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ORIGINAL ARTICLE
Heart Failure

Gender Difference in the Prognostic Value of N-Terminal Pro-B Type Natriuretic Peptide in Patients With Heart Failure

— A Report From the Korean Heart Failure Registry (KorHF) —

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Background: Very little data is available to evaluate the gender-specific role of N-terminal pro-B type natriuretic peptide (NT-proBNP). This study was performed to investigate whether there is a gender difference in the prognostic value of NT-proBNP in patients hospitalized for heart failure (HF).

Methods and Results: A total of 2,280 patients hospitalized with HF (67.9±14.3 years, 50.9% women) from the nationwide registry database were analyzed. Composite events including all-cause mortality and HF readmission were assessed. During the mean follow-up period of 1,245±824 days, there were 1,067 cases of composite events (49.7%). NT-proBNP levels were significantly higher in patients with events than those without in both genders (P<0.001 for each). A higher NT-proBNP level was an independent predictor of events (highest vs. lowest tertile: hazard ratio [HR], 1.74; 95% confidence interval [CI], 1.25–2.43; P=0.001) in men, even after controlling for potential confounders. However, NT-proBNP was not associated with the occurrence of composite events in women in the same multivariable analysis (P>0.05).

Conclusions: In patients with HF, the NT-proBNP level seems to be a more valuable marker in the prediction of long-term mortality and HF readmission in men than in women.

Key Words: Gender; Heart failure; N-terminal pro-B type natriuretic peptide; Prognosis

Heart failure (HF), a disabling condition with poor prognosis, is a huge burden of global health.[1] In spite of continued effort for the better management, the mortality and readmission rate of HF still remains high.[2] In order to improve the outcome of patients with HF, early identification of high-risk patients along with aggressive treatment is important.[3] For this purpose, N-terminal pro-B type natriuretic peptide (NT-proBNP) has been advocated as a valuable biomarker in patients with HF. NT-proBNP is elevated and its serum concentra-

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Table 1. Baseline Characteristics of Study Patients

Characteristic	Total (n=2,280)	Men (n=1,119)	Women (n=1,161)	P value*
Age, years	67.9±14.3	64.6±14.4	71.0±13.5	<0.001
BMI, kg/m^2	23.1±3.9	23.4±3.9	22.7±3.9	<0.001
SBP, mmHg	131±29	129±29	132±30	0.035
DBP, mmHg	77.9±18.2	78.2±19.0	77.7±17.3	0.459
Heart rate, beats/min	91.0±25.6	90.4±24.7	91.6±26.4	0.275
Previous medical history, %				
HF	30.2	30.5	29.8	0.715
Myocardial infarction	15.4	18.3	12.7	<0.001
Chronic kidney disease	8.9	9.7	8.2	0.130
Hypertension	47.4	44.9	49.8	0.019
Diabetes mellitus	30.5	30.4	30.7	0.885
Underlying conditions, %				
Ischemic	42.4	46.3	38.5	
Non-ischemic	51.9	48.1	55.6	0.001
Unknown	5.7	5.6	5.8	
Laboratory findings				
Hemoglobin, g/dL	12.4±2.3	13.1±2.3	11.6±2.0	<0.001
BUN, mg/dL	24.7±15.5	25.3±16.0	24.2±14.9	0.083
Creatinine, mg/dL	1.49±1.31	1.61±1.36	1.37±1.24	<0.001
Sodium, mEq/L	138±5	138±4	138±5	0.670
NT-proBNP, pg/mL	8,481±9,843	7,543±9,274	9,385±10,285	<0.001
Echocardiographic findings				
LVEDD, mm	56.7±10.2	59.3±10.2	54.1±9.6	<0.001
LVESD, mm	44.3±12.1	47.4±12.0	41.4±11.5	<0.001
LVEF, %	39.5±15.8	36.7±15.0	42.2±16.2	<0.001
Left atrial size, mm	56.6±32.2	56.0±32.9	57.3±31.6	0.603
Medications at discharge, %	n=2,148	n=1,048	n=1,100	
β-blockers	40.6	39.8	41.3	0.530
RAS-blockers	46.8	47.1	46.5	0.783

*P values were obtained from the comparisons between men and women. BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; HF, heart failure; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; NT-proBNP, N-terminal-pro-brain natriuretic peptide; RAS, renin-angiotensin system; SBP, systolic blood pressure.

tion is closely associated with mortality and hospitalization in patients with HF.[4–8]

There are substantial differences between men and women in the pathophysiology and disease manifestations of HF.[9–11] However, studies focusing on gender differences in biomarkers for HF have been scarce. Although several studies have indicated different blood levels of brain natriuretic peptide (BNP) or NT-proBNP between genders,[12–15] only a few studies have performed gender-specific analysis in the prognostic value of these biomarkers in HF. Nevertheless, their results are still conflicting.[12,16]

Data on gender differences for the prognostic value of NT-proBNP is essential for the interpretation of NT-proBNP results, and it would provide additional guidance of HF therapy. Therefore, the present study was performed to investigate whether there are gender differences in the ability of NT-proBNP levels to predict mortality and HF readmission in HF patients.

Methods

Study Population

Study data was derived from the nationwide registry of HF, involving 24 well-qualified cardiac centers in Korea.[17] Between June 2004 and April 2009, patients hospitalized for HF were asked to participate in the registry. HF on admission was diagnosed according to the Framingham criteria,[18] and the diagnosis was confirmed again at the time of hospital discharge. Patients' data was entered into the Korean Heart Failure (KorHF) Registry database via a web-based electronic data capture system that included an electronic case report form.[17] Data collection and audition were performed by the KorHF Registry Steering Committee at the Korean Society of Heart Failure. Among initially screened 3,427 patients with HF, NT-proBNP was available in 2,280 patients (66.5%), and these patients were analyzed in this study. This study complies with the Declaration of Helsinki, and the institutional review board at each participating hospital approved the study protocol. Written informed consent was obtained from each study patient.

Data Collection

Patient's height and body weight were measured at the time of admission. Body mass index (BMI) was calculated by dividing weight in kilograms by height squared in

meters. Systolic and diastolic blood pressure (SBP and DBP) and heart rate were measured by a trained nurse using an oscillometric device. Information on previous medical history or concomitant medical problems including HF, myocardial infarction, chronic kidney disease, hypertension and diabetes mellitus was obtained. HF etiology was classified as ischemic or non-ischemic. Major laboratory parameters suggested as prognostic markers in HF were measured using a venous blood sample. These parameters included hemoglobin, blood urea nitrogen, creatinine and sodium. Transthoracic echocardiography was performed, and left ventricular (LV) dimensions, LV ejection fraction (LVEF) and left atrial size were measured according to the current guidelines.[19] Medications at the time of discharge were also reviewed, and information on the use of β-blocker, renin-angiotensin system (RAS) blockers including angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker was collected.

Clinical Events

Three types of clinical events focused in this study were: (1) in-hospital mortality; (2) all-cause mortality after discharge; and (3) composite events including all-cause mortality and HF readmission during follow up. Clinical events were assessed by research coordinators by reviewing medical records, and telephone contact was performed if necessary using a standardized report form.

NT-ProBNP Measurement

NT-proBNP was measured at the time of admission with the electro-chemiluminescence immunoassay method using an Elecsys 2010 analyzer (Roche Diagnostics) or NT-proBNP assay for Dimension platform (Siemens Medical Solutions Diagnostics).[20]

Statistical Analysis

Continuous variables are presented as mean±standard deviation (SD), and categorical variables are expressed as percentages. Univariate comparisons between men and women were performed using Student's t-test for continuous variables and the chi-squared test for dichotomous variables. Age-adjusted mean values of NT-proBNP were compared between genders using analysis of covariance (ANCOVA). Multiple binary logistic regression analysis was performed to determine an independent association between NT-proBNP and in-hospital mortality. After excluding patients with in-hospital mortality, Cox proportional hazard analysis was performed to determine independent associations of NT-proBNP with mortality and composite events after discharge. The following variables were considered potential confounders and adjusted during the multivariable analyses:[17] age (<65 vs. ≥65 years), BMI (<23 vs. ≥23 kg/m^2),[21] prior history of HF, HF etiology, SBP (≥100 vs. <100 mmHg), heart rate (<100 vs. ≥100 beats/min), hemoglobin (≥12 vs. <12 g/dL),[22] creatinine (<2.0 vs. ≥2.0 mg/dL),[23] sodium (≥135 vs. <135 mEq/L), LVEF (≥50 vs. <50%) and HF medications at discharge. Kaplan-Meier survival curves with log-rank comparison were plotted to demonstrate different event rates according to NT-proBNP values in men and women. NT-proBNP was categorized into three groups based on tertiles during multivariable analysis and Kaplan-Meier survival analysis. A P value of <0.05 was considered statistically significant. All statistical analyses were conducted using SPSS version 18.0 (IBM Co., Armonk, NY, USA).

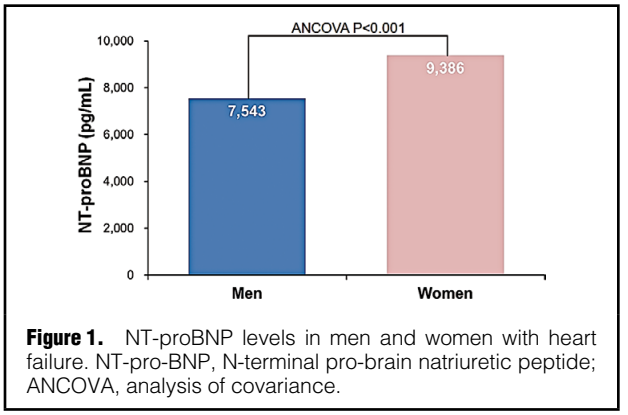

Figure 1. NT-proBNP levels in men and women with heart failure. NT-pro-BNP, N-terminal pro-brain natriuretic peptide; ANCOVA, analysis of covariance.

Results

Baseline Clinical Characteristics

The baseline clinical characteristics of the study patients are shown in **Table 1**. The mean age of the total study population was 67.9±14.3 years. The study patients consisted of 1,119 men (49.1%) and 1,161 women (50.9%). Women were older than men (71.0±13.5 vs. 64.6±14.4 years, P<0.001), and had smaller BMIs. SBP at the time of admission was higher in women than in men. The incidence of prior myocardial infarction was higher in men and the incidence of hypertension was higher in women. The incidence of ischemic etiology of HF was higher in men than in women. In laboratory findings, the hemoglobin level was lower and renal function was better in women than in men. Discharge medications including β-blocker

Table 2. Clinical Events

	Total	Men	Women	P value*
In-hospital mortality				
n	2,280	1,119	1,161	
In-hospital mortality, n (%)	132 (5.8)	71 (6.3)	61 (5.2)	0.276
Event after discharge				
n	2,148	1,048	1,100	
Mortality, n (%)	694 (32.3)	337 (32.1)	357 (32.4)	0.742
Mortality+HF admission, n (%)	1,067 (49.7)	503 (48.0)	564 (51.2)	0.129

*P values were obtained from the comparisons between men and women. HF, heart failure.

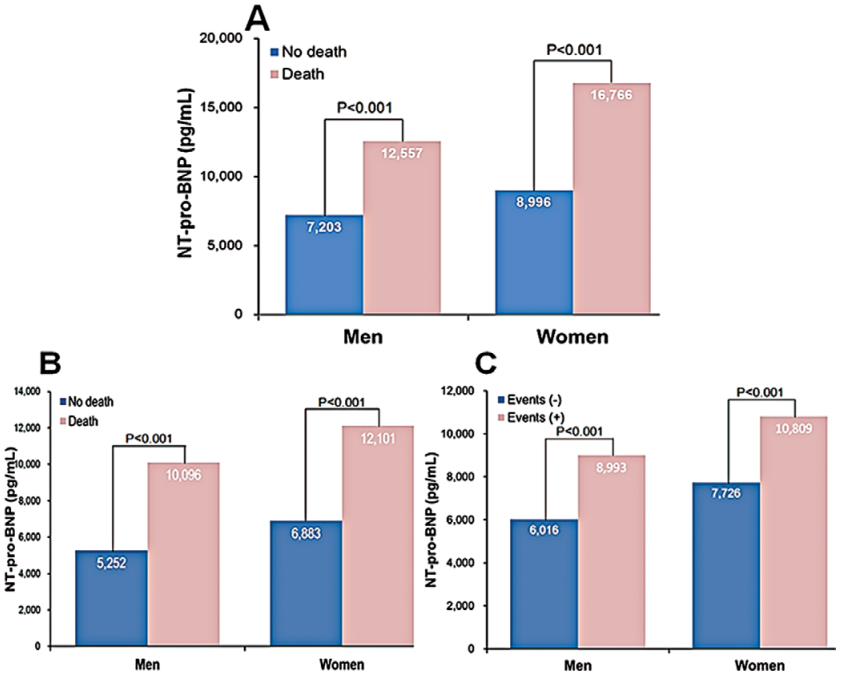

Figure 2. NT-proBNP levels according to in-hospital mortality (**A**) and all-cause mortality (**B**) and composite events (**C**) during follow up in men and women with heart failure. NT-pro-BNP, N-terminal-pro-brain natriuretic peptide.

Table 3. Independent Predictors for In-Hospital Mortality

Variable	Men		Women	
	OR (95% CI)	P value	OR (95% CI)	P value
Age ≥65 years	1.05 (0.47–2.35)	0.895	1.37 (0.48–3.91)	0.548
BMI ≥23 kg/m^2	1.48 (0.68–3.22)	0.314	1.18 (0.52–2.67)	0.680
Prior history of HF	1.36 (0.63–2.94)	0.427	3.03 (1.30–7.05)	0.010
Ischemic cause of HF	0.94 (0.52–1.68)	0.843	1.29 (0.70–2.38)	0.407
SBP <100 mmHg	2.31 (0.94–5.68)	0.067	1.84 (0.61–5.54)	0.278
Heart rate ≥100 beats/min	1.11 (0.50–2.46)	0.796	1.25 (0.54–2.88)	0.601
Hemoglobin <12 g/dL	1.36 (0.58–3.15)	0.471	1.12 (0.45–2.79)	0.805
Serum creatinine ≥2.0 mg/dL	3.14 (1.35–7.27)	0.008	4.92 (1.96–12.33)	0.001
Sodium <135 mEq/L	1.50 (0.67–3.35)	0.318	3.81 (1.71–8.50)	0.001
LVEF <50%	0.87 (0.34–2.24)	0.783	1.52 (0.58–4.02)	0.391
NT-proBNP				
Lowest tertile	1		1	
Middle tertile	1.21 (0.40–3.65)	0.728	1.05 (0.33–3.38)	0.925
Highest tertile	2.32 (0.80–6.68)	0.118	1.16 (0.36–3.72)	0.793

CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

and RAS-blockers were not different between genders. Women had a smaller LV size and better LV systolic function than men on echocardiographic examinations. The serum NT-proBNP level was significantly higher in women than in men, even after controlling for aging effect (9,385±10,285 vs. 7,543±9,274 pg/mL, ANCOVA, P<0.001) (**Figure 1**).

Clinical Events and NT-ProBNP

The incidences of clinical events are demonstrated in **Table 2**. A total of 132 patients (5.8%) died during initial hospitalization. There was no gender difference in in-hospital mortality (6.3% in men vs. 5.2% in women, P=0.276). During the mean follow-up duration of 1,245±824 days (median, 1,431 days; interquartile range, 418–1,979 days), there were 694 mortality cases (32.3%) and 1,067 cases of composite events (all-cause mortality+HF readmission) (49.7%). There were no gender differences in the occurrences of these events (mortality, 32.1% in men vs. 32.4% in women, P=0.742; composite events, 48.0% in men vs. 51.2% in women, P=0.129). NT-proBNP levels were significantly higher in patients with any events including in-hospital mortality (14,502±13,071 vs. 8,119±9,494 pg/mL, P<0.001), mortality after discharge (10,465±10,707 vs. 6,077±7,636 pg/mL, P<0.001) and composite events after discharge (9,374±10,145 vs. 6,864±8,620 pg/mL, P<0.001)

Table 4. Independent Predictors for Mortality After Discharge

Variable	Men		Women	
	HR (95% CI)	P value	HR (95% CI)	P value
Age ≥65 years	2.84 (1.94–4.17)	<0.001	2.31 (1.51–3.47)	<0.001
BMI ≥23 kg/m^2	0.65 (0.47–0.89)	0.007	0.72 (0.54–0.95)	0.024
Prior history of HF	1.77 (0.94–1.77)	0.104	1.03 (0.75–1.41)	0.825
Ischemic cause of HF	1.39 (1.02–1.89)	0.036	1.19 (0.88–1.62)	0.242
SBP <100 mmHg	0.82 (0.50–1.33)	0.425	1.25 (0.74–2.10)	0.395
Heart rate ≥100 beats/min	0.83 (0.59–1.17)	0.305	1.15 (0.85–1.55)	0.348
Hemoglobin <12 g/dL	1.37 (0.99–1.91)	0.056	1.15 (0.84–1.58)	0.371
Serum creatinine ≥2.0 mg/dL	1.56 (1.05–2.32)	0.026	2.25 (1.45–3.47)	<0.001
Sodium <135 mEq/L	0.96 (0.66–1.41)	0.858	2.02 (1.43–2.84)	<0.001
LVEF <50%	1.21 (0.81–1.79)	0.334	0.94 (0.69–1.28)	0.720
β-blocker use	0.83 (0.60–1.15)	0.267	1.08 (0.80–1.46)	0.575
RAS-blocker use	0.80 (0.58–1.09)	0.169	0.62 (0.46–0.84)	0.002
NT-proBNP				
Lowest tertile	1		1	
Middle tertile	1.84 (1.21–2.81)	0.004	0.79 (0.55–1.14)	0.223
Highest tertile	2.31 (1.49–3.56)	<0.001	1.41 (0.96–2.05)	0.075

Abbreviations as in Tables 1,3.

Table 5. Independent Predictors for Composite Events After Discharge

Variable	Men		Women	
	HR (95% CI)	P value	HR (95% CI)	P value
Age ≥65 years	1.81 (1.39–2.37)	<0.001	2.34 (1.71–3.19)	<0.001
BMI ≥23 kg/m^2	0.90 (0.71–1.15)	0.421	0.83 (0.66–1.04)	0.107
Prior history of HF	1.73 (1.35–2.21)	<0.001	1.50 (1.17–1.91)	0.001
Ischemic cause of HF	1.01 (0.79–1.29)	0.918	1.11 (0.87–1.42)	0.363
SBP <100 mmHg	0.58 (0.63–1.29)	0.904	1.23 (0.83–1.82)	0.285
Heart rate ≥100 beats/min	0.90 (0.69–1.17)	0.456	0.95 (0.75–1.21)	0.730
Hemoglobin <12 g/dL	1.24 (0.94–1.62)	0.117	0.92 (0.72–1.17)	0.537
Serum creatinine ≥2.0 mg/dL	1.41 (0.93–1.96)	0.035	1.59 (0.97–2.59)	0.110
Sodium <135 mEq/L	1.27 (0.94–1.71)	0.116	1.60 (1.20–2.13)	0.001
LVEF <50%	1.05 (0.78–1.41)	0.727	1.31 (1.02–1.68)	0.033
β-blocker use	0.86 (0.68–1.10)	0.253	0.97 (0.77–1.23)	0.852
RAS-blocker use	1.01 (0.78–1.27)	0.988	0.71 (0.56–0.91)	0.006
NT-proBNP				
Lowest tertile	1			
Middle tertile	1.51 (1.11–2.05)	0.007	0.93 (0.70–1.22)	0.610
Highest tertile	1.74 (1.25–2.43)	0.001	1.17 (0.87–1.56)	0.279

Abbreviations as in Tables 1,3.

than in those without. These results were consistent in both men (12,557±13,200 vs. 7,203±8,858 pg/mL, P<0.001 for in-hospital mortality [**Figure 2A**]; 10,096±10,011 vs. 5,252±7,036 pg/mL, P<0.001 for mortality after discharge [**Figure 2B**]; and 8,993±9,405 vs. 6,016±8,140 pg/mL, P<0.001 for composite events after discharge [**Figure 2C**]) and women (16,766±12,652 vs. 8,996±9,996 pg/mL, P<0.001 for in-hospital mortality [**Figure 2A**]; 12,101±11,275 vs. 6,883±8,104 pg/mL, P<0.001 for mortality after discharge [**Figure 2B**]; and 10,809±10,708 vs. 7,726±9,008 pg/mL, P<0.001 for composite events after discharge [**Figure 2C**]).

Prognostic Value of NT-ProBNP

Multivariable binary logistic regression analyses were performed to investigate independent predictors of in-hospital mortality (**Table 3**). Among potential variables, renal dysfunction (serum creatinine ≥2.0 mg/dL) was an independent predictor of in-hospital mortality in men (P<0.05). In women, prior history of HF, renal dysfunction (serum creatinine ≥2.0 mg/dL) and hyponatremia (serum sodium <135 mEq/L) were independent predictors of in-hospital mortality (P<0.05 for each). The predictive value of NT-proBNP in in-hospital mortality was not observed in either men or women in these multivariable analyses (P>0.05 for each). Multivariable Cox regression analyses were performed to investigate independent predictors of all-cause mortality after discharge (**Table 4**). Old age, low BMI, ischemic etiology of HF, and impaired renal function were independent predictors of mortality after discharge in men (P<0.05 for each). A higher NT-proBNP level was also

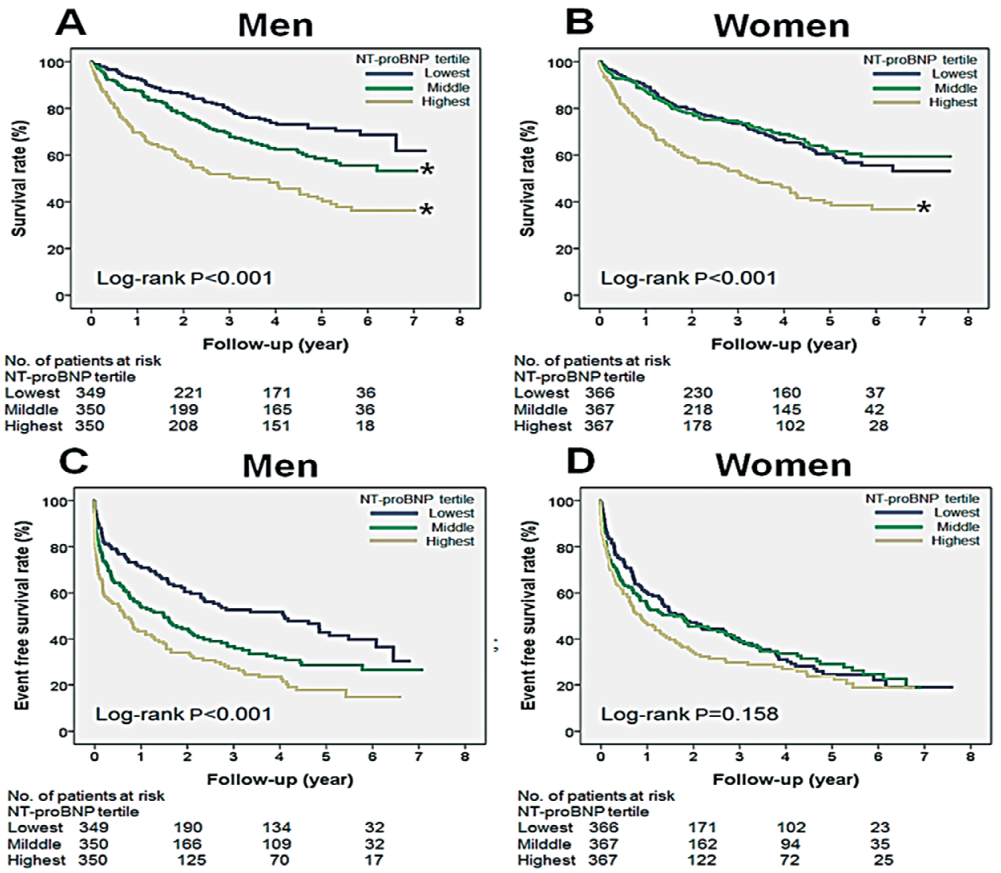

Figure 3. Survival rates (**A**,**B**) and event-free survival rates (**C**,**D**) according to NT-proBNP tertiles in men and women with heart failure. NT-pro-BNP, N-terminal-pro-brain natriuretic peptide.

significantly associated with mortality after discharge in men (highest vs. lowest tertile: hazard ratio [HR], 2.31; 95% confidence interval (CI), 1.49–3.56; P<0.001). In women, old age, low BMI, low serum sodium, impaired renal function and non-use of a RAS blocker were independently associated with mortality (P<0.05 for each). However, the same multivariable analysis showed that the predictive value of NT-proBNP was not significant in women (P>0.05). The independent predictors of composite events are shown in **Table 5**. Old age, HF history, and impaired renal function were associated with composite events in men (P<0.05 for each). A higher NT-proBNP was also an independent predictor of composite events in men (highest vs. lowest tertile: HR, 1.74; 95% CI, 1.25–2.43; P=0.001). In women, old age, HF history, low serum sodium, low LVEF and non-use of a RAS-blockers were associated with composite events (P<0.05 for each). However, NT-proBNP was not associated with the occurrence of composite events in women (P>0.05). Kaplan-Meier survival curves demonstrated that NT-proBNP value in the prediction of mortality was more pronounced in men compared to women (**Figure 3A**,**B**). Kaplan-Meier survival curves demonstrated significantly different composite event-free survival rates according to NT-proBNP tertiles in men (log-rank P<0.001) but not in women (log-rank P=0.158) (**Figure 3C**,**D**).

Discussion

The aim of this study was to investigate gender differences in the prognostic value of NT-proBNP in patients hospitalized for HF. There was no NT-proBNP value in the prediction of in-hospital mortality in either gender. The NT-proBNP level was independently associated with long-term clinical events including mortality and HF readmission in men. Otherwise, a higher NT-proBNP level was associated with a higher event rate in univariate analysis, but the prognostic power of NT-proBNP was diminished to be statistically insignificant after controlling for potential confounders in multivariable analysis in women.

The role of NT-proBNP in the prediction of future cardiovascular events in patients with HF has been widely acknowledged.[4–8] Our study also showed similar findings that NT-proBNP levels were a significant independent predictor of mortality and HF readmission in the total study population (data not shown). However, there has been limited data on gender-specific analysis of the prognostic value of NT-proBNP in HF. In our study, more specific analysis by gender stratification showed that long-term prognostic value of NT-proBNP was significant only in men but not in women. In agreement with our findings, Nakada et al demonstrated that high BNP levels were associated with long-term cardiovascular mortality and

HF admission in men but not in women among 748 consecutive patients with acute decompensated HF.[16] Meyer et al performed gender comparisons in 351 men and 215 women with HF, and demonstrated gender-stratified Kaplan-Meier survival curves for 3-year all-cause mortality based on NT-proBNP.[24] Much to our surprise, the survival graph patterns are very similar to those shown in our study (**Figure 3**). Duschek et al assessed the prognostic value of NT-proBNP in 205 elderly patients undergoing carotid endarterectomy, although they were not HF patients, and showed that the pre-operative plasma level of NT-proBNP is a predictive marker for long-term survival in men but not in women.[25] In contrast to those studies, a study by Christ et al involving 452 patients with acute dyspnea indicated that a higher BNP level was a more powerful predictor of death in women compared to men.[26] Hsich et al analyzed 99,930 HF patients, and showed that BNP levels were correlated with in-hospital mortality in both genders after controlling for 20 clinical variables.[12] However, gender difference in the prognostic values of BNP in long-term clinical outcomes were not assessed in that study.[12] Similar to this study, Franke et al followed up 2,019 men and 530 women with chronic HF for 5 years, and showed that NT-proBNP levels correlate well with survival rates in both genders.[27] However, the disproportion of men and women in this study should be considered when interpreting the results. In these current literatures, discrepancies regarding gender-related BNP or NT-proBNP values are mainly attributed to different study populations, clinical end-points, follow-up periods and HF management. These conflicting results warrant further well-designed studies in the future.

Mechanistic explanation for gender differences in prognostic value of NT-proBNP was not provided by our study. Complex pathophysiology such as different hormonal influences, gender-specific molecular mechanisms, co-morbidities, and psychosocial factors may play a role. Previous data suggest that the production and release of NT-proBNP are significantly different according to gender, and that sex hormones play a role interacting with regulation of neurohormones, including natriuretic peptide.[13,15,28] Specifically, it has been suggested that blood NT-proBNP levels are decreased by testosterone and increased by estrogen.[13] Indeed, age-adjusted NT-proBNP levels were significantly higher in women than in men in our study, which is in good agreement with the results of prior studies.[12–15] However, whether gender difference in NT-proBNP biology and its circulating levels influences the prognostic ability of NT-proBNP remains unclear. A plausible explanation is that different clinical characteristics such as age, BMI, blood pressure, HF etiology, laboratory findings and LV size and function between men and women might have an effect on the ability of NT-proBNP to predict future events. Nevertheless, gender differences in NT-proBNP value were obvious, even after controlling for these potential confounders in our multivariable analyses. A recent study by Kang et al analyzed 528 HFpEF and 1,142 HFrEF patients from the KorHF registry, and showed that the plasma level of NT-proBNP is a powerful prognostic factor in both HFpEF and HFrEF.[20] In addition, we controlled the effect of LVEF in multivariable analysis. Therefore, it may be hard to consider a higher incidence of HFpEF in women than in men as a potential mechanism for gender-specific value of NT-proBNP. Further investigations are needed to elucidate its underlying pathophysiology.

Our results suggest that NT-proBNP may be a more appropriate test to predict long-term future events in men compared to women. This information provides us with further insight into different biological bases of HF between men and women, and emphasizes the need of gender-specific approach for the best use of NT-proBNP.

Several limitations of our study should be addressed. As only 66.5% of patients with available NT-proBNP were selected from the registry database, there was a possibility of selection bias. The lack of data on sex hormones or menopausal status did not confer possible relationships between estrogen levels and the prognostic value of NT-proBNP. As all of our study patients were Korean, direct application of our results to other ethnic groups may therefore be difficult. Lack of information on the dosage and adherence of cardiovascular drugs, and device therapy such as implantable cardioverter-defibrillator or cardiac resynchronization therapy is another limitation of this study, because these factors might have an effect on patient outcomes.

In conclusion, NT-proBNP may be a stronger predictor of long-term mortality and HF re-admission in men than in women with HF. The gender effect should be considered in the use of NT-proBNP for the better management strategy in HF patients.

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Conflicts of Interest

The authors declare there is no conflict of interest associated with this manuscript.

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