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Original Article

Comparison of Natriuretic Peptide Levels in Sinus Rhythm and Atrial Fibrillation in Acute Heart Failure

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ABSTRACT

Background and Objectives: In chronic heart failure (HF), natriuretic peptide (NP) levels are higher in atrial fibrillation (AF) compared to sinus rhythm (SR). However, due to the loss of atrial contraction, AF patients are prone to hemodynamic decompensation at earlier stages. Since NP levels reflect disease severity, acutely decompensated AF patients may exhibit lower NP levels compared to SR patients, who retain greater hemodynamic reserve.
Methods: We analyzed 5,048 patients with acute HF from the Korea Acute Heart Failure registry with available NP data. NP levels and echocardiographic parameters were compared between AF and SR patients. The association of NP levels with in-hospital and one-year mortality was also assessed according to cardiac rhythm.
Results: Brain natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were measured in 2,027 and 3,021 patients, respectively. NP levels were lower in AF than in SR (median BNP, 740 vs. 1,044 pg/mL; median NT-proBNP, 4,420 vs. 5,198 pg/mL), particularly in HF with reduced or mildly reduced ejection fraction. A similar trend was observed regardless of HF onset or etiology. AF patients had smaller left ventricular (LV) end-diastolic diameter and larger left atrial size compared to SR patients. Higher NP tertiles were associated with increased in-hospital and one-year mortality in both groups.

Conclusions: In acute HF, NP levels are lower in AF than in SR. AF patients also exhibited smaller LV chamber sizes. Nevertheless, NP levels remain strong predictors of outcomes in both AF and SR patients.

Trial Registration: ClinicalTrials.gov Identifier: NCT01389843

Keywords: Atrial fibrillation; Heart failure; Natriuretic peptide

INTRODUCTION

Both brain natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are well-established prognostic markers in heart failure (HF), with elevated levels correlating with worse clinical outcomes.[1-4] In chronic HF, patients with atrial fibrillation (AF) compared to those in sinus rhythm (SR) have higher natriuretic peptide (NP) values.[5-11] This difference is often attributed to the hemodynamic and neurohormonal stress associated with AF.[7,12,13] Therefore, many clinical trials set higher NP cutoff values for AF than for SR in their inclusion criteria.[14-19]

While the role and prognostic value of NP in chronic HF are well established, its clinical significance in acute HF may differ, particularly between patients with AF and those in SR. In patients with AF, the absence of the atrial kick—which contributes approximately 20% to left ventricular (LV) filling—predisposes them to hemodynamic instability and increases their susceptibility to acute decompensation.[20,21] Consequently, these patients may experience decompensation at a lower trigger threshold; however, this does not necessarily correlate with reduced survival, which may instead be more closely linked to structural remodeling of the heart. Moreover, prior studies suggest that AF-related decompensations caused by reversible factors, such as tachycardia, were associated with better in-hospital outcomes than those with SR.[22]

Interpreting NP levels in acute HF can be complex due to the differentiation between "wet NP," which indicates fluid overload, and "dry NP," which signifies myocardial stress. This differentiation is not fully understood in the context of acute HF and is further complicated by the presence of AF, leading to questions about how these differences affect the interpretation and usefulness of NP as a biomarker. This study aims to investigate the differences in NP levels between patients with AF and those in SR admitted for acute HF. By clarifying these differences, the study seeks to improve the understanding of NP's clinical role and its potential prognostic implications in acute HF, ultimately refining its application as a biomarker in this population.

METHODS

Study design and population

The Korean Acute Heart Failure (KorAHF) registry was a prospective multicenter cohort study that consecutively enrolled 5,625 patients hospitalized for acute HF in 10 tertiary university hospitals across the country between March 2011 and December 2014. Detailed information on the study design and results has been previously reported (ClinicalTrials.gov NCT01389843).[23,24] Briefly, patients presenting with signs or symptoms of HF were eligible for the study if they met one of the following criteria: 1) lung congestion or 2) objective LV systolic dysfunction or structural heart disease. For the present study, we included only patients with available data on BNP or NT-proBNP levels.

The ethics committee and Institutional Review Board (IRB) of each hospital (Seoul National University Bundang Hospital, IRB No. B-1104-125-014) approved the study protocol. The study adhered to the Declaration of Helsinki.

Data collection and outcomes

Patients were defined as having AF if AF was documented on electrocardiogram (ECG) during the index admission. All echocardiographic studies were performed using a standard ultrasound machine with a 2.5-MHz probe. Standard techniques were employed to obtain M-mode, 2-dimensional, and Doppler measurements in accordance with the American Society of Echocardiography's guidelines.[25] LV ejection fraction (LVEF) was measured using Simpson's biplane method. If the Simpson's method was not possible, then LVEF was assessed using M-mode or visual estimation. The left atrial (LA) volume index (LAVI) was measured using the prolate ellipsoid method or biplane-modified Simpson method and adjusted for body surface area. LV end-diastolic diameter (LVEDD) was calculated from M-mode or two-dimensional images. LV end-diastolic volumes (LVEDVs) and LV end-systolic volumes (LVESVs) were measured from apical four- and two-chamber views. Most patients underwent echocardiography on the day of admission with the median time interval between admission and

echocardiographic exam being 1 day (interquartile range [IQR] of 0–2 days). Based on echocardiography findings, HF with reduced ejection fraction (HFrEF), HF with mildly reduced ejection fraction (HFmrEF), and HF with preserved ejection fraction (HFpEF) were defined as LVEF ≤40%, 41–49%, and ≥50%, respectively, in accordance with current HF guidelines.[26-28]

Levels of BNP or NT-proBNP were measured at the time of initial admission. Plasma was tested for BNP using the Biosite Triage assay, a point-of-care device that uses a fluorescence immunoassay technique (Biosite, San Diego, CA, USA). NT-proBNP measurements were performed using the electro-chemiluminescence immunoassay method with Elecsys® 2010 analyzer (Roche Diagnostics, Indianapolis, IN, USA) or using the assay for the Dimension platform (Siemens Medical Solutions Diagnostics, Erlangen, Germany).[29] Patients were categorized by cardiac rhythm and NP tertiles.

The primary outcome in this study was the difference in NP levels between patients with SR and those with AF. The secondary outcomes were in-hospital mortality and all-cause mortality within one year after discharge. Mortality data of patients who were lost to follow-up were collected from the Korean Statistical Information Service and Microdata Integrated Service managed by Statistics Korea, a government agency.

Statistical analysis

Categorical variables are reported as frequencies (percentages) and were compared using Pearson's χ^2 test. Continuous variables were tested for normality using the Shapiro-Wilk normality test. Continuous variables with normal distribution are expressed as means ± standard deviations and were compared using Student's t-test. Non-normally distributed continuous variables are presented as medians with IQRs and were compared using the Mann–Whitney U test or Kruskal-Wallis test.

In-hospital mortality and one-year mortality were analyzed according to tertiles of NP levels. Kaplan–Meier curves were plotted and compared using the log-rank test. Univariable and multivariable Cox proportional hazards regression models were used to evaluate the effects of NP levels on one-year all-cause mortality. Logistic regression models were employed to determine the predictors of the highest NP tertile in patients with acute HF. In the multivariable model, we included clinically relevant variables identified in previous studies or those found to be statistically significant in the univariable analysis, excluding variables with more than 20% missing data or those showing collinearity with other clinical variables. To quantify the predictive value of NP levels for in-hospital mortality, receiver operating characteristic curves were constructed, and the areas under the curves (AUCs) were compared using DeLong's test.

Statistical significance was set at a two-sided p value <0.05. Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA) and R programming version 4.2.3 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics according to cardiac rhythm

Among the 5,625 patients enrolled in the KorAHF registry, 5,048 patients with available BNP or NT-proBNP data were included in the current analysis. Of these, 2,027 patients had BNP measurements, and 3,021 had NT-proBNP measurements. Baseline characteristics according to cardiac rhythm are presented in the **Table 1**. Patients with AF were older and had a lower prevalence of de novo HF, ischemic etiology of HF, cardiomyopathy, diabetes mellitus, chronic kidney disease, and previous myocardial infarction compared to those with SR. However, patients with AF had a higher prevalence of valvular heart disease, tachycardia-induced HF, and cerebrovascular disease. They also exhibited a higher heart rate and hemoglobin levels compared to patients with SR.

NPs level and echocardiographic parameters according to rhythm

NP levels and echocardiographic parameters are presented in **Figures 1** and **2**, as well as **Table 1**. Patients with AF had significantly lower BNP levels (740 [433–1,300] vs. 1,044 [532–2,123] pg/mL, p<0.001) and NT-proBNP levels (4,420 [2,252–9,746] vs. 5,197 [2,088–13,582] pg/mL, p=0.011) compared with patients with SR. When stratified by LVEF, patients with HFrEF or HFmrEF had significantly lower BNP or NT-proBNP levels in those with AF compared to those with SR (**Table 2**). However, among patients with HFpEF, NP levels were similar to or higher in those with AF compared to those with SR. Patients with AF had lower BNP levels than those with SR, regardless of HF onset or etiology (**Figure 1C and D**). A similar trend was observed for NT-proBNP levels, although some comparisons did not reach statistical significance (**Figure 2C and D**). When stratified by AF type, NP levels tended to be lower in AF than in SR, regardless of AF type, although patients with paroxysmal AF tended to have higher NP levels than patients with persistent or permanent AF (**Supplementary Figure 1**).

Patients with AF showed higher LVEF, LA diameter, LAVI and e' velocity, as well as smaller LVEDD, LV end-systolic diameter (LVESD), LVEDV, LVESV and E/e' ratio compared to patients with SR (**Table 1**). When stratified by LVEF, patients with HFrEF showed

Table 1. Baseline characteristics of the study population by cardiac rhythm at admission

Variables	AF (n=1,762)	Sinus (n=3,286)	p value
Age (years)	70.8±12.5	67.5±15.3	<0.001
Men	897 (50.9)	1756 (53.4)	0.092
De novo	793 (45.0)	1875 (57.1)	<0.001
HF etiology			<0.001
Ischemic heart disease	375 (21.3)	1,517 (46.2)	
Cardiomyopathy	317 (18.0)	729 (22.2)	
Hypertensive	43 (2.4)	163 (5.0)	
Valvular heart disease	364 (20.7)	310 (9.4)	
Tachycardia-induced	490 (27.8)	65 (2.0)	
Other	173 (9.8)	502 (15.3)	
Height (cm)	160.5±9.6	160.2±9.5	0.427
Weight (kg)	60.7±13.2	60.0±13.0	0.098
Body mass index (kg/m^2)	23.4±3.9	23.2±3.9	0.092
Past medical history			
Hypertension	1,047 (59.4)	1,948 (59.3)	0.947
Diabetes mellitus	512 (29.1)	1,270 (38.6)	<0.001
Chronic kidney disease	752 (42.7)	1,533 (46.7)	0.008
Ischemic heart disease	372 (21.1)	1,053 (32.0)	<0.001
Previous myocardial infarction	196 (11.1)	623 (19.0)	<0.001
Valvular heart disease	377 (21.4)	313 (9.5)	<0.001
Cerebrovascular disease	330 (18.7)	436 (13.3)	<0.001
NYHA functional class			0.001
II	264 (15.0)	479 (14.6)	
III	690 (39.2)	1,122 (34.1)	
IV	808 (45.9)	1,685 (51.3)	
Physical exam			
Systolic BP (mmHg)	130.1±28.0	133.2±31.9	<0.001
Diastolic BP (mmHg)	80.4±18.8	78.5±19.1	0.001
Heart rate (beats per min)	97.0±30.2	91.4±23.5	<0.001
Laboratory findings			
Hemoglobin (g/dL)	12.7±2.2	12.2±2.3	<0.001
BUN (mg/dL)	21.5 (16.0–30.1)	21.4 (15.7–31.6)	0.629
Creatinine (mg/dL)	1.05 (0.83–1.41)	1.11 (0.84–1.61)	<0.001
BNP (pg/mL), (n=2,027)	740 (433–1,300)	1,044 (532–2,123)	<0.001
NT-proBNP (pg/mL), (n=3,021)	4,420 (2,252–9,746)	5,197 (2,088–13,582)	0.011
Echocardiographic parameters			
LVEF (%), (n=4,595)	40.2±15.7	36.0±15.3	<0.001
LVEDD (mm), (n=4,737)	55.9±9.6	58.2±10.2	<0.001
LVESD (mm), (n=4,577)	43.1±11.6	46.4±12.4	<0.001
LVEDV (mL), (n=3,436)	129 (90–173)	148 (107–197)	<0.001
LVESV (mL), (n=3,431)	73 (27–53)	96 (60–139)	<0.001
Left atrial diameter (mm), (n=4,680)	53.1±9.8	45.4±8.4	<0.001
LAVI (mL/m^2), (n=2,735)	68.8 (54.4–89.3)	49.9 (38.1–64.1)	<0.001
e' (cm/s), (n=4,079)	5.3 (4.2–7.0)	4.0 (3.2–5.3)	<0.001
E/e' (n=3,958)	18.1 (13.8–24.6)	19.3 (13.7–26.7)	0.009
Pulmonary arterial systolic pressure (mmHg), (n=3,355)	44.1±14.2	43.5±15.3	0.234
HF types (n=4,595)			<0.001
HFrEF	810 (51.3)	2,005 (66.5)	
HFmrEF	258 (16.3)	370 (12.3)	
HFpEF	512 (32.4)	640 (21.2)	
Pre-admission medications			
Renin-angiotensin system inhibitors	716 (40.6)	1,215 (37.0)	0.012
Beta-blockers	548 (31.1)	882 (26.8)	0.002
MRA	403 (22.9)	510 (15.5)	<0.001

Values are expressed as mean ± standard deviations, median (25th–75th percentile), or number (%).
AF = atrial fibrillation; HF = heart failure; NYHA = New York Heart Association; BP = blood pressure; BUN = blood urea nitrogen; BNP = B-type natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide; LVEF = left ventricular ejection fraction; LVEDD = left-ventricular end-diastolic diameter; LVESD = left-ventricular end-systolic diameter; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LAVI = left atrial volume index; HFrEF = heart failure with reduced ejection fraction; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; MRA = mineralocorticoid receptor antagonist.

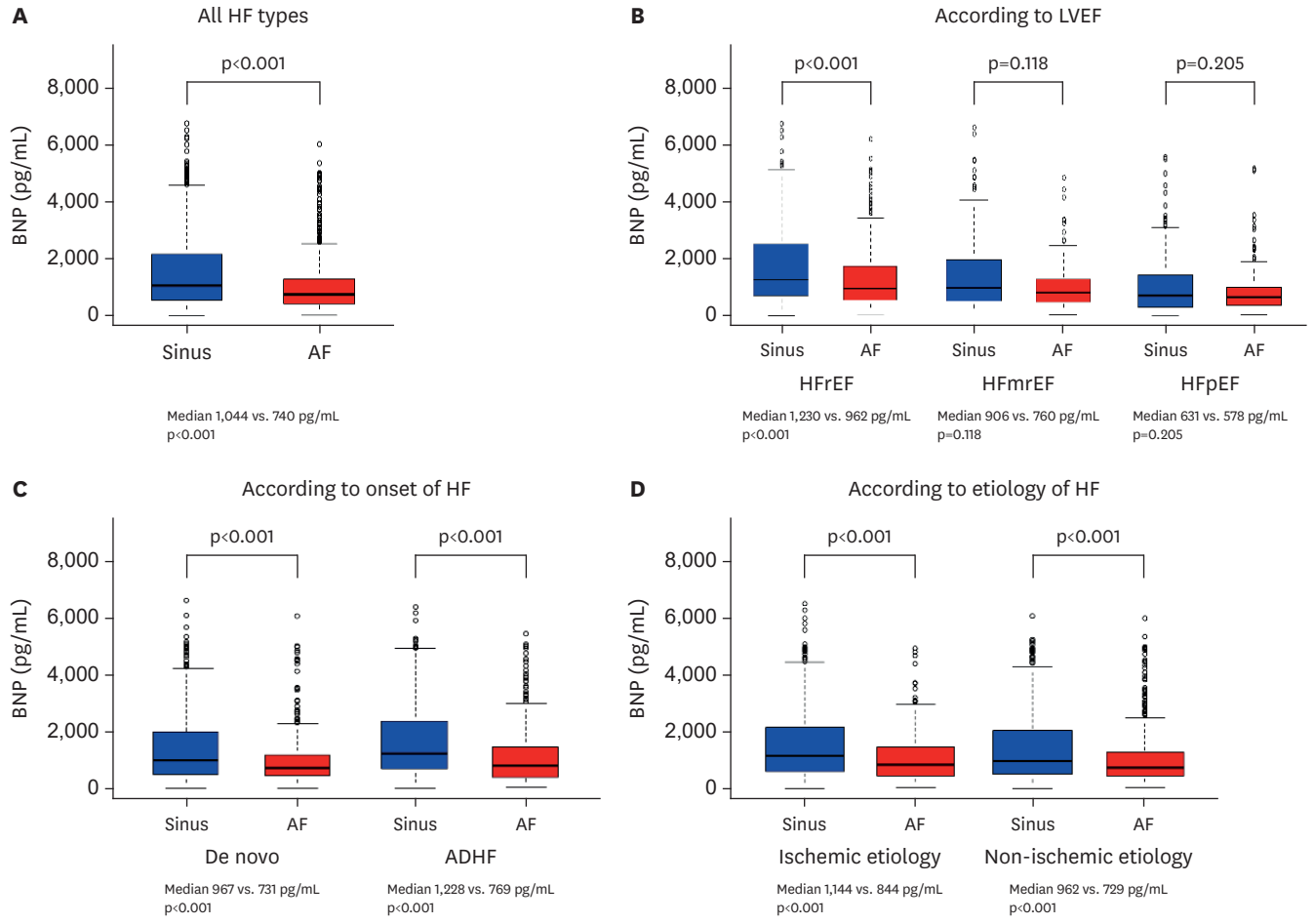

Figure 1. BNP levels by cardiac rhythm. Data from 2,027 acute heart failure patients with available BNP measurements were analyzed.
HF = heart failure; BNP = B-type natriuretic peptide; AF = atrial fibrillation; LVEF = left ventricular ejection fraction; HFrEF = heart failure with reduced ejection fraction; HFmrEF = heart failure with mild reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; ADHF = acute decompensated chronic heart failure.

a pattern similar to the overall population (**Table 2**). Among patients with HFmrEF and HFpEF, LVEDD and LVESD showed no significant differences between those with AF and SR. However, LA diameter and LAVI were higher in patients with AF compared to those with SR in these groups.

Impact of NP levels on clinical outcomes

Among patients with available BNP data, tertile 1 (T1) included values ≤602 pg/mL, tertile 2 (T2) ranged from 603–1,384 pg/mL, and tertile 3 (T3) included values ≥1,385 pg/mL. Among patients with available NT-proBNP data, T1 included values ≤2,968 pg/mL, T2 ranged from 2,969–8,417 pg/mL, and T3 included values ≥8,418 pg/mL.

A total of 235 patients (4.7%) died during the index admission. Patients with AF showed a trend toward a lower in-hospital mortality rate compared with patients with SR (3.9% vs. 5.1%; p=0.058). In-hospital mortality rates according to the tertiles of NP levels are shown in **Figure 3**. There was a clear increasing trend in in-hospital mortality across higher tertiles of NP levels. Additionally, when stratified by AF or SR, patients in the highest tertiles of NP levels demonstrated a trend toward the highest in-hospital mortality. The AUCs for predicting in-hospital mortality based on NP levels ranged from 0.6 to 0.7 and were similar between AF and SR (DeLong p>0.05) (**Supplementary Figure 2**).

Among 4,813 patients who discharged alive, 901 (18.7%) patients died within one year. After stratification by NP tertiles, a gradual increase in one-year mortality was observed with higher tertiles of NP levels, regardless of the cardiac rhythm (log-rank test, all p<0.01) (**Figure 4**). In the Cox proportional hazards regression analysis, after adjusting for significant covariates, including AF, age, sex, systolic blood pressure, chronic kidney disease, ischemic heart disease, LVEF, LVEDD, LA diameter and E/e' ratio, higher NT-proBNP tertiles was independently associated with increased

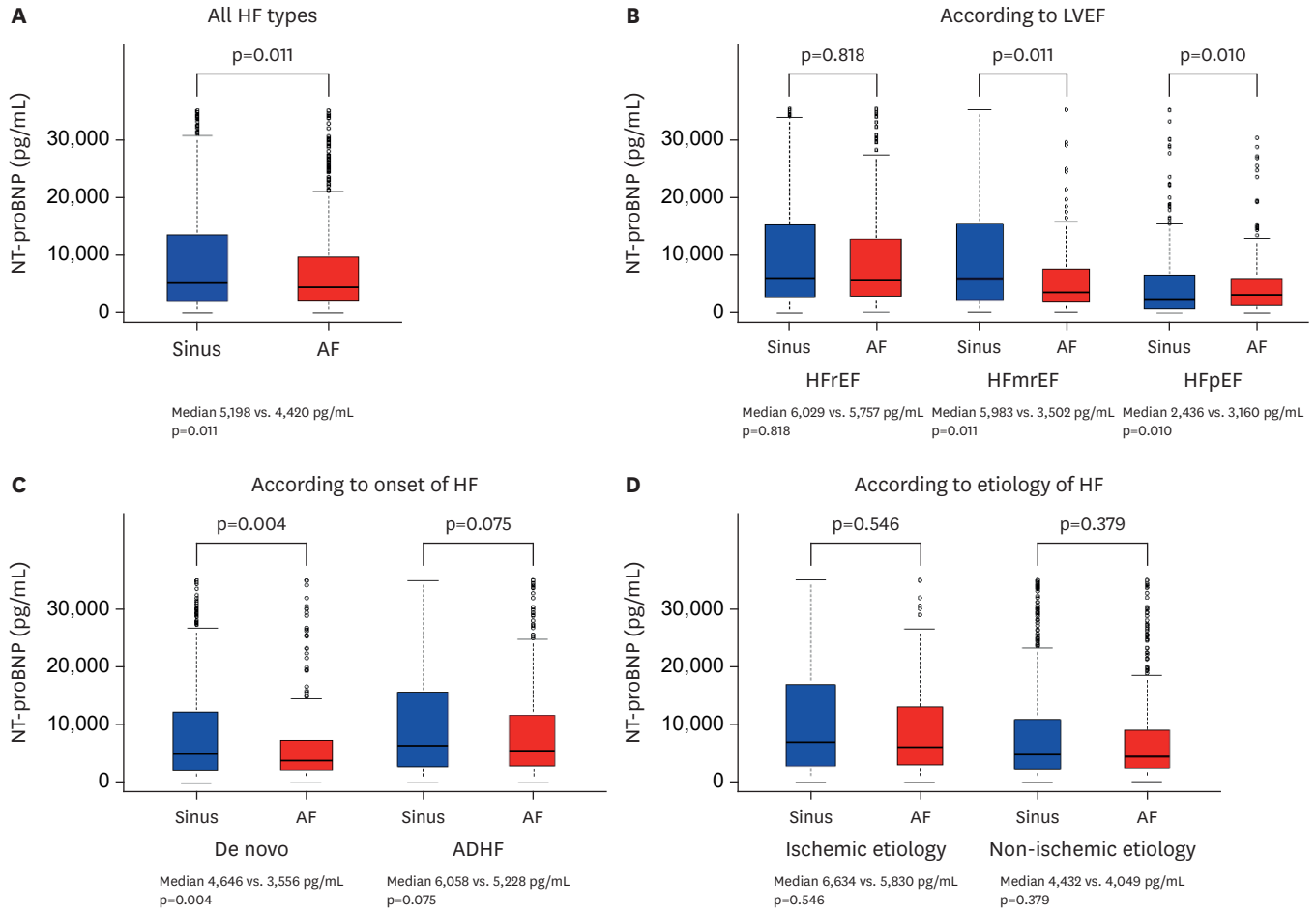

Figure 2. NT-proBNP levels by cardiac rhythm. Data from 3,021 acute heart failure patients with available NT-proBNP measurements were analyzed.
HF = heart failure; NT-proBNP = N-terminal pro-B-type natriuretic peptide; AF = atrial fibrillation; LVEF = left ventricular ejection fraction; HFrEF = heart failure with reduced ejection fraction; HFmrEF = heart failure with mild reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; ADHF = acute decompensated chronic heart failure.

post-discharge one-year mortality in the overall population (adjusted hazard ratio [HR], 1.79; 95% confidence interval (CI), 1.53–2.12), as well as in the subgroups of AF (adjusted HR, 2.28; 95% CI, 1.68–3.09) or SR (adjusted HR, 1.61; 95% CI, 1.32–1.95). A similar finding was observed when the analysis was conducted according to BNP tertiles.

Predictors of high NP tertiles

We performed multivariable logistic regression to identify predictors of highest NP tertiles, and the results are summarized in **Table 3**. Independent predictors of high NP tertiles in patients with acute HF included SR, lower body weight, higher creatinine levels, lower hemoglobin levels, higher LVEDD, lower LA diameter, and higher E/e' ratio. Notably, AF (odds ratio [OR], 0.80; 95% CI, 0.67–0.96) and smaller LVEDD (OR, 1.36; 95% CI, 1.24–1.48 per 10 mm increase) were independently associated with lower NP levels.

DISCUSSION

In this study, we investigated the differences in NP levels between patients with AF and those in SR who were hospitalized for acute HF using data from the KorAHF registry. Contrary to findings in chronic HF, NP levels, both BNP and NT-proBNP, were significantly lower in patients with AF than those in SR. This discrepancy was particularly evident in patients with HFrEF and HFmrEF, while no similar trend was observed in HFpEF. Despite these differences, NPs retained their prognostic value for all-cause mortality across both AF and SR groups. Echocardiographic findings revealed that patients with AF had smaller LVEDD and increased LA diameters, potentially contributing to the observed differences in NP levels.

A notable finding of this study was that patients with AF had lower NP levels than those with SR in the acute HF setting. This result contrasts with most studies on chronic HF, which have indicated

Table 2. Natriuretic peptide levels and echocardiographic parameters by cardiac rhythm in each type of HF

Variables	AF	Sinus	p value
HFrEF (n=2,815)	(n=810)	(n=2,005)	
BNP (pg/mL), (n=1,087)	962 (555–1,718)	1,230 (684–2,452)	<0.001
NT-proBNP (pg/mL), (n=1,728)	5,757 (2,965–12,796)	6,029 (2,820–15,190)	0.818
LVEF (%)	27.1±7.7	26.9±7.6	0.506
LVEDD (mm)	60.7±8.8	62.0±9.3	<0.001
LVESD (mm)	51.1±9.5	52.6±10.1	0.001
LVEDV (mL)	154 (113–201)	169 (127–216)	<0.001
LVESV (mL)	110 (78–146)	120 (89–159)	<0.001
Left atrial diameter (mm)	52.2±9.0	45.9±8.2	<0.001
LAVI (mL/m^2)	69.0 (55.0–89.9)	52.6 (40.5–66.1)	<0.001
e' (cm/s)	5.0 (4.0–6.0)	4.0 (3.0–5.0)	<0.001
E/e'	19.7 (14.8–25.6)	20.5 (14.9–28.0)	0.056
Pulmonary arterial systolic pressure (mmHg)	43.1±13.0	44.0±14.8	0.166
HFmrEF (n=628)	(n=258)	(n=370)	
BNP (pg/mL), (n=278)	760 (423–1,192)	906 (470–1,795)	0.118
NT-proBNP (pg/mL), (n=350)	3,502 (1,967–7,562)	5,983 (2,185–15,313)	0.011
LVEF (%)	45.0±2.5	44.6±2.4	0.052
LVEDD (mm)	53.6±7.5	53.8±7.5	0.739
LVESD (mm)	40.0±6.8	40.1±6.9	0.787
LVEDV (mL)	107 (76–144)	122 (86–156)	0.010
LVESV (mL)	58 (43–76)	66 (47–84)	0.009
Left atrial diameter (mm)	53.2±10.2	44.2±8.0	<0.001
LAVI (mL/m^2)	70.7 (53.9–87.2)	46.0 (35.6–58.4)	<0.001
e' (cm/s)	5.5 (4.4–7.0)	4.3 (3.3–5.5)	<0.001
E/e'	18.1 (13.3–25.0)	17.5 (12.4–25.7)	0.412
Pulmonary arterial systolic pressure (mmHg)	43.7±14.8	40.1±13.5	0.007
HFpEF (n=1,152)	(n=512)	(n=640)	
BNP (pg/mL), (n=537)	578 (313–894)	631 (247–1,268)	0.205
NT-proBNP (pg/mL), (n=615)	3,160 (1,545–6,116)	2,436 (845–6,697)	0.010
LVEF (%)	58.6±6.1	59.9±6.9	0.001
LVEDD (mm)	49.9±7.6	49.3±7.3	0.204
LVESD (mm)	32.5±6.2	31.8±6.4	0.059
LVEDV (mL)	101 (66–133)	101 (73–138)	0.520
LVESV (mL)	38 (26–51)	38 (27–52)	0.573
Left atrial diameter (mm)	55.1±10.4	45.2±9.2	<0.001
LAVI (mL/m^2)	68.7 (55.0–91.0)	45.9 (35.0–59.0)	<0.001
e' (cm/s)	6.0 (5.0–7.0)	5.0 (4.0–6.1)	<0.001
E/e'	16.7 (12.8–22.9)	17.0 (11.5–24.2)	0.448
Pulmonary arterial systolic pressure (mmHg)	46.2±15.2	43.7±17.0	0.021

Values are expressed as mean ± standard deviations, median (25th–75th percentile), or number (%).
HF = heart failure; AF = atrial fibrillation; HFrEF = heart failure with reduced ejection fraction; BNP = B-type natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide; LVEF = left ventricular ejection fraction; LVEDD = left-ventricular end-diastolic diameter; LVESD = left-ventricular end-systolic diameter; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LAVI = left atrial volume index; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction.

that AF is associated with higher NP levels,[5-11] leading many clinical trials on HF to establish higher NP thresholds for including patients with AF. AF is characterized by the loss of atrial contraction during late diastole, potentially resulting in up to a 20% reduction in diastolic filling.[13,20,30] In a healthy state, this loss does not present significant hemodynamic or clinical challenge because the majority of diastolic filling occurs during the early rapid filling phase due to ventricular relaxation. However, in HF, where ventricular relaxation is significantly impaired, the heart's capacity to compensate for this loss might be marginal. In patients with AF, the ability to tolerate additional stress is even further compromised. This limited compensatory reserve makes them highly susceptible to acute decompensation triggered by various stimuli, such as infection, tachycardia, or ischemia.[13] Also, AF can lead to an irregular heart rate or increased heart rate variability, making it more likely to cause hemodynamic instability and increasing the risk of acute decompensation. This explanatory framework is further supported by the finding that NP levels tended to be slightly higher in patients with paroxysmal AF than in those with persistent or permanent AF (**Supplementary Figure 1**).

NP is a neuro-hormone released from the ventricles in response to increased wall stress.[31] According to Laplace's law, wall stress is directly proportional to pressure and radius, and inversely

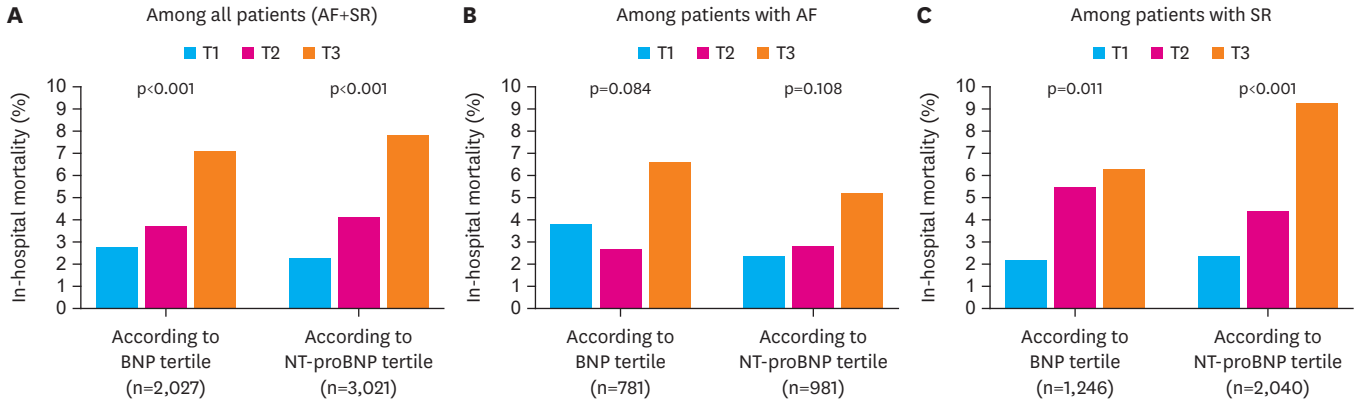

Figure 3. In-hospital mortality according to BNP or NT-proBNP tertiles. For each analysis, patients were divided into tertiles based on natriuretic peptide levels.
AF = atrial fibrillation; SR = sinus rhythm; BNP = B-type natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

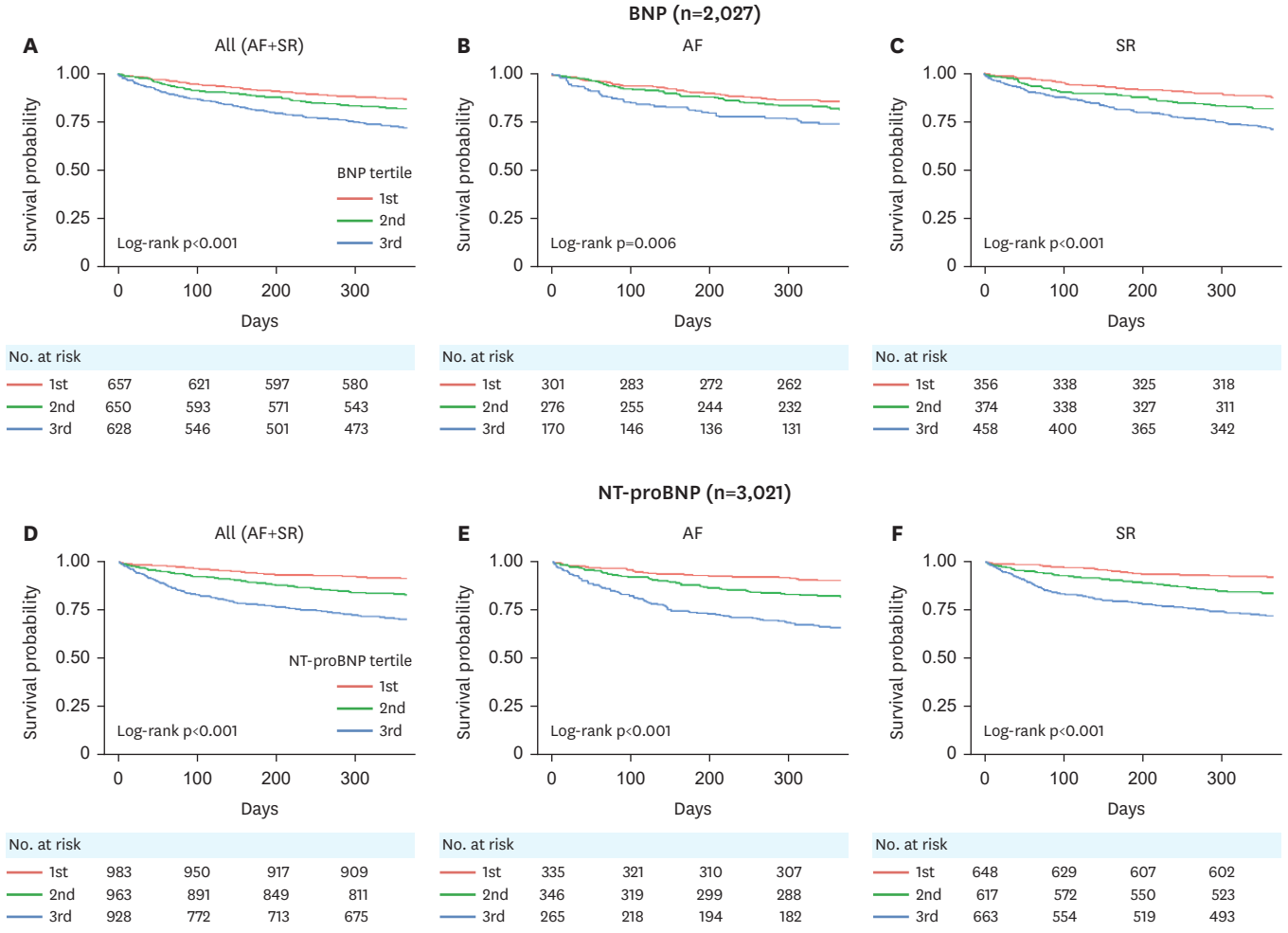

Figure 4. One-year mortality according to BNP and NT-proBNP tertiles.
AF = atrial fibrillation; SR = sinus rhythm; BNP = B-type natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

proportional to wall thickness. This study observed that patients with AF had smaller LVEDD compared to those with SR, which may account for their lower NP levels. Additionally, AF patients exhibited a larger LAVI than SR patients. AF is part of the spectrum of atrial cardiomyopathy, which can cause or exacerbate HF. Therefore, a larger LA size in AF patients serves as a marker of the

Table 3. Multivariable logistic regression for predictors of highest natriuretic peptides tertiles

Variables	OR	95% CI	p value
Atrial fibrillation (vs. sinus rhythm)	0.80	0.67–0.96	0.017
Age (per 10 years increase)	1.05	0.99–1.12	0.090
Male (vs. female)	0.91	0.76–1.09	0.326
Weight (per 1 kg increase)	0.96	0.95–0.97	<0.001
Diabetes mellitus	0.89	0.76–1.05	0.183
Creatinine (per 1 mg/dL increase)	2.31	2.07–2.58	<0.001
Hemoglobin (per g/dL increase)	0.94	0.91–0.98	0.004
LVEDD (per 10 mm increase)	1.36	1.24–1.48	<0.001
Left atrial diameter (per 1 mm increase)	0.99	0.98–1.00	0.029
E/e' (per 1 increase)	1.01	1.01–1.02	<0.001

An analysis was conducted using the highest tertile of brain natriuretic peptide or the highest tertile of N-terminal pro-B-type natriuretic peptide as the dependent variable.
OR = odds ratio; CI = confidence interval; LVEDD = left-ventricular end-diastolic diameter.

cardinal pathological changes associated with LA cardiomyopathy in AF patients, which may occur without the presence of HF. This finding also supports the notion that "AF begets AF."

By integrating the physiological and anatomical characteristics of AF patients, we propose the following hypothesis: 1) AF patients are more prone to hemodynamic decompensation compared to those in SR; 2) in acute HF, AF patients exhibit less structural remodeling than SR patients due to earlier hemodynamic decompensation, as reflected by smaller LV diameters; and 3) consequently, AF patients may have lower in-hospital mortality rates, since mortality is more closely linked to advanced structural remodeling, whereas morbidity, such as worsening HF, is primarily driven by hemodynamic instability.

AF patients may differ not only in rhythm but also exhibit a distinct clinical and anatomical profile—characterized by older age, more frequent valvular or tachycardia-induced cardiomyopathy, smaller LV dimensions, and lower NP levels—suggesting a different trajectory or stage of HF. While some of these features may indicate less advanced HF, others (e.g., larger LA size, higher pulmonary artery systolic pressure in HFpEF) might suggest that AF-related AHF may represent a qualitatively different syndrome rather than merely a milder form.

We demonstrated that NP levels were higher in SR compared to AF in patients with HFrEF, but this difference was not observed in HFpEF. This finding aligns with echocardiographic parameters, as HFrEF patients in SR had larger LVEDD than those in AF, whereas no significant differences were seen in HFpEF. Given that LVEDD is a significant predictor of elevated NP levels, these results support our hypothesis regarding the complex interplay between NP levels, cardiac rhythm, and HF types. Additionally, the lack of significant NP differences in HFpEF highlights the complex regulation of NPs in this phenotype, likely influenced by factors such as diastolic dysfunction and atrial remodeling. Nevertheless, NP levels are influenced by various complex factors, making it essential to consider underlying comorbidities, the etiology of HF, and medications. These findings emphasize the need for careful interpretation of NP levels in patients with AF, particularly in the context of acute HF.

As shown in **Table 1**, patients with AF had a lower prevalence of ischemic etiology of HF. However, patients with ischemic etiology of HF showed higher NP levels compared with those with non-ischemic etiology (**Figures 1** and **2**). Therefore, the difference in the proportion of ischemic etiology of HF may partially explain the overall lower NP levels in patients with AF. Nonetheless, as shown in **Figures 1** and **2**, NP levels remained consistently lower in patients with AF compared to those with SR, regardless of ischemic etiology, which aligns with our main argument. Additionally, tachycardia-induced HF, a condition characterized by relatively less advanced cardiac structural remodeling, was more prevalent among patients with AF, which may explain the relatively low NP levels in patients with AF compared to those with SR.

Our study has several notable strengths. AF was documented by ECG, ensuring accurate rhythm classification. Furthermore, the KorAHF study, as a large, prospective cohort study, enabled us to identify triggers for acute decompensation in all patients. These triggers were prospectively collected, confirmed, and adjudicated by investigators, enhancing the reliability of the data. However, some limitations should be acknowledged. We cannot rule out the possibility that some patients experienced new-onset AF during their acute HF admission. Additionally, despite the prospective design, we were unable to fully eliminate potential confounding factors that may have influenced the study results. Besides the patient's cardiac rhythm, NP levels may also be affected by underlying comorbidities, the etiology of HF, and HF medications including renin-angiotensin system inhibitor, beta-blocker and diuretics. The study's generalizability may also be limited, as it exclusively included patients hospitalized for acute HF in East

Asia. Our study population did not include patients treated with newer HF therapies, such as sacubitril/valsartan or sodium-glucose cotransporter 2 inhibitors, as these drugs were not available at the time of enrollment. Consequently, it remains uncertain whether our findings hold true in the context of these therapies. Nonetheless, approximately 50% of the patients were de novo cases, and similar findings were observed, suggesting that the results may still be applicable.

In conclusion, acute HF patients with AF had lower NP levels than those with SR. They have smaller LV diameter which was a significant predictor of lower NP levels. Nevertheless, NP levels remain strong predictors of outcomes in both AF and SR patients.

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

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SUPPLEMENTARY MATERIALS

Supplementary Figure 1
Natriuretic peptide levels by sinus rhythm or AF type.

Supplementary Figure 2
Receiver operating characteristic curve for in-hospital mortality according to natriuretic peptide levels.

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