operating characteristic (ROC) analysis. For body mass index, the best cut-off value was 22.3 $kg/m^2$

**Table III.** Cox Proportional Hazard Analyses in the Non-CKD Group

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | *P* | HR | 95% CI | *P* |
| BMI | 0.783 | 0.711-0.862 | < 0.001 | 0.669 | 0.562-0.798 | < 0.001 |
| eGFR | 0.999 | 0.979-1.020 | NS | | | |
| Uric acid | 1.346 | 1.089-1.664 | < 0.01 | 1.132 | 0.834-1.536 | NS |
| Hb | 0.736 | 0.603-0.900 | < 0.01 | 1.356 | 0.964-1.907 | NS |
| Na | 0.838 | 0.765-0.917 | < 0.001 | 1.065 | 0.908-1.249 | NS |
| Log BNP | 4.028 | 3.021-5.860 | < 0.001 | 3.542 | 2.308-5.435 | < 0.001 |
| LVEF | 0.943 | 0.924-0.961 | < 0.001 | 1.009 | 0.974-1.045 | NS |
| LAD | 1.026 | 1.003-1.044 | < 0.05 | 1.049 | 1.004-1.096 | < 0.05 |
| DcT | 0.983 | 0.977-0.990 | < 0.001 | 0.988 | 0.996-1.003 | NS |
| Peak $VO_2$ | 0.761 | 0.695-0.834 | < 0.001 | 0.942 | 0.847-0.998 | < 0.05 |
| Diuretics use | 12.664 | 5.464-22.613 | < 0.001 | 1.275 | 0.228-7.125 | NS |

Abbreviations as in Table I. The data were adjusted for age and gender.

**Table IV.** Cox Proportional Hazard Analyses in the CKD Group

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | *P* | HR | 95% CI | *P* |
| BMI | 0.967 | 0.899-1.031 | NS | | | |
| Hb | 0.785 | 0.694-0.889 | < 0.001 | 0.920 | 0.889-0.988 | < 0.05 |
| eGFR | 0.965 | 0.946-0.985 | < 0.01 | 1.106 | 0.989-1.031 | NS |
| Uric acid | 1.161 | 1.025-1.316 | < 0.05 | 1.160 | 1.0011-1.282 | < 0.05 |
| Na | 0.873 | 0.812-0.938 | < 0.001 | 0.976 | 0.8497-1.062 | NS |
| log BNP | 1.818 | 1.407-2.350 | < 0.001 | 1.452 | 1.117-1.889 | < 0.01 |
| LVEF | 0.980 | 0.964-0.996 | < 0.05 | 0.993 | 0.974-1.012 | NS |
| LAD | 1.027 | 1.003-1.052 | < 0.05 | 1.015 | 0.980-1.050 | NS |
| DcT | 0.994 | 0.991-0.998 | < 0.01 | 0.996 | 0.989-1.237 | NS |
| Peak $VO_2$ | 0.758 | 0.696-0.824 | < 0.0001 | 0.844 | 0.741-0.962 | < 0.01 |
| Diuretics use | 2.779 | 1.424-5.425 | < 0.01 | 1.190 | 0.659-2.821 | NS |

Abbreviations as in Table I. The data were adjusted for age and gender.

(sensitivity: 0.698; specificity: 0.660; area under the curve, AUC: 0.734). In Kaplan-Meier analysis, patients with a body mass index ≤ 22.3 kg/$m^2$ had significantly higher cardiac event rates than those with a body mass index > 22.3 kg/$m^2$ (Figure 2A). The cut-off value for log BNP was similarly determined by ROC analysis as 5.47 (sensitivity: 0.833; specificity: 0.827; AUC: 0.907). Patients with higher log BNP (≥ 5.47) had significantly higher cardiac event rates than those with < 5.47 as demonstrated by Kaplan-Meier analysis (Figure 2B). The best cut-off values for LAD and peak $VO_2$ were 42.8 mm and 14.8 mL/kg/minute, respectively, in the ROC analysis (sensitivity: 0.718; specificity: 0.632; AUC: 0.688 and sensitivity: 0.791; specificity: 0.712; AUC: 0.818). As shown in Figure 2C, patients with a larger LAD (≥ 42.8 mm) had significantly higher cardiac event rates than those with a smaller LAD (< 42.8 mm). Compared to patients with peak $VO_2$ > 14.8 mL/kg/minute, patients with peak $VO_2$ ≤ 14.8 mL/kg/minute had significantly higher cardiac events (Figure 2D).

**Risk stratification of CHF patients in the CKD group:** In the CKD group, patients with CHF were risk-stratified by independent prognostic factors, namely uric acid, hemoglobin, log BNP, and peak $VO_2$, obtained by the multivariate Cox proportional hazard analysis. The best cut-off values determined by the ROC analysis for uric acid, hemoglobin, log BNP, and peak $VO_2$ were 7.12 mg/dL (sensitivity: 0.625; specificity: 0.550; AUC: 0.602), 12.1 g/dL (sensitivity: 0.600; specificity: 0.650; AUC: 0.650), 5.45 (sensitivity 0.667; specificity 0.620; AUC: 0.679), and 13.5 mL/kg/minute (sensitivity: 0.775; specificity: 0.629; AUC: 0.773), respectively. In Kaplan-Meier analysis, patients with higher uric acid (≥ 7.12 mg/dL) had significantly higher cardiac event rates than those with lower uric acid (< 7.12 mg/dL) as demonstrated in Figure 3A. Compared with patients with Hb > 12.1 g/dL, patients with Hb < 12.1 g/dL had significantly higher cardiac events by Kaplan-Meier analysis (Figure 3B). Patients with higher log BNP (≥ 5.45) had significantly higher cardiac event rates as shown in Figure 3C. Patients with peak $VO_2$ ≤ 13.5 mL/kg/minute had significantly higher cardiac event rates than patients with peak $VO_2$ > 13.5 mL/kg/minute (Figure 3D).

## Discussion

In the present study, cardiac event rates were significantly higher in the CKD group than in the non-CKD group as previously reported. In the non-CKD group, Cox proportional hazard regression analysis demonstrated that body mass index, log BNP, LAD, and peak $VO_2$ were independent parameters for predicting cardiac events. In contrast, uric acid, hemoglobin, log BNP, and peak $VO_2$ were independent prognostic factors in the CKD group.

**Impact of plasma BNP level and exercise capacity in CHF:** Plasma BNP levels and peak $VO_2$ are well known strong prognostic factors in CHF.[9-11] In the present study, plasma BNP levels and peak $VO_2$ were independent prognostic factors in both the CKD and non-CKD groups. However, it has been shown that the plasma BNP level is affected by many factors that include age, gender, body mass index, cardiac hypertro-

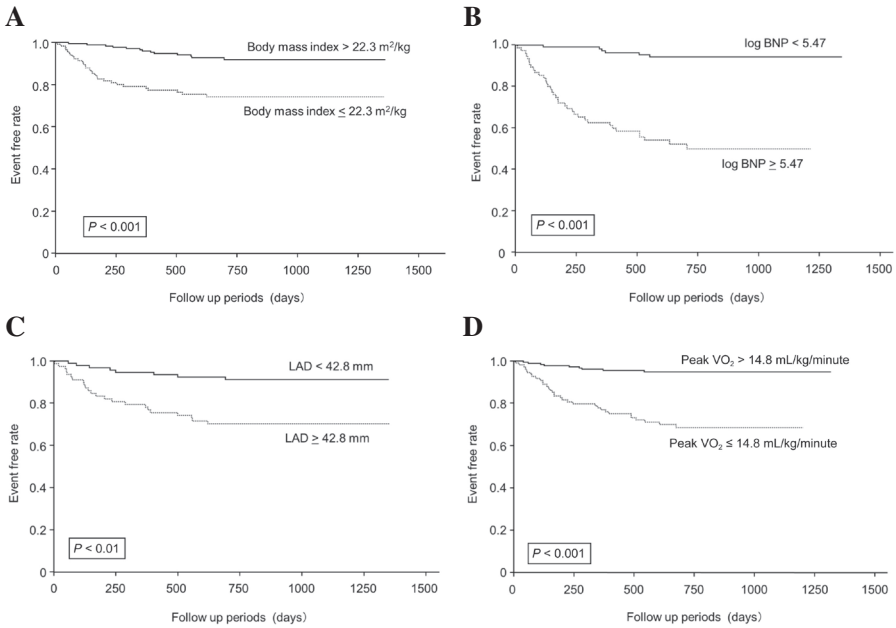


**Figure 2.** Comparisons of event free rates by body mass index (**A**), log BNP (**B**), LAD (**C**), and peak $VO_2$ (**D**) with Kaplan-Meier survival analysis in patients without CKD. Cut-off values were determined by ROC analysis. Event free curves were compared using a log-rank test.

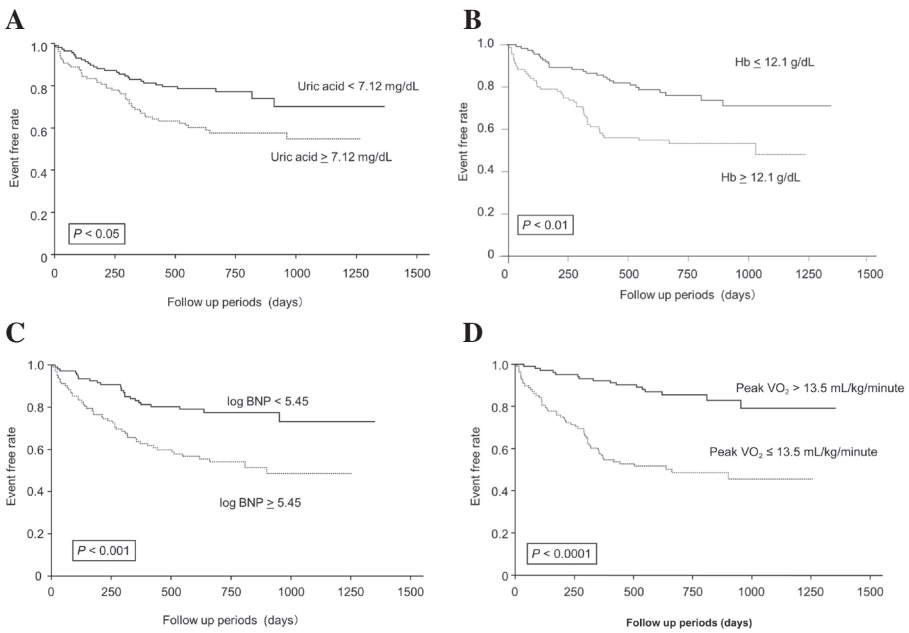


**Figure 3.** Comparisons of event free rates by uric acid (**A**), hemoglobin (**B**), log BNP (**C**), and peak $VO_2$ (**D**) with Kaplan-Meier survival analysis in patients with CKD. Cut-off values were determined by ROC analysis. Event free curves were compared using a log-rank test.

phy, and renal function, in addition to cardiac overload and dysfunction. Decreased clearance of BNP from the kidney has been found to affect plasma BNP levels to a lesser extent than NT-pro BNP in CHF patients with renal dysfunction.[12] Therefore, we should pay attention when interpreting plasma BNP levels in CHF patients with CKD.

In the present study, peak $VO_2$ similarly showed important prognostic values in both groups. These findings suggested that peak $VO_2$ may be an important factor for predicting cardiac events in both CHF and CKD.

**Distinct prognostic factors between CHF patients with and without CKD:** It is now widely accepted that CHF and CKD share a number of common risk factors and pathophysiological pathways such as activation of the renin-angiotensin- aldoster-

one system, sympathetic nervous system, inflammation, oxidative stress.[4] Also, recent studies have demonstrated that CKD increases the risk of cardiovascular events.[3] In CHF, a high incidence of renal dysfunction has been reported, and impaired renal function is a strong predictor of mortality.[13] These findings indicate that CHF and CKD were each capable of causing or worsening the other. They form a vicious linkage that can lead to their progression, supporting the concept of the cardiorenal syndrome.[14] In this study, prognostic factors were different between CHF patients with and without CKD. Therefore, we should consider these data when managing CHF patients with CKD.

Hemoglobin was an independent prognostic factor of cardiac events in CHF and CKD in the present study. Lower hemoglobin concentration is reported to be associated with increased mortality in patients with CHF.[15] In addition, worsening renal function leads to lower hemoglobin concentration.[16] Anemia, CHF and CKD are each capable of causing or worsening each other, and form a vicious circle which can result in progressive them?? (cardio-renal anemia syndrome).[17]

In the present study, uric acid level was an independent prognostic factor of cardiac events in CHF patients with CKD. It has been shown that high levels of uric acid are associated with mortality in CHF.[18] Moreover, serum uric acid is an index of impaired oxidative metabolism in CHF. In CHF patients, hyperuricemia is explained by not only renal function and diuretic use, but also by activation of xanthine oxidase.[19] On the other hand, hyperuricemia independently worsens renal function in normal subjects. Renal urate anion exchanger regulates the blood urate level.[20] Xanthine oxidase activity and impaired renal excretion lead to high serum uric acid levels in CHF and CKD. It has been reported that therapeutic interventions with xanthine oxidase inhibitors like allopurinol lead to a favorable clinical outcome.[21]

BMI has been reported to be an independent risk factor for mortality in CHF.[22] However, in the present study, BMI was an independent predictor related to cardiac events in the non-CKD group, but not in the CKD group. One possible reason for this may be that patients with CKD developed fluid overload in early phase,[23] and fluid accumulation and wasting possibly coexisted in the CKD group.

**Study limitations:** This study was performed in a single center, and may not reflect the general population of patients with CHF and CKD. All subjects underwent cardiopulmonary exercise testing, and CHF patients who could not perform exercise testing were excluded. Therefore, the subjects in this study were from a relatively younger population and had preserved exercise tolerance, and thus cardiac event rates might be lower than previous studies, including those with exercise intolerance. In addition, our conclusions might not be totally applicable to patients with poor renal function as patients with end-stage renal disease were excluded.

**Conclusions:** Peak $VO_2$ and plasma BNP levels were independent factors for predicting cardiac events in both the CKD and non-CKD groups. However, LAD and body mass index were independent prognostic factors in the non-CKD group, but not in the CKD group. On the other hand, levels of uric acid and hemoglobin were prognostic factors related to cardiac events in the CKD group, but not in the non-CKD group. Therefore, we should take these discrepancies into consideration when managing CHF patients with CKD.

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