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Prognostic Utility and Cutoff Differences in NT-proBNP Levels Across Subgroups in Heart Failure With Preserved Ejection Fraction: Insights From the PURSUIT-HFpEF Registry

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ABSTRACT

Objectives: N-terminal pro brain natriuretic peptide (NT-proBNP) is a biomarker for myocardial stress that is used in diagnosing and prognosticating heart failure (HF). However, its interpretation is complicated by clinical factors. This study aims to clarify the prognostic value of NT-proBNP in patients with heart failure with preserved ejection fraction (HFpEF), and risk-prediction cutoffs considering various clinical factors.

Methods: The study used data from the prospective, multicenter, observational Asian HFpEF registry. Patients with acute decompensated HF and left ventricular ejection fraction ≥ 50% were included. NT-proBNP levels were measured at discharge. The primary endpoint was a composite of all-cause death and hospitalization due to HF within 1 year after discharge.

Results: A total of 1231 patients (83 [77–87] years old, 551 [45%] male) were enrolled, and 916 eligible patients were analyzed. The median NT-proBNP level was 1060 pg/m. In a multivariable logistic regression model, NT-proBNP was significantly associated with the primary endpoint (adjusted OR for log-transformed NT-proBNP: 2.71, 95% CI: 1.78–4.18; $P < 0.001$). Subgroup analysis revealed varying NT-proBNP distributions and differential safety cutoffs (329–929 pg/mL) at sensitivity of 0.8 based on factors such as atrial fibrillation and chronic kidney disease, maintaining its discriminatory performance (area under the curve: 0.587–0.734).

Conclusions: NT-proBNP levels at discharge are a significant prognostic marker for HFpEF. Although NT-proBNP levels showed different distributions in various subgroups, and cutoff values were distinctive for each, the prognostic utility was found to be equivalent in almost all subgroups and had similar moderate discriminative performance. The

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See page 779 for disclosure information.

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study highlights the necessity of personalized NT-proBNP cutoffs for better management of and prognostication for patients with HFpEF. (*J Cardiac Fail 2025;31:771–780*)

Key Words: HFpEF, acute heart failure, biomarker, NT-proBNP.

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Introduction

N-terminal pro brain natriuretic peptide (NT-proBNP) levels are reliably measured in clinical practice as biomarkers reflecting myocardial stress, and they have been used for the diagnosis of heart failure (HF), understanding the status and predicting the prognoses of patients with HF with both reduced and preserved ejection fraction (HFrEF and HFpEF).[1–3] However, it has been reported that NT-proBNP levels are confounded by clinical indicators, such as age, body mass index (BMI), cardiac hypertrophy, atrial fibrillation (AF), and estimated glomerular filtration rate (eGFR).[4–6] Because of the variance in NT-proBNP levels influenced by these factors, clinicians often find difficulty in interpreting the value of NT-proBNP.

A study from the BIOS (Biomarkers In Heart Failure Outpatient Study) consortium tested the prognostic role of NT-proBNP levels stratified by BMI.[7] In the study, lower optimal risk-prediction cutoffs were observed in obese patients. Similarly, it is highly probable that several clinical factors, such as AF and chronic kidney disease (CKD), influence the optimal risk-prediction cutoffs of NT-proBNP. However, the optimal risk-prediction cutoffs of NT-proBNP, considering such influencing factors, have not been well investigated to date. Furthermore, HFpEF has multifactorial pathophysiology, which further complicates the utility of NT-proBNP in our clinical practice.[8]

The objectives of this study were: (1) to examine the prognostic impact of NT-proBNP levels in patients with HFpEF; and (2) to examine differences in the distribution of NT-proBNP and the risk-prediction cutoff values of NT-proBNP in various subgroups of patients with HFpEF.

Methods

Study Subjects

Patients' data were obtained from the prospective multicenter observational study of Asian patients with HFpEF. In the study, patients aged ≥ 20 years who were hospitalized due to acute decompensated HF (ADHF) with preserved left ventricular ejection fraction ≥ 50%, as measured by echocardiography on admission, were registered. ADHF was diagnosed on the basis of the Framingham heart failure criteria, and NT-proBNP ≥ 400 pg/mL or brain natriuretic peptide ≥ 100 pg/mL according to laboratory data on admission. Details of inclusion and exclusion criteria are summarized in Supplementary Table 1. Between June 2016 and February 2022, 1231 patients were enrolled. In this study, we excluded patients with in-hospital death, those on dialysis, those with missing survival data, those with planned follow-up not yet achieved, and those with missing NT-proBNP data. The study was conducted in compliance with the ethical principles stated in the Declaration of Helsinki, and the study protocol was approved by the ethics committees of all participating hospitals. All patients provided written informed consent before participating in the study.

Data Collection

We collected data including detailed medical histories, comorbidities, clinical frailty scales, New York Heart Association classes, laboratory data, and transthoracic echocardiographic data. The clinical frailty scale was assessed on admission. New York Heart Association class data, laboratory data and transthoracic echocardiographic data were obtained at discharge. Details are described in the Supplementary Appendix.

Measurement of NT-proBNP Levels

We measured NT-proBNP levels after stabilization of HF status at discharge. Venous blood was collected into an ethylene diamine tetra-acetic acid anticoagulation tube and processed immediately after sampling. The tests were performed in a local laboratory that used the Elecsys NT-proBNP assay (Roche, Mannheim, Germany).

Clinical Endpoints

The primary endpoint of this study was a composite of all-cause death and hospitalization due to HF within 1 year after discharge. After discharge, enrolled patients were followed-up at the out-patient clinic in each hospital. Clinical follow-up data were obtained either by direct contact with patients or by telephone or e-mail contact with their families.

Statistical Analysis

All statistical analyses were performed using R software (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria). A P value of < 0.05 was considered statistically significant. The following information is a brief description; details are shown in the Supplementary Appendix.

Data are presented using complete case analyses. Categorical variables are expressed as counts (percentages)

and compared with the χ^2 test or the Fisher exact test. Continuous variables are expressed as mean (SD) or median (interquartile range) and are compared using the Student *t* test, the Mann-Whitney U test or the Kruskal-Wallis test, as appropriate. The normality of distribution of continuous data was assessed using Q-Q plots with 95% confidence intervals (CIs).

Logistic regression models were used to analyze the prognostic impact of NT-proBNP levels by calculating the univariable and multivariable-adjusted odds ratios (ORs) and 95% CI. Both spline and linear models were considered (Supplementary Fig. 1). Details of the model selection process are provided in the Supplementary Appendix. We ultimately adopted the linear model in the logistic regression model. Covariates in the multivariable logistic regression model are listed in Supplementary Table 2. These covariates were selected based on previous findings.[8] The variance inflation factors for all independent variables were below 2, indicating the absence of multicollinearity. In the multivariable model, to evaluate the impact of potential confounders, we incrementally adjusted for all covariates, adding them 1 by 1 to the univariable model and assessing the change in the OR of log-transformed NT-proBNP levels. Subsequently, a fully adjusted model incorporating all covariates simultaneously was constructed to evaluate the independent effect of NT-proBNP levels.

Multiple linear regression analysis was used to identify correlates of log-transformed NT-proBNP levels with clinical factors, aiming to explore the mechanisms underlying the elevation of NT-proBNP levels. Variables in the multivariable linear regression model are listed in Supplementary Table 3. These variables were selected based on clinical consensus and the previous findings.[4,5] The variance inflation factors for all independent variables were below 2, indicating the absence of multicollinearity.

We stratified the study population into subgroups according to age, sex, BMI, history of AF, history of diabetes, history of hypertension, eGFR, left ventricular mass index (LVMI), and tricuspid annular plane systolic excursion (TAPSE). The distribution of NT-proBNP levels was compared across subgroups. The criteria for stratification were based on consensus from previous reports and established guidelines.[9–12] To assess the predictive value of NT-proBNP lvels in various subgroups of people with HFpEF, we used the AUC of ROC curves. In this study, we aimed to propose a reference value that acts as a safety threshold to prevent adverse events, and we examined differences in cutoffs among subgroups. Therefore, we have defined a clinically safe cutoff to prevent death and rehospitalization due HF by using a sensitivity of 0.8. This safety cutoff was decided based on the consensus of our research team, considering the clinical significance. We also computed the corresponding specificity, positive predictive value and negative predictive value, as well. To evaluate the generalizability of this safety cutoff, we conducted cross-validation. Details are described in the Supplementary Appendix. To assess the difference and its 95% CI in the safety cutoffs among subgroups, the bootstrap method was employed (bias corrected and accelerated percentile method, n = 1000). Additionally, we examined cutoff values at sensitivities of 0.7 and 0.9, closest to the top left corner of the ROC curve, as reference values. In each subgroup, the primary endpoint was assessed according to the stratification of each cutoff in a time-to-first-event fashion by using the Kaplan-Meier method and was compared by using the log-rank test.

Results

Baseline Patient Characteristics

A total of 1231 patients were enrolled in this HFpEF study (83 [77, 87] years, 551 [45%] male). Of the overall cohort, 916 patients were analyzed to assess the prognostic value of NT-proBNP levels (Fig. 1). Patients' baseline characteristics are shown in Table 1. The Q-Q plots for continuous variables are shown in Supplementary Fig. 2. The median level of NT-proBNP levels was 1060 [475, 2348] pg/mL. The clinical characteristics of patients included and those excluded due to missing NT-proBNP data are summarized in Supplementary Table 4.

The Prognostic Impact of NT-proBNP

The mean follow-up duration was 2.2 ± 1.3 years. The primary endpoint occurred in 261 patients within 1 year (all-cause death, 104 patients; and hospitalization for HF, 191 patients). Details regarding the causes of death are summarized Supplementary Fig. 3.

In univariable analysis, NT-proBNP levels were significantly associated with the primary endpoint (OR for log-transformed NT-proBNP; 3.70, 95% CI: 2.68−5.16; $P < 0.001$). When adjusted for cholinesterase, the OR of log-transformed NT-proBNP levels decreased the most (adjusted OR for log-transformed NT-proBNP 2.98, 95% CI: 2.13−4.22; $P < 0.001$) (Supplementary Table 5). Although the risk estimate decreased, NT-proBNP levels remained an independent predictor of the primary endpoint, even after fully adjusting for all covariates (adjusted OR for log-transformed NT-proBNP: 2.71, 95% CI: 1.78−4.18; $P < 0.001$) (Table 2).

Correlates of NT-proBNP Levels With Clinical Factors

Correlates of NT-proBNP levels are shown in Table 3. AF, log-transformed C-reactive protein, LVMI, and TRPG (tricuspid regurgitation pressure gradient) were positively associated with NT-proBNP levels, and BMI, eGFR, albumin, cholinesterase, and TAPSE were negatively associated.

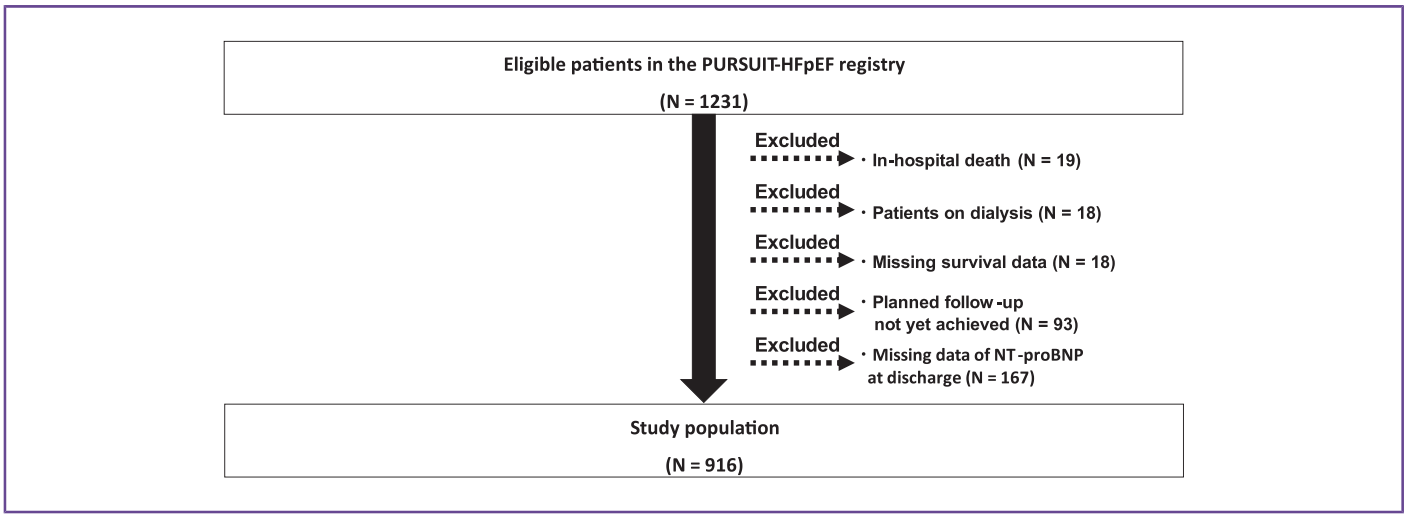


Fig. 1. Patients' flowchart.

Differential Distribution of NT-proBNP Levels in Subgroups of HFpEF

Fig. 2 illustrates histograms showing the distribution of NT-proBNP levels in various subgroups divided by hospital discharge data. The levels of NT-proBNP were significantly different according to age, BMI, history of AF, eGFR, LVMI, and TAPSE. On the other hand, there were no significant differences in sex and comorbidities, such as diabetes and hypertension.

Discriminative Power of NT-proBNP and Safety Cutoffs in Various Subgroups of Patients With HFpEF

The AUC (95% CI) for NT-proBNP levels in various subgroups are shown in Fig. 3. In almost all subgroups, NT-proBNP levels had moderate to fair discriminatory power (ranging from 0.60−0.80) for the primary endpoint, although the safety cutoffs varied. In the cross-validation process, the safety cutoff was confirmed to be reasonably consistent across the entire dataset (Supplementary Table 6). The cutoff values at sensitivities of 0.7, 0.9 and closest to the top left corner of the ROC curve are shown in Supplementary Fig. 4. The Kaplan-Meier analysis revealed that in almost all subgroups, each safety cutoff of NT-proBNP levels successfully stratified the patients (Fig. 4).

Discussion

The main findings of the present study can be summarized as follows: (1) NT-proBNP levels at discharge were associated with the prognoses of patients with HFpEF; and (2) when patients with HFpEF were divided into various subgroups stratified by age, sex, BMI, and comorbidities such as AF and CKD, the prognostic power of NT-proBNP levels was preserved for almost all subgroups, whereas the safety cutoffs of NT-proBNP differed by subgroups.

Prognostic Utility of NT-proBNP

In clinical practice, it is often difficult to predict precisely the prognoses of patients with HFpEF, because patients with HFpEF have, in general, a complex combination of various pathological conditions, including both cardiac and extra-cardiac stress. In our analysis, when adjusting for cholinesterase, the OR for log-transformed NT-proBNP levels substantially decreased from 3.70 to 2.98. Although high NT-proBNP levels basically reflect cardiac burden, low cholinesterase levels mainly reflect extra-cardiac burdens, such as malnutrition and inflammation. Low cholinesterase levels are significantly associated with poor prognosis in HFpEF.[13] This suggests that the prognosis in HFpEF is influenced not only by cardiac burden but also by extra-cardiac burdens, such as malnutrition and inflammation. The association between NT-proBNP levels and prognosis for patients with HFpEF, after adjusting every covariate, including extra-cardiac factors, is of great importance.

Additionally, in the analysis of the correlation between NT-proBNP levels and clinical factors (Table 3), NT-proBNP levels independently correlated not only with cardiac factors such as tricuspid regurgitation pressure gradient and TAPSE but also with extra-cardiac factors, including nutritional indicators such as BMI and albumin, as well as inflammation, anemia and renal dysfunction. NT-proBNP levels could capture comprehensively complicated pathophysiological conditions, including cardiac and extra-cardiac burdens, and could have prognostic significance in HFpEF.

Subgroup-specific Distribution of NT-proBNP

Several reports have been published concerning the differential distribution of NT-proBNP levels in subgroups of patients with HF. NT-proBNP levels are elevated in elderly patients and in those with lupus, CKD and/or AF.[4,5,7] In our study, elderly patients, those underweight, those with

Table 1 Patients' backgrounds

Characteristics	All Patients (n = 916)	Data Missing (%)
Age (years)	83 [77, 87]	0
Male sex	404 (44.1)	0
Body mass index (kg/m^2) at hospital discharge	21.5 [19.0, 24.3]	0.7
NYHA evaluated at hospital discharge		1.1
I	309 (34.1)	
II	529 (58.4)	
III	64 (7.1)	
IV	4 (0.4)	
Clinical frailty scale ≥ 5 evaluated at hospital admission	261 (28.6)	0.2
Worsening Reasons for Heart Failure		
Too much intake	252 (27.5)	0
Poor drug compliance	62 (6.8)	0
Physical fatigue	84 (9.2)	0
Infection	162 (17.7)	0
Arrythmia	246 (26.9)	0
Ischemia	25 (2.7)	0
Poor blood pressure control	134 (14.6)	0
Medical History		
Atrial fibrillation	470 (51.3)	0
Myocardial infarction	62 (6.9)	1.4
Hypertension	773 (84.6)	0.2
Diabetes mellitus	300 (33.0)	0.8
COPD	67 (7.7)	4.5
Medication at Hospital Discharge		
ACE-i/ARBs	487 (53.2)	0
Beta-blockers	497 (54.3)	0
Diuretics	767 (83.7)	0
MRA	372 (40.6)	0
SGLT2-inhibitors	54 (5.9)	0.1
Laboratory Data at Hospital Discharge		
Albumin (g/dL)	3.4 [3.1, 3.7]	0.8
Hemoglobin (g/dL)	11.3 [10.1, 12.7]	0
Sodium (mEq/L)	140 [137, 141]	0.1
Potassium (mEq/L)	4.3 [3.9, 4.6]	0
Chloride (mEq/L)	103 [100, 106]	0.7
eGFR (mL/min/1.73m^2)	41.7 [30.3, 54.7]	0.1
eGFR ≥ 60	159 (17.4)	
60 > eGFR ≥ 30	533 (58.3)	
30 > eGFR	223 (24.4)	
NT-proBNP (pg/mL)	1060 [475, 2348]	0
Cholinesterase (U/L)	207 [170, 254]	9.1
C-reactive protein (mg/dL)	0.3 [0.1, 0.8]	0.4
Echocardiography at Hospital Discharge		
LVDd (mm)	46 [41, 50]	2.5
LVEF (%)	61 [56, 66]	10.8
LAVI (mL/m^2)	50 [37, 65]	13.1
LVMI (g/m^2)	102 [84, 124]	3.1
TAPSE (mm)	17.3 [14.7, 20.2]	10.5
Mean E/e'	12.5 [9.6, 16.7]	10
TRPG (mmHg)	27 [22, 33]	9.7

Data are shown as median [interquartile range] or number (percentage).

ACE-i, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease; E, early diastolic velocity on transmitral doppler; e', early diastolic velocity of the mitral valve annulus; eGFR, estimated glomerular filtration rate; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVDd, left ventricular diastolic diameter; LVMI, left ventricular mass index; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SGLT2 inhibitors, sodium glucose cotransporter2 inhibitor; TAPSE, tricuspid annular plane systolic excursion; TRPG, tricuspid regurgitation pressure gradient.

AF, CKD, cardiac hypertrophy, and/or right heart dysfunction had significantly higher NT-proBNP levels, which is in line with previous findings.[4,5,7] On the other hand, differential optimal risk-prediction cutoffs of NT-proBNP levels were reported only in the BIOS study. That study (n = 12,763) tested the prognostic role of NT-proBNP levels stratified by BMI.[7] NT-proBNP levels inversely correlated with BMI. The best cutoffs of NT-proBNP levels for 5-year all-cause death prediction were lower as BMI increased (3785 ng/L, 2193 ng/L, 1554 ng/L, 1045 ng/L, 755 ng/L, and 879 ng/L, for underweight, normal weight, overweight, and mildly, moderately and severely obese patients, respectively). Although the study provided important insights into the practical use of NT-proBNP levels, there remains a large evidence gap in this topic. First, the BIOS study included mainly patients with HFrEF (76%). The applicability of the findings to those with HFpEF may be limited. It is known that patients with HFpEF show lower NT-proBNP levels than patients with HFrEF.[3] Second, the Asian patients with HFpEF were critically different from those in the United States and Europe in terms of body weight. The median BMI in our cohort

Table 2 Prognostic impact of NT-proBNP

	OR (95%CI)	*P* value
Univariable logistic regression analysis		
Log-transformed NT-proBNP (pg/mL)	3.70 (2.68-5.16)	<0.001
Multivariable logistic regression model		
Log-transformed NT-proBNP (pg/mL)	2.71 (1.78-4.18)	<0.001

CI, confidence interval; NT-proBNP, N-terminal pro-brain natriuretic peptide; OR, odds ratio.

Table 3 Correlation between NT-proBNP and clinical factors

	β-Coefficient [95% confidence interval]	*P* value
Age (years)	−0.0019 [−0.0052, 0.0014]	0.267
Male sex	−0.0237 [−0.0802, 0.0328]	0.412
Body mass index	−0.0166 [−0.0235, −0.0098]	<0.001
NYHA ≥ 2	0.0443 [−0.0128, 0.1014]	0.129
Clinical frailty scale ≥ 5	0.0382 [−0.0237, 0.1001]	0.227
Atrial fibrillation	0.0978 [0.0414, 0.1543]	0.001
Hypertension	−0.0526 [−0.1279, 0.0226]	0.170
Diabetes mellitus	0.0307 [−0.0268, 0.0882]	0.296
COPD	−0.0090 [−0.1099, 0.0920]	0.862
eGFR (mL/min/1.73m^2)	−0.0091 [−0.0106, −0.0076]	<0.001
Albumin (g/dL)	−0.1731 [−0.2445, −0.1016]	<0.001
Cholinesterase (U/L)	−0.0013 [−0.0018, −0.0008]	<0.001
Log-transformed CRP (mg/dL)	0.0555 [0.0115, 0.0995]	0.014
Hemoglobin (g/dL)	0.0098 [−0.0065, 0.0260]	0.241
LVMI	0.0029 [0.0021, 0.0037]	<0.001
TRPG (mmHg)	0.0059 [0.0029, 0.0088]	<0.001
TAPSE (mm)	−0.0157 [−0.0223, −0.0092]	<0.001

COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; TAPSE, tricuspid annular plane systolic excursion; TRPG, tricuspid regurgitation pressure gradient.

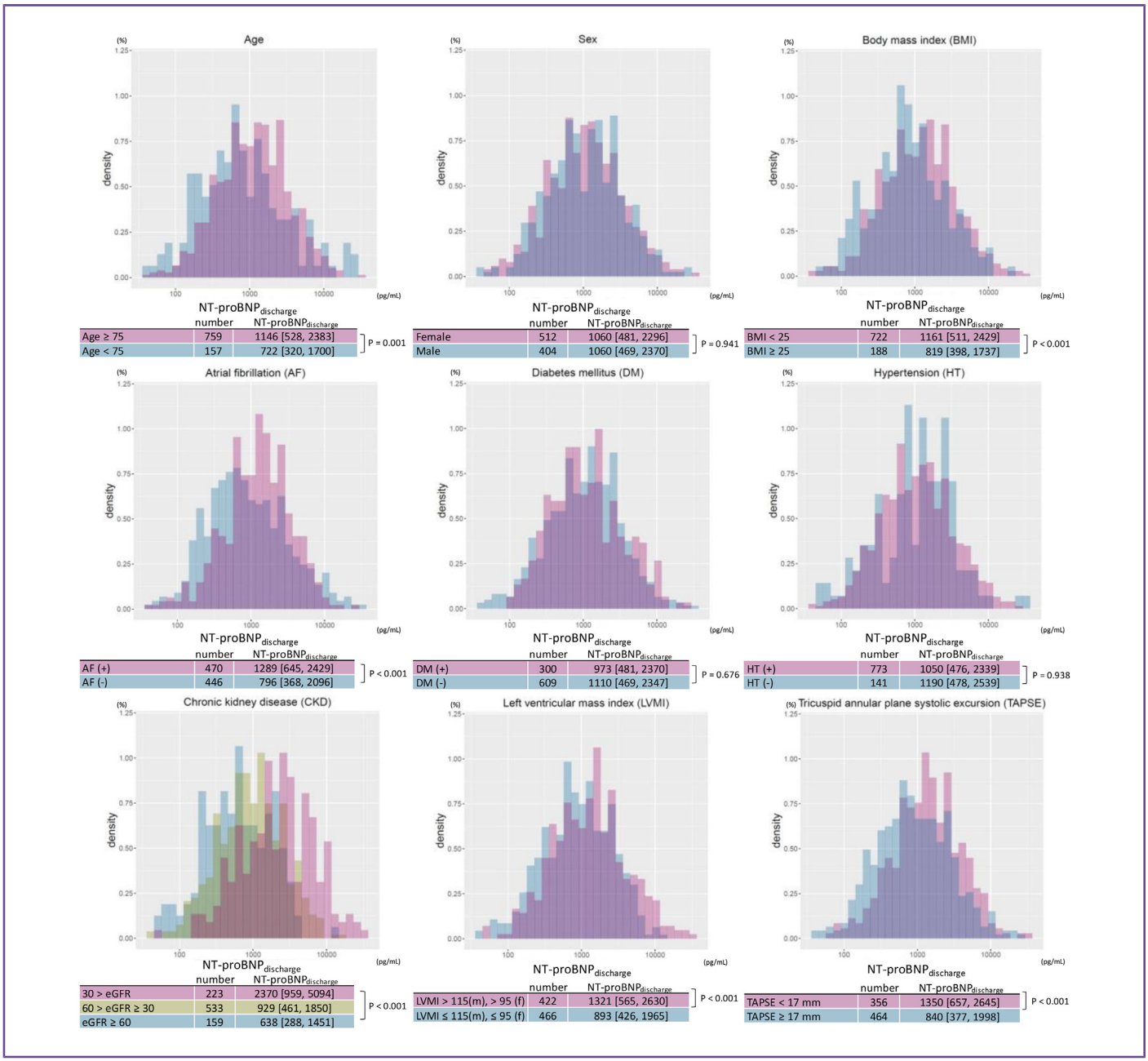


Fig. 2. Differential distribution of NT-proBNP in various patient subgroups. The distribution of NT-proBNP levels in various subgroups is shown using a histogram. In the histogram, the x-axis shows NT-proBNP taken on a logarithmic axis, and the y-axis shows the percentage of patients in each subgroup. AF, atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate (mL/min/1.73m^2); f, female; HT, hypertension; LVMI, left ventricular mass index; m, male; TAPSE, tricuspid annular plane systolic excursion (mm).

was 21.5, whereas in the U.S. and Europe, it is as high as 30.[14] Third, in spite of the fact that several clinical factors, such as AF and CKD, other than body weight might influence the risk-prediction cutoffs of NT-proBNP levels, this point has not been investigated so far.

Our investigation delineates the safety target NT-proBNP cutoff value during hospitalization due to ADHF for the prevention of death and recurrent admissions due to HF, marking the first report on its risk-prediction values and the differences in various subgroups of Asian patients with HFpEF. Notably, the prognostic power of NT-proBNP levels is preserved across subgroups differentiated by age, sex, BMI, and comorbidities such as AF and CKD, despite varying safety cutoffs. Our study, prioritizing a sensitivity of 0.8, aims to establish a safety-target NT-proBNP cutoff value to mitigate rehospitalization risks during inpatient care of those with ADHF. We found that the safety cutoffs were influenced by the presence or absence of complications, a trend generally consistent with previous reports on the mechanism.[15,16] This underscores the robust prognostic utility of NT-proBNP levels, which transcends the heterogeneity of the HFpEF population. The

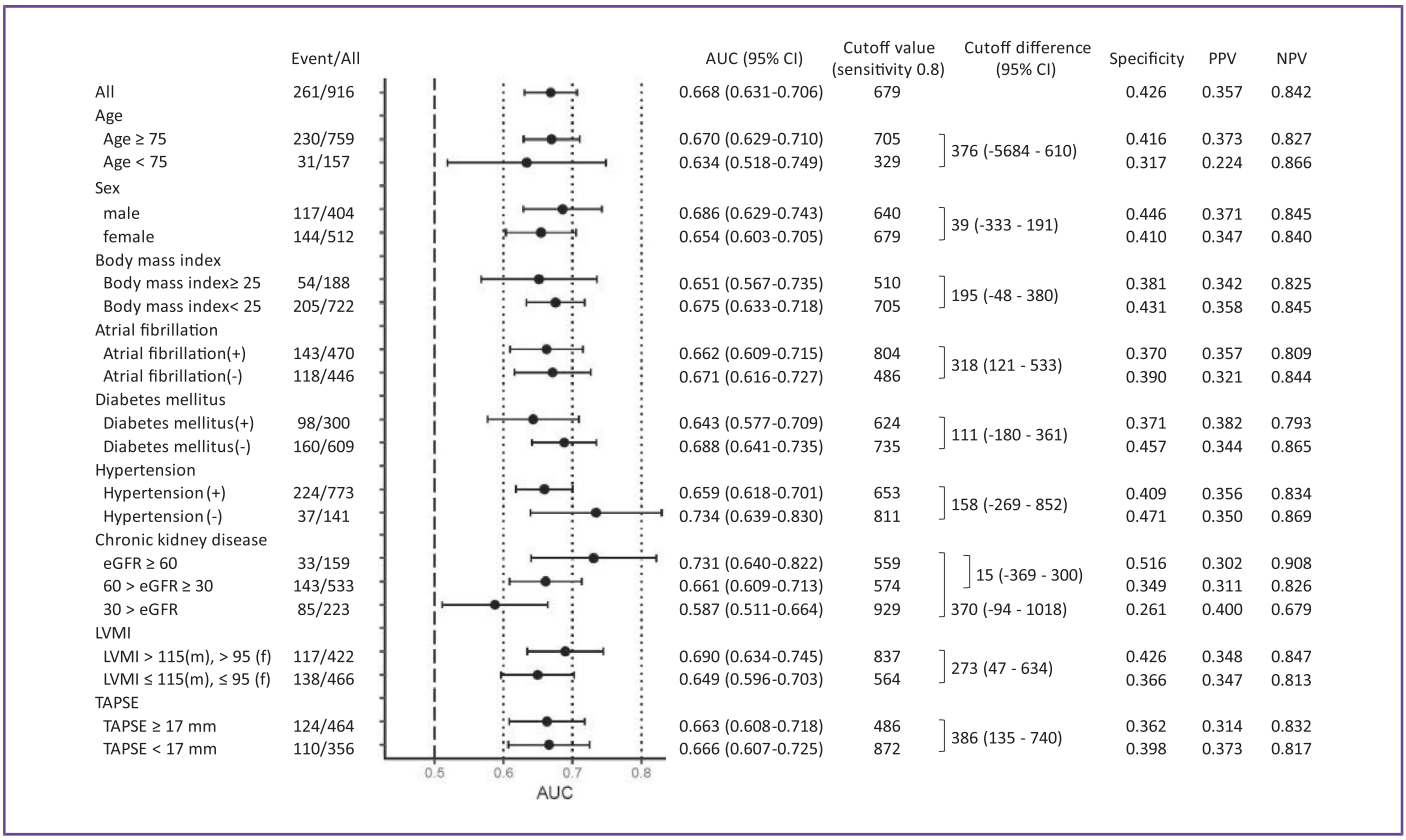


Fig. 3. Differential safety NT-proBNP cutoffs at a sensitivity of 0.8 in various subgroups of HFpEF. C-statistics (area under the curve) and a 95% confidence interval of NT-proBNP for the primary endpoint are shown in a forest plot. We have defined a clinically optimal safety cutoff value to prevent rehospitalization due to heart failure, with a sensitivity of 0.80. We also computed the corresponding specificity, positive predictive value and negative predictive value, as well. Although the cutoff values of NT-proBNP levels differed in various subgroups of patients with HFpEF, the discriminative power was, overall, maintained at a moderate level. eGFR, estimated glomerular filtration rate (mL/min/1.73m^2); f, female; LVMI, left ventricular mass index[10]; m, male; PPV, positive predictive value; NPV, negative predictive value; TAPSE, tricuspid annular plane excursion.

variation in safety cutoff values across subgroups highlights the complex nature of HFpEF, indicating the need for a tailored approach to risk stratification based on patient-specific factors and comorbid conditions. The use of NT-proBNP levels in guiding in-hospital and post-discharge management and risk stratification in patients with HFpEF suggests the potential for enhancing personalized care strategies.

Integrating NT-proBNP levels into the prognostic assessment of patients with HFpEF aligns with the multifactorial approach required for managing this condition. This integration also emphasizes the need for continued research into the pathophysiological mechanisms of HFpEF and the role of biomarkers in these dynamics. Additionally, combining NT-proBNP levels with other biomarkers, such as tumor necrosis factor-alpha and growth and differentiation factor 15, which are gaining attention for their potential correlation with HF, may improve the discriminatory ability to help patients with HFpEF. This combination highlights the evolving landscape of HF diagnostics and the potential for more refined treatment strategies.[8]

Study Limitations

Several limitations in this study must be acknowledged. First, the generalizability of the findings to other regions and ethnicities is limited due to differing races, social health care systems and the dietary habits in Japan compared with those of other countries. Although we performed cross-validation (Supplementary Table 6), further large-scale external validation studies should be conducted. Second, the safety NT-proBNP cutoff values presented in this study for differing groups of patients require caution in interpretation and clinical application. In particular, safety cutoffs in cases with multiple comorbidities (eg, AF and CKD) are not specified. Third, due to the missing data of NT-proBNP levels at discharge, only 74.4% of the overall population were included in the present study. As presented in Supplementary Table 4, there were some differences in clinical characteristics between the patients included in and excluded from this analysis, which might have resulted in a potential selection bias. Fourth, our registry did not enroll patients with acute coronary syndromes or severe valvular disease. Fifth, the diagnosis of secondary cardiomyopathy, such as cardiac amyloidosis, was at

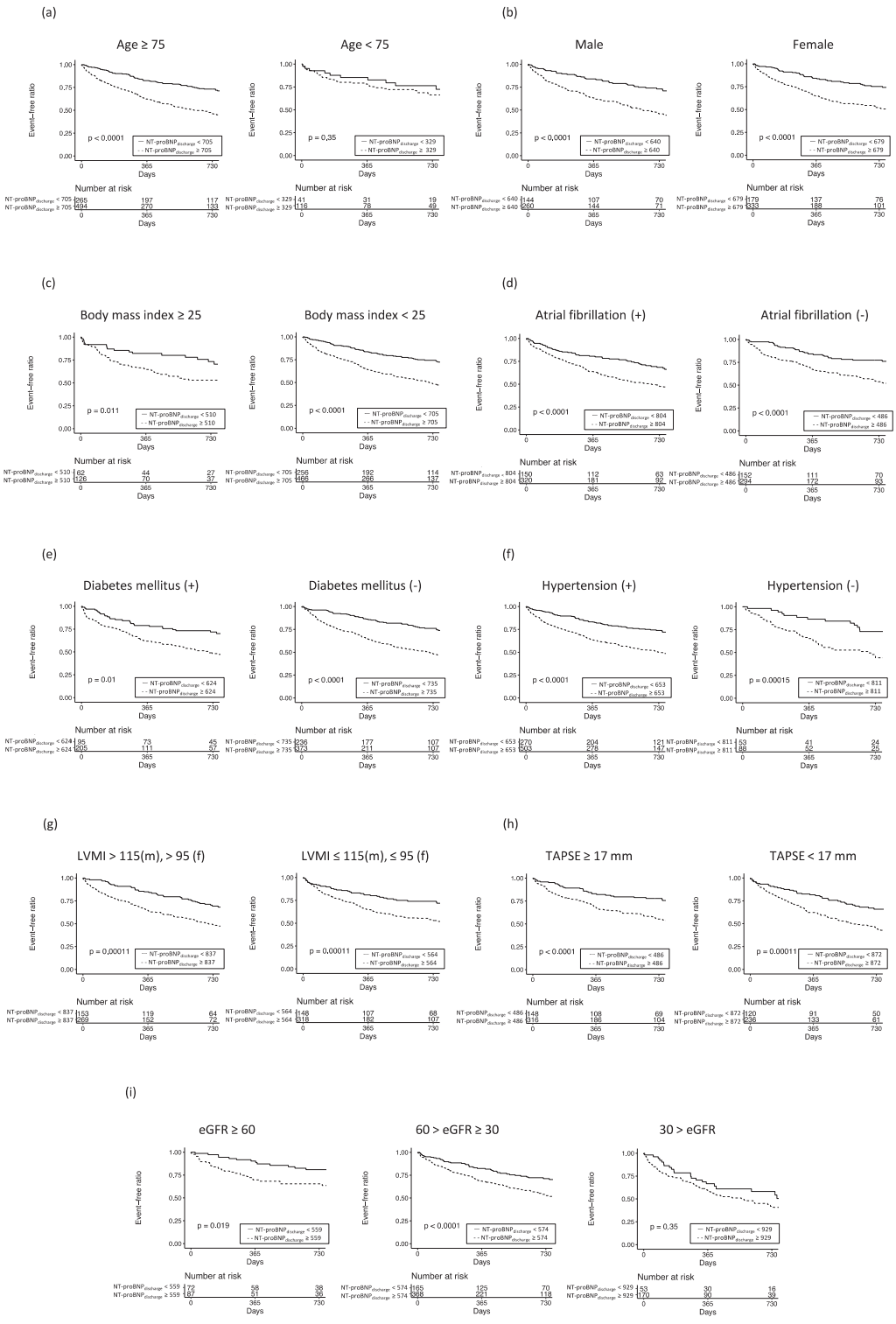


Fig. 4. Kaplan-Meier curves demonstrating the composite endpoint across subgroups, stratified by specific cutoff values. The Kaplan-Meier analysis for comparing the composite of all-cause death and hospitalization for heart failure in 2 groups divided by each optimal cutoff value of NT-proBNP in each subgroup. Panels indicate the stratifications by (a) age, (b) sex, (c) body mass index, (d) atrial fibrillation, (e) diabetes mellitus, (f) hypertension, (g) LVMI, (h) TAPSE, and (i) eGFR. eGFR, estimated glomerular filtration rate (mL/min/1.73m^2). f, female; LVMI; left ventricular mass index[10]; m, male; TAPSE, tricuspid annular plane excursion.

physicians' discretion and was not made systematically. Therefore, the primary disease was not fully identified. Sixth, our study was conducted between 2016 and 2022, before the evidence for use of sodium glucose cotransporter 2 inhibitors (SGLT2-is) was established.[17] SGLT2-is were prescribed only to patients with diabetes, which resulted in a low prescription rate for SGLT2-is. Seventh, although we believe that the sensitivity of 0.8 offers a practical safety line in managing HFpEF, this threshold is exploratory and is not a universally accepted standard. Finally, the small sample size, especially of the subgroup analysis stratified by renal dysfunction, might not have enough statistical power. Results should be interpreted with caution. Further large-scale global studies are needed to address these limitations.

Conclusions

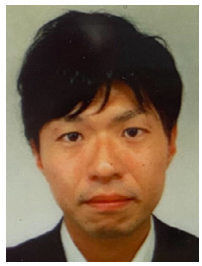
This study demonstrated that in patients with HFpEF who are hospitalized for ADHF, NT-proBNP levels at discharge were significantly associated with a composite of all-cause death and hospitalization due to HF. Although NT-proBNP levels showed different distributions in the various patient subgroups, and cutoff values were distinctive for each, the prognostic utility was found to be equivalent in most HFpEF subgroups and had similarly moderate discriminative performance. The differences in safety cutoffs across subgroups can suggest the necessity of personalized NT-proBNP targets for better management of and prognostication for people with HFpEF.

Declaration of Generative AI and AI-assisted Technologies in the Writing Process

During the preparation of this work, we used ChatGPT to edit English. After using this tool, we reviewed and edited the content as needed, and we take full responsibility for the content of the publication.

Lay Summary

This study found that NT-proBNP level, a heart-stress marker, is useful in predicting the risk of death or readmission due to heart failure in patients hospitalized for acute decompensation for heart failure with preserved ejection fraction when measured at the time they are discharged from the hospital. The study shows that the levels of this marker vary among patients and suggests different cutoff points for adverse events based on specific health conditions, such as atrial fibrillation, obesity and kidney disease. This helps doctors to personalize treatment so as to better manage and predict outcomes for patients with heart failure.



Disclosures

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CRediT authorship contribution statement

DAISUKE SAKAMOTO: Writing – original draft. **YOHEI SOTOMI:** Writing – review & editing. **YUKI MATSUOKA:** Writing – review & editing. **DAISAKU NAKATANI:** Writing – review & editing. **KATSUKI OKADA:** Writing – review & editing. **AKIHIRO SUNAGA:** Writing – review & editing. **HIROTA KIDA:** Writing – review & editing. **TAIKI SATO:** Writing – review & editing. **TETSUHISA KITAMURA:** Writing – review & editing. **MASAHIRO SEO:** Writing – review & editing. **MASAMICHI YANO:** Writing – review & editing. **TAKAHARU HAYASHI:** Writing – review & editing. **AKITO NAKAGAWA:** Writing – review & editing. **YUSUKE NAKAGAWA:** Writing – review & editing. **SHUNSUKE TAMAKI:** Writing – review & editing. **YOSHIO YASUMURA:** Writing – review & editing. **TAKAHISA YAMADA:** Writing – review & editing. **SHUNGO**

HIKOSO: Writing – review & editing. YASUSHI SAKATA: Writing – review & editing, Supervision, Project administration.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2024.10.440.

References

1. Zegard A, Naneishvili T, Viyapurapu R, Desai P, White S, Patel PA, et al. Diagnostic yield of a heart failure referral pathway using N-terminal pro-brain natriuretic peptide. Open Heart 2023;10.
2. Zhang X, Wan Y, Karunathilaka N, Chan W, Kostner K, Hartel G, et al. Prognostic utility of serum NT-proBNP (fragments 1-76aa and 13-71aa) and galectin-3 in predicting death and re-hospitalisation due to cardiovascular events in patients with heart failure. Heart Vessels 2023.
3. Salah K, Stienen S, Pinto YM, Eurlings LW, Metra M, Bayes-Genis A, et al. Prognosis and NT-proBNP in heart failure patients with preserved versus reduced ejection fraction. Heart 2019;105:1182–9.
4. Nasab Mehrabi E, Toupchi-Khosroshahi V, Athari SS. Relationship of atrial fibrillation and N terminal pro brain natriuretic peptide in heart failure patients. ESC Heart Failure. n/a.
5. Ozkan B, Grams ME, Coresh J, McEvoy JW, Echouffo-Tcheugui JB, Mu SZ, et al. Associations of N-terminal pro-B-type natriuretic peptide, estimated glomerular filtration rate, and mortality in US adults. Am Heart J 2023;264:49–58.
6. Myhre PL, Vaduganathan M, Claggett BL, Anand IS, Sweitzer NK, Fang JC, et al. Association of natriuretic peptides with cardiovascular prognosis in heart failure with preserved ejection fraction: secondary analysis of the TOPCAT randomized clinical trial. JAMA Cardiol 2018;3:1000–5.
7. Vergaro G, Gentile F, Meems LMG, Aimo A, Januzzi Jr JL, Richards AM, et al. NT-proBNP for risk prediction in heart failure: identification of optimal cutoffs across body mass index categories. JACC Heart Fail 2021;9:653–63.
8. Sotomi Y, Tamaki S, Hikoso S, Nakatani D, Okada K, Dohi T, et al. Pathophysiological insights into machine learning-based subphenotypes of acute heart failure with preserved ejection fraction. Heart 2023.
9. KDIGO 2024 Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int 2024;105:S117–314.
10. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1–39. e14.
11. Ogawa W, Hirota Y, Miyazaki S, Nakamura T, Ogawa Y, Shimomura I, et al. Definition, criteria, and core concepts of guidelines for the management of obesity disease in Japan. Endocr J 2024;71:223–31.
12. Hanyu H, Koyama Y, Umekida K, Momose T, Watanabe S, Sato T. Factors and brain imaging features associated with cognition in oldest-old patients with Alzheimer-type dementia. J Neurol Sci 2024;458:122929.
13. Seo M, Yamada T, Tamaki S, Hikoso S, Yasumura Y, Higuchi Y, et al. Prognostic significance of serum cholinesterase level in patients with acute decompensated heart failure with preserved ejection fraction: insights from the PURSUIT-HFpEF registry. J Am Heart Assoc 2020;9:e014100.
14. Steinberg BA, Zhao X, Heidenreich PA, Peterson ED, Bhatt DL, Cannon CP, et al. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. Circulation 2012;126:65–75.
15. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. Circulation 2017;136:6–19.
16. Glisic M, Rojas LZ, Asllanaj E, Vargas KG, Kavousi M, Ikram MA, et al. Sex steroids, sex hormone-binding globulin and levels of N-terminal pro-brain natriuretic peptide in postmenopausal women. Int J Cardiol 2018;261:189–95.
17. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med 2022;387:1089–98.