

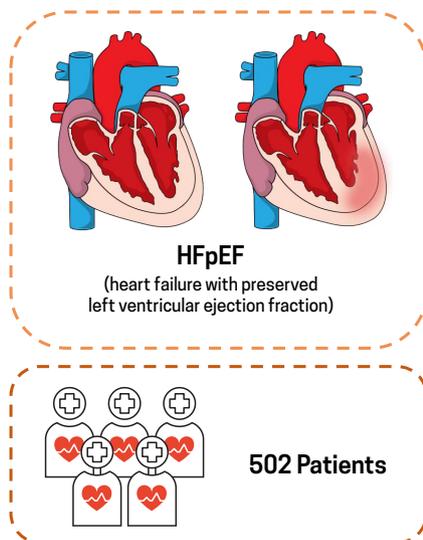


HFA-PEFF scores: prognostic value in heart failure with preserved left ventricular ejection fraction

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HFA-PEFF scores: prognostic value in heart failure with preserved left ventricular ejection fraction



HFA-PEFF score

CVD events
HF-related events

Intermediate score group
(score 2-4)
High score group
(score 5-6)



ROC curve
for HF-related event

AUC 0.633
Se 57.8%, Sp 67.4%
Cut off 4.5

Decision curve analysis

Base model: 40%
+ HFA-PEFF score
Combined model: 60%

HFA-PEFF scores may be useful
for predicting HF-related events in HFpEF patients.

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Background/Aims: The Heart Failure Association (HFA)-PEFF score is recognized as a simple method to diagnose heart failure (HF) with preserved ejection fraction (HFpEF). This study aimed to evaluate the relationship between HFA-PEFF scores and cardiovascular outcomes in HFpEF patients.

Methods: A total of 502 consecutive HFpEF patients were prospectively observed for up to 1,500 days. Cardiovascular outcomes were compared between two groups of patients, defined by their HFA-PEFF scores: those who scored 2–4 (the intermediate-score group) and those who scored 5–6 group (the high-score group). Overall, 236 cardiovascular events were observed during the follow-up period (median, 1,159 days).

Results: Kaplan-Meier analysis showed that there were significant differences in composite cardiovascular events and HF-related events between the intermediate-score group and the high-score group ($p = 0.003$ and $p < 0.001$, respectively). Multivariate Cox proportional hazards analysis showed that the HFA-PEFF scores significantly predicted future HF-related events (hazard ratio, 1.66; 95% confidence interval [CI], 1.11 to 2.50; $p = 0.014$); receiver operating characteristic analysis confirmed this relationship (area under the curve, 0.633; 95% CI, 0.574 to 0.692; $p < 0.001$). The cutoff HFA-PEFF score for the identification of HF-related events was 4.5. Decision curve analysis revealed that combining the HFA-PEFF score with conventional prognostic factors improved the prediction of HF-related events.

Conclusions: HFA-PEFF scores may be useful for predicting HF-related events in HFpEF patients.

Keywords: Heart failure; Prognosis; Follow-up studies

INTRODUCTION

Accumulating clinical studies have shown that approximately half of the clinically presenting cases of heart failure (HF) have HF with normal or preserved left ventricular (LV) ejection fraction (EF) [1]. Various diagnostic criteria have been proposed by various papers: (1) clinical presentation of HF symptoms; (2) normal or preserved LVEF; and (3) LV diastolic dysfunction demonstrated by Doppler echocardiography or cardiac catheterization. The above three points are now considered standard diagnostic criteria [2]. We have already reported that vascular function [3,4], blood electrolytes [5,6], Heavy, Hypertensive, atrial Fibrillation, Pulmonary hypertension, Elder, Filling pressure (H₂FPEF) scores [7], nutrition indexes [8], and diastolic late mitral annular velocity determined by echocardiography [9] are potent prognostic factors for patients who have HF with preserved EF (HFpEF). Hypertension causes the majority of HFpEF cases. The pathological conditions that can accompany HFpEF are diverse, and it has many comorbidities, including not only cardiovascular but also non-cardiovascular diseases, and this fact contributes to the high rates of hospitalization and death in HFpEF patients [10].

In the past year, the Heart Failure Association (HFA) of the European Society of Cardiology proposed a new diagnostic algorithm for HFpEF, incorporating the HFA-PEFF diagnostic

algorithm [11]. This algorithm is composed of four steps. In the second step, the HFA-PEFF score is calculated for each patient (Supplementary Table 1). If the HFA-PEFF score is ≥ 5 , HFpEF is diagnosed, and if the score is ≤ 1 , HFpEF can be excluded. If the HFA-PEFF score is 2 to 4, representing an intermediate probability of HFpEF, functional testing is recommended in the third step. This stepwise diagnostic approach from initial clinical assessment to more specialized tests is expected to be useful [11]. The HFA-PEFF score is well validated as a tool for the diagnosis of HFpEF [12]. These concepts were comprehensively reviewed in a recent article [13].

Recently, Sotomi et al. [14] investigated the prognosis in 408 HFpEF patients and reported the association between HFA-PEFF scores and future HF-related events. Thus, we investigated the value of HFA-PEFF scores in predicting subsequent cardiovascular events in HFpEF patients at our institutions. The aim of the study is to assess this scoring system for overall CVD event prediction and not merely for HF outcomes.

METHODS

This study was a prospective, single-center observational study.

Ethics statement

All procedures were conducted in accordance with the Declaration of Helsinki and its amendments. The study protocol was approved by the Institutional Review Board of Kumamoto University (approval number, Senshin 2,225). This study is registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000036884). There is no written consent because we obtained the consent of the participants by using “the opt-out material.” Opt-out materials are available at the following address: <https://kumadai-junnai.com/wp-content/uploads/houkatsu.pdf>.

Study design and patients

We prospectively investigated 948 consecutive patients with HF who were hospitalized in Kumamoto University Hospital between January 2007 and September 2013. We recorded each patient’s medical history and relevant clinical character-

istics. We excluded 443 patients for the following reasons: severe valvular disease (n = 118), chronic renal failure requiring hemodialysis (n = 65), systemic inflammatory disease (n = 5), acute renal failure with dehydration (n = 1), and not meeting the diagnostic criteria for HFpEF as subsequently described (including HF with a reduced LVEF [HFrEF], n = 251). We subsequently calculated the HFA-PEFF score of each of these HFpEF patients, and the subjects were subdivided into low-score (0–1), intermediate-score (2–4), and high-score (5–6) groups according to the original concepts of HFA-PEFF scoring as described below. We excluded patients with insufficient data (n = 3), and we also excluded the low-score group (n = 3) because this group had a low probability of having HFpEF. Finally, the remaining 502 patients were enrolled in this study and followed for up to 1,500 days to track the occurrence of composite cardiovascular events and HF-related events. A flow chart of the study is shown in Fig. 1.

Definition of HFpEF

HFpEF was clinically defined according to the European Society of Cardiology task force, as follows: (1) symptoms or signs of HF; (2) normal or mildly reduced LVEF (LVEF > 50% and LV end-diastolic volume index < 97 mL/m²); (3) evidence of abnormal LV relaxation, filling, diastolic distensibility, and diastolic stiffness.

We excluded HFpEF patients who had shown even a transient reduction in EF. Hence, HFpEF patients whose LVEF was < 50% and was improved by optimal medical therapy were not included in the present study. In our study, we stratified patients by the ratio of early transmitral flow velocity to early diastolic mitral annular velocity (E/e’), classified as either a ≥ 15 ratio or a ratio between 8 and 15; we also stratified patients by plasma brain-type natriuretic peptide (BNP) levels, with a cutoff of 100 pg/mL. Physicians further confirmed that the patients had HF by determining their New York Heart Association (NYHA) functional class [15], which was assessed by the standard questionnaire while the patients were in stable condition after optimal therapy.

Calculation of the HFA-PEFF score

The calculation of the HFA-PEFF score has been described previously [11]. In brief, the score has functional, morphological, and biomarker domains. Within each domain, a major criterion is worth 2 points, and a minor criterion is worth 1 point (Supplementary Table 1).

A total score ≥ 5 points is considered to be diagnostic

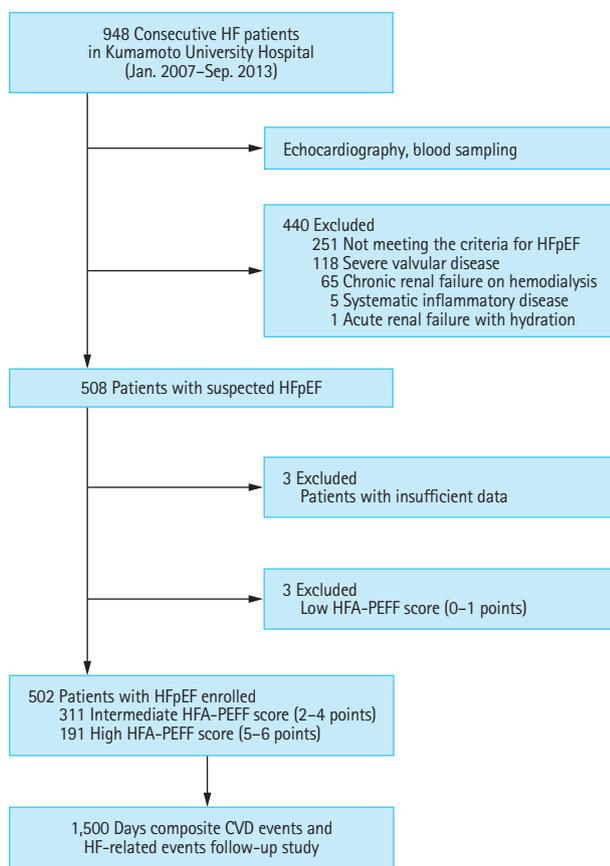


Figure 1. Flow chart showing the enrollment protocol. HF, heart failure; HFpEF, HF with preserved left ventricular ejection fraction; HFA-PEFF, Heart Failure Association-PEFF; CVD, cardiovascular disease.

of HFpEF, while a score of ≤ 1 point is considered to make a diagnosis of HFpEF very unlikely and to mandate investigations for alternative causes. Patients with an intermediate score (2–4 points) need further evaluation [11]. We subsequently calculated the HFA-PEFF scores of these HFpEF patients, and the subjects were subdivided into low- (0–1), intermediate- (2–4), and high-score (5–6) groups.

Clinical parameters

The clinical parameters have been described previously [16–18].

Echocardiographic examinations

The patients underwent echocardiography while they were in stable condition after admission; the examinations were performed by experienced cardiac sonographers who had no knowledge of the study data. The methods have been described in detail previously [9].

Biomarker measurement

Early-morning fasting blood samples were obtained while the patients were in stable condition. The patients' BNP levels were analyzed using a commercially available assay (Abbott Japan, Matsudo, Japan) in the hospital clinical laboratory on admission. The estimated glomerular filtration rate (eGFR) was calculated using the Japanese Society of Nephrology formula [19].

Follow-up and outcomes

Patients were followed up prospectively at our outpatient clinics or by a primary care physician every month until July 2017 or until the occurrence of a cardiovascular event, including the following: cardiovascular death, hospitalization for HF decompensation, nonfatal myocardial infarction (MI), unstable angina pectoris, coronary revascularization for a new diagnosis of angina or in-stent restenosis after percutaneous coronary intervention, and nonfatal ischemic stroke. Cardiovascular death was defined as death within 30 days of a documented cardiovascular event, sudden death without apparent non-cardiovascular causes, MI, death from HF, or death from stroke. Hospitalization for HF decompensation was defined as having occurred if the patient was admitted for at least an overnight stay in the hospital because of HF with typical symptoms and had objective signs of worsening HF requiring intravenous drug administration. MI was diagnosed by an increase or decrease in cardiac biomarkers (plasma creatine kinase-MB or cardi-

ac troponin) above the 99th percentile of the upper limit of the normal range together with evidence of myocardial ischemia and at least 1 of the following symptoms: electrocardiographic changes (new ST-T changes, left bundle branch block, or pathological Q wave), imaging evidence of new viable myocardial loss, or a new regional wall motion abnormality [20]. Unstable angina pectoris was diagnosed according to new or accelerating symptoms of myocardial ischemia accompanied by new ischemic ST-T-wave changes. Ischemic stroke was diagnosed according to a documented focal neurological deficit with radiological evidence of brain infarction, excluding intracranial hemorrhage. The primary and secondary endpoints were composite cardiovascular event (cardiovascular death, hospitalization for HF decompensation, and nonfatal stroke) occurrence and HF-related event (hospitalization for HF decompensation) occurrence, respectively, at 1,500 days. Cardiovascular events were ascertained by reviewing medical records and were confirmed by direct contact with the patients, their families, and physicians or by an annual telephone interview with each patient. An Events Committee comprising at least three independent physicians reviewed all events to avoid intraobserver biases.

Statistical analysis

Continuous variables are expressed as the mean \pm standard deviation for normally distributed variables according to the Shapiro-Wilk test. Variables with a nonnormal distribution are expressed as the median value with the interquartile range. Categorical variables are presented as frequencies and percentages. Intergroup differences in categorical variables were determined using Fisher's exact test. Differences in continuous variables were analyzed by the unpaired *t* test or the Mann-Whitney *U* test, as appropriate. Missing data were excluded from the analyses. A Kaplan-Meier curve was used to determine the cumulative incidence of composite cardiovascular events and HF-related events. The log-rank test was used to compare the incidence of these events between the two groups. The Cox proportional hazards model was used to estimate the hazard ratios (HRs) for HF-related events by univariate and multivariate analyses. We selected variables that were statistically significant in the univariate analyses ($p < 0.05$) and excluded variables that would cause internal correlations. The factors of plasma BNP level, *E/e'* ratio, maximum velocity of tricuspid regurgitation (TRVmax) and LVMI were components of the HFA-PEFF score, and we expected that plasma BNP level, *E/e'*, tricuspid regur-

Table 1. Baseline characteristics of HFpEF patients according to group determined by HFA-PEFF scores

Characteristic	Enrolled HFpEF patients (n = 502)	Intermediate score group (n = 311)	High score group (n =191)	p value
Age, yr	71.6 ± 9.5	70.8 ± 8.8	73.0 ± 10.3	0.014
Male sex	274 (55)	188 (60)	86 (45)	0.001
BMI, kg/m ²	24.1 ± 3.6	24.1 ± 3.4	24.2 ± 4.0	0.903
Previous hospitalization for HF	86 (17)	36 (12)	50 (26)	< 0.001
NYHA III or IV	86 (17)	29 (9)	57 (30)	< 0.001
Diabetes mellitus	156 (31)	107 (34)	49 (26)	0.036
Hypertension	392 (78)	247 (79)	145 (76)	0.358
Dyslipidemia	391 (78)	243 (78)	148 (77)	0.865
IHD	266 (53)	177 (57)	89 (47)	0.025
Atrial fibrillation	142 (28)	85 (27)	57 (30)	0.545
SBP, mmHg	130.2 ± 21.3	128.9 ± 18.7	132.4 ± 24.9	0.086
DBP, mmHg	71.0 ± 13.1	71.3 ± 11.8	70.6 ± 15.1	0.590
Hemoglobin, g/dL	12.8 ± 1.9	13.1 ± 1.8	12.3 ± 1.9	< 0.001
hs-CRP, mg/L	0.45 ± 2.0	0.32 ± 1.3	0.64 ± 2.7	0.131
eGFR, mL/min/1.73 m ²	62.3 ± 19.5	66.1 ± 18.7	56.0 ± 19.3	< 0.001
BNP, pg/mL	176.8 ± 292.2	90.9 ± 185.0	316.2 ± 370.8	< 0.001
LVEF, %	62.7 ± 5.8	63.4 ± 5.4	61.5 ± 6.3	< 0.001
SVI, mL/m ²	40.4 ± 9.9	40.4 ± 9.0	40.4 ± 11.3	0.979
LAD, mm	39.6 ± 7.1	38.1 ± 6.5	41.9 ± 7.3	< 0.001
LVMI, g/m ²	130.5 ± 41.3	118.3 ± 32.6	150.3 ± 46.1	< 0.001
E/e'	17.6 ± 5.1	16.7 ± 3.8	19.1 ± 6.3	< 0.001
TR-PG, mmHg	25.3 ± 8.0	25.0 ± 7.5	25.8 ± 8.9	0.371
PAP, mmHg	31.6 ± 9.1	31.2 ± 8.6	32.3 ± 10.0	0.254
Diuretics	122 (24)	53 (17)	69 (36)	< 0.001
ACE-I or ARB	313 (62)	194 (62)	119 (62)	0.986
CCB	290 (58)	182 (59)	108 (57)	0.664
Beta-blocker	224 (45)	137 (44)	87 (46)	0.744
Statin	333 (66)	216 (69)	117 (61)	0.063
HFA-PEFF score	4.2 ± 1.1	3.4 ± 0.59	5.3 ± 0.46	< 0.001

Values are presented as mean ± standard deviation or number (%).

HFpEF, heart failure with preserved ejection fraction; BMI, body mass index; HF, heart failure; NYHA, New York Heart Association; IHD, ischemic heart disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; SVI, stroke volume index; LAD, left atrium diameter; LVMI, left ventricular mass index; E/e', the ratio of early transmitral flow velocity to early diastolic mitral annular velocity; TR-PG, tricuspid regurgitation pressure gradient; PAP, pulmonary artery systolic pressure; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; HFA-PEFF, Heart Failure Association-PEFF.

gitation pressure gradient, pulmonary artery pressure, and LVMI would cause internal correlations with the HFA-PEFF score variable. Furthermore, the estimates of Harrell's C-statistics in the Cox proportional hazards regression models

were compared after the addition of high HFA-PEFF score to conventional factors identified in the subanalysis of the Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction (I-PRESERVE) trial [21,22]. The factors are age,

Table 2. Cardiovascular events according to HFA-PEFF score

Variable	Enrolled HFpEF patients (n = 502)	Intermediate score group (n = 311)	High score group (n = 191)	<i>p</i> value
Total cardiovascular events	236 (47)	135 (43)	101 (53)	0.039
Cardiovascular death	31 (6)	16 (5)	15 (8)	0.244
Hospitalization for HF decompensation	109 (22)	46 (15)	63 (33)	< 0.001
Non-fatal myocardial infarction	6 (1)	4 (1)	2 (1)	0.811
Unstable angina pectoris	15 (3)	10 (3)	5 (3)	0.703
Coronary revascularization	60 (12)	48 (15)	12 (6)	0.001
Nonfatal ischemic stroke	15 (3)	11 (4)	4 (2)	0.358

Values are presented as number (%).

HF, heart failure.

previous hospitalization for HF, diabetes mellitus (DM), and BNP level; however, we excluded BNP level because plasma BNP is a component of the HFA-PEFF score. Therefore, we defined age, previous hospitalization for HF and DM as the 3 prognostic factors (PF3). We also assessed the incremental effects of adding a high HFA-PEFF score to the PF3 to predict HF-related events using the net reclassification improvement (NRI). The categorical NRI has been described previously [23,24]. Decision curve analysis (DCA) was used to quantify the clinical usefulness of the prediction models [25]. A $p < 0.05$ was considered statistically significant. Harrell's C-statistic, NRI, and integrated discrimination improvement (IDI) were calculated by the R package PredictABEL (R Foundation for Statistical Computing, Vienna, Austria). The DCA analysis was performed using the R package ggplot2. The software SPSS version 26.0 (IBM Japan, Tokyo, Japan) was used for other statistical analyses.

RESULTS

Clinical characteristics of enrolled patients with HFpEF

A total of 502 patients with HFpEF were enrolled in this study. The numbers of patients (percentage) with intermediate and high scores were 311 (62.0%) and 191 (38.0%), respectively. The baseline characteristics of the HFpEF patients are shown in Table 1. Overall, the patients had a mean age of 71.6 ± 9.5 years, and 55% were male. The prevalence rates of DM and ischemic heart disease (IHD) were reduced in the high-score group. Plasma BNP levels, left atrial diameter, LVMI, and E/e' were significantly increased in the high-

score group. Hemoglobin and eGFR levels were significantly reduced in the high-score group. While the rate of diuretic prescription was significantly increased in the high-score group, the other drugs, including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, beta blockers and statins, were prescribed at similar rates in both groups.

Cardiovascular events at follow-up

Overall, 236 cardiovascular events were recorded during the follow-up period (median, 1,157 days). Table 2 shows the details of cardiovascular events during follow-up. We found a significantly higher rate of hospitalization for HF decompensation events in the high-score group than in the intermediate score group ($p < 0.001$). We also found a significantly higher rate of coronary revascularization in the high-score group than in the intermediate-score group ($p = 0.001$); however, other events did not differ in frequency between the two groups.

Kaplan-Meier curves

We performed a Kaplan-Meier analysis and observed that there were significant differences in the rates of composite cardiovascular events and HF events between the two groups ($p = 0.003$ and $p < 0.001$, respectively) (Fig. 2).

Cox proportional hazards analyses

Table 3 shows the results of univariate and multivariate Cox proportional hazards analyses for HF-related events. Univariate Cox proportional hazards analysis identified previous hospitalization for HF (HR, 2.30; 95% confidence interval [CI], 1.51 to 3.50; $p < 0.001$), NYHA III or IV (HR, 2.83;

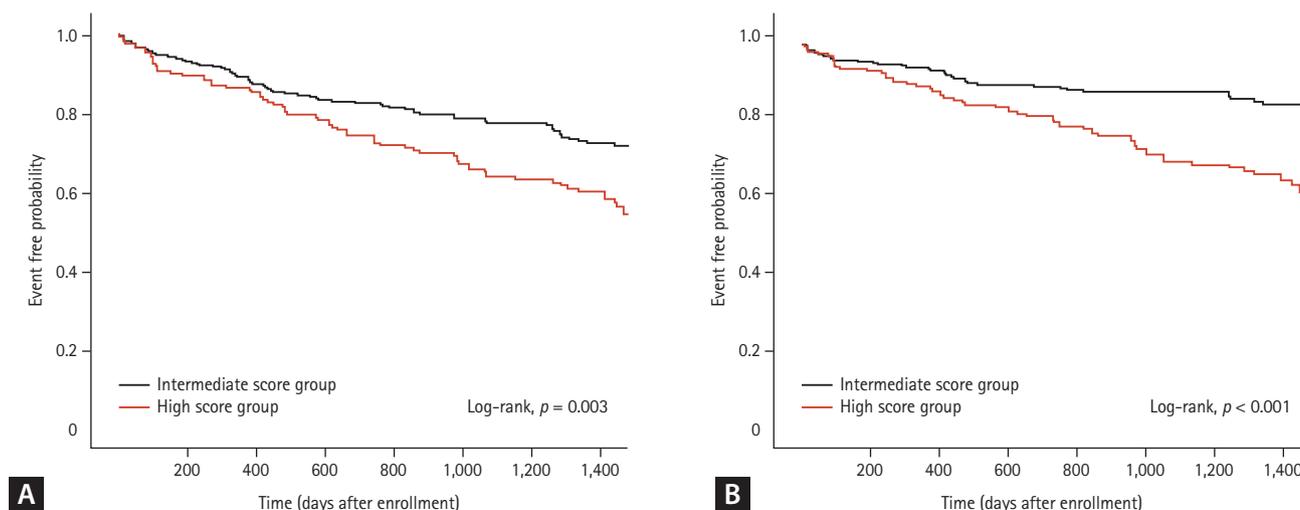


Figure 2. Kaplan-Meier analyses after 1,500 days of follow-up for composite cardiovascular disease (CVD) events and heart failure (HF)-related events according to Heart Failure Association (HFA)-PEFF scores. (A) Composite CVD events. (B) HF related events. The 0 time point on the x-axis indicates the day the patient was discharged following the qualifying cardiovascular event.

95% CI, 1.89 to 4.23; $p < 0.001$), presence of hypertension (HR, 0.57; 95% CI, 0.38 to 0.85; $p = 0.007$), presence of IHD (HR, 0.56; 95% CI, 0.38 to 0.82; $p = 0.003$), presence of atrial fibrillation (AF; HR, 1.76; 95% CI, 1.20 to 2.59; $p = 0.004$), hemoglobin level (HR, 0.85; 95% CI, 0.76 to 0.94; $p = 0.001$), high HFA-PEFF score (HR, 2.18; 95% CI, 1.49 to 3.19; $p < 0.001$), TRVmax > 2.8 m/sec, and high BNP level as significant factors associated with HF-related events. In a multivariate Cox proportional hazard analysis that included PF3 by forced-entry logistic regression (Model 1), previous hospitalization for HF (HR, 2.02; 95% CI, 1.32 to 3.10; $p = 0.001$) and a high HFA-PEFF score (HR, 1.98; 95% CI, 1.35 to 2.92; $p = 0.001$) were independently and significantly associated with HF-related events. Multivariate Cox proportional hazards analysis using the abovementioned significant factors from the univariate analysis (Model 2) identified NYHA III or IV (HR, 1.70; 95% CI, 1.07 to 2.70; $p = 0.026$), hemoglobin levels (HR, 0.87; 95% CI, 0.79 to 0.97; $p = 0.011$) and a high HFA-PEFF score (HR, 1.66; 95% CI, 1.11 to 2.50; $p = 0.014$) as independent predictors of HF-related events in patients with HFpEF.

Receiver operating characteristic analysis for HF-related events and HFA-PEFF score

Receiver operating characteristic (ROC) curves were constructed to assess the ability of the HFA-PEFF score to predict

HF-related events (Fig. 3). The area under the curve of the HFA-PEFF score for the detection of HF-related events was 0.633 (95% CI, 0.574 to 0.692; $p < 0.001$). When a cutoff value of 4.5 was applied to HFA-PEFF scores, the sensitivity and specificity were 57.8% and 67.4%, respectively, for the detection of HF-related events.

Harrell's C-statistic for regression models, continuous NRI and IDI

The value of Harrell's C-statistic for PF3 was 0.598 (95% CI, 0.539 to 0.657); after an HFA-PEFF score ≥ 5 was added as a factor, the value was 0.630 (95% CI, 0.571 to 0.689; $p = 0.021$). We reclassified the risk of HF-related events after adding an HFA-PEFF score ≥ 5 to PF3; the continuous NRI was 27.3% ($p = 0.007$), and the IDI was 4.1% ($p < 0.001$) (Table 4).

DCA of PF3 and combined model

We analyzed the DCA of PF3 and the combined model to predict 1,500-day HF-related events in patients. Fig. 4 shows the DCA for PF3 and the combined model. Both models were useful between 0% and 40%. However, the combined model was superior to PF3 for a threshold probability of 40% to 60% (Fig. 4).

Table 3. Cox proportional hazards regression analyses for HF event outcome within 1,500 days follow-up

Variable	Univariate regression			Multivariate regression					
	HR	95% CI	<i>p</i> value	Model 1 (I-PRESERVE)			Model 2		
				HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
Age, yr	1.01	0.99–1.03	0.381	1.00	0.99–1.02	0.658			
Male sex (yes)	0.78	0.53–1.13	0.190						
BMI, kg/m ²	0.97	0.92–1.02	0.242						
Previous hospitalization for HF (yes)	2.30	1.51–3.50	< 0.001	2.02	1.32–3.10	0.001	1.43	0.89–2.30	0.143
NYHA III or IV (yes)	2.83	1.89–4.23	< 0.001				1.70	1.07–2.70	0.026
Diabetes mellitus (yes)	0.83	0.55–1.28	0.403	0.92	0.60–1.41	0.696			
Hypertension (yes)	0.57	0.38–0.85	0.007				0.65	0.42–1.01	0.054
Dyslipidemia (yes)	0.82	0.53–1.28	0.379						
IHD (yes)	0.56	0.38–0.82	0.003				0.74	0.48–1.13	0.158
Atrial fibrillation (yes)	1.76	1.20–2.59	0.004				1.21	0.78–1.87	0.390
SBP, mmHg	1.00	0.99–1.01	0.473						
DBP, mmHg	1.00	0.98–1.01	0.570						
Hemoglobin, g/dL	0.85	0.76–0.94	0.001				0.87	0.79–0.97	0.011
hs-CRP, mg/L	1.03	0.97–1.10	0.317						
eGFR, mL/min/1.73 m ²	1.00	0.99–1.01	0.863						
LVEF, %	0.98	0.95–1.01	0.150						
SVI, mL/min	0.99	0.97–1.01	0.169						
ACE-I or ARB (yes)	1.24	0.83–1.85	0.290						
CCB (yes)	0.72	0.50–1.05	0.084						
Beta-blocker (yes)	1.03	0.71–1.50	0.889						
Statin (yes)	0.73	0.50–1.07	0.108						
High HFA-PEFF score (yes)	2.18	1.49–3.19	< 0.001	1.98	1.35–2.92	0.001	1.66	1.11–2.50	0.014
TRVmax, m/sec (> 2.8)	1.93	1.24–3.02	0.004						
Averaged E/e' (≥ 15)	0.84	0.50–1.43	0.526						
High LVMI ^a (yes)	1.40	0.96–2.04	0.080						
LV wall thickness, mm (≥ 12)	1.40	0.95–2.07	0.092						
RWT (> 0.42)	1.02	0.66–1.59	0.915						
High BNP ^b (yes)	1.94	1.33–2.82	0.001						

Model 1: age, previous hospitalization for HF, diabetes mellitus and HFA-PEFF score; Model 2: variables of statistical significance in the univariate analyses (*p* < 0.05).

HF, heart failure; I-PRESERVE, Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction; HR, hazard ratio; CI, confidence interval; BMI, body mass index; NYHA, New York Heart Association; IHD, ischemic heart disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; SVI, stroke volume index; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; HFA-PEFF, Heart Failure Association-PEFF; TRVmax, maximum velocity of tricuspid regurgitation; E/e', the ratio of early transmitral flow velocity to early diastolic mitral annular velocity; LVMI, left ventricular mass index; LV, left ventricular; RWT, relative wall thickness; BNP, brain natriuretic peptide.

^aHigh LVMI was defined as more than 149 and 122 g/m² in men and women, respectively.

^bHigh BNP was defined as more than 80 and 240 pg/mL in patients with sinus rhythm and atrial fibrillation, respectively.

Kaplan-Meier curves in subgroup analyses

The HFA-PEFF score differs depending on whether the patient has sinus rhythm (SR) or AF. Thus, we divided the Kaplan-Meier analysis by separately assessing the prognostic relevance of this score in patients with AF and in patients with SR (Supplementary Fig. 1). The Kaplan-Meier analyses showed that, among patients with SR, the high-score group had a higher risk of composite cardiovascular events than the AF group ($p = 0.015$) (Supplementary Fig. 1A). Additionally, these analyses showed that there was no significant difference in composite cardiovascular events between the AF patients in the intermediate and high groups ($p = 0.064$) (Supplementary Fig. 1B). Additionally, they showed that the

high-score group had a higher risk of HF-related events than the intermediate-score group whether the patients had SR or AF (SR, $p = 0.001$, Supplementary Fig. 1C; AF, $p = 0.008$, Supplementary Fig. 1D).

Additional Cox proportional hazards analyses in the short term

Supplementary Table 2 shows the results of univariate and multivariate Cox proportional hazards analyses for HF-related events at 365, 730, and 1,095 days. Multivariate Cox proportional hazard analyses revealed that a high HFA-PEFF score was an independent and significant predictor of HF-related events at 1,095 days but not at 365 or 730 days.

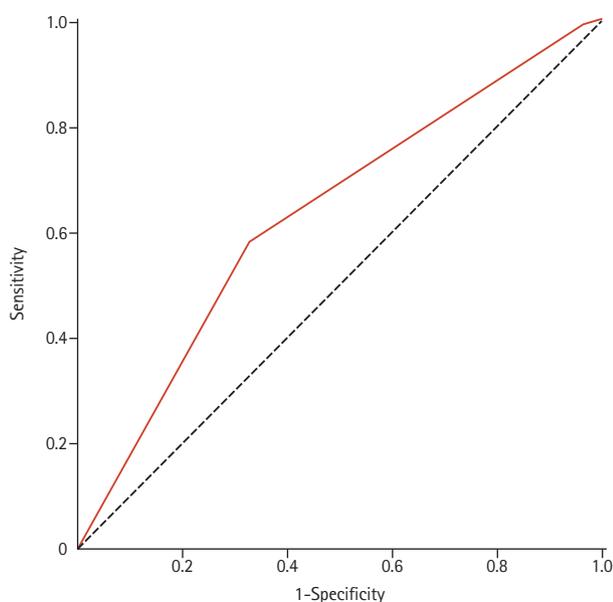


Figure 3. Receiver operating characteristic curves of Heart Failure Association (HFA)-PEFF scores for the prediction of heart failure-related events.

DISCUSSION

The main undertaking in this study was to classify the prognosis of HFpEF patients by HFA-PEFF score, and the main findings of this study were as follows. (1) The Kaplan-Meier curve revealed that the higher the HFA-PEFF score was, the higher the incidence of composite cardiovascular disease events and HF-related events. (2) Multivariate Cox proportional hazards analysis revealed that the HFA-PEFF score was an independent and significant predictor of clinical outcomes in HFpEF patients. (3) The cutoff HFA-PEFF score for HF-related events was 4.5. (4) The NRI and IDI were significant when an HFA-PEFF score ≥ 5 was added to the PF3. (5) DCA revealed that combining the HFA-PEFF score with conventional prognostic factors improved the prediction of HF-related event risk.

Observational studies report that HFpEF accounts for nearly half of all cases of HF. The percentage of HF patients in Japan with an LVEF of 50% or more was 50.6% in the

Table 4. Harrell's C-statistics, NRI, and IDI for the Cox hazard model to predict heart failure-related events in patients with HFpEF by the addition of HFA-PEFF score ≥ 5 to the PF3

	Harrell's C-statistic			NRI			IDI		
	Value	95% CI	<i>p</i> value	Value	95% CI	<i>p</i> value	Value	95% CI	<i>p</i> value
PF3	0.598	0.539–0.657							
PF3 + HFA-PEFF score ≥ 5	0.630	0.571–0.689	0.021	0.273	0.158–0.379	0.007	0.041	0.009–0.088	< 0.001

PF3: age + diabetes mellitus + previous hospitalization for HF.

NRI, net reclassification improvement; IDI, integrated discrimination improvement; HFpEF, heart failure with preserved ejection fraction; HFA-PEFF, Heart Failure Association-PEFF; PF3, 3 prognostic factors; CI, confidence interval.

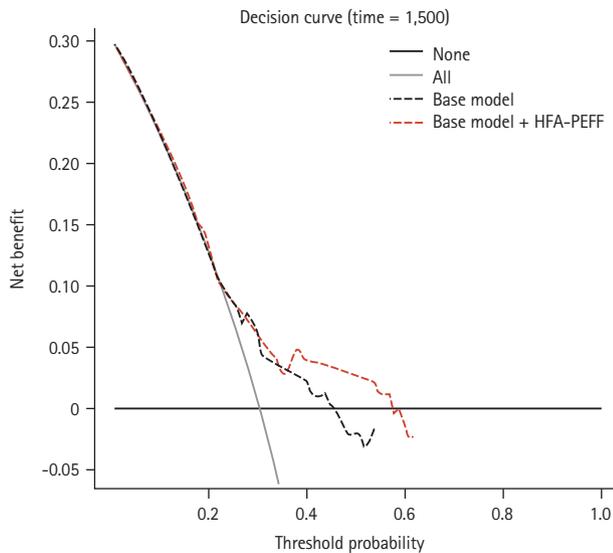


Figure 4. Decision curve analysis for 3 prognostic factors (PF3) and combined model. The black dotted curve indicates the PF3 model. The red dotted curve indicates the PF3 + Heart Failure Association (HFA)-PEFF ≥ 5 model.

Chronic Heart Failure Analysis and Registry in the Tohoku District (CHART)-1 study [26] and 68.7% in the subsequent CHART-2 study [27]. Regarding the prognosis of HFpEF, there was no significant difference in all-cause mortality or in the rate of rehospitalization due to exacerbation of HFrEF in the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) study [28]. A meta-analysis showed that the prognosis of HFpEF is somewhat better than that of HFrEF [29], and similar analysis results were reported in the CHART-2 study [30]. However, the abovementioned meta-analysis [29] showed that the difference in prognosis between HFpEF and HFrEF decreases as age increases. In any case, it should be noted that there is a high proportion of patients with HFpEF in the world, the prognosis is similar to or worse than that of HFrEF, and HFpEF will increase in the super-aging society of the future.

Regarding the patient baseline characteristics (Table 1), it is unclear why women made up a majority of patients with high HFA-PEFF scores; however, we speculate that the reason may be as follows: HFpEF causes diastolic dysfunction as a result of HF risk factors such as obesity, hypertension, diabetes, and AF that cause increased inflammation and oxidative stress, resulting in vascular endothelial damage, myocardial hypertrophy, and myocardial fibrosis [31]. Since the

progression of LV diastolic disorder is remarkable in women over 60 years of age [32], elderly women are considered to be at high risk for HFpEF onset. The reason why the risk of IHD decreases as the HFA-PEFF score increases is thought to be that patients with high HFA-PEFF scores are likely to be in a state of HF or have a history of HF (which the HFA-PEFF scale was originally designed to assess), as shown by the administration of vasodilators or statins (Table 1). Therefore, the onset of IHD might be suppressed. Other components of the results are considered to be proportional to the severity of HF.

In the Cox proportional hazards analyses (Table 3), the presence of hypertension and the hemoglobin level were positive and negative independent predictors, respectively, and were considered to be influenced by age. The calculation methods for the HFA-PEFF score are concise; however, the final score does not reflect which factors influenced the endpoint or to what extent because it is calculated through linear equations with various coefficients. In the univariate analyses, the hypertension and IHD were protective against HF-related events (HR, 0.57 for hypertension and 0.56 for IHD). The reason is not clear, but we speculate the following explanation. Accumulating clinical studies have demonstrated that hypotensive agents (angiotensin receptor blockers [33], mineralocorticoid receptor antagonists [34], and diuretics [35]) and dyslipidemia drugs such as statins [36,37] are effective for the prevention and treatment of HF. The effects of these drugs are thought to suppress HF events.

The H₂FPEF score is a composite score to diagnose symptomatic euvoletic patients with HFpEF using a weighted score based on six variables that range from 0 to 9 [38]. The H₂FPEF score demonstrated predictive value for future HF-related events both in HFpEF patients and in non-HF patients with cardiovascular risk factors [39-41]. We have already reported that the H₂FPEF score is a useful marker for the prediction of cardiovascular and HF-related events in HFpEF patients in the same cohort [7]. Selvaraj et al. [42] reported the usefulness of the H₂FPEF score and HFA-PEFF score for clinical outcomes in HFpEF patients. They analyzed a community-based epidemiological study, the Atherosclerosis Risk In Communities (ARIC) study. However, the subjects of the ARIC study were patients without other common cardiopulmonary causes of dyspnea. In addition, the subjects were 67 to 90 years old. Therefore, the participants in the ARIC study must be considered a limited cohort. In

contrast, the subjects in the present study were all Asian and ranged in age from 32 to 90 years old. In other words, the cohort in the present study reflects the general population.

Considering that HFA-PEFF scoring was originally developed to improve the accuracy of HFpEF diagnosis, it is distinctly possible that the phase of HF differs between the intermediate- and high-score groups. The high-score group had a significantly larger proportion of NYHA III to IV and a higher BNP level than the intermediate-score group; thus, the phase of HF appears to be different, and patients in the high-score group are considered to have a worse prognosis because their HF is more severe. Moreover, a high HFA-PEFF score was an independent and significant predictor of HF-related events at 1,095 days but not at 365 or 730 days (Supplementary Table 2). These results suggest that HFpEF patients should be followed up for at least 3 years. When we compared the incremental prognostic performance of the HFA-PEFF score versus the available individual standard parameters, high TRVmax and high BNP level were significantly associated with HF-related events as well as high HFA-PEFF scores in univariate Cox proportional hazards analyses (Table 3). However, since the NRI and IDI were significant when an HFA-PEFF score ≥ 5 was added to PF3 (Table 4), we believe that a high HFA-PEFF score has incremental prognostic value.

This study is an innovative study to investigate the association of a new marker, the HFA-PEFF score, with future HF-related events in HFpEF patients. Each component of the HFA-PEFF score is simple, and the assessment is not only easy in clinical practice but also well validated and inexpensive, which indicates that the score can be widely applied. If this score further predicts subsequent cardiovascular events in HFpEF patients, it will also represent a useful clinical indicator for general clinicians as well as cardiologists. Although the HFA-PEFF score is highly likely to have clinical value, large-scale clinical studies are required to confirm its value. Therefore, additional detailed, prospective, multicenter studies are warranted to verify the precision and usefulness of this measure.

The present study has some limitations. First, it was a single-center study with a relatively small sample size. Therefore, a larger, multiracial, multicenter study is required for confirmation. Second, we could not compare the prognostic performance of the HFA-PEFF score and the 2016 American Society of Echocardiography/European Association of Cardiovascular Imaging (ASE/EACVI) score [43] in determin-

ing the risk of HF-related hospitalization or mortality due to the lack of left atrium (LA) volume index data. The 2016 ASE/EACVI algorithm enables echocardiographic estimation of LA pressure and grading of diastolic dysfunction based largely on mitral inflow pattern. Third, in the present study, it was difficult to analyze the outcomes by cause of death due to the lack of detailed data on the causes of death. Finally, it is unclear which factors contribute—and to what extent they contribute—to a poor HF prognosis. Thus, further pathophysiological and molecular physiological studies, including animal experiments, are warranted. Additional detailed, large-scale clinical studies may be required to verify our results.

In conclusion, the HFA-PEFF score, which can be easily and accurately calculated, may be useful for predicting 1,500-day composite cardiovascular events as well as HF-related events in HFpEF patients. Although there are many factors that affect the prognosis of HFpEF patients and there is still a need for large-sample multicenter studies to confirm the prognostic value of the HFA-PEFF score for these patients, our results might provide substantial insights into the prognosis of patients with HFpEF.

KEY MESSAGE

1. The higher the Heart Failure Association (HFA)-PEFF score was, the higher the incidence of composite cardiovascular disease events and heart failure (HF)-related events.
2. The HFA-PEFF score was an independent and significant predictor of clinical outcomes in HF with preserved ejection fraction (HFpEF) patients.
3. The cutoff HFA-PEFF score for HF-related events was 4.5.
4. Therefore, the HFA-PEFF scores may be useful for predicting HF-related events in HFpEF patients.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Supplementary Table 1. Calculation of HFA-PEFF score

Parameter	HFA-PEFF score			
	Major		Minor	
	Value	Point	Value	Point
Functional	Septal e' < 7 cm/sec or lateral e' < 10 cm/sec or average E/e' ≥ 15 or TR Vmax > 2.8 m/sec (PASP > 35 mmHg)	2	Average E/e' 9–14 or GLS < 16%	1
Morphological	LAVI > 34 mL/m ² or LVMI ≥ 149/122 g/m ² (M/W) + RWT > 0.42	2	LAVI 29–34 mL/m ² or LVMI ≥ 115/95 g/m ² (M/W) or RWT > 0.42 or LV wall thickness ≥ 12 mm	1
Biomarker				
SR	NT-proBNP > 220 pg/mL or BNP > 80 pg/mL	2	NT-proBNP 125–220 pg/mL or BNP 35–80 pg/mL	1
AF	NT-proBNP > 660 pg/mL or BNP > 240 pg/mL	2	NT-proBNP 365–660 pg/mL or BNP 105–240 pg/mL	1

Adapted from Kim et al. [13].

HFA-PEFF, heart Failure Association-PEFF; e', early diastolic mitral annular velocity; E, early transmitral flow velocity; TR V, tricuspid regurgitation velocity; PASP, pulmonary artery systolic pressure; GLS, left ventricular global longitudinal strain; LAVI, left atrial volume index; LVMI, left ventricular mass index; RWT, relative wall thickness; LV, left ventricle; SR, sinus rhythm; NT-proBNP, N-terminal pro-B-type natriuretic peptide; BNP, B-type natriuretic peptide; AF, atrial fibrillation.

Supplementary Table 2. Cox proportional hazards regression analyses for HF event outcome within 365, 730, and 1,095 days follow-up

Variable	Univariate regression			Multivariate regression					
				Model 1 (I-PRESERVE)			Model 2		
	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
365 Days									
Age, yr	0.99	0.96–1.02	0.596	0.99	0.96–1.02	0.412			
Male sex (yes)	0.92	0.49–1.74	0.804						
BMI, kg/m ²	0.98	0.89–1.07	0.586						
Previous hospitalization for HF (yes)	2.63	1.34–5.13	0.005	2.30	1.16–4.57	0.017	1.18	0.52–2.67	0.696
NYHA III or IV (yes)	2.95	1.53–5.70	0.001				2.05	0.98–4.30	0.057
Diabetes mellitus (yes)	0.58	0.27–1.27	0.177	0.65	0.30–1.43	0.287			
Hypertension (yes)	0.52	0.27–1.02	0.059						
Dyslipidemia (yes)	0.69	0.34–1.40	0.307						
IHD (yes)	0.35	0.17–0.70	0.003				0.40	0.19–0.85	0.018
Atrial fibrillation (yes)	1.92	1.01–3.65	0.048				1.03	0.50–2.12	0.931
SBP, mmHg	0.98	0.97–1.00	0.041				0.99	0.97–1.00	0.063
DBP, mmHg	0.99	0.96–1.01	0.298						
Hemoglobin, g/dL	0.94	0.80–1.12	0.492						
hs-CRP, mg/L	0.96	0.75–1.22	0.714						
eGFR, mL/min/1.73 m ²	1.01	0.99–1.02	0.286						
LVEF, %	0.94	0.89–1.00	0.036				0.95	0.90–1.01	0.102
SVI, mL/min	0.98	0.95–1.01	0.236						
ACE-I or ARB (yes)	0.93	0.48–1.79	0.838						
CCB (yes)	0.73	0.39–1.38	0.327						
Beta-blocker (yes)	1.39	0.73–2.62	0.316						
Statin (yes)	0.69	0.36–1.32	0.260						
High HFA-PEFF score (yes)	1.83	0.97–3.46	0.063	1.59	0.83–3.05	0.164			
TRVmax, m/sec (> 2.8)	1.25	0.54–2.91	0.599						
Averaged E/e' (≥ 15)	1.45	0.51–4.08	0.485						
High LVMI ^a (yes)	1.03	0.54–1.98	0.926						
LV wall thickness, mm (≥ 12)	1.41	0.73–2.73	0.307						
RWT (> 0.42)	1.21	0.56–2.64	0.629						
High BNP ^b (yes)	1.87	0.99–3.53	0.055						
730 Days									
Age, yr	1.00	0.97–1.03	0.986	1.00	0.97–1.02	0.694			
Male sex (yes)	0.75	0.46–1.23	0.249						
BMI, kg/m ²	0.97	0.90–1.04	0.325						
Previous hospitalization for HF (yes)	2.80	1.67–4.70	< 0.001	2.47	1.45–4.20	0.001	1.46	0.79–2.73	0.230
NYHA III or IV (yes)	3.04	1.82–5.07	< 0.001				1.95	1.07–3.54	0.029
Diabetes mellitus (yes)	0.68	0.38–1.21	0.185	0.76	0.42–1.36	0.355			
Hypertension (yes)	0.54	0.32–0.90	0.019				0.69	0.40–1.20	0.186
Dyslipidemia (yes)	0.70	0.40–1.21	0.198						

Supplementary Table 2. Continued

Variable	Univariate regression			Multivariate regression					
				Model 1 (I-PRESERVE)			Model 2		
	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
IHD (yes)	0.40	0.25–0.70	0.001				0.61	0.32–1.16	0.129
Atrial fibrillation (yes)	2.02	1.22–3.32	0.006				1.15	0.65–2.03	0.627
SBP, mmHg	1.00	0.98–1.00	0.209						
DBP, mmHg	1.00	0.98–1.02	0.859						
Hemoglobin, g/dL	0.89	0.78–1.02	0.096						
hs-CRP, mg/L	0.98	0.84–1.14	0.758						
eGFR, mL/min/1.73 m ²	1.00	0.99–1.01	0.926						
LVEF, %	0.96	0.92–1.00	0.037				0.97	0.93–1.02	0.252
SVI, mL/min	0.98	0.96–1.01	0.203						
ACE-I or ARB (yes)	1.41	0.83–2.42	0.208						
CCB (yes)	0.65	0.44–1.07	0.090						
Beta-blocker (yes)	1.00	0.61–1.64	0.999						
Statin (yes)	0.54	0.33–0.89	0.015				0.86	0.48–1.52	0.601
High HFA-PEFF score (yes)	1.85	1.13–3.04	0.015	1.58	0.95–2.63	0.079	1.29	0.76–2.19	0.351
TRVmax, m/sec (> 2.8)	1.40	0.75–2.61	0.294						
Averaged E/e' (≥ 15)	0.80	0.42–1.54	0.505						
High LVMI ^a (yes)	1.44	0.88–2.36	0.150						
LV wall thickness, mm (≥ 12)	1.14	0.67–1.93	0.634						
RWT (> 0.42)	0.88	0.51–1.54	0.655						
High BNP ^b (yes)	1.77	1.08–2.90	0.023						
1,095 Days									
Age, yr	1.01	0.99–1.03	0.436	1.00	0.98–1.02	0.886			
Male sex (yes)	0.78	0.51–1.20	0.253						
BMI, kg/m ²	0.96	0.91–1.02	0.207						
Previous hospitalization for HF (yes)	2.28	1.43–3.64	0.001	1.87	1.16–3.01	0.011	1.10	0.63–1.92	0.738
NYHA III or IV (yes)	2.89	1.84–4.53	< 0.001				1.71	1.02–2.89	0.044
Diabetes mellitus (yes)	0.86	0.54–1.38	0.538	0.98	0.61–1.57	0.926			
Hypertension (yes)	0.62	0.39–0.99	0.048				0.72	0.44–1.19	0.206
Dyslipidemia (yes)	0.83	0.51–1.36	0.466						
IHD (yes)	0.51	0.33–0.79	0.002				0.65	0.40–1.06	0.084
Atrial fibrillation (yes)	1.77	1.14–2.74	0.011				1.21	0.74–2.00	0.450
SBP, mmHg	1.00	0.99–1.01	0.464						
DBP, mmHg	1.00	0.99–1.02	0.815						
Hemoglobin, g/dL	0.85	0.76–0.96	0.006				0.89	0.79–1.00	0.055
hs-CRP, mg/L	1.04	0.97–1.12	0.246						
eGFR, mL/min/1.73 m ²	1.00	0.98–1.01	0.413						
LVEF, %	0.96	0.92–0.99	0.019				0.97	0.93–1.01	0.117
SVI, mL/min	0.98	0.96–1.01	0.182						
ACE-I or ARB (yes)	1.46	0.91–2.32	0.116						
CCB (yes)	0.68	0.44–1.04	0.071						

Supplementary Table 2. Continued

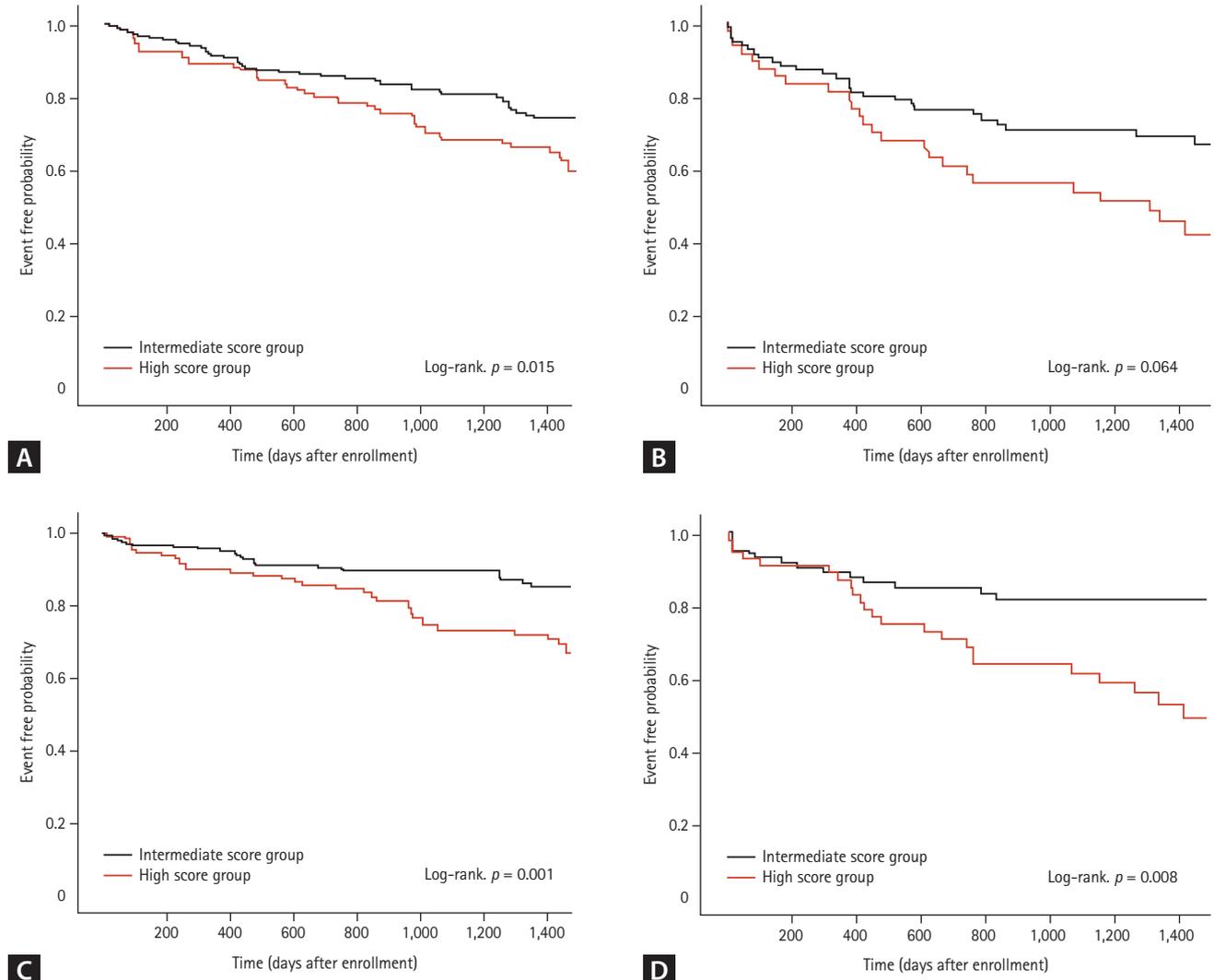
Variable	Univariate regression			Multivariate regression						
				Model 1 (I-PRESERVE)			Model 2			
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value	
Beta-blocker (yes)	1.03	0.67–1.58	0.892							
Statin (yes)	0.68	0.44–1.05	0.082							
High HFA-PEFF score (yes)	2.67	1.72–4.13	< 0.001	2.41	1.54–3.78	< 0.001	1.97	1.23–3.16	0.005	
TRVmax, m/sec (> 2.8)	1.66	0.98–2.81	0.062							
Averaged E/e' (≥ 15)	0.91	0.51–1.65	0.763							
High LVMI ^a (yes)	1.46	0.95–2.23	0.086							
LV wall thickness, mm (≥ 12)	1.37	0.88–2.15	0.164							
RWT (> 0.42)	0.86	0.53–1.39	0.534							
High BNP ^b (yes)	2.34	1.52–3.60	< 0.001							

Model 1: age, previous hospitalization for HF, diabetes mellitus and HFA-PEFF score; Model 2: variables of statistical significance in the univariate analyses (*p* < 0.05).

HF, heart failure; I-PRESERVE, Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction; HR, hazard ratio; CI, confidence interval; BMI, body mass index; NYHA, New York Heart Association; IHD, ischemic heart disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; SVI, stroke volume index; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; HFA-PEFF, Heart Failure Association-PEFF; TRVmax, maximum velocity of tricuspid regurgitation; E/e', the ratio of early transmitral flow velocity to early diastolic mitral annular velocity; LVMI, left ventricular mass index; LV, left ventricular; RWT, relative wall thickness; BNP, brain natriuretic peptide.

^aHigh LVMI was defined as more than 149 and 122 g/m² in men and women, respectively.

^bHigh BNP was defined as more than 80 and 240 pg/mL in patients with sinus rhythm and atrial fibrillation, respectively.



Supplementary Figure 1. Kaplan-Meier analyses after 1,500 days of follow-up for the endpoints according to HFA-PEFF scores in enrolled patients. (A) Composite cardiovascular disease (CVD) events in sinus rhythm (SR) patients. (B) Composite CVD events in atrial fibrillation (AF) patients. (C) Heart failure (HF)-related events in SR patients. (D) HF-related events in AF patients.