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Original Article

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The Impact of Body Mass Index on the Prognostic Value of N-Terminal proB-Type Natriuretic Peptide in Patients with Heart Failure: an Analysis from the Korean Heart Failure (KorHF) Registry

Hack-Lyoung Kim, MD, PhD[1], Myung-A Kim, MD, PhD[1], Sohee Oh, PhD[2], Dong-Ju Choi, MD, PhD[3], Seongwoo Han, MD, PhD[4], Eun-Seok Jeon, MD, PhD[5], Myeong-Chan Cho, MD, PhD[6], Jae-Joong Kim, MD, PhD[7], Byung-Su Yoo, MD, PhD[8], Mi-Seung Shin, MD, PhD[9], Seok-Min Kang, MD, PhD[10], Shung Chull Chae, MD, PhD[11], Kyu-Hyung Ryu, MD, PhD[4], and on behalf of the Korean Heart Failure Registry

[1]Division of Cardiology, Department of Internal Medicine, Boramae Medical Center, Seoul National University College of Medicine, Seoul, Korea
[2]Department of Biostatistics, Boramae Medical Center, Seoul, Korea
[3]Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea
[4]Department of Cardiovascular Medicine, Dongtan Sacred Heart Hospital, College of Medicine, Hallym University, Hwaseong, Korea
[5]Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University College of Medicine, Seoul, Korea
[6]Department of Internal Medicine, Chungbuk National University College of Medicine, Cheongju, Korea
[7]Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[8]Department of Internal Medicine, Yonsei University Wonju Christian Hospital, Wonju, Korea
[9]Department of Internal Medicine, Gachon University Gil Hospital, Incheon, Korea
[10]Department of Internal Medicine, Yonsei University Severance Hospital, Seoul, Korea
[11]Department of Internal Medicine, Kyungpook National University College of Medicine, Daegu, Korea

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Correspondence to
Myung-A Kim, MD, PhD
Division of Cardiology, Department of Internal Medicine, Boramae Medical Center, Seoul National University College of Medicine, 20, Boramae-ro 5-gil, Dongjak-gu, Seoul 07061, Korea.
E-mail: kma@snu.ac.kr

ORCID iDs
Hack-Lyoung Kim
https://orcid.org/0000-0002-6703-1472
Myung-A Kim
https://orcid.org/0000-0002-3064-7118
Sohee Oh
https://orcid.org/0000-0002-3010-448X
Dong-Ju Choi
https://orcid.org/0000-0003-0146-2189
Seongwoo Han
https://orcid.org/0000-0002-0327-5021
Eun-Seok Jeon
https://orcid.org/0000-0002-9946-5611
Myeong-Chan Cho
https://orcid.org/0000-0002-0047-0227
Jae-Joong Kim
https://orcid.org/0000-0002-2714-2282

ABSTRACT

Background and Objectives: Although an inverse correlation between the level of amino (N)-terminal pro-brain natriuretic peptide (NT-proBNP) and body mass index (BMI) has been reported, the impact of BMI on the prognostic value of NT-proBNP has not been well addressed.
Methods: A total of 1,877 patients (67-year-old and 49.9% females) hospitalized for acute heart failure (HF) with documented NT-proBNP levels at baseline were included. Patients were classified into 2 groups by BMI (nonobese: BMI<23 kg/m^2 and overweight or obese: BMI≥23 kg/m^2). Clinical events during the follow-up including all-cause mortality and HF readmission were assessed.
Results: During the median follow-up of 828 days (interquartile range, 111–1,514 days), there were 595 cases of total mortality (31.7%), 600 cases of HF readmission (32.0%), and 934 cases of composite events (49.8%). In unadjusted analyses, higher NT-proBNP level was associated with all-cause mortality and composite events (all-cause mortality and HF readmission) in both patients with BMI<23 kg/m^2 and those with BMI≥23 kg/m^2. In adjusted analyses controlling for potential confounders, however, a higher NT-proBNP level was

Byung-Su Yoo
https://orcid.org/0000-0002-3395-4279
Mi-Seung Shin
https://orcid.org/0000-0002-0273-0109
Seok-Min Kang
https://orcid.org/0000-0001-9856-9227
Shung Chull Chae
https://orcid.org/0000-0002-9871-6976
Kyu-Hyung Ryu
https://orcid.org/0000-0001-9329-2716

Conflict of Interest
The authors have no financial conflicts of interest.

Author Contributions
Conceptualization: Kim HL, Kim MA; Data curation: Oh S, Choi DJ, Han S, Jeon ES, Cho MC, Kim JJ, Yoo BS, Shin MS, Kang SM, Chae SC, Ryu KH; Formal analysis: Kim HL, Oh S; Resources: Choi DJ, Jeon ES, Cho MC, Ryu KH; Supervision: Kim MA; Validation: Kim MA; Writing - original draft: Kim HL; Writing - review & editing: Han S, Kim JJ, Yoo BS, Shin MS, Kang SM, Chae SC.

associated with all-cause mortality and composite events in patients with BMI<23 kg/m^2, but not in those with BMI≥23 kg/m^2.
Conclusions: The prognostic value of NT-proBNP was more significant in nonobese patients than in overweight and obese patients in this HF population. BMI should be considered when NT-proBNP is used for risk estimation in HF patients.

Keywords: Body mass index; Heart failure; NT-proBNP; Prognosis; Obesity

INTRODUCTION

Although methods for the prevention and management of heart failure (HF) have been much improved during recent several decades, HF is highly prevalent and HF outcome is still poor.[1] Obesity is one of the risk factors for cardiovascular disease and HF.[2] The prevalence of obesity is constantly increasing, and it becomes a major public health concern globally.[3] As a cardiac biomarker, the diagnostic and prognostic value of amino (N)-terminal pro-brain natriuretic peptide (NT-proBNP) is well established.[4-6] Recently, inverse relationship between NT-proBNP and body mass index (BMI) has been reported.[7][8] Decreased production and increased clearance of natriuretic peptide in obese patients has been suggested as possible mechanisms.[9-11] On this background, it can be postulated that the prognostic utility of NT-proBNP may differ between obese and nonobese patients, which have also raised concerns about the prognostic value of NT-proBNP in obese patients with HF. However, it is not well-determined whether the prognostic power of NT-proBNP is modified by BMI. Although there are several observational studies on this issue, most studies are performed in Western countries, and their results are still conflicting.[12-14] Therefore, this study was performed to investigate the effect of BMI on the predictive value of NT-proBNP in Korean patients with HF.

METHODS

Study population

Study data was derived from the Korean Heart Failure (KorHF) Registry, which included participation of 24 well-qualified cardiac centers in Korea. Information regarding the KorHF Registry has previously been described.[15] Briefly, patients hospitalized for HF between June 2004 and April 2009 were enrolled in the registry. HF on admission was diagnosed according to the Framingham criteria,[16] and the diagnosis was confirmed at the time of hospital discharge. Patients' data was entered into the KorHF Registry database via a web-based electronic data capture system that included an electronic case report form.[15] Data collection and audition were performed by the KorHF Registry Steering Committee at the Korean Society of HF. Among 3,427 patients with HF initially screened, both BMI and NT-proBNP were available in 2,280 (66.5%), who were analyzed in this study. This study complies with the Declaration of Helsinki, and the Institutional Review Board (IRB) at each participating hospital approved the study protocol (IRB number of Boramae Medical Center was 07-2019-39). Written informed consent was obtained from each study patient.

BMI criteria

Patient's height and body weight were measured at the time of admission. BMI was calculated by dividing weight in kilograms by height squared in meters. For Korean population, there is an increase in morbidity from the BMI of 23 kg/m^2 and an increase in mortality from the BMI

of 25 kg/m^2. According to the Korean guideline, overweight is defined as a BMI of 23 to 24.9 kg/m^2, and obesity as a BMI≥25 kg/m^2.[17] As only 28.9% of the patients had a BMI≥25 kg/m^2, we used a BMI of 23 kg/m^2 for the stratification in this study. About half of patients (48.4%) had BMI of≥23 kg/m^2 in this study.

Data collection

Systolic and diastolic blood pressures 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 was classified etiologically as ischemic or non-ischemic. Major laboratory parameters suggested as prognostic markers in HF were measured using 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 and left atrial size were measured according to the current guidelines.[18] Medications at the time of discharge were also reviewed, and information on the use of beta-blocker, renin-angiotensin system-blockers including angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker was collected.

NT-proBNP testing

NT-proBNP was measured at the time of admission with the electro-chemiluminescence immunoassay method using an Elecsys 2010 analyzer (Roche Diagnostics, Basel, Switzerland) or NT-proBNP assay for Dimension platform, Siemens Medical Solutions Diagnostics.[19]

Clinical events

Two types of clinical events were focused in this study, which included all-cause mortality and composite events including all-cause mortality and HF readmission during the follow-up. Clinical events were assessed by research coordinators through reviewing medical records and telephone contact was performed if needed, using the standardized report form. HF readmission was defined as hospitalization for clinical manifestations of worsening HF resulting in the new administration of intravenous drugs, mechanical or surgical intervention, or hemodialysis for the management of HF.

Statistical analysis

Continuous variables are presented as mean±standard deviation, and categorical variables are expressed as percentages. Univariate comparisons between patients with BMI≥23 kg/m^2 and those with BMI<23 kg/m^2 were performed using Student's t-test for continuous variables and the χ^2 test for dichotomous variables. The mean values of NT-proBNP were compared among patients according to the BMI criteria using analysis of variance. Scatter plots were used to demonstrate correlation between log-transformed NT-proBNP and BMI. Correlation coefficients were obtained using Pearson's correlation. 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: age, systolic blood pressure, heart rate, hypertension, ischemic etiology of HF, blood levels of hemoglobin, sodium, and creatinine, LV ejection fraction, and medications including beta-blocker and renin-angiotensin system blocker. Kaplan-Meier survival curves with log-rank comparison were plotted to demonstrate different event rates according to NT-proBNP values in patients with BMI≥23 kg/m^2 and those with BMI<23 kg/m^2. For adjustment for confounding factors, Cox

regression survival plots were generated. NT-proBNP was categorized into 3 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 Corp., Armonk, NY, USA).

RESULTS

Baseline clinical characteristics of the study patients

The baseline clinical characteristics of the study patients according to BMI are shown in **Table 1**. Patients with BMI≥23 kg/m^2 were older, male dominant and had worse cardiovascular risk profiles including higher blood pressure, and higher prevalence of hypertension and diabetes mellitus than those with BMI<23 kg/m^2. Beta-blocker and RAS blocker were more frequently prescribed to patients with BMI≥23 kg/m^2 than to those with BMI < 23 kg/m^2. The NT-proBNP levels were significantly higher in patients with BMI≥23 kg/m^2 than in those with BMI<23 kg/m^2 (6,259±8,086 vs. 9,690±10,238 pg/mL, p<0.001). There was an inverse relationship between the NT-proBNP level and BMI (p<0.001) (**Figure 1**).

Prognostic value of NT-proBNP according to BMI

During the median follow-up of 828 days (interquartile range, 111–1,514 days), there were 595 cases of all-cause mortality (31.7%), 600 cases of HF readmission (32.0%), and 934 cases of composite events (49.8%). Unadjusted and adjusted risks of NT-proBNP for mortality are

Table 1. Baseline characteristics of study patients

Characteristic	BMI<23 kg/m^2 (n=968)	BMI≥23 kg/m^2 (n=909)	p value
Age (years)	70.1±13.4	64.3±14.5	<0.001
Female (sex)	54.9	44.7	<0.001
Systolic blood pressure (mmHg)	129±29	133±29	<0.001
Diastolic blood pressure (mmHg)	76.7±16.8	79.8±19.0	<0.001
Heart rate (beat/min)	91.6±25.4	88.7±25.5	0.016
Combined medical conditions			
Hypertension	43.2	53.4	<0.001
Diabetes mellitus	27.9	34.3	0.003
Previous heart failure	32.2	29.5	0.238
Previous myocardial infarction	16.1	15.2	0.578
Underlying conditions			0.041
Ischemic	39.5	35.2	
Non-ischemic	48.7	49.5	
Unknown	11.9	15.3	
Laboratory findings			
Hemoglobin (g/dL)	12.0±2.2	12.9±2.3	<0.001
Blood urea nitrogen (mg/dL)	24.8±15.1	23.4±14.5	0.049
Creatinine (mg/dL)	1.47±1.33	1.47±1.30	0.964
Sodium (mEq/L)	138±5	139±4	0.060
NT-proBNP (pg/mL)	9,690±10,238	6,259±8,086	<0.001
Echocardiographic findings			
LV end-diastolic dimension (mm)	57.2±10.3	57.8±10.1	0.001
LV end-systolic dimension (mm)	44.3±12.1	43.9±12.2	0.354
LV ejection fraction (%)	38.8±15.5	40.2±16.2	0.063
Left atrial size (mm)	56.6±28.9	56.8±30.1	0.001
Medications at discharge			
Beta-blocker	38.5	45.1	0.010
Renin-angiotensin system blocker	45.8	51.9	0.008

Data are expressed as the mean±standard deviation or number (%).
BMI = body mass index; NT-proBNP = N-terminal pro-B-type natriuretic peptide; LV = left ventricular.

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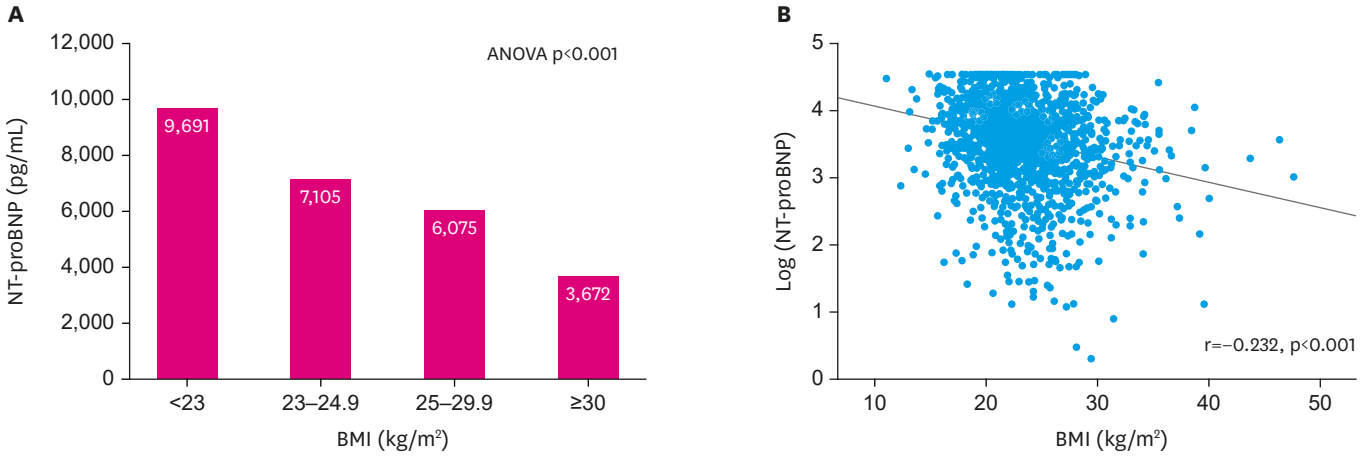

Figure 1. Association between BMI and NT-proBNP. (A) The mean value of NT-proBNP according to the category of BMI, (B) scatter plot showing the negative correlation between BMI and log (NT-proBNP) concentration.
NT-proBNP = amino (N)-terminal pro-brain natriuretic peptide; BMI = body mass index; ANOVA = analysis of variance.

demonstrated in **Table 2**. In unadjusted analyses, a higher NT-proBNP level was associated with increased mortality risk in the total population, and in both patients with BMI<23 kg/m^2 and BMI≥23 kg/m^2. In adjusted analyses controlling for potential confounders, a higher NT-proBNP level was associated with increased mortality risk in the total population (highest vs. lowest tertile; hazard ratio [HR], 1.76; 95% confidence interval [CI], 1.34–2.31; p<0.001) and in patients with BMI<23 kg/m^2 (highest vs. lowest tertile; HR, 2.24; 95% CI, 1.54–3.25; p<0.001) but not in those with BMI≥23 kg/m^2 (p>0.05). Unadjusted and adjusted risks of NT-proBNP for composite events is shown in **Table 3**. In unadjusted analyses, a higher NT-proBNP level was associated with increased composite event risk in the total population, and in both patients with BMI<23 kg/m^2 and BMI≥23 kg/m^2. In adjusted analyses controlling for potential confounders, a higher NT-proBNP level was associated with increased composite event risk in the total population (highest vs. lowest tertile; HR, 1.39; 95% CI, 1.12–1.72; p=0.002) and in patients with BMI<23 kg/m^2 (highest vs. lowest tertile; HR, 1.50; 95% CI, 1.12–2.00; p=0.006) but not in those with BMI≥23 kg/m^2 (p>0.05). Kaplan-Meier curves demonstrates different prognostic value of NT-proBNP in mortality and composite events (**Figure 2**) according to BMI. Differences in survival and event-free survival rates according to NT-proBNP tertiles were more obvious in patients with BMI<23 kg/m^2 than in those with BMI≥23 kg/m^2. Even after controlling for the effects of potential confounders, prognostic value of NT-proBNP in the prediction of survival was greater in in patients with BMI<23 kg/m^2 than in those with BMI≥23 kg/m^2 (**Figure 3**).

DISCUSSION

Considering the increasing prevalence of both obesity and HF, understanding the relationship between BMI and the prognostic value of NT-proBNP is essential. Using the nation-wide HF registry, present study showed that there was an inverse relationship between BMI and NT-proBNP. More importantly, our data demonstrated that the prognostic value of NT-proBNP was greater in HF patients with BMI<23 kg/m^2 than in those with BMI≥23 kg/m^2. This result provides additional evidence regarding an influence of BMI on the utility of the NT-proBNP assay for the prognosis of patients with HF.

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Table 2. Unadjusted and adjusted risk of NT-proBNP for mortality

Subgroup	Unadjusted		Adjusted*	
	HR (95% CI)	p value	HR (95% CI)	p value
Total population				
Lowest tertile (2–2,467 pg/mL)	1		1	
Middle tertile (2,470–7,295 pg/mL)	1.28 (1.08–1.53)	0.004	1.19 (0.91–1.56)	0.185
Highest tertile (7,309–35,000 pg/mL)	1.80 (1.52–2.14)	<0.001	1.76 (1.34–2.31)	<0.001
BMI<23 kg/m^2				
Lowest tertile (13–3,165 pg/mL)	1		1	
Middle tertile (3,166–9,800 pg/mL)	1.30 (1.03–1.64)	0.023	1.46 (1.02–2.07)	0.035
Highest tertile (9,838–35,000 pg/mL)	1.98 (1.58–2.48)	<0.001	2.24 (1.54–3.25)	<0.001
BMI≥23 kg/m^2				
Lowest tertile (2–1,947 pg/mL)	1		1	
Middle tertile (1,957–5,596 pg/mL)	1.38 (1.06–1.80)	0.016	1.19 (0.77–1.82)	0.417
Highest tertile (5,609–35,000 pg/mL)	1.57 (1.21–2.05)	0.001	1.27 (0.82–1.98)	0.278

HR = hazard ratio; CI = confidence interval; BMI = body mass index; NT-proBNP = N-terminal pro-B-type natriuretic peptide.
*Adjusted for age, sex, systolic blood pressure, heart rate, hypertension, ischemic etiology of heart failure, blood level of hemoglobin, sodium, and creatinine, left ventricular ejection fraction, and medications including beta-blocker and renin-angiotensin system blocker.

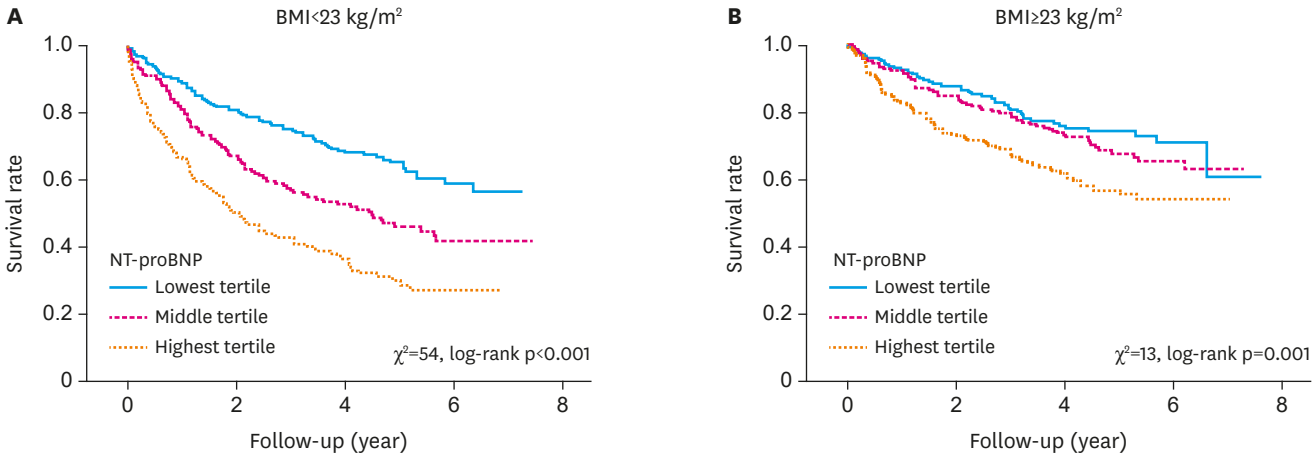
Table 3. Unadjusted and adjusted risk of NT-proBNP for composite events

Subgroup	Unadjusted		Adjusted*	
	HR (95% CI)	p value	HR (95% CI)	p value
Total population				
Lowest tertile (2–2,467 pg/mL)	1		1	
Middle tertile (2,470–7,295 pg/mL)	1.41 (1.11–1.78)	0.004	1.19 (0.97–1.45)	0.087
Highest tertile (7,309–35,000 pg/mL)	2.21 (1.76–2.77)	<0.001	1.39 (1.12–1.72)	0.002
BMI<23 kg/m^2				
Lowest tertile (13–3,165 pg/mL)	1		1	
Middle tertile (3,166–9,800 pg/mL)	1.70 (1.26–2.29)	<0.001	1.11 (0.84–1.45)	0.452
Highest tertile (9,838–35,000 pg/mL)	2.81 (2.11–3.75)	<0.001	1.50 (1.12–2.00)	0.006
BMI≥23 kg/m^2				
Lowest tertile (2–1,947 pg/mL)	1		1	
Middle tertile (1,957–5,596 pg/mL)	1.21 (0.82–1.77)	0.324	1.30 (0.96–1.77)	0.082
Highest tertile (5,609–35,000 pg/mL)	1.86 (1.29–2.68)	0.001	1.16 (0.83–1.63)	0.360

HR = hazard ratio; CI = confidence interval; BMI = body mass index; NT-proBNP = N-terminal pro-B-type natriuretic peptide.
*Adjusted for age, sex, systolic blood pressure, heart rate, hypertension, ischemic etiology of heart failure, blood level of hemoglobin, sodium, and creatinine, left ventricular ejection fraction, and medications including beta-blocker and renin-angiotensin system blocker.

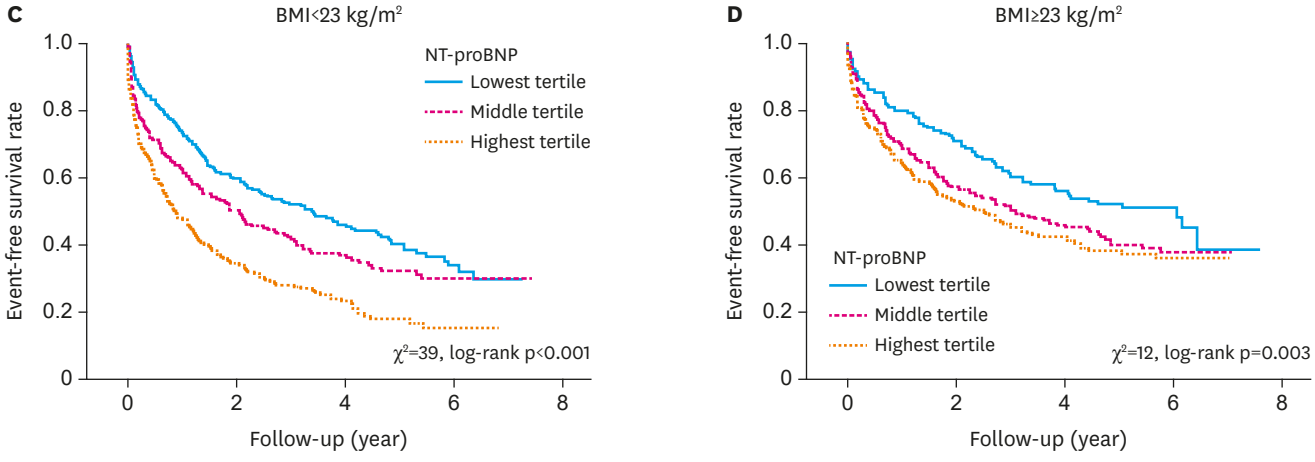
Previous studies indicated that the NT-proBNP level is lower in patients with higher BMI than in those with normal or lower BMI.[7][8] Our data also confirmed that the NT-proBNP level decreased in relation to increase in BMI. Underlying pathophysiology for the association between obesity and lower NT-proBNP level is not fully defined. As possible mechanisms, it has been suggested that release of natriuretic peptide decreased from the heart,[9][10] while clearance of this biomarker increased in obese patients.[11] Additional studies are needed to identify clear mechanisms why the NT-proBNP level is low in obese individuals.

It has been clearly demonstrated that NT-proBNP is a strong prognostic marker for worse cardiovascular outcomes in HF patients.[4-6] However, most of these studies did not consider the BMI effect. Similar findings were also obtained from our study in the total HF patients without stratification by BMI; NT-proBNP concentrations were well able to identify those at high risk for worse cardiovascular outcome. However, when we stratified study patients into 2 groups according to BMI (<23 kg/m^2 vs. ≥23 kg/m^2), prognostic value of NT-proBNP was different between the 2 groups. Similar finding was reported in the other study. In 8,217 patients with chronic HF, Nadruz et al.[12] showed that the ability of NT-proBNP to predict prognosis was attenuated in moderately or severe obese patients. In contrast, Bayes-Genis et al.[13] showed that the prognostic value of NT-proBNP remained irrespective of BMI categories.



No. of patients at risk				
Lowest tertile	323	182	136	57
Middle tertile	323	144	97	47
Highest tertile	322	125	76	42

No. of patients at risk				
Lowest tertile	303	162	121	50
Middle tertile	303	186	140	49
Highest tertilea	303	161	116	46



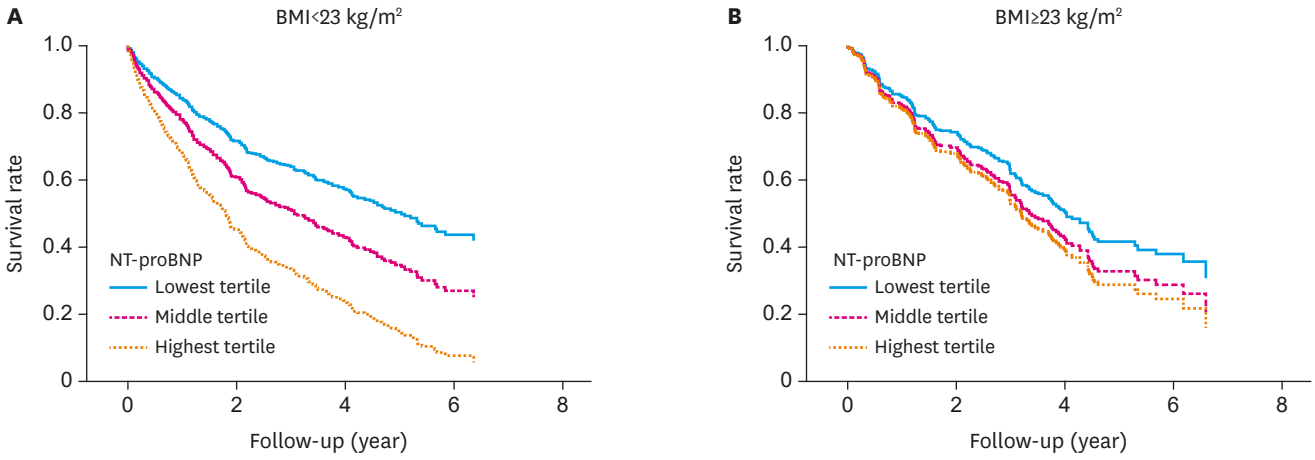
No. of patients at risk				
Lowest tertile	323	143	97	30
Middle tertile	323	112	67	32
Highest tertile	322	83	50	24

No. of patients at risk				
Lowest tertile	303	139	97	35
Middle tertile	303	139	101	47
Highest tertilea	303	121	83	36

Figure 2. Kaplan-Meier survival curves showing survival and event-free survival rates according to NT-proBNP tertiles. Survival rates in patients with BMI<23 kg/m² (A) and those with BMI≥23 kg/m² (B), and event-free survival rates in patients with BMI<23 kg/m² (C) and those with BMI≥23 kg/m² (D).
NT-proBNP = amino (N)-terminal pro-brain natriuretic peptide; BMI = body mass index.

In that study, however, they included patients who presented with dyspnea in the emergency department rather than those with confirmed HF, the number of enrolled patients was smaller (n=1,103) than in ours (n=2,280), and multivariate analysis differed from ours in that only age and sex were corrected. Another study including patients with decompensated HF found that the prognostic value of NT-proBNP was not modified by BMI.[14] However, it should be cautious to interpret the results because our study also involved a relatively small number of patients (n=686), and the duration of follow-up of clinical events was also short (=180 days).

Considering high prevalence and poor prognosis of HF, risk stratification using reliable biomarkers is very important for individualized therapy. For this, it is first necessary to know



No. of patients at risk				
Lowest tertile	323	182	136	57
Middle tertile	323	144	97	47
Highest tertile	322	125	76	42

No. of patients at risk				
Lowest tertile	303	162	121	50
Middle tertile	303	186	140	49
Highest tertilea	303	161	116	46

Figure 3. Cox plots showing survival rates according to NT-proBNP tertiles in patients with BMI<23 kg/m² (A) and those with BMI≥23 kg/m² (B) after adjustment for confounding clinical covariates. Clinical covariates adjusted were age, sex, systolic blood pressure, heart rate, hypertension, ischemic etiology of heart failure, blood level of hemoglobin, sodium, and creatinine, left ventricular ejection fraction, and medications including beta-blocker and renin-angiotensin system blocker.
NT-proBNP = amino (N)-terminal pro-brain natriuretic peptide; BMI = body mass index.

in what circumstances the utility of NT-proBNP is maximized, and in what circumstances the effectiveness of the biomarker is reduced. Because HF and obesity continue to increase globally, HF is highly prevalent in obese patients,[20] and the use of NT-proBNP is widely spread, it is very important for clinicians to understand the possible confounding impact of obesity on the validity of NT-proBNP for the adequate application of this biomarker. Finding the underlying mechanisms explaining lower level and prognostic value of NT-proBNP in overweight and obese patients may provide an important step in understanding the cardiovascular risk of obesity. Because the NT-proBNP level is low in patients with greater BMI, diagnosis of HF in obese individuals with NT-proBNP alone will increase false negative rate. In addition, the finding of lower prognostic value of NT-proBNP in overweight and obese patients has raised question whether NT-proBNP could work as a prognostic marker in patients with high BMI. For the physician using NT-proBNP to estimate the risk of HF patients, it would be better to avoid making an important decision only with NT-proBNP concentration especially in overweight and obese patients. Other prognostic biomarkers such as troponin or ST2, and echocardiographic parameters, such as LV ejection fraction or E/e′ should be combined to ascertain the correct estimation of long-term cardiovascular outcomes.

There are several limitations in this study. There might be some selection bias because only HF patients who were hospitalized were included in this study. In addition, only 66.5% of patients with available data on BMI and NT-proBNP were selected in our study. The lack of information on central obesity and BMI change during hospitalization is another limitation to this study. Also, mechanisms explaining the less prognostic value of NT-proBNP in patients with higher BMI could not be suggested. Finally, patients in our study are all Koreans, and thus, our results may be difficult to apply to other ethnic groups.

The prognostic value of NT-proBNP was greater in nonobese than in overweight and obese Korean patients with HF. BMI should be considered NT-proBNP is used for risk estimation in this population. Further studies are needed to confirm our findings.

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