

Relationship between serum brain natriuretic peptide and heart function in patients with chronic kidney disease

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Background/Aims: Brain natriuretic peptide (BNP) levels are known to be elevated in patients with chronic kidney disease (CKD) and normal heart function. Therefore, the present study was performed to examine the effectiveness of BNP level in diagnosing heart failure in patients with CKD and to determine its effects on survival rate and prognosis.

Method: A total of 182 patients with CKD who visited the hospital due to dyspnea of NYHA class II were included in the study. BNP levels were measured and echocardiography was performed to divide the subjects into groups with and without heart failure. Their BNP levels, clinical courses, and survival rates were analyzed retrospectively.

Results: When BNP level was ≥ 858.5 pg/mL in CKD patients, heart failure could be diagnosed with sensitivity and specificity of 77% and 72%, respectively. Survival rate of the group with BNP levels of ≥ 858.8 pg/mL was significantly lower than that of the group with BNP level below this threshold ($p=0.012$) and multivariate analysis showed that BNP level, age, and sex affected survival rate in the group with BNP level ≥ 858.8 pg/mL.

Conclusions: BNP levels of patients with CKD showed a positive correlation with creatinine levels, and the critical point of BNP level for diagnosis of heart failure was 858.5 pg/mL. As the survival rate in patients with BNP level above the critical point was significantly low, this level was a useful indicator for predicting their prognosis. Care should be taken in interpreting BNP level because patients with stage 5 CKD may show a high concentration of BNP without heart failure.

Key Words: Brain natriuretic peptide; Congestive heart failure; Chronic kidney disease

INTRODUCTION

Heart failure and coronary artery disease are major causes of death in patients with chronic kidney disease (CKD)¹⁾. Measurement of serum level of brain natriuretic peptide (BNP) is helpful for diagnosis and treatment of heart failure in patients with normal kidney function²⁾ and is known to be a useful test for the differential diagnosis of the concurrent presence of heart failure in patients visiting emergency care centers with the chief

complaint of respiratory distress³⁾. However, as the synthesis of BNP is increased within myocardial cells and BNP clearance in the kidney is decreased due to the increased water content in the body in patients with impaired renal function, the concentration of serum BNP is elevated in comparison to patients with normal kidney function. Therefore, different criteria must be applied in subjects with impaired vs. normal renal function^{4, 5)}. It is also necessary to examine whether the concentration of serum BNP affects the survival and prognosis in patients with CKD in

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the same manner as in normal controls.

The present study was performed to examine the usefulness of serum BNP concentration in the diagnosis of heart failure and to determine its effects on the survival and prognosis in patients with impaired kidney function.

MATERIALS AND METHODS

Patients

Serum BNP concentration was measured and echocardiography was performed in 182 patients with a ≥ 6 -month history of impaired renal function (glomerular filtration rate [GFR] < 60 mL/min/1.73 m²) who had been diagnosed with CKD. The patients were recruited when they visited the Department of Internal Medicine (Division of Nephrology) between May 2001 and May 2006, with a chief complaint of respiratory distress greater than New York Heart Association (NYHA) class II. A retrospective analysis was performed. The patient diagnoses included 59 cases of CKD stage III, 52 cases of CKD stage IV, and 71 cases of CKD stage V, of whom 38 and 23 were undergoing hemodialysis and peritoneal dialysis, respectively (Figure 1).

Methods

The following laboratory tests were performed: body index, ECG, chest radiography, arterial blood gas analysis, serum electrolyte, complete blood cell count, and serum chemistry for renal and hepatic function tests. Measurement of BNP level was performed at the time of initial outpatient visit for patients with CKD who were not undergoing dialysis. Measurements were performed prior to dialysis because the serum BNP concentration was reported to be elevated prior to and to decrease following dialysis as a result of the removal of fluids in dialysis patients^{12, 13}. Blood samples of 3-5 mL were collected in test tubes containing a minimal amount of EDTA and centrifuged; the serum was isolated. Quantitative measurements were obtained by immunofluorescence labeling using a BNP kit (Triage[®]; Biosite, San Diego, CA, USA), with upper and lower limits of detection of 5,000 pg/mL and 5 pg/mL, respectively.

Echocardiography was performed during the hospitalization period. On M-mode test, the left ventricular diameter and ejection fraction at both end-diastole and end-systole were measured. The relaxation function was evaluated by Doppler ultrasonography. Renal function was assessed based on creatinine clearance (Ccr) in 24-h urinalysis. In accordance with the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, patients were classified as CKD stage III (Ccr 30-59 mL/min/1.73 m²), CKD stage IV (Ccr 15-29 mL/min/1.73 m²), and CKD stage V (Ccr < 15 mL/min/1.73 m² or patients

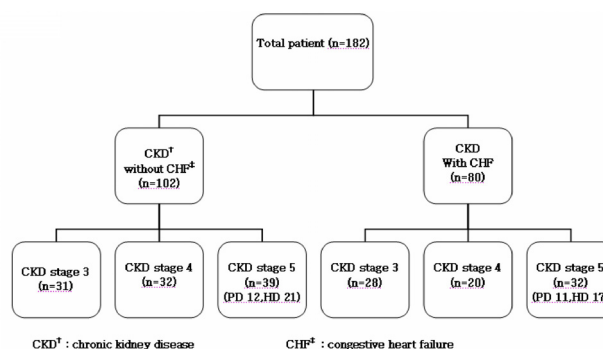


Figure 1. The classification of all patients.

undergoing renal replacement therapy). Diagnostic criteria for heart failure were based on history, radiological findings, and echocardiographic findings, which included clinical symptoms fulfilling Framingham's criteria, left ventricular ejection fraction of less than 50% on echocardiography, and left ventricular diameter at end-diastole greater than 5.5 cm. Patients with past histories of chronic obstructive pulmonary disease, liver cirrhosis, malignant tumor, or multiple trauma were excluded from the present analysis. A follow-up study was performed based on hospitalization records, medical records, and telephone interview to confirm whether any of the patients had died. For analysis of patient survival, considering death as the final event, all cases in which transfer or loss to follow-up occurred were treated as having dropped out of the study. The total patient population was divided into two groups: those with impaired and those with normal heart function. The serum BNP concentration, serological and hematological findings, clinical manifestations, concurrent diseases, and echocardiographic findings were compared between the two groups, and the correlations between serum BNP concentration and other echocardiographic findings were also analyzed. Based on these findings, a retrospective analysis was performed for the factors associated with clinical course and patient survival.

Statistical analysis

Statistical analyses were performed using SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA). All data are expressed as means \pm standard deviation (mean \pm SD). Student's *t*-test and the χ^2 test were used for comparison of continuous and discontinuous variables, respectively, between the two groups. Multiple logistic regression analysis was performed to identify the correlations between the parameters associated with heart failure. Simple linear regression analysis was performed to identify the correlation between serum BNP concentration and renal function. An inter-group comparison of the correlation between the serum BNP concentration and echocardiographic findings was performed. To confirm the accuracy of measure-

Table 1. Basic characteristics and clinical findings of patients

Variable	Total (n=182)	CRF [†] with CHF [‡] (n=80)	CRF without CHF (n=102)	<i>p</i> value
Age	60.3±13.4	60±15	60±12	NS
BMI [†]	22.9±3.3	22.3±3.1	23.2±3.4	NS
Systolic BP	150.2±22.6	146±20.9	152.3±23.2	NS
Diastolic BP	87.8±13.5	87.2±13.5	88.1±13.5	NS
LVH in EKG	79 (43%)	29 (36%)	50 (49%)	NS
Cardiomegaly on X-ray	84 (46%)	47 (59%)	37 (36%)	0.0001
Pulmonary congestion on X-ray	71 (39%)	42 (53%)	29 (28%)	0.001
Survival duration (month)	50.3±35.6	35.8±28.1	51.6±32.1	0.026

CRF[†], chronic renal failure; CHF[‡], congestive heart failure; BMI[†], body mass index

ment of BNP level in diagnosis of heart failure in patients with renal failure, receiver operating characteristic (ROC) curve analysis was performed. The cut-off value was defined as the value with the highest sensitivity and specificity on the ROC curve. Patients were also divided into two groups based on whether BNP level was above or below the cut-off value. In these two groups, analysis of patient survival was performed using the Kaplan-Meier method. Statistical significance was set at $p < 0.05$.

RESULTS

Patient characteristics.

A total of 182 patients, including 99 men and 83 women with a mean age of 60 ± 13 years, were included in the present study. Patients were divided into two groups based on the presence or absence of heart failure: the heart failure group ($n=80$) and the normal heart function group ($n=102$). Mean age was 60 ± 15 years in the heart failure group and 60 ± 12 years in the normal heart function group; this age difference was not statistically significant. Underlying diseases for heart failure included 41 cases of hypertension (51%), 27 cases of ischemic heart disease (33%), ten cases of dilated cardiomyopathy (12%), and two cases of valvular heart disease (4%). In the heart failure group, underlying diseases for ischemic heart disease included 19 cases of stable angina (70%), four cases of ischemic heart failure (15%), three cases of acute myocardial infarction (11%), and one case of unstable angina (4%). The most prevalent cause of kidney disease was diabetic nephropathy (97 cases, 54%), followed by hypertensive nephropathy (64 cases, 35%), glomerulonephritis (15 cases, 8%), polycystic kidney disease (two cases, 1%), and idiopathic causes (four cases, 2%). In the heart failure group, the causes of renal disease included 41 cases of diabetic nephropathy (51%), 28 cases of hypertensive nephropathy (34%), and seven cases of glomerulonephritis (9%). In the normal heart function group, the causes of renal disease

included 56 cases of diabetic nephropathy (55%), 36 cases of hypertensive nephropathy (35%), and eight cases of glomerulonephritis (7%). Thus, diabetic nephropathy was the most prevalent cause of renal disease in both groups. Twenty-eight (35%), 20 (25%), and 32 (40%) patients in the heart failure group, and 31 (30%), 32 (31%), and 39 (39%) patients in the normal heart function group had stage 3, stage 4, and stage 5 CKD, respectively (Figure 1).

Vital signs and clinical symptoms (Table 1)

In the total patient population, mean systolic blood pressure was 150.2 ± 22.6 mmHg and mean diastolic blood pressure was 87.8 ± 13.5 mmHg. There were no significant differences in systolic or diastolic pressure between the heart failure and normal heart function groups (146 ± 20.9 mmHg vs. 152.3 ± 23.2 mmHg, $p=0.078$, and 87.2 ± 13.5 mmHg vs. 88.1 ± 13.5 mmHg, $p=0.684$, respectively). The difference in number of patients with left ventricular hypertrophy on ECG between the heart failure and normal heart function groups was not significant (29 vs. 50, respectively, $p=0.375$). Plain chest radiography findings suggestive of pulmonary edema were observed in 42 patients in the heart failure group and in 29 patients in the normal heart function group; this difference was significant ($p=0.001$). In addition, findings suggestive of cardiac hypertrophy were observed in 47 patients in the heart failure group and in 37 patients in the normal heart function group; this difference was significant ($p=0.0001$).

Laboratory findings (Table 2)

Mean hemoglobin level in the total patient population was 10.2 ± 5.5 g/dL. It was 9.9 ± 1.9 g/dL in the heart failure group and 10.4 ± 6.7 g/dL in the normal heart function group; this difference was not statistically significant ($p=0.533$). On liver function test, there were no significant differences in the mean levels of the following parameters between the heart failure group and the normal heart group, respectively: total protein (6.4 ± 0.9 g/dL; 6.2 ± 1.0 vs. 6.5 ± 0.9 g/dL, $p=0.257$); total

Table 2. Laboratory findings of patients

Variable	Total (n=182)	CRF with CHF (n=80)	CRF without CHF (n=102)	<i>p</i> value
Hb* (g/dL)	10.2±5.5	9.9±1.9	10.4±6.7	NS
Hct† (%)	29.2±5.3	29.1±5.2	29.4±5.5	NS
Protein (g/dL)	6.4±0.9	6.2±1.0	6.5±0.9	NS
Albumin (g/dL)	3.3±0.6	3.2±0.7	3.4±0.6	NS
Cholesterol (mg/dL)	166.1±50.1	167.2±52.3	165.5±49.1	NS
AST (U/L)	33.2±97.9	38.6±12.8	23.1±12.9	NS
ALT (U/L)	26.8±68.6	31.1±24.3	18.9±16.2	NS
Calcium (mg/dL)	9.3±2.3	8.85±1.1	10.1±9.4	NS
Phosphate (mg/dL)	5.6±6.8	5.2±3.5	6.4±10.5	NS
Sodium (mmol/L)	135.2±12.2	133.7±15.1	136.0±3.9	NS
Potassium (mmol/L)	4.5±0.9	4.6±0.9	4.5±0.9	NS
BUN (mg/dL)	54.5±28.7	57.1±31.6	53.0±26.9	NS
Creatinine (mg/dL)	6.2±3.8	5.9±4.0	6.3±3.75	NS
Residual Ccr (ml/min)	33.0±12.6	33.7±12.8	32.6±12.5	NS
CK‡ (U/L)	133.7±172.6	174.4±259.3	111.4±91.6	0.023
LDH§ (U/L)	284.1±114.5	291.0±105.7	280.3±119.3	NS
CKMB (ng/mL)	7.1±19.4	7.9±15.1	6.0±28.8	NS
Troponin-I (ng/mL)	1.2±2.1	2.1±7.2	0.4±1.7	0.014
CRP (mg/dL)	2.7±4.8	2.9±5.6	2.3±3.2	NS
BNP¶ (pg/mL)	1,667.5±1,914.2	3,003.6±1,967.1	942.9±1,441.8	0.0001

Hb*, hemoglobin; Hct†, hematocrit; CK‡, creatine kinase; LDH§, lactate dehydrogenase; CRP||, C-reactive protein; BNP¶, brain natriuretic peptide

albumin (3.3±0.6 g/dL; 3.2±0.7 vs. 3.4±0.6 g/dL, $p=0.082$); total cholesterol (166.1±50.1 mg/dL; 167.2±52.3 vs. 165.5±49.1 mg/dL, $p=0.827$); and triglyceride (141.7±79.6 mg/dL; 134.8±81.5 vs. 145.6±78.6 mg/dL, $p=0.395$). On kidney function test, there were no significant differences between the heart failure group and the normal heart group, respectively, in the mean levels of BUN (54.5±28.7 mg/dL; 57.1±31.6 vs. 53.1±26.9 mg/dL, $p=0.388$) or creatinine (6.2±3.8 mg/dL; 5.9±4.0 vs. 6.3±3.7 mg/dL, $p=0.543$). Furthermore, the mean serum electrolyte concentrations were as follows for the heart failure group and the normal heart group, respectively: Na⁺, 135.2±12.2 mmol/L; K⁺, 4.5±0.9 mmol/L; Cl⁻, 104.3±6.4 mmol/L; Ca²⁺, 9.3±2.3 mmol/L; and PO₄³⁻, 5.6±6.8 mmol/L. There were no significant differences in these values between the two groups. Mean concentration of serum BNP was 1,667.4±1,914.1 pg/mL, and this parameter showed a significant difference between the heart failure group and the normal heart group, respectively (3,003.5±1,967.1 pg/mL vs. 942.8±1,441.8 pg/mL, $p=0.0001$). The overall glomerular filtration rate (GFR) was 33.1±12.6 mL/min on average, and was not significantly different between the heart failure group and the normal heart group, respectively (33.7±12.8 mL/min vs. 32.6±12.5 mL/min, $p=0.584$).

Other concurrent diseases

Cerebral infarction and stroke were concurrently present in eight patients in the heart failure group and in 18 patients in the

normal heart function group. However, this difference was not significant ($p=0.612$). Cardiac arrhythmia was more prevalent in the heart failure group (five cases) than in the normal heart function group (two cases) ($p=0.032$). Peripheral vascular occlusive diseases were concurrently present in two patients in each groups, but this difference was not significant ($p=0.536$). Thirty-seven patients in the heart failure group and 59 patients in the normal heart function group had a history of smoking; this difference was not significant ($p=0.341$). Thirty-five and 55 patients in the heart failure group and the normal heart function group, respectively, had a past history of alcoholism; this difference was not significant ($p=0.298$).

Drug use history

Nitrate drugs were administered to 38 patients in the heart failure group and 33 patients in the normal heart function group. The difference between the two groups was not significant ($p=0.229$). Angiotensin converting enzyme inhibitor (ACE-I) was administered to 65 patients in the heart failure group and 78 patients in the normal heart function group, and the difference between the two groups was not significant ($p=0.344$). Angiotensin receptor blocker (ARB) was administered to 41 patients in the heart failure group and 45 patients in the normal heart function group, and the difference was not significant ($p=0.873$). Both beta blockers and diuretics were administered at significantly higher frequencies in the heart failure group than in the normal heart function group (63 vs. 57 patients, $p=0.017$,

Table 3. Echocardiographic findings of patients.

Variable	Total (n=182)	CRF with CHF (n=80)	CRF without CHF (n=102)	<i>p</i> value
Ejection fraction	56.0±15.6	39.5±10.4	59.3±8.8	0.001
LVMl ¹	166.7±48.9	186.5±46.2	166.1±50.7	0.04
IVSd ²	1.15±0.26	1.04±0.2	1.2±0.2	0.001
LVDs ³	3.89±0.97	4.7±0.8	3.4±0.6	0.002
LVDd ⁴	5.58±0.74	5.9±0.7	5.3±0.6	0.001
PWDd ⁵	1.14±0.26	1.04±0.3	1.2±0.1	0.002
LA ⁶	4.88±0.63	4.9±0.6	4.8±0.5	NS
DT ⁷	198.2±60.6	159±49.9	220.9±54.8	0.002
Pericardial effusion	63 (35%)	31 (39%)	32 (31%)	NS
RWMA ⁸	45 (25%)	30 (38%)	15 (15%)	0.001

LVMl¹, left ventricular mass index; IVSd², end diastolic interventricular septum thickness; LVDs³, end-systolic left ventricular diameter; LVDd⁴, end-diastolic left ventricular diameter; PWDd⁵, end-diastolic posterior wall thickness; LA⁶, left atrium; DT⁷, deceleration time; RWMA⁸, regional wall motion abnormality

and 67 vs. 48, *p*=0.003, respectively).

Echocardiography (Table 3)

On echocardiography, mean overall ejection fraction (EF) in the total study population was 56.0±15.6%; the value was significantly lower in the heart failure group than in the normal heart function group (39.5±10.4% vs. 59.3±8.8%, respectively, *p*=0.00). Mean overall left ventricular mass index (LVMl) in the total study population was 176.6±48.9 g/m², and the value was significantly higher in the heart failure group than in the normal heart function group (186.5±46.2 vs. 166.1±50.7 g/m², respectively, *p*=0.04). Mean overall left ventricular end-systolic diameter (LVESD) was 3.8±0.9 mm (4.7±0.8 vs. 3.4±0.6 mm); mean overall left ventricular end-diastolic diameter (LVEDD) mm was 5.5±0.7 mm (5.9±0.7 vs. 5.3±0.6 mm); mean overall left ventricular interseptal thickness at end-systole was 1.1±0.2 mm (1.0±0.2 vs. 1.2±0.2 mm); and mean overall left ventricular posterior wall thickness at end-diastole was 1.1±0.2 mm (1.0±0.2 vs. 1.2±0.2 mm). The differences in these parameters between the two groups were all statistically significant (*p*=0.00). Mean overall fractional shortening (FS) was 31.8±10.3%, and was significantly lower in the heart failure group than in the normal heart function group (20.9±6.6 vs. 37.5±6.7%, *p*=0.00). Local motor disturbances were more prevalent in the heart failure group than in the normal heart function group (30 vs. 15 cases, respectively, *p*=0.00). The numbers of cases in which pericardial effusion was classified as "mild" or "severe" were 28 and 3 in the heart failure group and 28 and 4 in the normal heart function group, respectively; these differences were not statistically significant (*p*=0.542).

Causes of death

Of the total of 80 patients in the heart failure group, 38 had died, six were lost to follow-up, and 36 were currently being

followed-up at the Outpatient Clinic of the Department of Nephrology. Of the total of 102 patients in the normal heart function group, 31 had died, eight were lost to follow-up, and 63 were currently being followed-up at the Outpatient Clinic of the Department of Nephrology. The most prevalent cause of death was cardiovascular disease, accounting for 30 deaths in the total study population (26 vs. 4 cases in the heart failure and normal heart function groups, respectively). This was followed by 14 cases of sepsis (3 vs. 11 cases), 11 of idiopathic causes (3 vs. 8 cases), six cases of cachexia (all in the normal cardiac function group), five cases of stroke or cerebrovascular hemorrhage (4 vs. 1 case), one case of gastrointestinal bleeding (in the normal heart function group), and one case of malignant tumor (in the heart failure group).

Correlation between renal function and serum BNP concentration (Figure 2)

(1) Difference in serum BNP concentration between the two groups in patients with CKD stage 3

The serum BNP concentration was 205.7±273.4 pg/mL in the normal heart function group and 1,618.4±1,237.7 pg/mL in the heart failure group. Thus, it was significantly elevated in the heart failure group (*p*=0.004).

(2) Difference in serum BNP concentration between the two groups in patients with CKD stage 4

The serum BNP concentration was 284.0±435.6 pg/mL in the normal heart function group and 2,713.0±2,023.3 pg/mL in the heart failure group. Thus, it was significantly elevated in the heart failure group (*p*=0.000).

(3) Difference in serum BNP concentration between the two groups in patients with CKD stage 5

The serum BNP concentration was 1,275.3±1,634.5 pg/mL

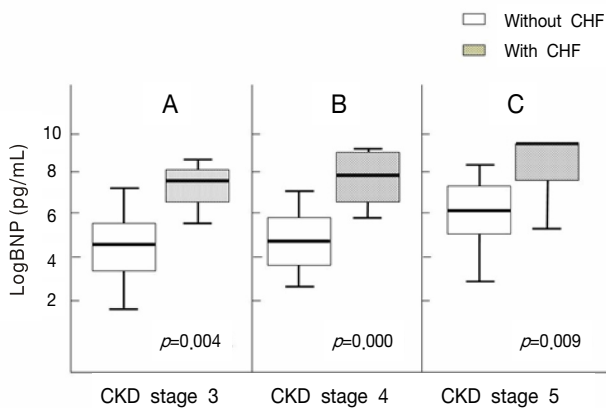


Figure 2. Box plot of serum BNP levels in CKD stage 3 (A), CKD stage 4 (B), and stage 5 (C) according to heart function.

in the normal heart function group and $3,519.1 \pm 1,935.8$ pg/mL in the heart failure group. Thus, it was significantly elevated in the heart failure group ($p=0.009$).

(4) Serum BNP concentration depending on hemodialysis

A comparison of BNP level depending on hemodialysis was performed in all patients with renal failure, without considering heart function. The results indicated BNP levels of $2,008.4 \pm 2,036.1$ pg/mL and $1,319.0 \pm 1,723.3$ pg/mL in patients who were and who were not receiving hemodialysis, respectively ($p=0.015$).

(5) Difference in serum BNP concentration depending on CKD stage in the normal heart function group

In patients in the normal heart function group with chronic

renal failure, the concentrations of serum BNP at CKD stages 3, 4, and 5 were 205 ± 273.4 , 284 ± 435.6 , and $1,275 \pm 1,634.5$ pg/mL, respectively. There was no significant difference between CKD stage 3 and stage 4. However the differences between CKD stage 4 and stage 5 and between CKD stage 3 and stage 5 were significant ($p=0.018$ and $p=0.006$, respectively).

(6) Difference in serum BNP concentration depending on CKD stage in the heart failure group

In patients in the heart failure group with chronic renal failure, the concentrations of serum BNP at CKD stages 3, 4, and 5 were $1,618 \pm 1,237.7$, $2,713 \pm 2,023.3$, and $3,519 \pm 1,935.8$ pg/mL, respectively. There were no significant differences between CKD stage 3 and stage 4 or between CKD stage 4 and 5. However, the difference between CKD stage 3 and stage 5 was significant ($p=0.011$).

Correlations between serum BNP concentration and other parameters (Figure 3)

(1) Correlation between serum BNP concentration and left ventricular ejection fraction on echocardiography

There was a significant inverse correlation between serum BNP concentration and left ventricular ejection fraction in patients with CKD ($R^2=0.172$, $p=0.001$).

(2) Correlation between serum BNP concentration and patient survival

There was a significant inverse correlation between serum BNP concentration and survival in patients with CKD ($R^2=0.099$, $p=0.012$).

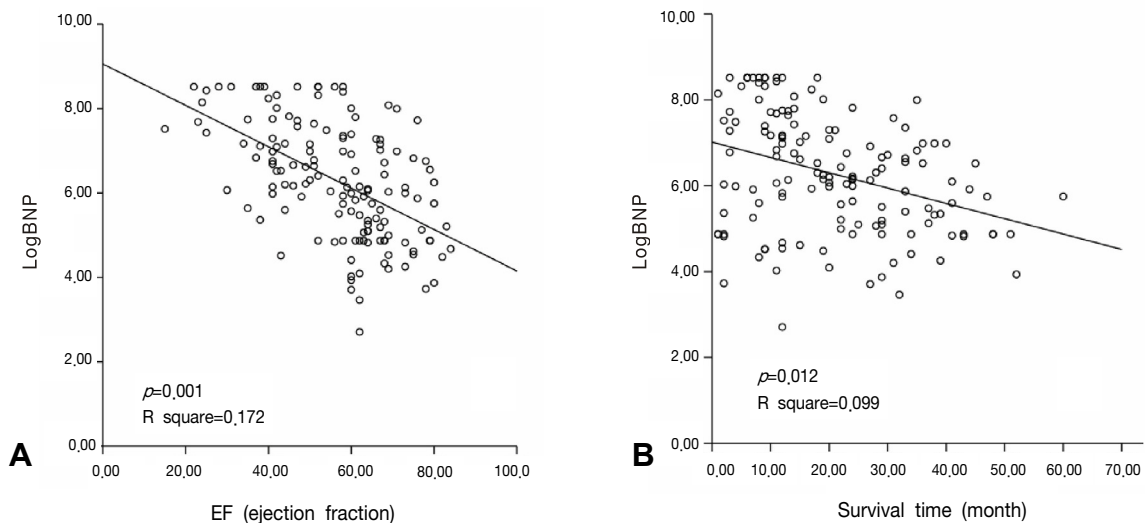


Figure 3. Scatter plots of log BNP with ejection fraction (A) and duration of survival (B).

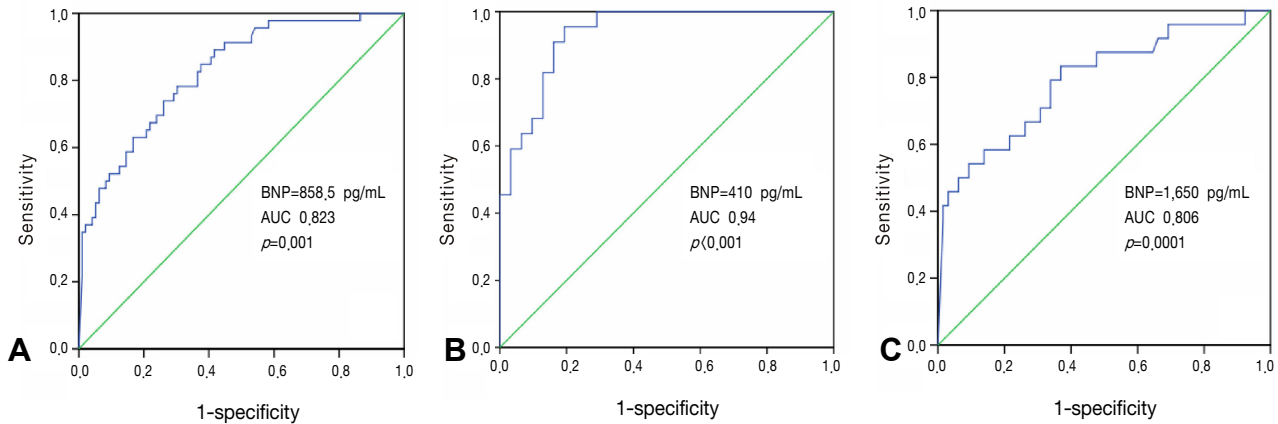


Figure 4. The accuracy and reference value of serum BNP for diagnosing CHF in all patients (A), in CKD stage 3-4 (B), and CKD stage 5 (C) by ROC curve.

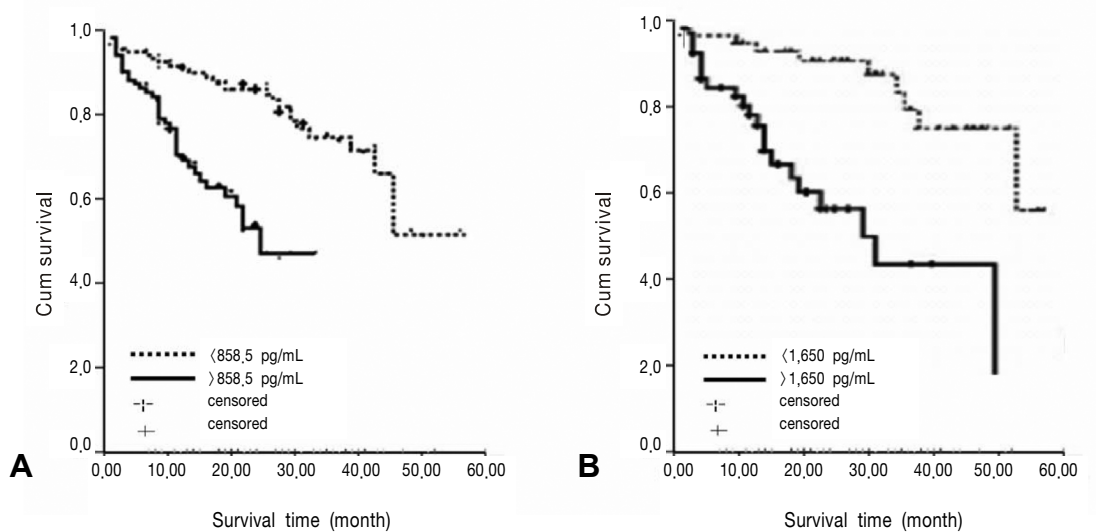


Figure 5. The cumulative survival rate using Kaplan-Meier method in patients with CKD stage 3-5 (A) and with renal replacement treatment (B) classified according to serum BNP level.

(3) Correlation between serum BNP concentration and LVMI on echocardiography

There was a significant positive correlation between serum BNP concentration and LVMI in patients with CKD ($R^2=0.205$, $p=0.002$).

Diagnostic value of BNP level in detecting heart failure in patients with renal failure (Figure 4)

(1) ROC curve of total patient population

In the total patient population, when BNP level was 858.5 pg/mL and the area under the curve (AUC) was 0.823, a diagnosis of heart failure was made with sensitivity of 77% and specificity of 72%.

(2) ROC curve of patients with CKD stages 3 or 4

In patients with CKD stages 3 or 4, when BNP level was 410 pg/mL and the AUC was 0.94, a diagnosis of heart failure was made with sensitivity of 82% and specificity of 90%.

(3) ROC curve of patients with CKD stage 5

In patients with CKD stage 5, when BNP level was 1,650 pg/mL and the AUC was 0.806, a diagnosis of heart failure was made with sensitivity of 74% and specificity of 76%.

Analysis of patient survival (Figure 5)

(1) In all patients (CKD stage 3-5), patient survival was significantly lower in the group with BNP level higher than 858.8 pg/mL ($p=0.012$).

Table 4. Multivariable analysis of risk factors for CHF

Variable	BNP > 858.5 pg/mL				BNP < 858.5 pg/mL			
	H.R. (Exp B)	ρ value	CI [†] (95%)		H.R. (Exp B)	ρ value	CI (95%)	
			lower	upper			lower	upper
BNP	1,001	0,017	0,999	1,004	1,000	0,334	1,000	1,000
Age	1,025	0,022	1,001	1,051	1,032	0,035	1,001	1,065
Sex	1,198	0,630	0,579	2,463	1,334	0,478	0,601	2,961
DM [‡]	1,225	0,623	0,545	2,750	0,781	0,425	0,427	1,434
Albumin (g/dL)	0,581	0,051	0,337	1,003	0,489	0,035	0,251	0,950
LVMl [§] (g/m ²)	0,996	0,259	0,989	1,003	0,988	0,107	0,974	1,002
Residual CCr (mL/min)	1,004	0,758	0,979	1,030	0,986	0,388	0,954	1,019
EF [¶] (%)	0,978	0,263	0,942	1,017	0,886	0,631	0,841	1,262

DM[‡], diabetes mellitus; LVMl[§], left ventricular mass index; CCr^{||}, creatinine clearance; EF[¶], ejection fraction

(2) In patients who underwent renal replacement therapy, survival analysis showed that patient survival was significantly lower in the group with BNP level higher than 1,650 pg/mL ($\rho=0,004$).

Multivariate analysis (Table 4)

In all patients, group assignment was made based on the cut-off value of BNP level of 858.5 pg/mL obtained from the ROC curve. Multivariate analysis was performed to identify the independent factors affecting patient survival in each group. In the group with BNP level exceeding 858.5 pg/mL, the factors associated with patient survival included BNP level and age. In this group, however, sex, diabetes mellitus, left ventricular mass index, left ventricular ejection fraction, and residual renal function were not independent factors affecting patient survival. In the group with BNP level less than 858.5 pg/mL, the factors associated with patient survival were age and albumin level. In this group, however, other parameters were not independent factors affecting patient survival.

DISCUSSION

In patients visiting the outpatient clinic with a chief complaint of respiratory distress, it is critical to determine whether the etiology is of cardiogenic or non-cardiogenic origin to decide on an appropriate treatment plan and to estimate prognosis. Respiratory distress symptoms are of nonspecific origin, which cannot be differentially diagnosed based on an interview or routine laboratory tests. Echocardiography is costly and requires highly trained personnel. Accordingly, simplified methods have been developed for measurement of serum BNP concentration and their use has become widespread in the assessment of cardiac function^{6,7}. BNP is a peptide hormone that is secreted in response to muscular relaxation in the left ventricle and is converted to two biologically active forms: c-BNP and N-

terminal pro-BNP. N-terminal pro-BNP has a longer half-life and is more biologically stable than c-BNP, and it has greater clinical significance⁹. Recent studies have shown that these natriuretic peptides accurately indicate the treatment response and prognosis as well as fulfill the requirements for a diagnosis of heart failure⁹.

Left ventricular hypertrophy and left ventricular dysfunction are present concurrently in 60-80% and approximately 15% of patients with CKD, respectively. A number of studies have been performed to examine the diagnostic value of BNP level in detecting cardiogenic respiratory distress¹⁰. In some studies, the serum BNP concentration was not increased in comparison to the normal value in patients with chronic renal diseases who had normal kidney function and showed no left ventricular hypertrophy on echocardiography⁵. According to most of these studies, however, the volume of water content was elevated and renal clearance of BNP was decreased in patients with CKD compared to patients with normal kidney function. It has also been reported that serum BNP concentration is elevated in patients with chronic renal failure compared to those with normal kidney function^{11,12}. However, the serum BNP concentration has also been shown to be associated with left ventricular dysfunction and left ventricular hypertrophy in patients with CKD or end-stage renal disease. Similar to observations in patients with normal kidney function, the serum BNP concentration has been reported to be a prognostic indicator of the occurrence of cardiovascular disease and death in patients with CKD or end-stage renal disease¹³⁻¹⁵.

There is still a great deal of controversy regarding the cut-off value of BNP level in the diagnosis of heart failure in patients with CKD. Only a small number of studies have examined the effects of BNP level on survival rate in these patients. Kim *et al.*⁷ maintained that a diagnosis of cardiac failure could be made with sensitivity and specificity of 77% and 71%, respectively, using a BNP cut-off value of higher than 600 pg/L in patients with chronically impaired kidney function. McCullough *et al.*²

reported that it would be appropriate to apply a diagnostic value of approximately 200 pg/mL in cases with GFR lower than 60 mL/min/1.73 m². Wang et al.¹⁰ noted that a diagnosis of cardiac failure could be made with sensitivity and specificity of 66% and 70%, respectively, using a BNP cut-off value of higher than 829 pg/L in patients with CKD in whom systolic heart failure was absent. According to these authors, when the renal function was classified as moderate renal failure (60)Ccr \geq 30 mL/min), severe renal failure (30)Ccr \geq 15 mL/min) and end-stage renal failure (Ccr $<$ 15 mL/min), comparison of BNP level can be problematic. In cases with concurrent heart failure, however, the serum BNP concentration was significantly elevated in patients with renal failure of corresponding severity (1,183 \pm 1,056, 2,205 \pm 1,470, 3,209 \pm 1,900 pg/mL). In the present study, a diagnosis of heart failure could be made with sensitivity and specificity of 77% and 72%, respectively, in the total CKD patient population when the concentration of serum BNP exceeded 858.5 pg/mL. In comparison with other studies, our figures were relatively high. This may be explained by the fact that McCullough et al. excluded the dialysis group, unlike the present study, and Kim et al. used a BNP upper limit of 2,000 pg/mL (vs. 5,000 pg/mL in the present study). In our series, BNP level depending on the CKD stage was elevated with no relation to cardiac dysfunction in CKD stage 5. This may have been due to the effects of left ventricular hypertrophy, impairment of relaxation function, hemoglobin, albumin, and drugs used in treatment⁴.

There have been many recent studies of the correlations between BNP level, cardiac function, and patient prognosis. Kim et al.⁷ and Takayoshi et al.¹⁴ reported that the concentration of serum BNP was inversely correlated with left ventricle ejection fraction. Nitta et al.¹⁵ reported that the mean serum BNP concentration was higher in hemodialysis patients than in normal healthy subjects, and there was an inverse correlation between the serum BNP concentration and the left ventricular function. The results of the present study also indicated an inverse correlation between the serum BNP concentration and left ventricle ejection fraction on echocardiography. This study also indicated that serum BNP concentration shows an inverse correlation with patient survival and a positive correlation with left ventricular mass index (LVMI).

In the present study, the cumulative survival rates were calculated based on the serum BNP concentration, which can be used for diagnosis of heart failure. The results revealed a significant difference in patient survival, indicating that the concentration of serum BNP is a prognostic indicator for prediction of patient survival in patients with chronic renal failure as well as those with normal kidney function. In another study examining the correlation between serum BNP concentration and patient survival in patients with CKD, Yoichi et al.⁵ analyzed the incidence of heart disease in patients with CKD who had normal

heart function. These authors reported significant differences in the incidence of cardiac disease and patient survival based on a BNP cut-off value of 150 pg/mL. Wendy et al.¹² reported that the incidence of heart disease increased and there are significant differences in patient survival based on a cut-off value of 175 pg/mL. Moreover, other studies have also indicated that the serum BNP concentration is a useful indicator for diagnosis of left ventricular hypertrophy or left ventricular dysfunction in hemodialysis patients with CKD. Furthermore, it has also been reported that the serum BNP concentration is a powerful indicator for prediction of prognosis in patients in whom cardiovascular diseases are accompanied by left ventricular hypertrophy or left ventricular dysfunction^{17, 18}.

In the present study, the serum BNP concentration showed a positive correlation with that of serum creatinine in patients with CKD. Here, the cut-off value of BNP level was 858.5 pg/mL. In addition, there were significant differences in serum BNP concentration depending on the presence of heart failure at identical CKD stages. In patients with CKD stage 5, however, the serum BNP concentration was relatively high with no relation to the presence of heart failure, in comparison to those with CKD stage 3 or 4. These results indicate that assessment of cardiac function based on the concentration of serum BNP depending on each CKD stage will be useful for determining prognosis as well as for planning treatment in patients with CKD.

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