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ORIGINAL ARTICLE

N-terminal Pro-brain Natriuretic Peptide Level as a Prognostic Predictor in Elderly Patients in a Convalescent Rehabilitation Ward

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Objective: N-terminal pro-brain natriuretic peptide (NTproBNP) levels were investigated to predict outcomes for elderly patients in a convalescent rehabilitation ward. **Methods:** The study included 75 patients aged at least 75 years who were admitted to the convalescent rehabilitation ward of Naruto-Yamakami Hospital. Based on NTproBNP levels on admission, the patients were divided into those with NTproBNP levels ≥400 pg/ml (Group A) and those with NTproBNP levels <400 pg/ml (Group B). Patients were also divided into three groups according to their outcomes: Group I, death-related discharge or emergency transfer; Group II, home discharge; and Group III, medical/nursing care continuation. Group A patients were further divided, according to the time course of NTproBNP levels, into Group A-I (levels increased) and A-II (levels unchanged/decreased). The correlation coefficients between outcomes and each measurement index were determined, and discriminant analysis was performed among the groups. **Results:** The NTproBNP level on hospitalization was significantly higher in Group I than in Groups II and III. There were significantly more death-related discharges and emergency transfers in Group A than in Group B and in Group A-I than in Group A-II. In discriminant analysis, assuming the outcome to be a dependent variable in Group A-I and Group A-II, the canonical correlation was 0.81 ($P<0.05$). **Conclusion:** The study findings suggest that NTproBNP levels are useful for predicting patient outcomes.

Key Words: convalescent rehabilitation ward; elderly people; NTproBNP; rehabilitation outcome

INTRODUCTION

Patients with orthopedic disorders, cerebrovascular disorders, and disuse atrophy after surgery or pneumonia are frequently admitted to a convalescent rehabilitation ward. Elderly rehabilitation patients often have systemic diseases; therefore, a sudden change in overall status or disease may lead to emergency transfer (ET) or death-related discharge (DD) during the stay in a convalescent rehabilitation ward. These sudden events may create anxiety and subsequent distrust in patients or their families. Consequently, it is important to gather information about patient risk levels and to share the findings with the patient and family in the early hospitalization period.

In planning a rehabilitation program, clinicians predict prognosis and outcome based on patient facility with activities of daily living (ADL), functional status, attributes, comorbidities, and social background.[1–3] However, few studies have examined systemic factors predictive of clinical outcomes. Cardiac activity is a factor that can affect the prognosis of rehabilitation. There is much latent left ventricular dysfunction in elderly patients, in particular. Furthermore, chronic heart failure reportedly exacerbates cerebrovascular disorders, dementia, fractures, and pneumonia and reduces cardiac activity.[4–7] Here, we focused on N-terminal pro-brain natriuretic peptide (NTproBNP), a biomarker used to

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support the diagnosis of heart failure, and examined whether NTproBNP levels could predict clinical and discharge outcomes in elderly patients.

METHODS

Patients

The subjects of this study were 75 patients (24 men, 51 women) aged at least 75 years who were admitted to the convalescent rehabilitation ward of Naruto-Yamakami Hospital between January and December 2016. Serum NTproBNP levels were evaluated within 1 week of hospitalization in all cases, and ≥400 pg/ml was defined as a high level according to the cutoff value identified by the Japanese Heart Failure Society.[8] In patients with high NTproBNP levels, the examination was repeated once a month. Rehabilitation programs were implemented at an intensity equivalent to a Borg scale score of 11–13, and were increased regularly according to patient response.

This study was approved by our institutional review board, and informed consent was obtained from all the patients.

Subgroup Analysis

Figure 1 is a flow chart depicting the grouping of the study patients. Patients were divided into three groups based on their outcomes: Group I, death-related discharge (DD) or emergency transfer (ET) for advanced medical care; Group II, discharge to home or a nursing facility; and Group III, medical/nursing care continuation in special elderly care nursing home or a medical institution for chronic conditions. DD and ET patients were grouped together, with DD being the most severe form of ET; neither DD nor ET patients were able to complete convalescent rehabilitation.

The following parameters were extracted from medical charts as factors that may affect outcomes: serum albumin (Alb) and creatinine (Cr) levels, history of cardiovascular diseases (CVD) such as atrial fibrillation (Af) and ischemic heart disease (IHD), functional independence measure (FIM) scores, age, sex, indication for rehabilitation, and duration of hospitalization.

Based on the initial NTproBNP levels, the patients were also divided into a high-level group (≥400 pg/ml; Group A) and a low-level group (<400 pg/ml; Group B). These groups were compared for each measurement index and patient outcome. Furthermore, we selected the 28 patients from Group A who were hospitalized for >1 month and who underwent blood tests more than once, and divided them into two groups: Group A-I contained the 15 patients with an increase between the initial and final NTproBNP levels and Group A-II contained the 13 patients whose NTproBNP levels stayed the same or decreased.

The characteristics of each measurement index, including patient outcomes, were compared between the two groups. Furthermore, we evaluated the correlation between patient outcomes and each measurement index and conducted multivariate analysis using discriminant analysis. In discriminant analysis, we considered patient outcome to be the dependent factor and the change in logarithm of NTproBNP, the FIM gain, and the final FIM level to be independent factors that were highly correlated with patient outcomes.

Statistical Analysis

We used IBM SPSS Statistics ver. 21 for the statistical analyses and performed tests of normality and homoscedasticity using the chi-squared test, Mann-Whitney U test, Kruskal-Wallis test, Bonferroni test, Welch's *t*-test, one-way analysis of variance, Tukey's test, Student's *t*-test, Spearman's rank correlation coefficient, and multivariate analysis. Values of $P<0.05$ were considered statistically significant. NTproBNP levels were logarithmically converted and tested for stabilization of dispersion.

RESULTS

Patient Characteristics

Table 1 shows the subject characteristics. The average (±SD) age of the 75 patients (24 men, 51 women) was 85.8 ± 5.3 years. The rehabilitation indication was locomotive disease in 41 patients, cerebrovascular disease in 11, and disuse atrophy in 23. The mean hospitalization period was 79.6 ± 40.0 days, the initial FIM score was 55.7 ± 29.4 points, the final FIM score was 66.7 ± 32.9 points, and the FIM gain was 10.4 ± 14.6 points. The mean initial NTproBNP level was 1102.7 ± 1696.6 pg/ml, the initial Alb level was 3.32 ± 0.68 g/dL, the final Alb level was 3.05 ± 0.70 g/dL, the change in Alb was −0.27 ± 0.53 g/dL, and the initial Cr level was 0.71 ± 0.44 mg/dL. Fourteen patients (18.7%) experienced death-related discharge (n=6) or emergency transfer (n=8). The causes of death in the six fatal cases were exacerbation of chronic heart failure in three patients, exacerbation of chronic renal failure in two, and exacerbation of chronic obstructive pulmonary disease in one. None of the eight emergency transfer cases was attributable to heart disease: two patients had hemorrhage of the digestive tract, one had acute cholecystitis, one had threatened rupture of an abdominal aortic aneurysm, one had recurrent cerebral infarction, one

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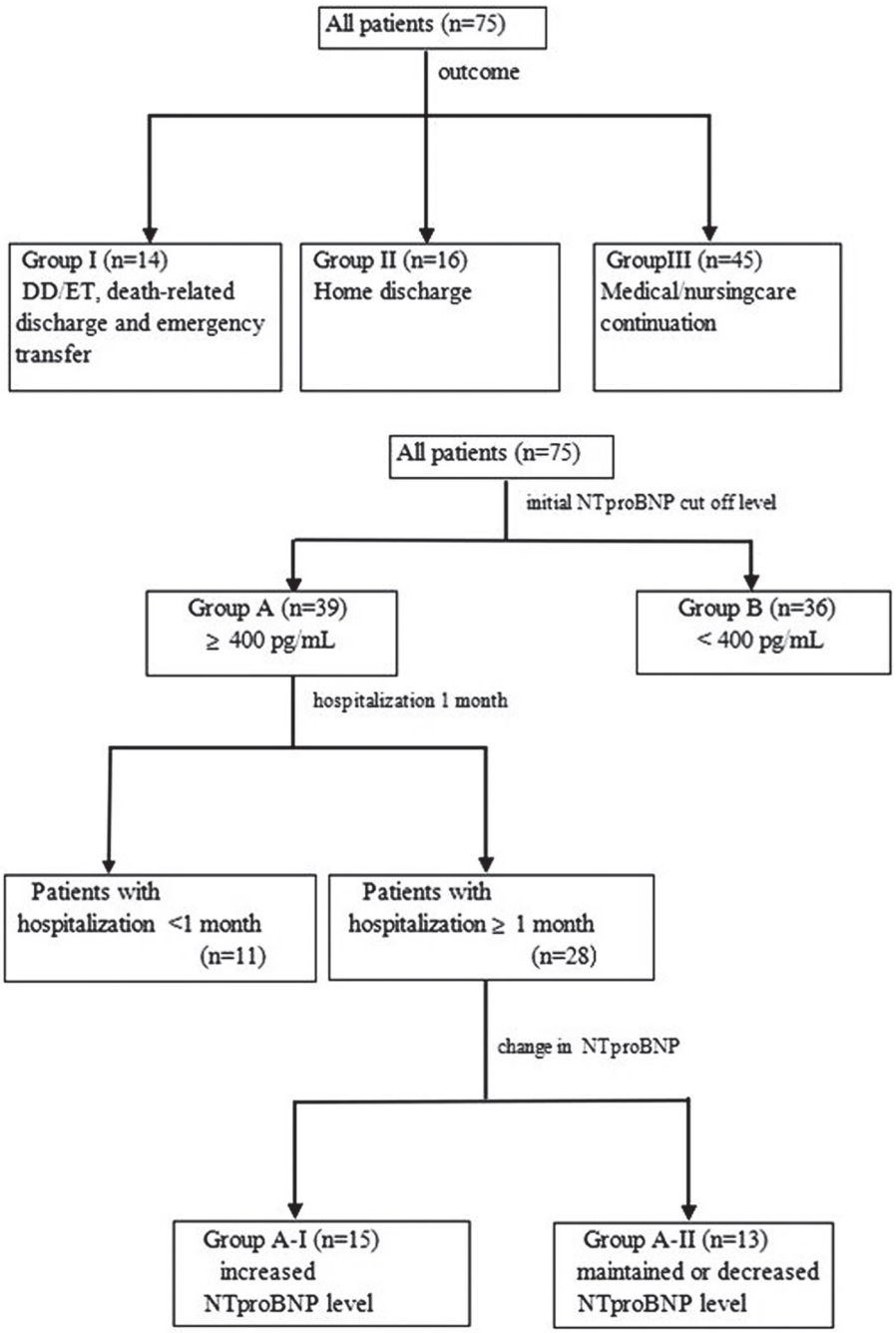

Fig. 1. Flow chart showing the grouping of study patients.

had a femoral neck fracture, one had hip prosthesis dislocation, and one had ileus.

Accuracy of Measurement Indices as Predictors of DD/ET

Table 1 shows the accuracy of each measurement index as a predictor of DD/ET. A high initial NTproBNP level was found in 39 patients; of these, 13 (33.3%) experienced DD/ET. The accuracy of the negative likelihood ratio (LR–) was 0.127 and that of the positive likelihood ratio (LR+) was 2.09 (sensitivity 92.9%, specificity 55.7%, positive predictive value 33.3%, and negative predictive value 97.1%). Of the 24 patients with cardiovascular disease (CVD), 9 (37.5%) experienced DD/ET. The accuracy of LR– was 0.473, and that of LR+ was 2.61 (sensitivity 64.3%, specificity 75.4%, positive predictive value 37.5%, and negative predictive value 90.2%).

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Table 1. Patient characteristics and the accuracy of measurement indices as predictors of DD/ET

Characteristic		Value
Participants (n)		75
Age (year, mean ± SD)		85.8 ± 5.3
Sex (n, male/female)		24/51
Disease (n)	Locomotive	41
	Cerebrovascular	11
	Disuse atrophy	23
Hospitalization (days, mean ± SD)		79.6 ± 40.0
Initial FIM (points, mean ± SD)		55.7 ± 29.4
Final FIM (points, mean ± SD)		66.7 ± 32.9
FIM gain (points, mean ± SD)		10.4 ± 14.6
Total ADL assistance[a] (n, %)		28 (37.3%)
Initial NTproBNP (pg/ml, mean ± SD)		1102.7 ± 1696.6
Initial Alb (g/dL, mean ± SD)		3.32 ± 0.68
Final Alb (g/dL, mean ± SD)		3.05 ± 0.70
Change in Alb (g/dL, mean ± SD)		−0.27 ± 0.53
Initial Cr (mg/dL, mean ± SD)		0.71 ± 0.44
DD[b]/ET[c] (n, %)		14 (18.7%)
DD (n)		6[b]
ET (n)		8[c]

Method	Patients (n)	DD/ET (n, %)	Accuracy (LR–, LR+)	S (%)	Sp (%)	PPV (%)	NPV (%)
Initial high NTproBNP	39	13, 33.3	0.127, 2.09	92.9	55.7	33.3	97.1
CVD history	24	9, 37.5	0.473, 2.61	64.3	75.4	37.5	90.2
Af[d]	15						
IHD[e]	13						
Total ADL assistance	28	9, 32.1	0.518, 2.07	64.3	68.9	32.1	89.4
RD	15	4, 26.7	0.871, 1.59	28.6	82.0	26.7	83.3

SD, standard deviation; S, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; RD, renal dysfunction with estimated glomerular filtration rate <50% (Cr value: ≥1.2 mg/ml in men and ≥0.9 mg/ml in women).
[a] Patients with an initial FIM score <36 points.
[b] Exacerbation of chronic heart failure, n=3; exacerbation of chronic renal failure, n=2; exacerbation of chronic obstructive pulmonary disease, n=1.
[c] Gastrointestinal disease, n=2; gastrointestinal surgery, n=2; neurosurgery, n=1; cardiovascular surgery, n=1; orthopedic surgery, n=2.
[d] Chronic Af, n=13; paroxysmal Af, n=2.
[e] IHD, Angina pectoris, n=12; old myocardial infarction, n=1.

A total of 28 patients required assistance with ADLs, with an initial FIM score <36 points; of these, 9 (32.1%) experienced DD/ET. The accuracy of LR– was 0.518, and that of LR+ was 2.07 (sensitivity 64.3%, specificity 68.9%, positive predictive value 32.1%, and negative predictive value 89.3%). Of the 15 patients with renal dysfunction (RD), 4 (26.7%) experienced DD/ET. The accuracy of LR– was 0.871, and that of LR+ was 1.59 (sensitivity 28.6%, specificity 82.0%, positive predictive value 26.7%, and negative predictive value 83.3%).

Comparison of Patient Characteristics According to Outcome

Table 2 compares patient characteristics among the three groups classified by outcome. Group I contained 14 cases (18.7%), Group II contained 16 cases (21.3%), and Group III contained 45 cases (60.0%). Because the data for the initial NTproBNP were unequally dispersed, we used the logarithmic values to ensure statistical stability (**Fig. 2**). The logarithm transformed initial NTproBNP values were normally distributed. Among Groups I, II, and III, significant differ-

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Table 2. Comparison of patient characteristics according to group and outcome

Characteristic	Group I[a] n=14	Group II[b] n=16	Group III[c] n=45	P value	Multiple comparisons
Age (years, mean ± SD)	85.9 ± 4.7	84.8 ± 5.5	86.2 ± 5.4	ns*	-
Sex (male/female)	8/6	4/12	12/33	ns**	-
Disease (n)					
Locomotive	4	13	24		
Cerebrovascular	4	0	7	ns**	-
Disuse atrophy	6	3	14		
Hospitalization (days, mean ± SD)	43.4 ± 35.1	76.3 ± 31.5	92.0 ± 37.1	<0.05*	I< II, III*****
FIM (points, mean ± SD)					
Initial	42.2 ± 24.0	80.2 ± 27.3	51.2 ± 26.6	<0.05*	I, III< II*****
Final	47.4 ± 28.0	96.3 ± 24.3	62.1 ± 30.1	<0.05*	I, III< II*****
Gain	5.2 ± 17.1	16.1 ± 12.1	10.9 ± 14.0	<0.05*	I< II, III*****
Total ADL assistance (n)	9	1	18	<0.05**	II< I, III**
Initial NTproBNP (pg/ml, mean ± SD)	2683.0 ± 2433.8	649.0 ± 609.4	772.4 ± 1365.1	<0.05***	II, III< I******
Logarithm of initial NTproBNP (mean ± SD)	3.26 ± 0.45	2.56 ± 0.57	2.56 ± 0.48	<0.05****	II, III< I******
Alb (g/dL, mean ± SD)					
Initial	3.02 ± 0.53	3.32 ± 0.58	3.41 ± 0.72	ns*	-
Final	2.50 ± 0.81	3.21 ± 0.46	3.16 ± 0.67	ns*	-
Change in Alb	−0.52 ± 0.69	−0.11 ± 0.42	−0.25 ± 0.48	ns*	-
Initial Cr (mg/dL, mean ± SD)	0.95 ± 0.35	0.86 ± 0.60	0.71 ± 0.37	ns*	-
RD (n)	4	3	8	ns**	-
CVD (n)	9	4	10	<0.05**	II, III< I**
Af	6	3	6	<0.05**	II, III< I**
IHD	3	2	8	ns**	-
Symptomatic CHF treatment on 1st day of hospitalization	6	5	16	ns**	-
Oxygen (n)	3	1	6	ns**	-
Diuretic (n)	5	5	11	ns**	-

ns, not significant; -, not calculated.

[a] Group I, death-related discharge and emergency transfer; [b] Group II, home discharge; [c] Group III, medical/nursing care continuation.

*Kruskal-Wallis test; **χ^2 test; ***one-way analysis of variance; ****Student's *t*-test; *****Bonferroni test; ******Tukey test.

ences were seen in the duration of hospitalization, the initial FIM level, the final FIM level, the FIM gain, the number of patients requiring total ADL assistance, the initial NT-proBNP level, the logarithm of the initial NTproBNP, CVD, and Af. In multiple comparisons, the duration of hospitalization in Group I was significantly shorter and the FIM gain was significantly smaller, while the initial NTproBNP level and logarithm of initial NTproBNP level were significantly higher. Moreover, there were significantly more patients with CVD and Af in Group I. In Group II, the initial and final FIM levels were significantly high, and few patients required total ADL assistance. There were no significant differences in the other parameters among the three groups.

Discriminant Analysis (All Patients) and Correlation Coefficients Between Outcomes and Major Indexes

Table 3 shows the correlation coefficients between the outcomes and the major indexes and discriminant analysis for all patients. The correlation coefficients with patient out-

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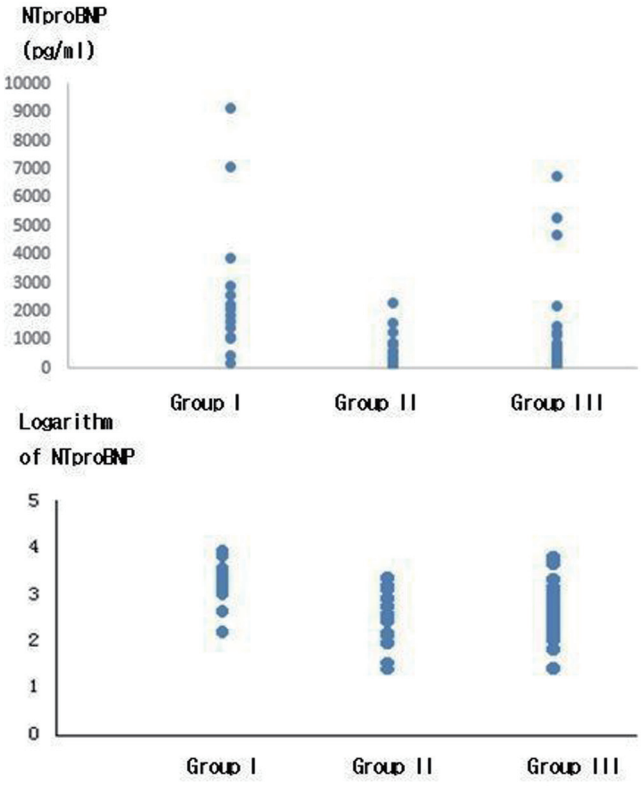

Fig. 2. Scatter plots of the initial NTproBNP levels and the logarithm of the initial NTproBNP levels. In the test for homoscedasticity, initial NTproBNP values were found not to be equally dispersed (P<0.05). We obtained stabilization of the dispersion by calculating the logarithm of the initial NTproBNP (P >0.05).

comes were significantly high for the final FIM level, the initial FIM level, the logarithm of the initial NTproBNP level, and the final Alb level. In discriminant analysis, assuming patient outcome as the dependent variable and items with high correlation coefficients as independent variables, the canonical correlation was 0.54, the significance was P<0.05, and the distinction hitting ratio was 80%.

Comparison of Patient Characteristics According to the NTproBNP Cutoff Level

Table 4 compares the characteristics of Group A and Group B, which were classified according to the NTproBNP cutoff level of 400 pg/ml. In Group A, more patients experienced DD/ET, had higher initial Cr levels, and more prevalent CVD, Af, symptomatic chronic heart failure (CHF) treatment on day 1, and the need for diuretic on day 1 (all P<0.05). Moreover, the duration of hospitalization was significantly shorter in Group A than in Group B (P<0.05).

Comparison of Patient Characteristics According to the Change in NTproBNP Levels

Table 5 compares the patient characteristics of Groups A-I and A-II, classified according to the change in NTproBNP among patients with high initial NTproBNP levels. In Group A-I, significantly more patients experienced DD/ET. The accuracy of LR– was 0 and the accuracy of LR+ was 2.62 (sensitivity 100.0%, specificity 61.9%, PPV 46.7%, and NPV 100.0%). The FIM gain and final Alb levels were also significantly lower in Group A-I than in Group A-II,

Discriminant Analysis and Correlations Between Outcomes and Major Indexes for Groups A-I and A-II.

Table 6 shows the correlation between outcomes and major items and discriminant analysis in Groups A-I and A-II. The correlation coefficients were significant for changes in the logarithm of NTproBNP level, the logarithm of the final NTproBNP level, the FIM gain, the final FIM level, the logarithm of the initial NTproBNP level, and the initial FIM level (all P<0.05). We conducted discriminant analysis assuming patient outcome as a dependent variable and items with high correlation coefficients as independent variables. However, considering multicollinearity, we excluded the logarithm of the initial NTproBNP level and the initial FIM as independent variables. In the discriminant analysis, the canonical correlation was 0.81, the significant probability was P<0.05,

Table 3. Correlation coefficients between outcomes and major indexes and discriminant analysis in all patients

Independent variable	Value (mean ± SD)	Correlation coefficient	P value
Final FIM (points)	66.7 ± 32.9	−0.488	<0.05
Initial FIM (points)	55.7 ± 29.4	−0.408	<0.05
Logarithm of initial NT-proBNP	2.69 ± 0.56	0.34	<0.05
Final Alb (g/dL)	3.05 ± 0.70	−0.282	<0.05
Dependent variable	Canonical correlation	P value	Distinction hitting ratio
Outcome	0.54	P<0.05	80%

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Table 4. Comparison of characteristics in Groups A and B classified according to an NTproBNP cutoff level of 400 pg/ml

	Group A[a] (n=39)	Group B[b] (n=36)	P value
Initial NTproBNP (pg/ml)	1934.2 ± 2021.3	202.0 ± 102.6	-
DD/ET (n)	6/7	0/1	<0.05**
Home discharge (n)	7	7	ns**
Medical/nursing care continuation (n)	19	28	ns**
Age (years, mean ± SD)	86.4 ± 4.5	85.2 ± 6.0	ns*
Sex (male/female)	14/25	10/26	ns**
Disease (n)			
Locomotive	23	18	
Cerebrovascular	5	6	ns**
Disuse atrophy	11	12	
Hospitalization (days, mean ± SD)	68.0 ± 37.6	92.1 ± 38.8	<0.05*
Initial FIM (points, mean ± SD)	56.9 ± 29.3	54.4 ± 29.4	ns*
Final FIM (points, mean ± SD)	65.7 ± 31.9	67.7 ± 33.9	ns*
FIM gain (points, mean ± SD)	8.8 ± 14.1	13.3 ± 14.9	ns*
Total ADL assistance (n)	14	14	ns**
Initial Alb (g/dL, mean ± SD)	3.22 ± 0.64	3.48 ± 0.72	ns*
Final Alb (g/dL, mean ± SD)	2.94 ± 0.83	3.24 ± 0.60	ns*
Change in Alb (g/dL, mean ± SD)	−0.28 ± 0.59	−0.24 ± 0.48	ns*
Initial Cr (mg/dL, mean ± SD)	0.91 ± 0.50	0.65 ± 0.30	<0.05*
CVD (n)	18	5	<0.05**
Af	14	1	<0.05**
IHD	8	5	ns**
Symptomatic CHF treatment on 1st day of hospitalization	19	8	<0.05**
Oxygen (n)	5	5	ns**
Diuretic (n)	7	4	<0.05**

[a] Group A, patients with NTproBNP >400 mg/dL.
[b] Group B, patients with NTproBNP <400 mg/dL.
*Mann-Whitney U-test; **χ^2 test.

and the distinction hitting ratio was 92.9%.

DISCUSSION

Significance of NTproBNP

BNP and NTproBNP are biomarkers secreted by the ventricles as a result of myocardial stress-extension. The levels of these markers increase in patients with left ventricular systolic and diastolic dysfunction and are used for adjuvant diagnosis, prognostic expectation of heart failure, and effect measurement of heart rehabilitation. NTproBNP has been studied extensively because of its long half-life, high blood levels, and availability for measurement at the same time as serum BNP. Moreover, both markers have the same clinical significance and tendency to increase with heart load.[9] However, NTproBNP is more susceptible to the effects of renal function than BNP is: NTproBNP levels tend to be high in patients with impaired renal function. When investigating diastolic left ventricular dysfunction, Sonoda et al. stated that, for NTproBNP levels <56.5 pg/ml, normal left ventricular diastolic function can be established in patients with coronary artery disease, and maintained left ventricular systolic function can be established in those without a history of heart failure with 100% sensitivity, 52.5% specificity, a positive predictive value of 56.1%, and a negative predictive value of 100%. They also stated that they were able to diagnose extension disorder with a sensitivity of 62.5%, a specificity of 93.9%, a positive predictive value of 66.7%, and a negative predictive value of 92.8% if the NTproBNP level was ≥244.5 pg/ml.[10] The Japanese Heart Failure Society cutoff value for NTproBNP in the diagnosis of heart failure is 400 pg/ml. In particular, there is a possibility of

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Table 5. Comparison of patient characteristics in Groups A-I and A-II, classified according to the change in NTproBNP in patients with a high initial NTproBNP level

	Group A-I[a] (n=15)	Group A-II[b] (n=13)	P value
Change in NTproBNP (pg/ml)	2593.5 ± 5137.9	−1091.2 ± 1782.8	-
Initial NTproBNP (pg/ml)	1969.7 ± 1757.0	1785.8 ± 1883.2	ns*
DD[c]/ET[d](n)	3/4	0/0	<0.05**
Home discharge (n)	3	3	
Medical/nursing care continuation (n)	5	10	
Age (years, mean ± SD)	86.4 ± 4.6	87.7 ± 4.5	ns***
Sex (male/female)	5/10	2/11	ns**
Disease (n)			
Locomotive	7	11	
Cerebrovascular	4	1	ns**
Disuse atrophy	4	1	
Hospitalization (days, mean ± SD)	82.4 ± 30.8	88.9 ± 19.9	ns***
Initial FIM (points, mean ± SD)	48.3 ± 27.7	53.1 ± 16.9	ns***
Final FIM (points, mean ± SD)	54.0 ± 34.0	73.0 ± 20.0	ns***
FIM gain (points, mean ± SD)	5.8 ± 10.0	20.1 ± 16.2	<0.05***
Total ADL assistance (n)	8	3	ns**
Initial Alb (g/dL, mean ± SD)	3.12 ± 0.77	3.42 ± 0.39	ns***
Final Alb (g/dL, mean ± SD)	2.63 ± 1.06	3.19 ± 0.38	<0.05***
Change in Alb (g/dL, mean ± SD)	−0.51 ± 0.79	−0.24 ± 0.36	ns***
Initial Cr (mg/dL, mean ± SD)	0.83 ± 0.41	1.03 ± 0.70	ns***
CVD (n)	9	5	ns**
Af	7	4	ns**
IHD	2	4	ns**
Symptomatic CHF treatment on 1st day of hospitalization	9	8	ns**
Oxygen (n)	3	0	ns**
Diuretic (n)	8	8	ns**

Method	Patients (n)	DD/ET (n, %)	Accuracy (LR−, LR+)	S (%)	Sp (%)	PPV (%)	NPV (%)
Increased NTproBNP	39	13, 33.3	0.00, 2.62	100.0	61.9	46.7	100.0

[a] Group A-I, patients whose NTproBNP level increased.
[b] Group A-II, patients whose NTproBNP level was maintained or decreased.
[c] DD, exacerbation of chronic renal failure (with exacerbation of CHF), n=2; exacerbation of CHF, n=1.
[d] ET, exacerbation of CHF, n=1; gastrointestinal disease, n =1; neurosurgery, n=1; cardiovascular surgery (aortic disease), n=1.
*Welch's *t*-test; **χ^2 test; *** Mann-Whitney U-test.

heart failure requiring treatment when NTproBNP levels reach 900 pg/ml; heart failure requiring treatment is likely when the level is ≥900 pg/ml, and heart failure is unlikely if the level is <125 pg/ml.[8] Furthermore, some reports have stated that NTproBNP is useful as a prognostic indicator of cardiovascular events such as acute coronary syndrome, postoperative cardiovascular disease, and stable coronary artery disease.[11,12] Fukuda et al. reported that a numerical formula based on blood BNP concentrations in chronic heart failure patients at discharge could predict prognosis after discharge with a high probability.[13] In other words, a high NTproBNP level may indicate heart failure requiring treatment and may also identify a poor outcome. However, it is known that NTproBNP increases in patients with renal dysfunction and decreases in those with obesity.[14] Therefore, it is necessary to consider not only heart disease but also other

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disorders.

Association Between NTproBNP Increase and Cardiovascular Disease

In this study, higher NTproBNP levels appear to indicate cardiovascular complications, especially Af (**Tables 2, 4**). In Af and IHD, it is known that NTproBNP levels are as high as the levels found in renal dysfunction, and the histories of these diseases should be confirmed.

Initial NTproBNP Level as a Prognostic Marker

A high initial NTproBNP level was observed in 39 patients (52%) at hospitalization, including 13 patients who experienced DD/ET (**Table 4**). These 13 cases accounted for 92.9% of the total 14 DD/ET cases (**Table 1**). As a prognostic marker, high initial NTproBNP level was considered to be better than a history of CVD, the initial FIM level, or the presence of RD. Of these four markers, the prognostic accuracy of high initial NTproBNP level (an LR– of 0.127) was considerably superior, making it the most suitable of the four markers for screening (**Table 1**). In addition, the correlation coefficient and discriminant analysis indicated that the initial NTproBNP level can be used for prognostic prediction of DD/ET in combination with the initial FIM values in the initial stage of hospitalization (**Table 3**). Considering that the reported prevalence of chronic heart failure in those aged ≥80 years is 10%, the accuracy of high initial NTproBNP levels at hospitalization for determining the risk of DD/ET will likely prove helpful in screening for chronic heart failure.[4)]

Association Between Heart Failure and Diseases Leading to DD/ET

Many studies have investigated the association between heart failure and various diseases. Pasini et al. reported that patients with chronic heart failure commonly had infections with *Candida* and had pathogens such as *Campylobacter*, *Shigella*, *Salmonella*, and *Yersinia* in the intestine at levels several to a dozen times higher than those of healthy persons.[5)] Ezekowitz et al. reported that the risk of fracture in heart failure patients is four times higher than that in healthy persons, whereas the risk of hip fracture, in particular, is six times higher.[6)] Furthermore, heart failure increases the risk of stroke. In the Framingham study by Kannel et al., the risk of stroke as a result of heart failure increased by 3.9 times in those in their 50s, 2.4 times in those in their 60s, and 2.2 times in those in their the 70s.[4)] Haeusler et al. reported that the morbidity and mortality associated with cerebral infarction in heart failure patients were considerably higher than those in non-heart failure patients.[7)] Sauve et al. reported that the risk of cognitive dysfunction increased by more than four times in chronic heart failure patients.[15)] In other words, these studies showed that heart failure increases the risk of infection, fracture, and stroke, and can be a factor in physical-functional and medical prognosis during rehabilitation.

In this study, almost all cases (13 of 14) of death-related discharge or emergency transfer had a high initial NTproBNP level and heart disease, i.e., chronic heart failure and arrhythmia or coronary artery disease (**Table 1**). Moreover, in fatal cases, the initial NTproBNP level was high; however, all cases were complicated by heart failure, and the causes of death were exacerbation of chronic heart failure, chronic renal failure, or chronic obstructive pulmonary disease (**Table 1**). However, the direct cause for emergency transfer was something other than heart disease in all eight cases. Therefore, in cases of chronic heart failure, the incidence of complications that could lead to death or emergency hospital transfer seemed to be higher than that in cases without chronic heart failure. In addition, chronic heart failure symptoms occur frequently in patients aged ≥75 years, according to the Framingham study.[4)] Therefore, for elderly people with chronic heart failure, it is necessary to consider diseases and trauma specific to the elderly.

Change in NTproBNP Level as a Prognostic Marker

Significantly more patients experienced DD/ET in Group A-I than in A-II. Moreover, the accuracy of increased NTproBNP levels was considered to indicate excellent screening ability (**Table 5**). Furthermore, the correlation coefficients and discriminant analysis in the follow-up groups (A-I and A-II) suggested that changes in NTproBNP levels, in combination with FIM gains, could be used for prognostic prediction of DD/ET (**Table 6**). The FIM gain was significantly greater in Group A-II than in Group A-I (**Table 5**). Therefore, regardless of the history of CVD or renal dysfunction, decreases in NTproBNP levels indicate that CHF is controllable, the risk of DD/ET is reduced, and ADL can be improved. Therefore, changes in NTproBNP were considered useful not only for determining medical prognosis but also as a predictor of rehabilitation efficacy. Okubo et al. reported that cardiac rehabilitation intervention improved ADLs and decreased NTproBNP levels in inpatients with exacerbation of heart failure and reduced the risk of readmission due to heart failure.[16)] Therefore, to predict outcomes, it may be useful to monitor changes over time in

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Table 6. Correlation between outcomes and major items and discriminant analysis in Groups A-I and A-II

Measurement item		Value (mean ± SD)	Correlation coefficient	P value
1 Change in logarithm of NTproBNP		2.75 ± 0.68	0.625	<0.05
2 Logarithm of final NTproBNP (pg/ml)		3.12 ± 0.49	0.624	<0.05
3 FIM gain (points)		12.4 ± 15.1	−0.561	<0.05
4 Final FIM (points)		62.9 ± 30.0	−0.523	<0.05
5 Logarithm of initial NTproBNP (pg/ml)		3.12 ± 0.36	0.489	<0.05
6 Initial FIM (points)		50.5 ± 23.7	−0.454	<0.05
7 Final Alb (g/dL)		3.05 ± 0.70	−0.223	ns
Dependent variable	Independent variable	Canonical correlation	P value	Distinction hitting ratio
Outcome	1–4	0.81	P<0.05	92.9%

FIM and in the NTproBNP level.

Method of NTproBNP Follow-up

It is important to examine chest X-rays and electrocardiograms in patients with high NTproBNP levels at hospitalization to determine the exacerbation of heart failure or Af. Moreover, in NTproBNP follow-up, chest X-rays seemed desirable for patients with increased NTproBNP levels to check for the exacerbation of heart failure even if there were no apparent symptoms. This would enable earlier treatment of increased congestion or pleural effusion on chest X-ray. In contrast, a decrease in NTproBNP level indicated decreased risk of DD/ET and improvement in ADLs.

Medical Therapy in Patients with High Initial NTproBNP Level (Group A)

Significantly more Group A than Group B patients had heart failure symptoms such as edema or decreased oxygen saturation and consequently received diuretic drugs on the first day of hospitalization (**Table 4**). Therefore, it was considered that the reason that the number experiencing DD/ET was significantly greater in Group A than in Group B was that there were more patients with heart failure symptoms in Group A.

Medical Therapy in Patients Whose NTproBNP Level Increased (Group A-I)

There was no significant difference in the number of patients with heart failure symptoms at hospitalization between Group A-I and A-II. However, the number experiencing DD/ET was significantly higher in group A-I (**Table 5**). This fact suggests that heart failure treatment for group A-I was not appropriately performed. Furthermore, it was also possible that nutrition management and infection control were inadequate, because final Alb levels were significantly lower in group A-I than in group A-II. The calorie intake was calculated with reference to resting energy expenditure, activity coefficients, and stress factors by the doctor and nutritionist at the time of admission. However, it was considered that reassessment for changes in stress coefficient during treatment was not sufficient, and that the calorie requirement might have been underestimated. Moreover, recurrent infection in these patients might have influenced heart failure.

Limitations of the Current Study

This study had several limitations: (1) data were from a single facility and the sample size was small, (2) CVD evaluation was inadequate: echocardiography was not performed for evaluation of valvular disease, and (3) assessment of the impact of infection on heart failure was inadequate and should be examined in a future study.

CONCLUSION

In summary, high initial NTproBNP levels and increases in NTproBNP level are useful for screening for a risk of DD/ET. In contrast, low initial NTproBNP levels and decreases in NTproBNP level indicate that CHF is controllable, the risk of DD/ET is reduced, and ADL can improve. Therefore, our study showed that the NTproBNP level is useful for predicting patient outcomes.

CONFLICTS OF INTEREST

The authors have no conflicts of interest directly relevant to the content of this article.

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