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Factors Related to N-Terminal Pro-B-Type Natriuretic Peptide as a Biomarker for Heart Failure

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Purpose: This study aimed to examine the relationships between the N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels with the sociodemographic and clinical factors, self-care behaviors, and the physical symptom experiences in patients with heart failure. **Methods:** This cross-sectional study utilized a convenience sample of adult outpatients and inpatients who attended a cardiology department in a tertiary hospital in Seoul, Korea. The data from 154 patients with heart failure were collected using a questionnaire, and their clinical data were extracted from their electronic medical records. **Results:** Compared with the patients with high NT-proBNP levels, those with low NT-proBNP levels had significantly lower physical symptom experiences scores. Patients with low- and mid-NT-proBNP levels were more likely to be employed compared with those with high NT-proBNP levels. Patients with low NT-proBNP levels had higher left ventricular ejection fractions, and were less likely to have arrhythmias and comorbidities. **Conclusion:** The results from this study showed that patients with more severe heart failure had higher physical symptom experiences scores; hence, individualizing treatment approaches based on heart failure severity is necessary.

Key Words: *Heart failure; Biomarkers; Symptom assessment*
국문주요어: 심부전, 바이오마커, 증상

INTRODUCTION

1. Background

Heart failure is associated with a variety of clinical symptoms that result from a structural or functional disability, and a reduced capacity to pump blood into and out of the ventricles [1]. Advances in medical technologies mean that the causes of heart failure associated with uncontrollable hypertension and ischemic heart diseases, including myocardial infarction, valvular heart disease, and dilated cardiomyopathy, can be treated successfully. Despite successful treatment, the number of patients with long-term chronic heart failure has increased every year, and an aging population and the high rates of hypertension and diabetes mellitus have augmented this phenomenon [2]. Approximately 26 million individuals worldwide and 1 million individuals in Korea suffer from heart failure, and these numbers are expected to increase by 25.0% by 2030 [3-5]. Heart failure is a cause of hospitalization in the USA and Europe, resulting in over 1 million admissions [5]. In Korea, heart failure frequently leads to hospitalization and high treatment costs which are more than 800 billion won per year [4].

Patients with heart failure experience physical symptoms, including fatigue, dyspnea, and generalized edema, depending on the condition's severity. These physical symptoms can have psychological effects, for example, anxiety, depression, and reduced self-efficacy, which can hinder daily activities, work, and a person's social life [6]. Heart failure is difficult to cure, and its characteristics often include recurrent cycles of deterioration and improvement. Consequently, rehospitalization rates con-

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tinue to rise, and they approach 30% within 60-90 days of discharge [7]. This negatively affects a patient's quality of life, and it increases the burden on families and other caregivers [6]. Hence, it is an important social and economic issue [3].

Most patients have difficulties recognizing the signs and symptoms of heart failure, because the symptoms are unspecific and they are often mistaken for normal changes associated with aging or comorbidities [6, 8]. Failing to recognize the early symptoms and to seek treatment can result in more severe disease and hospitalization, because of delays associated with symptom management and reporting the symptoms to health care providers [9]. Consequently, treatment and recovery are delayed, because help was not sought until the symptoms were more severe. Delaying treatment can lower the physical, psychological, and social aspects of a patient's quality of life. Therefore, it is essential to understand the individual clinical factors and indicators involved to facilitate the recognition of differences among patients with heart failure and to enable a systematic approach towards assessing the symptoms to be followed [10].

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is secreted by the heart's ventricles in response to volume expansion and the pressure load [11]. The serum NT-proBNP test is recommended as a diagnostic tool for heart failure by the American Heart Association [12]. Therefore, this test is widely used as a screening and/or diagnostic tool for patients with heart failure. Moreover, NT-proBNP is a reliable biomarker for grading the severity of heart failure and for predicting the readmission and mortality risks in patients with heart failure [13]. The results from previous studies have shown that the NT-proBNP levels increase in normal individuals in association with being female and older, which indicates that the cut-off levels should be stratified according to age and sex [14, 15].

Adhering to self-care management protocols is an important aspect of heart failure treatment [18, 20, 23]. The findings from a previous study that investigated self-care and the NT-proBNP levels indicated that better self-care management was associated with reduced NT-proBNP levels [16]. This study's findings also showed that self-care maintenance, which included adherence behaviors that maintained physiologic homeostasis, self-care management that involved symptom evaluation and treatment, and self-care confidence that assessed a patient's perceived ability to engage in the self-care process, may reduce myocardial stress; however, the potential correlates that were pertinent to patients with heart failure with physical symptom experiences were not explored. Despite the significance of NT-proBNP as a biomarker for patients with heart failure, the relationships between NT-proBNP and self-care behaviors and physical symptom experiences have rarely been investigated.

Identifying the relationships between a biomarker for heart failure and associated factors, including self-care and physical symptom experiences, will help nurses to recognize the differences between individual patients with heart failure and to consider symptom management strategies for their patients. Consequently, efficient management of and appropriate self-care among patients with risk factors may lead to symptom reductions and, ultimately, to positive clinical outcomes. Therefore, determining the relationships between the NT-proBNP levels and the relevant factors could enable differences in the NT-proBNP levels to be recognized, based on the characteristics of patients with heart failure, and provide a more comprehensive understanding of the symptoms.

2. Purpose

The purpose of this study was to identify the patients' characteristics, self-care behaviors, and physical symptom experiences in association with NT-proBNP, and to determine whether or not the NT-proBNP levels differed among the factors investigated.

METHODS

1. Study Design

This cross-sectional study aimed to examine the relationships between the NT-proBNP levels and related factors of patients with heart failure. The study utilized a convenience sample of adult outpatients and inpatients who attended a cardiology department in a tertiary hospital in Seoul, Korea.

2. Setting and Study Sample

The clinical data were extracted from the electronic medical records (EMRs) of 154 patients with heart failure who attended a tertiary medical center. The general rule for calculating the sample size for multinomial logistic regression is a minimum ratio of 10 cases to each independent variable, with a minimum sample size of 100 or 50 [17]. In this study, 12 independent variables, including age and sex, were incorporated into the multivariate models. The sample size to the number of independent variables ratio was 12.8 to 1, which was greater than the minimum ratio required.

Patients who were diagnosed with heart failure and were aged 18 years or older, those who could communicate without any problems, and those with a stable hemodynamic status were included in the study. Patients who had undergone heart transplantations after being diagnosed with heart failure, those who had temporary heart failure with clearly defined causes, such as sepsis, anemia, or thyrotoxicosis, patients with normal left ventricular ejection fractions (LVEFs) (>60%), and those with acute aortic dissections and idiopathic pulmonary hypertension were excluded from the study.

3. Instruments

1) Sociodemographic and Clinical Data

The patients' sociodemographic data were obtained by using a questionnaire that gathered data about the patient's sex, age, marital status, education, employment status, and monthly income. The patients' clinical data were extracted from the patients' EMRs, and they included data that described the New York Heart Association (NYHA) functional classification (FC) that graded the severity of the functional limitations associated with physical activity, the cause of heart failure, the LVEF, the presence of arrhythmias, the types and numbers of prescribed medications, the heart surgery and percutaneous coronary intervention histories, the comorbidities, the numbers of emergency room visits and rehospitalizations within 1 year, and the NT-proBNP level. The NYHA FC places patients in one of four categories; Class I, II, III, and IV meaning 'No symptoms of heart failure', 'Symptoms with moderate exertion', 'Symptoms with minimal exertion', and 'Symptoms at rest' respectively.

2) Self-Care Behaviors

The self-care behaviors were measured using the nine-item European Heart Failure Self-care Behavior (EHFScB-9) scale, an instrument that was developed for patients with heart failure by Jaarsma et al. [21] and that was translated, reverse-translated, and expert-verified by Son et al. [20]. The EHFScB-9 scale includes items that address multiple components associated with self-care behaviors for heart failure, including weight measurements, reporting to a healthcare provider when body weight increases, fluid restrictions, consumption of a low-sodium diet, and compliance with prescribed medicines. The patients responded to the questionnaire using a five-point Likert scale with answers that ranged from 1 = "completely disagree" to 5 = "completely agree". The overall self-care behavior score was calculated from the means of all of the questions. A higher score indicated better self-care behaviors. The EHFScB-9 scale showed reliability in the study by Jaarsma et al. [21] (Cronbach's $\alpha = 0.85$) and in this study (Cronbach's $\alpha = 0.65$). Content validity and construct validity were established by Jaarsma et al. [21].

3) Physical Symptom Experiences

The physical symptom experiences caused by heart failure were measured using parts of the instrument developed by Riegel et al. [18] and modified by Song et al. [19]. The instrument is based on a four-point Likert scale, and it consists of 10 physical symptom items, including dyspnea, leg/ankle edema, anorexia, and fatigue. The instrument was modified by our research team to assess the symptoms, and to report the frequency and intensity of each symptom separately. The patients responded to the questionnaire using the four-point Likert scale, and the responses ranged from "none" (0 points) to "severe" (4 points) for both frequency and intensity; therefore, the mean of the two scores for each symptom ranged from 0 to 4. The overall physical symptom experiences score was calculated from the means of the scores for each symptom. The scale showed reliability in a previous study (Cronbach's $\alpha = 0.84$) [20] and in this study (Cronbach's $\alpha = 0.85$).

4. Data Collection

The data were collected from October 2013 to November 2013 from heart failure outpatients and inpatients who attended the circulatory internal medicine and cardiology departments at Samsung Medical Center, which is a tertiary medical center in Seoul, Korea. The self-administered survey questionnaires and the EMRs were used to collect the data.

5. Data Analyses

A total of 154 patients were included in the final analyses, with a 91% rate of return. The data collected were encoded and processed into statistical data using IBM®SPSS® software, version 20.0 (IBM Corporation, Armonk, NY, USA), and all of the analyses were carried out using a significance level of $p < .05$. The sociodemographic and clinical characteristics of the patients and the major variables were analyzed using univariate analysis for inclusion in the regression model to examine related factors to NT-proBNP groups. The continuous variables, such as self-care behaviors and physical symptom experiences were anaylzed using an analysis of variance (ANOVA). And the categorical variables, such as NYHA classification, the cause of heart failure, the LVEF, the presence

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of arrhythmias, the types and numbers of prescribed medications, the history of heart surgery and percutaneous coronary intervention histories, the comorbidities, the numbers of emergency room visits and rehospitalizations within 1 year were analyzed using Pearson's chi-square test. The Scheffé post-hoc test was used for multiple-comparison for the ANOVA results. The previous studies have suggested that cut-off levels could be determined by stratifying the patients according to age, sex, and renal function [14, 15]. However, these cut-off values could not be used in this study, because the number of patients in some groups was too small. Furthermore, the distribution of the NT-proBNP levels was skewed, therefore, the frequencies in each group were disproportionate. Thus, we divided the patients into three equal groups based on the NT-proBNP levels, i.e. tertiles. The significant variables identified in the univariate analysis were included as independent variables and the three NT-proBNP groups were included as dependent variables in the multinomial logistic regression. The multinomial logistic regression was adjusted for age and sex.

6. Ethical Considerations

This study was approved by Samsung Medical Center's Institutional Review Board (Approval number: 2013-09-049-001). The research objectives, the methods, and the study's duration were explained to the patients, and the patients were provided with detailed information regarding their participation in the research.

RESULTS

1. Overall Sociodemographic and Clinical Characteristics of the Patients

The patients' mean ± standard deviation (SD) age was 60.8 ± 15.4 years, and 91 patients (59.1%) were male. Most of the patients were married (107 patients; 69.5%), and 54 (35.1%) patients were employed (Table 1). Sixty-three patients (40.9%) had arrhythmias, and most of the patients (107 patients; 69.5%) were categorized as NYHA classes I or II. The mean ± SD number of prescribed medications was 5.1 ± 2.3. One-third of the participants (57 patients; 37.0%) had been hospitalized more than once within the previous year, because of heart failure, and 41 patients (26.6%) had visited the emergency room at least once within the previous year. The patients' mean ± SD LVEF was 44.8 ± 17.7%. The most frequent comorbidity was diabetes (38 patients; 24.7%) (Table 2). The distribution of the NT-proBNP levels was skewed, and the median NT-proBNP level was 702.1 pg/mL. The patients were divided into three groups based on

Table 1. Sociodemographic Characteristics of the N-Terminal Pro-B-Type Natriuretic Peptide Groups (N = 154)

Characteristic	n (%)	Low group (n = 52) n (%)	Mid group (n = 51) n (%)	High group (n = 51) n (%)	χ^2	*p*
Sex					1.907	.385
Male	91 (59.1)	28 (53.8)	29 (56.9)	34 (66.7)		
Female	63 (40.9)	24 (46.2)	22 (43.1)	17 (33.3)		
Age (year), Mean ± SD	60.82 ± 15.43				10.369	.035
< 50	35 (22.7)	15 (28.8)	13 (25.5)	7 (13.7)		
50-65	52 (33.8)	22 (42.3)	11 (21.6)	19 (37.3)		
> 65	67 (43.5)	15 (28.8)	27 (52.9)	25 (49.0)		
Spouse					2.751	.253
Yes	107 (69.5)	32 (61.5)	39 (76.5)	36 (70.6)		
No	47 (30.5)	20 (38.5)	12 (23.5)	15 (29.4)		
Education					0.793	.992
≤ Elementary school	35 (22.7)	10 (19.2)	12 (23.5)	13 (25.5)		
Middle school	20 (13.0)	7 (13.5)	6 (11.8)	7 (13.7)		
High school	46 (29.9)	16 (30.8)	15 (29.4)	15 (29.4)		
≥ College	53 (34.4)	19 (36.5)	18 (35.3)	16 (31.4)		
Employment status					13.891	.001
Employed	54 (35.1)	26 (50.0)	20 (39.2)	8 (15.7)		
Unemployed	100 (64.9)	26 (50.0)	31 (60.8)	43 (84.3)		
Monthly income (1,000 won)					3.52	.172
< 2,000	53 (34.4)	18 (34.6)	13 (25.5)	22 (43.1)		
≥ 2,000	101 (65.6)	34 (65.4)	38 (74.5)	29 (56.9)		

SD = Standard deviation.

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their NT-proBNP levels, as follows: Low: < 380 pg/mL; Mid: ≥ 380- < 1289 pg/mL; and High: ≥ 128998 pg/mL.

2. Sociodemographic and Clinical Characteristics of the N-Terminal Pro-B-Type Natriuretic Peptide Groups

The patients in the High group were older than those in the Mid and Low groups (χ^2 = 10.369; p = .035), and those in the Low group were more likely to be employed (χ^2 = 13.891; p = .001) (Table 1). A high NT-proBNP level was associated with a higher incidence of arrhythmia (χ^2 = 27.063; p < .001), a higher NYHA FC (χ^2 = 30.661; p < .001), the administration of a higher number of medicines (χ^2 = 18.808; p = .001), more frequent readmissions (χ^2 = 13.647; p = .001), and more frequent visits to the emergency room within the previous year (χ^2 = 16.368; p < .001). The LVEF was significantly associated with the NT-proBNP level, and patients in the High group were more likely to have lower LVEFs compared with those in the Mid and Low groups (χ^2 = 16.880; p < .001) (Table 2).

3. Self-care Behavior and Physical Symptom Experiences Scores for the N-Terminal Pro-B-Type Natriuretic Peptide Groups

The average overall scores for the self-care behaviors ranged from 1.8

Table 2. Clinical Characteristics of the N-Terminal Pro-B-Type Natriuretic Peptide Groups (N = 154)

Characteristic	n (%)	Low group (n = 52) n (%)	Mid group (n = 51) n (%)	High group (n = 51) n (%)	χ^2	p
Cause of heart failure					1.582	.453
Ischemic	33 (21.4)	12 (23.1)	8 (15.7)	13 (25.5)		
Non-ischemic	121 (78.6)	40 (76.9)	43 (84.3)	38 (74.5)		
Arrhythmias					27.063	< .001
Yes	63 (40.9)	7 (13.5)	24 (47.1)	32 (62.7)		
No	91 (59.1)	45 (86.5)	27 (52.9)	19 (37.3)		
NYHA FC					30.661	< .001
Class I or II	107 (69.5)	45 (86.5)	41 (80.4)	21 (41.2)		
Class III	34 (22.1)	6 (11.5)	8 (15.7)	20 (39.2)		
Class IV	13 (8.4)	1 (1.9)	2 (3.9)	10 (19.6)		
History of heart surgery					3.833	.147
Yes	19 (12.3)	4 (7.7)	5 (9.8)	10 (80.4)		
No	135 (87.7)	48 (92.3)	46 (90.2)	41 (19.6)		
History of PCI					2.045	.360
Yes	22 (14.3)	7 (13.5)	5 (9.8)	10 (19.6)		
No	132 (85.7)	45 (86.5)	46 (90.2)	41 (80.4)		
BMI (kg/m^2)					4.813	.307
< 18.5	8 (5.2)	2 (3.8)	2 (3.9)	4 (7.8)		
18.5-24.9	89 (57.8)	28 (53.8)	27 (52.9)	34 (66.7)		
> 25	57 (37.0)	22 (42.3)	22 (43.1)	13 (25.5)		
Number of medicines, Mean ± SD	5.05 ± 2.29				18.808	.001
1-3	38 (24.8)	19 (36.5)	15 (29.4)	4 (7.8)		
4-6	73 (47.4)	26 (50.0)	23 (45.1)	24 (47.1)		
≥ 7	43 (27.9)	7 (13.5)	13 (25.5)	23 (45.1)		
Rehospitalization within 1 year					13.647	.001
Yes	57 (37.0)	12 (23.1)	16 (31.4)	22 (43.1)		
No	97 (63.0)	40 (76.9)	35 (68.6)	29 (56.9)		
ER visits within 1 year					16.368	< .001
Yes	41 (26.6)	8 (15.4)	9 (17.6)	24 (47.1)		
No	113 (73.4)	44 (84.6)	42 (82.4)	27 (52.9)		
LVEF (%), Mean ± SD	44.77 ± 17.65				16.88	< .001
< 45%	73 (47.4)	17 (32.7)	20 (39.2)	36 (70.6)		
≥ 45%	81 (52.6)	35 (67.3)	31 (60.8)	15 (29.4)		
Comorbidities					9.185	.010
Yes	62 (40.3)	15 (28.8)	18 (35.3)	29 (56.9)		
No	92 (59.7)	37 (71.2)	33 (64.7)	22 (43.1)		

NYHA FC = New York Heart Association functional classification; PCI = Percutaneous coronary intervention; BMI = Body mass index; SD = Standard deviation; ER = Emergency room; LVEF = Left ventricular ejection fraction.

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to 4.8, which was based on a five-point scale, the average score was 3.5±0.5, and there were no significant differences among the NT-proBNP groups. The highest scored item was "I take my medication as prescribed" and the lowest scored item was "I limit the amount of fluids" (Table 3). The physical symptom experiences scores ranged from 0 to 4, and the average score was 1.2±0.7. The average scores for symptom frequency and symptom intensity were 1.2±0.7 and 0.9±0.6, respectively. Approximately 85.1% of the patients reported that they experienced "fatigue", which was scored with the highest frequency and intensity. The patients in the High group had higher scores for physical symptom experiences ($F=21.635$, $p<.001$). All of the physical symptom experiences scores, except for those for "sleep disturbance" and "chest pain or chest tightness", were significantly higher in the High group (Table 3). There were no differences between the Low and the Mid groups with respect to the physical symptom experiences scores.

Table 3. Self-care Behavior and Physical Symptom Experiences Scores in the N-Terminal Pro-B-Type Natriuretic Peptide Groups (N=154)

Characteristic	All cases (n=154)	Low group[a] (n=52)	Mid group[b] (n=51)	High group[c] (n=51)	F	*p*
	Mean±SD	Mean±SD	Mean±SD	Mean±SD		
Self-care behavior	3.49±0.53	3.47±0.50	3.51±0.57	3.47±0.52	0.106	.900
Physical symptom experiences	1.22±0.74	0.83±0.50	0.98±0.73	1.65±0.77	$21.352^{a,b<c}$	<.001
Fatigue	2.09±1.16	1.89±1.13	1.91±1.19	2.46±1.08	$4.136^{a<c}$	.018
Dyspnea during activities	1.69±1.26	1.29±1.00	1.42±1.34	2.37±1.15	$13.141^{a,b<c}$	<.001
Sleep disturbance	1.37±1.28	1.26±1.19	1.21±1.32	1.65±1.30	1.84	.162
Chest pain or chest tightness	1.13±1.08	0.96±0.95	1.06±1.14	1.38±1.13	2.148	.120
Anorexia	1.10±1.26	0.56±0.93	0.96±1.19	1.78±1.32	$14.947^{a,b<c}$	<.001
Leg/ankle edema	1.03±1.19	0.74±1.01	0.86±1.13	1.48±1.31	$6.036^{a,b<c}$	.003
Nausea	1.00±1.15	0.77±0.98	0.84±1.11	1.40±1.26	$4.86^{a,b<c}$	.009
Dyspnea while lying	0.80±1.13	0.32±0.59	0.57±0.91	1.52±1.38	$20.16^{a,b<c}$	<.001
Dyspnea while resting	0.70±1.00	0.32±0.57	0.58±0.86	1.22±1.24	$12.754^{a,b<c}$	<.001
Dyspnea while sleeping	0.59±1.02	0.18±0.50	0.39±0.73	1.22±1.34	$17.86^{a,b<c}$	<.001

Table 4. Multinomial Logistic Regression for the N-Terminal Pro-B-Type Natriuretic Peptide Groups* (N=154)

Predictor	Low group vs. High group (reference group)		Mid group vs. High group (reference group)	
	AOR	95% CI	AOR	95% CI
Employed (reference group: no)				
Yes	5.16	(1.07-24.78)	4.90	(1.20-20.08)
Arrhythmia (reference group: no)				
Yes	0.04	(0.01-0.18)	0.38	(0.12-1.25)
NYHA FC (reference group: I or II)				
Class III	0.59	(0.09-3.80)	0.32	(0.07-1.48)
Class IV	1.00	(0.04-25.16)	0.22	(0.02-2.76)
Number of medicines (reference group: ≥1-3)				
4-6	1.30	(0.21-7.94)	0.39	(0.08-2.03)
7	1.38	(0.17-11.40)	0.66	(0.11-3.98)
Rehospitalized within 1 year (reference group: no)				
Yes	1.07	(0.22-5.12)	1.67	(0.41-6.79)
ER visited within 1 year (reference group: no)				
Yes	1.00	(0.18-5.44)	0.48	(0.11-2.13)
LVEF (reference group: <45%)				
≥45%	9.44	(2.21-40.27)	2.59	(0.74-9.06)
Comorbidity (reference group: no)				
Yes	0.19	(0.05-0.75)	0.30	(0.09-1.01)
Self-care	1.02	(0.32-3.25)	0.89	(0.32-2.48)
Physical symptom experiences	0.13	(0.03-0.50)	0.35	(0.12-1.03)

*Age and sex were adjusted.
AOR=Adjusted odds ratio; CI=Confidence interval; NYHA FC=New York Heart Association functional classification; ER=Emergency room; LVEF=Left ventricular ejection fraction.

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4. Factors Associated With the N-Terminal Pro-B-Type Natriuretic Peptide Level

The significant variables identified by the univariate analysis were included as the independent variables and the NT-proBNP groups were included as the dependent variables in the multinomial logistic regression. Age and sex were the confounding factors, and self-care was added as an independent variable, because it was a major factor in this study. The regression analysis was preceded by Pearson's correlation to identify multicollinearity between the independent variables. The correlation coefficient was 0.02-0.60, which indicated that independence was maintained between the variables that were considered to be independent during this research.

The High group was used as the reference group, and the adjusted odds ratios (ORs) for age, sex, the employment status, arrhythmias, the NYHA FC, the number of medicines, rehospitalizations within 1 year, emergency room visits within 1 year, the LVEF, comorbidities, self-care behaviors, and the physical symptom experiences were used in the final model (Table 4). Compared with the patients in the High group, the patients in the Low group were 5.16-times more likely to be employed (95% confidence interval [CI] = 1.07-24.78) and those in the Mid group were 4.90-times more likely to be employed (95% CI = 1.20-20.08). The occurrence of arrhythmias was lower in the Low group compared with the High group (OR, 0.04; 95% CI = 0.01-0.18). Compared with the patients in the High group, the patients in the Low group were 9.44-times more likely to have a higher LVEF ($\geq$ 45%) than a lower LVEF ($<$45%) (95% CI = 2.21-40.27) and they were less likely to have comorbidities (OR, 0.19; 95% CI = 0.05-0.75). The patients in the Low group experienced fewer physical symptoms compared with the patients in the High group (OR, 0.13; 95% CI = 0.03-0.50).

DISCUSSION

This study examined the relationships between the patients' NT-proBNP levels and their sociodemographic and clinical characteristics, self-care behaviors, and physical symptom experiences.

The patients in the High group were older than those in the Mid and Low groups. Previous studies' findings have demonstrated that age and being female independently predict NT-proBNP levels in the normal range [14-16]; therefore, the NT-proBNP levels should be stratified according to age and sex to determine the cut-off values for patients.

There were statistically significant differences among the NT-proBNP groups with respect to several clinical factors. We determined that arrhythmias, a higher NYHA class, a higher number of medicines, rehospitalization, emergency room visits, a lower LVEF, and comorbidities were significantly associated with high NT-proBNP levels, which concurs with the findings from other studies on patients with heart failure [14, 16, 22].

Patients in the High group were more likely to have higher physical symptom experiences scores, but we were unable to identify a relationship between NT-proBNP and self-care behaviors. The results from a previous study [23] suggested that patients who implemented better self-care behaviors reduced their symptoms and that the tendency of those with more severe symptoms to implement better self-care behaviors was counterproductive. Therefore, we speculate that better self-care may have led to lower physical symptom experiences scores in our study, which could lead to lower biomarker levels.

Multinomial logistic regression showed that compared with the patients in the High group, the patients in the Low and Mid groups were more likely to be employed. Compared with the patients in the High group, more patients in the Low group did not have arrhythmias, low LVEFs ($<$45%), or any comorbidities, and they had lower physical symptom experiences scores. Given that the patients in the Low and Mid groups were more likely to be employed than those in the High group, the severity of the illness may have affected the employment prospects of the patients with heart failure.

We found that the patients with high NT-proBNP levels were more likely to have arrhythmias, which might be attributed to the irregular ventricular rhythms and the pathophysiology of atrial fibrillation (AF) that includes hypertrophy, fibrosis, and inflammation in patients with arrhythmias [24]. The findings from a meta-analysis showed that patients with AF had higher baseline NT-proBNP levels and that NT-proBNP could be a biomarker for predicting the recurrence of AF [24]. AF is the most common complex arrhythmia, and it is associated with increases in morbidity from stroke and heart failure, a poor prognosis, and an increase in mortality [25]. Accordingly, treatment strategies for patients with AF and concomitant heart failure focus on preventing thromboembolism and rhythm control.

Patients with heart failure and preserved LVEFs are generally considered to have better prognoses than those patients with reduced LVEFs. However, a recent study reported that mortality is not necessarily low in patients with acute decompensated heart failure and preserved LVEFs,

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and that it appears to depend on the NT-proBNP levels [26]. Most studies have focused on left ventricular (LV) systolic dysfunction that is assessed by means of an impaired ejection fraction (EF). However, the independent association between the NT-proBNP level and the LV diastolic function that was determined in the present study suggests that LV diastolic dysfunction is a major determinant of elevated NT-proBNP levels in patients with preserved EFs [27]. Therefore, it is necessary to consider the LV diastolic function in addition to the LVEF to precisely assess heart function.

Elevated NT-proBNP levels are associated with comorbidities that include chronic renal failure, type 2 diabetes, anemia, and acute coronary syndrome [28, 29]. In this study, the most frequent comorbidity was diabetes, and patients in the Low group (NT-proBNP < 380 mg/mL) were less likely to have comorbidities compared with the patients in the High group. The findings from several studies have shown that health care providers must consider underlying diseases that include diabetes, renal failure, and right ventricular dysfunction secondary to chronic pulmonary disease or acute pulmonary embolism, in patients with NT-proBNP concentrations that are between 100 pg/mL and 500 pg/mL [29].

The physical symptom experiences score was significantly associated with the NT-proBNP levels. We were unable to identify any studies that had directly addressed the relationships between physical symptom experiences and NT-proBNP. Moreover, studies that have investigated tailored interventions based on symptom experiences are sparse, which suggests that further studies are warranted to measure these factors and develop individualized interventions.

One randomized controlled trial compared NT-proBNP-guided care with standard care management, that is, without NT-proBNP guidance, in patients with heart failure. In the NT-proBNP-guided care arm, an additional goal was to lower and sustain the NT-proBNP levels, and additional clinic visits and medication adjustments occurred. This study's findings suggested that serial changes in the NT-proBNP levels were a risk for adverse outcomes, and that NT-proBNP-assisted treatments were associated with improvements in the clinical outcomes [22]. Another study's findings showed that NT-proBNP-guided therapy was safe in elderly and highly comorbid patients [30]. This could be attributed to the more intense medical therapy for heart failure that was administered to the NT-proBNP-guided group. Further studies are needed to investigate whether treatment and nursing guidance based on the NT-proBNP levels help to improve outcomes in a way that is more specifically suited to the individual needs of the patients. Longitudinal studies are needed to determine whether self-care influences heart failure biomarkers.

The present study has some limitations. First, the findings from this study cannot be generalized, because the research was based on convenience sampling from patients at a single hospital, and most of the patients were outpatients with minor symptoms. Therefore, similar studies in patients with different heart failure severities are required in the future. Second, the patients were enrolled over a relatively short period of time and the influence of seasonal variations on the symptoms of heart failure was not considered. Third, this study did not measure other heart failure biomarkers and psychological factors; hence, further research must be undertaken that includes psychological factors. Fourth, we could not consider age, sex, or renal function when the NT-proBNP groups were defined, because of the small number of patients, and this may have led to false-positive or false-negative results.

CONCLUSION

Compared with the patients with high NT-proBNP levels, those with low NT-proBNP levels had significantly lower physical symptom experiences scores. More patients with low and mid NT-proBNP levels were likely to be employed compared with the patients with high NT-proBNP levels. Patients with low NT-proBNP levels had higher LVEFs and were less likely to have arrhythmias and comorbidities. These findings suggest that health care providers should understand individual patients' clinical factors in order to assess the severity of the heart failure.

Importantly, individualizing treatment approaches based on the severity of the heart failure in patients is necessary, because the results from the current study have demonstrated that the patients with more severe heart failure had higher physical symptom experiences scores. Further studies are warranted to investigate whether nursing guidance using biomarkers, including NT-proBNP, which is more specifically suited to the needs of individual patients, can help to improve outcomes. The results from this study may provide a scientific basis for nursing intervention in the future that accounts for the characteristics of patients with heart failure.

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