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ORIGINAL RESEARCH

Predictors and Outcomes of Heart Failure With Preserved Ejection Fraction in Patients With a Left Ventricular Ejection Fraction Above or Below 60%

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BACKGROUND: Although potential therapeutic candidates for heart failure with preserved ejection fraction (HFpEF) are emerging, it is still unclear whether they will be effective in patients with left ventricular ejection fraction (LVEF) of 60% or higher. Our aim was to identify the clinical characteristics of these patients with HFpEF by comparing them to patients with LVEF below 60%.

METHODS AND RESULTS: From a multicenter, prospective, observational cohort (PURSUIT-HFpEF [Prospective Multicenter Obsevational Study of Patients with Heart Failure with Preserved Ejection Fraction]), we investigated 812 consecutive patients (median age, 83 years; 57% women), including 316 with 50% ≤ LVEF <60% and 496 with 60% ≤ LVEF, and compared the clinical backgrounds of the 2 groups and their prognoses for cardiac mortality or HF readmission. Two hundred four adverse outcomes occurred at a median of 366 days. Multivariable Cox regression tests adjusted for age, sex, heart rate, atrial fibrillation, estimated glomerular filtration rate, N-terminal pro-B-type natriuretic peptide, and prior heart failure hospitalization revealed that systolic blood pressure (hazard ratio [HR], 0.925 [95% CI, 0.862–0.992]; *P*=0.028), high-density lipoprotein to C-reactive protein ratio (HR, 0.975 [95% CI, 0.944–0.995]; *P*=0.007), and left ventricular end-diastolic volume index (HR, 0.870 [95% CI, 0.759–0.997]; *P*=0.037) were uniquely associated with outcomes among patients with 50% ≤ LVEF <60%, whereas only the ratio of peak early mitral inflow velocity to velocity of mitral annulus early diastolic motion e′(HR, 1.034 [95% CI, 1.003–1.062]; *P*=0.034) was associated with outcomes among patients with 60% ≤ LVEF.

CONCLUSIONS: Prognostic factors show distinct differences between patients with HFpEF with 50% ≤ LVEF <60% and with 60% ≤ LVEF. These findings suggest that the 2 groups have different inherent pathophysiology.

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Key Words: heart failure with preserved ejection fraction ■ left ventricular ejection fraction ■ prognostic factor

Although several therapeutic drugs have been established for heart failure (HF) with reduced ejection fraction (HFrEF),[1] the discovery of a therapeutic strategy for heart failure with preserved ejection fraction (HFpEF) has been long awaited. The positive result of the EMPEROR-Preserved

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CLINICAL PERSPECTIVE

What Is New?

- This is the first large observational study focusing on the differences between patients with heart failure with preserved ejection fraction (HFpEF) with 50% ≤ left ventricular ejection fraction (LVEF) <60% and those with 60% ≤ LVEF from a prospective multicenter registry in East Asia (PURSUIT-HFpEF [Prospective Multicenter Obsevational Study of Patients with Heart Failure with Preserved Ejection Fraction]).
- Left ventricular end-diastolic volume index, heart rate, and hemoglobin concentration were significantly different between patients with HFpEF whose LVEF was below or above 60%.
- Although systolic blood pressure, high-density lipoprotein/C-reactive protein ratio, and left ventricular end-diastolic volume index were characteristic prognostic factors in patients with HFpEF with LVEF below 60%, ratio of peak early mitral inflow velocity to velocity of mitral annulus early diastolic motion e′ was uniquely highlighted in patients with LVEF above 60%.

What Are the Clinical Implications?

- These highlighted factors may allow us to propose possible hypotheses as to the cause of the different treatment effects of angiotensin receptor-neprilysin inhibitor and sodium-glucose cotransporter 2 inhibitor on patients with HFpEF with lower and higher LVEF, observed in the PARAGON-HF (Prospective Comparison of ARNI With ARB Global Outcomes in HF With Preserved Ejection Fraction) and EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction) trials.
- The ratio of peak early mitral inflow velocity to velocity of mitral annulus early diastolic motion e′ was particularly shown to be important for the prognosis of patients with HFpEF with LVEF above 60%, for whom a reliable therapeutic response has not been well established. Further investigations of what this parameter reflects among them will help us to find better ways to manage these difficult-to-treat patients.

Nonstandard Abbreviations and Acronyms

E/e′	ratio of peak early mitral inflow velocity to velocity of mitral annulus early diastolic motion e′
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
LAVI	left atrial volume index
LVEDVI	left ventricular end-diastolic volume index
LVMI	left ventricular mass index
SVI	stroke volume index
TAPSE	tricuspid annular plane systolic excursion

(Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction) study,[2] which showed that empagliflozin reduced the combined risk of cardiovascular death and HF hospitalization in patients with HFpEF, provided welcome hope for a treatment strategy for these patients. Despite the excellent main result, subgroup analysis revealed that effective results were limited to patients with left ventricular (LV) ejection fraction (LVEF) <50% and with LVEF ≥50% to <60%, and that no benefit accrued to patients with LVEF ≥60%. The PARAGON-HF (Prospective Comparison of ARNI With ARB Global Outcomes in HF With Preserved Ejection Fraction) study[3] made the important suggestion of an angiotensin receptor–neprilysin inhibitor as a potential treatment choice for HFpEF. Although the main result was unfortunate, subgroup analysis showed that patients with LVEF ≤57% (median of participants) accrued a beneficial effect, but those with >57% did not.

The results of these latest trials have led to reconsideration of the clinical implications of LVEF in patients with HFpEF. The different therapeutic effects between upper and lower LVEF patients could have resulted from pathophysiological differences between the 2 populations. A recent HF classification based on LVEF was proposed partly on the basis of treatment strategies, and the consensus statement for this defines HFpEF as LVEF ≥50%.[4] We propose that efforts to establish effective treatment strategies overall for patients with HFpEF would benefit from a focus on the differences between patients with HFpEF with lower and higher LVEF.

As shown between patients with HFrEF and HFpEF, prognostic factors also likely differ between populations that pathophysiologically differ with regard to LVEF.[5] We previously reported several prognostic factors among hospitalized East Asian patients with HFpEF based on a prospective multicenter observational cohort, including sex,[6] blood pressure,[7] high-density lipoprotein (HDL) to CRP (C-reactive protein) ratio,[8] diastolic dysfunction,[9] LV filling pressure,[10,11] and right ventricular to pulmonary circulation coupling evaluated with tricuspid annular plane systolic excursion

(TAPSE) to pulmonary arterial systolic pressure (PASP) ratio.[12,13]

In the present exploratory study, we aimed to compare clinical characteristics, including these factors which we previously focused and reported as important prognostic markers, between patients with HFpEF with lower and higher LVEF. We also aimed to suggest potential pathophysiological differences between them, which might lead to the different pharmacological effects of the featured drugs.

METHODS

The authors declare that all supporting data are available within the article and its supplemental files.

Study Protocol and Setting

The PURSUIT-HFpEF (Prospective Multicenter Obsevational Study of Patients with Heart Failure with Preserved Ejection Fraction) registry is a prospective, multicenter, observational cohort study that enrolled consecutive patients who were hospitalized for acute decompensated heart failure. Details of the registry have been described previously.[14] Briefly, in collaboration with 31 hospitals in Japan, we enrolled consecutive acute decompensated patients with HF who met the Framingham criteria[15] and the following on admission: (1) LVEF ≥50%, and (2) NT-proBNP (N-terminal pro-B-type natriuretic peptide) ≥400 pg/mL or brain natriuretic peptide ≥100 pg/mL. Major exclusion criteria were age <20 years, severe valvular disease or acute coronary syndrome on admission, life expectancy <6 months because of prognosis for a noncardiac disease, or previous heart transplantation. The anonymized data were transferred to Osaka University Hospital for analysis via a data capture system connected with electronic medical records.[16] Written informed consent was received from each participating patient. This study conformed to the principles of the Declaration of Helsinki and was approved by the institutional review board of each participating facility. It was registered under the Japanese UMIN Clinical Trials Registration (UMIN000021831).

Study Population

The 1095 patients with HFpEF were registered from June 2016 to December 2020. Of all participants, we excluded 17 patients who died in the hospital, 7 who were diagnosed as having cardiac amyloidosis, and 30 with hypertrophic cardiomyopathy. We excluded an additional 162 patients whose LVEF at discharge was missing and 67 whose LVEF was <50%. Finally, 812 patients whose LVEF was above 50% at discharge were analyzed in this study (Figure 1).

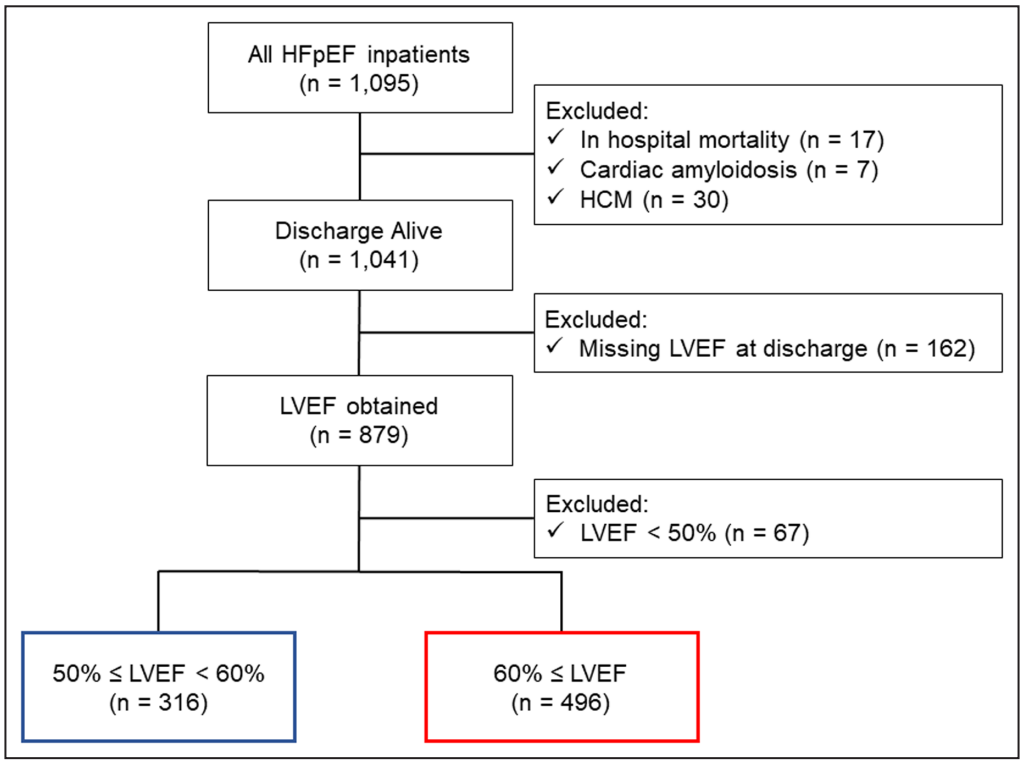

Figure 1. Patients analyzed in this study.
Tree chart of the patient-selection process. HCM indicates hypertrophic cardiomyopathy; HFpEF, heart failure with preserved ejection fraction; and LVEF, left ventricular ejection fraction.

Laboratory Tests and Echocardiography

Laboratory and echocardiographic data were obtained at discharge. Comprehensive echocardiographic examinations were performed by trained cardiac sonographers in accordance with the American Society of Echocardiography guidelines.[17] In patients with atrial fibrillation (AF), recordings of 5 to 7 consecutive beats were recommended. Measurement of systolic or diastolic parameters for 1 beat occurring after 2 serial beats with average RR interval or 1 beat with an average Doppler wave contour with an average velocity was also permitted in accordance with previous studies.[18] LVEF, LV end-diastolic volume index (LVEDVI), and stroke volume index (SVI) were calculated with the biplane Simpson method using apical 2- and 4-chamber views. Left atrial volume index (LAVI) was also calculated with the biplane Simpson method. LV mass index (LVMI) was estimated with the Devereux formula.[19] Each parameter was indexed by body surface area. Relative wall thickness and cardiac remodeling category were defined according to the guideline.[17] The ratio of peak early mitral inflow velocity to the velocity of mitral annulus early diastolic motion e′ (E/e′) was calculated with the mean e′ velocity obtained from the septal and lateral sides of the mitral annulus. TAPSE and right ventricular dimension were obtained using a right ventricular focused apical 4-chamber view, and PASP was estimated using diameter/collapsibility of the inferior vena cava and tricuspid regurgitation pressure gradient.[12]

Clinical Outcome Measurement

The primary outcome was measured as a composite of cardiac mortality or HF rehospitalization. Duration of the follow-up period was calculated from the day of discharge until an outcome, or to the time of last patient contact. Outpatient management after discharge was at the discretion of the attending physician at each facility. Outcomes and last patient contacts were generally checked up on at least once a year until 5 years after the discharge by confirming the last visits to each facility or by contact by telephone or mail interview to the patients, their family members, or the latest attending physicians.

Statistical Analysis

Continuous variables are presented as medians and interquartile ranges of 25% to 75% and were compared using the Kruskal-Wallis test. Categorical variables are presented as numbers with percentages and were compared using Pearson χ^2 test. The clinical end point was assessed with the Kaplan-Meier method and compared with the log-rank test for dichotomized groups divided by categorical variables and median values of continuous variables among the whole population. Cox proportional hazards regression models were used to calculate hazard ratios (HRs) and 95% CIs for associations between clinical factors of interest and outcome. These factors comprised fundamental background (age and sex); well-established prognostic factors for patients with HFpEF[20] (HF history, AF, diabetes, estimated glomerular filtration rate [eGFR], NT-proBNP, and the diastolic function markers[21] of LAVI, LVMI, and E/e′), including prognostic factors reported from our previous investigations in this registry (systolic blood pressure,[7] HDL/CRP,[8] and TAPSE/PASP ratios[12,13]), and background factors that significantly differed between the 2 groups (heart rate, hematocrit, and LVEDVI). We used multivariable Cox proportional hazards regression analysis with statistical interaction terms to test for effect modification (described as *P* for interaction) in each LVEF-categorized group. We then provided the stratified analysis to explore associations within each group. Multivariable Cox regression tests on outcomes for distinctive and interactive prognostic factors in each subgroup were performed using the covariates of age, sex, heart rate, AF, eGFR, log-transformed NT-proBNP, and prior HF hospitalization history. Although we studied lots of subgroup analyses, we considered corrections for multiple analyses were unnecessary because of the exploratory purpose. All statistical tests were 2-sided, and $P<0.05$ as well as P for interaction <0.10 were regarded as statistically significant. Statistical analysis was performed using JMP Pro 13.2.1 (SAS Institute, Chicago, IL) or R software version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Characteristics

Demographic and clinical characteristics of the patients are summarized in Table 1. In the overall population of 812, the median age was 83 years, 57% were women, and 23% had a history of prior HF. The major potential triggers for HF worsening were arrhythmia (237 cases, 29%) and excessive sodium/water intake (220 cases, 27%) (Table S1). They consisted of 316 patients (39%) with 50% ≤ LVEF <60% ($LVEF_{50-60}$) and 496 (61%) with 60% ≤ LVEF ($LVEF_{60-}$). The $LVEF_{50-60}$ and $LVEF_{60-}$ groups did not significantly differ in basic characteristics, including age ($LVEF_{50-60}$ versus $LVEF_{60-}$, 82 versus 83 years, $P=0.204$), sex (women of 53% versus 59%, $P=0.087$), prior HF history (24% versus 22%, $P=0.589$), and frequency of each comorbidity. Furthermore, although SVI (31.5 versus 32.5 mL/m^2, $P=0.075$), LAVI (50 versus 49 mL/m^2, $P=0.758$), E/e′ (12.2 versus 12.6, $P=0.384$), and LVMI (104 versus 101 mL/m^2, $P=0.103$) were not statistically different, LVEDVI (57 versus 50 mL/m^2, $P<0.001$) was

Table 1. Patient Characteristics

Characteristic	Overall, n=812	Missing	50% ≤ LVEF <60%, n=316	60% ≤ LVEF, n=496	*P* value
Age, y	83 [77–87]	0	82 [76–87]	83 [78–87]	0.204
Sex, women	472 (57)	0	168 (53)	294 (59)	0.087
HF history	182 (23)	16	74 (24)	108 (22)	0.589
Hypertension	693 (86)	3	264 (84)	429 (87)	0.306
Diabetes	269 (33)	4	98 (31)	171 (34)	0.368
Dyslipidemia	345 (43)	4	124 (39)	221 (45)	0.142
Coronary artery disease	147 (18)	6	60 (19)	87 (18)	0.609
Pacemaker implantation	64 (8)	1	24 (8)	40 (8)	0.802
Stroke	111 (14)	6	38 (12)	73 (15)	0.272
Sleep apnea	39 (5)	76	14 (5)	25 (5)	0.763
Chronic obstructive pulmonary disease	61 (8)	36	18 (6)	43 (9)	0.126
Chronic kidney disease	324 (40)	6	131 (42)	193 (39)	0.482
Malignancy	99 (12)	11	36 (12)	63 (13)	0.591
Data at discharge					
Systolic blood pressure, mm Hg	119 [107–132]	0	118 [106–130]	120 [107–132]	0.376
Heart rate, bpm	70 [61–78]	0	72 [62–80]	69 [60–78]	0.019
Atrial fibrillation	297 (37)	1	112 (35)	185 (37)	0.578
Hemoglobin, g/dL	11.2 [10.0–12.5]	1	11.4 [10.3–13.0]	11.1 [9.7–12.3]	0.002
Hematocrit, %	34.2 [30.8–38.1]	1	35.0 [31.3–39.4]	33.7 [30.1–37.6]	0.002
eGFR, mL/min per 1.73 m^2	42 [30–55]	13	44 [32–56]	42 [29–54]	0.396
HDL, mg/dL	43 [35–52]	79	43 [35–52]	43 [36–52]	0.986
CRP, mg/dL	0.29 [0.11–0.80]	10	0.29 [0.11–0.83]	0.28 [0.11–0.79]	0.743
HDL/CRP	148 [51–385]	81	150 [48–407]	145 [53–374]	0.588
NT-proBNP, pg/mL	1048 [466–2369]	92	1290 [584–2720]	880 [371–2005]	<0.001
LVDd, mm	45 [41–50]	0	46 [41–51]	45 [41–49]	0.011
LVEDV, mL	77 [58–100]	18	82 [63–109]	74 [57–97]	<0.001
LVEDVI, mL/m^2	53 [41–66]	23	57 [43–71]	50 [40–63]	<0.001
LVMI, g/m^2	102 [85–121]	8	104 [85–125]	101 [86–119]	0.103
Relative wall thickness	0.43 [0.37–0.50]	2	0.42 [0.36–0.49]	0.43 [0.38–0.50]	0.130
Remodeling category		8			0.558
Normal geometry	236 (29)		91 (29)	145 (30)	
Concentric remodeling	188 (23)		76 (24)	112 (23)	
Eccentric hypertrophy	149 (19)		64 (20)	85 (17)	
Concentric hypertrophy	231 (29)		83 (26)	148 (30)	
LVEF, %	62 [57–66]	0	55 [53–58]	65 [62–69]	<0.001
SVI, mL/m^2	32.2 [25.2–40.6]	23	31.5 [24.0–39.2]	32.5 [25.6–41.2]	0.075
LAVI, mL/m^2	49 [36–64]	79	50 [36–63]	49 [36–64]	0.758
E/e′, mean	12.5 [9.8–16.8]	51	12.2 [9.5–16.9]	12.6 [10.0–16.8]	0.384
RVD, mm	32 [28–36]	92	32 [28–36]	32 [27–36]	0.456
TAPSE, mm	17.5 [14.8–20.4]	50	16.8 [13.2–19.0]	18.0 [15.4–21.2]	<0.001
PASP, mm Hg	31 [26–38]	93	30 [25–38]	32 [26–39]	0.025
TAPSE/PASP	0.55 [0.42–0.72]	117	0.55 [0.40–0.72]	0.55 [0.43–0.73]	0.280
Medication at discharge					
Antiplatelet	242 (30)	1	97 (31)	145 (29)	0.670
ACEi or ARB	457 (56)	0	176 (56)	281 (57)	0.789
Calcium channel blocker	416 (51)	1	147 (47)	269 (54)	0.030

(*Continued*)

Table 1. Continued

Characteristic	Overall, n=812	Missing	50% ≤ LVEF <60%, n=316	60% ≤ LVEF, n=496	*P* value
β-Blocker	456 (56)	1	195 (62)	261 (53)	0.012
Loop diuretics	640 (79)	0	249 (79)	391 (79)	0.991
Tolvaptan	136 (17)	0	49 (16)	87 (18)	0.449
Mineralocorticoid receptor antagonist	317 (39)	0	145 (46)	172 (35)	0.001
SGLT2 inhibitor	50 (6)	2	20 (6)	30 (6)	0.883
Statins	278 (34)	0	104 (33)	174 (35)	0.512
Digitalis	31 (4)	1	14 (4)	17 (3)	0.471
Warfarin	100 (12)	0	39 (12)	61 (12)	0.692
DOAC	386 (48)	0	157 (50)	229 (46)	0.292

Values are given as median [interquartile range] or n (%). Between-group comparisons were performed using the Kruskal-Wallis test or Pearson χ^2 test. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRP, C-reactive protein; DOAC, direct oral anticoagulants; E/e′, ratio of peak early mitral inflow velocity to velocity of mitral annulus early diastolic motion e′; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol; HF, heart failure; LAVI, left atrial volume index; LVDd, left ventricular diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PASP, pulmonary arterial systolic pressure; RVD, right ventricular dimension; SGLT2, sodium-glucose cotransporter 2; SVI, stroke volume index; and TAPSE, tricuspid annular plane systolic excursion.

significantly lower in the $LVEF_{60-}$ group of patients regardless of their lower heart rate (72 versus 69 bpm, *P*=0.005). Patients in the $LVEF_{60-}$ group showed lower NT-proBNP (1290 versus 880 pg/mL, *P*<0.001) despite a higher PASP (30 versus 32 mm Hg, *P*=0.025). TAPSE (16.8 versus 18.0 mm, *P*<0.001), reflecting right ventricular contractility, was higher in the $LVEF_{60-}$ group of patients, whereas TAPSE/PASP ratio (0.55 versus 0.55 mm/mm Hg, *P*=0.280) was not statistically different between the groups. Hemoglobin concentration (11.4 versus 11.1 g/dL, *P*=0.002) and hematocrit (35.0% versus 33.7%, *P*=0.002) was significantly lower in the $LVEF_{60-}$ group. Among the potential triggers for HF worsening, cardiac ischemia was more frequently observed in the $LVEF_{50-60}$ group (15 cases, 5%) than $LVEF_{60-}$ group (11 cases, 2%) (*P*=0.046; Table S1).

Prognostic Factors on Clinical Outcome

Among the 812 patients, 204 patients (79 [25%] in the $LVEF_{50-60}$ group and 125 [25%] in the $LVEF_{60-}$ group; Table 2) reached the clinical outcome of cardiac mortality or HF rehospitalization with a median (interquartile range) follow-up of 366 days (93–720 days). Survival curve analysis showed that prognosis of the $LVEF_{60-}$ group did not differ to that of the $LVEF_{50-60}$ group (log-rank *P*=0.7970; Figure 2).

Sex (log-rank *P* of overall, $LVEF_{50-60}$, and $LVEF_{60-}$: 0.6506, 0.8793, and 0.4357, respectively), diabetes (log-rank *P*: 0.9079, 0.3790, and 0.3971, respectively), SVI (log-rank *P*: 0.9326, 0.1026, and 0.1716, respectively), and LVMI (log-rank *P*: 0.5803, 0.6446, and 0.2997, respectively) were not distinctive prognostic factors in any of the overall, $LVEF_{50-60}$, or $LVEF_{60-}$ groups (Figure S1). On the other hand, HF history (log-rank *P*: <0.0001, 0.0011, and <0.0001, respectively), AF (log-rank *P*: 0.0025, 0.0498, and 0.0216, respectively), NT-proBNP (log-rank *P*: <0.0001, <0.0001, and 0.0002, respectively), eGFR (log-rank *P*: 0.0004, 0.0356, and 0.0037, respectively), and TAPSE/PASP ratio (log-rank *P*: 0.0007, 0.0135, and 0.0191, respectively) were significantly associated with the prognosis in all 3 groups (Figure S2). In addition, systolic blood pressure (log-rank *P*: 0.3250, 0.0034, and 0.2809, respectively), heart rate (log-rank *P*: 0.033, 0.0063, and 0.1115, respectively), HDL/CRP ratio (log-rank *P*: 0.5632, 0.0133, and 0.2117, respectively), and LVEDVI (log-rank *P*: 0.5608, 0.0380, and 0.3988, respectively) were particularly significant prognostic factors in the $LVEF_{50-60}$ group (Figure 3). In contrast, LAVI (log-rank *P*: 0.0053, 0.1841, and 0.0115, respectively), E/e′ (log-rank *P*: 0.0015, 0.6977, and 0.0002, respectively), and hematocrit (log-rank *P*: 0.0203, 0.2901, and 0.0286, respectively) were specific and significant prognostic factors in the $LVEF_{60-}$ group (Figure 4).

Univariable Cox regression models showed similar results (Figure 5). LVEF itself was not a significant prognostic factor for the overall population (HR, 0.962 [95% CI, 0.862–1.073] in 5% increments; *P*=0.491), for the $LVEF_{50-60}$ group (HR, 0.740 [95% CI, 0.501–1.097] in 5% increments; *P*=0.133), and for the $LVEF_{60-}$ group (HR, 0.986 [95% CI, 0.809–1.189] in 5% increments; *P*=0.887). Moreover, multivariable Cox regression analyses also showed that LVEF did not predict adverse events even after adjusted by sex for the overall population (HR, 0.960 [95% CI, 0.859–1.071] in 5% increments; *P*=0.469), for the $LVEF_{50-60}$ group (HR, 0.739 [95% CI, 0.497–1.100] in 5% increments; *P*=0.135), and for the $LVEF_{60-}$ group (HR, 0.984 [95% CI, 0.806–1.187] in 5% increments; *P*=0.869).

Distinctive prognostic factors for the $LVEF_{50-60}$ group were systolic blood pressure (HR, 0.896 [95%

Table 2. Adverse Outcomes

Outcome	Overall, n=812	Missing	50% ≤ LVEF <60%, n=316	60% ≤ LVEF, n=496	*P* value
All-cause death	143 (18)	0	56 (18)	87 (18)	0.947
Cardiac death	55 (7)	0	24 (8)	31 (6)	0.457
HF rehospitalization	193 (24)	0	75 (24)	118 (24)	0.985
Cardiac death+HF rehospitalization	204 (25)	0	79 (25)	125 (25)	0.949

Values are given as n (%). Between-group comparisons were performed using Pearson χ^2 test. HF indicates heart failure; and LVEF, left ventricular ejection fraction.

CI, 0.835–0.959] in 5-mm Hg increments; *P*=0.001), heart rate (HR, 1.099 [95% CI, 1.013–1.188] in 5-bpm increments; *P*=0.023), HDL/CRP ratio (HR, 0.961 [95% CI, 0.926–0.987] in 50-unit increments; *P*<0.001), LVEDVI (HR, 0.878 [95% CI, 0.782–0.980] in 10-mL/m^2 increments; *P*=0.019), and SVI (HR, 0.891 [95% CI, 0.802–0.984] in 5-mL/m^2 increments; *P*=0.023), whereas those for the $LVEF_{60-}$ group were hematocrit (HR, 0.733 [95% CI, 0.616–0.867] in 5% increments; *P*<0.001), eGFR (HR, 0.823 [95% CI, 0.743–0.909] in 10-mL/min per 1.73 m^2 increments; *P*<0.001), and E/e′ (HR, 1.038 [95% CI, 1.012–1.060] in 1-unit increments; *P*=0.004). Among these factors, systolic blood pressure (*P* for interaction, 0.004), hematocrit (*P* for interaction, 0.026), eGFR (*P* for interaction, 0.053), HDL/CRP ratio (*P* for interaction, 0.027), LVEDVI (*P* for interaction, 0.008), SVI (*P* for interaction, 0.011), and E/e′ (*P* for interaction, 0.047) had significant interactions for outcome with an effect modification by the LVEF categorization.

Both survival curve analysis and univariable Cox regression models showed that systolic blood pressure, HDL/CRP ratio, and LVEDVI were particularly distinctive prognostic factors for the $LVEF_{50-60}$ group, and that hematocrit and E/e′ were also for the $LVEF_{60-}$ group. Multivariable Cox regression models were analyzed to adjust the predictability of these factors with age, sex, heart rate, AF, eGFR, NT-proBNP, and prior HF history (Table 3). Although systolic blood pressure (HR, 0.925 [95% CI, 0.862–0.992] in 5-mm Hg increments; *P*=0.028), HDL/CRP ratio (HR, 0.975 [95% CI, 0.944–0.995] in 50-unit increments; *P*=0.007), and LVEDVI (HR, 0.870 [95% CI, 0.759–0.997] in 10-mL/m^2 increments; *P*=0.037) were revealed to be unique and statistically significant after adjustment for other factors in the $LVEF_{50-60}$ group, only E/e′ (HR, 1.034 [95% CI, 1.003–1.062] in 1-unit increments; *P*=0.034) was in the $LVEF_{60-}$ group. It should be also noted that only LVEDVI in the $LVEF_{50-60}$ group (*P* for interaction, 0.011) had significant interaction for outcome with an effect modification by the LVEF categorization.

DISCUSSION

In this study, we examined differences in clinical characteristics and prognostic factors between patients with LVEF below and above 60% in the PURSUIT-HFpEF, an East Asian prospective, multicenter, observational study. The major finding was that LVEDVI, heart rate and hemoglobin concentration were significantly

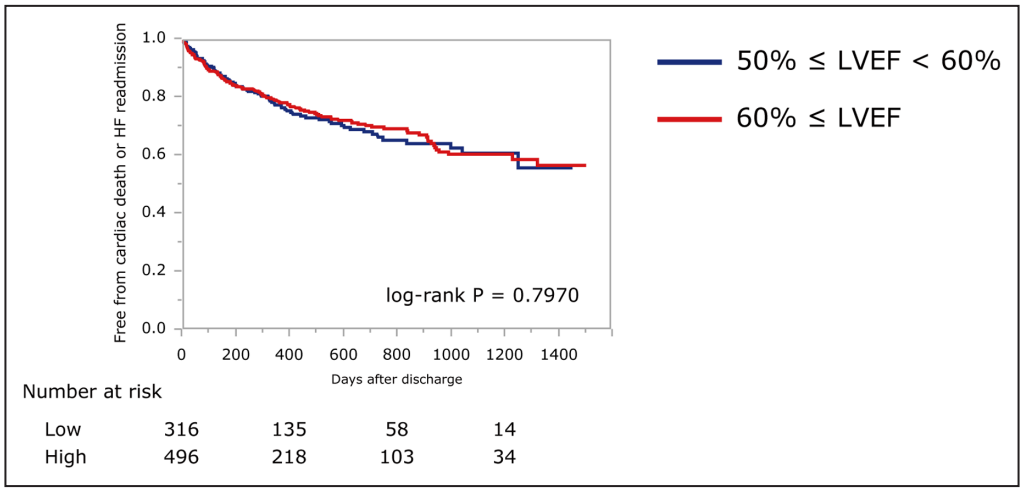

Figure 2. Kaplan-Meier curves of patients with HFpEF whose LVEF was below or above 60%.
HF indicates heart failure; HFpEF, heart failure with preserved ejection fraction; and LVEF, left ventricular ejection fraction.

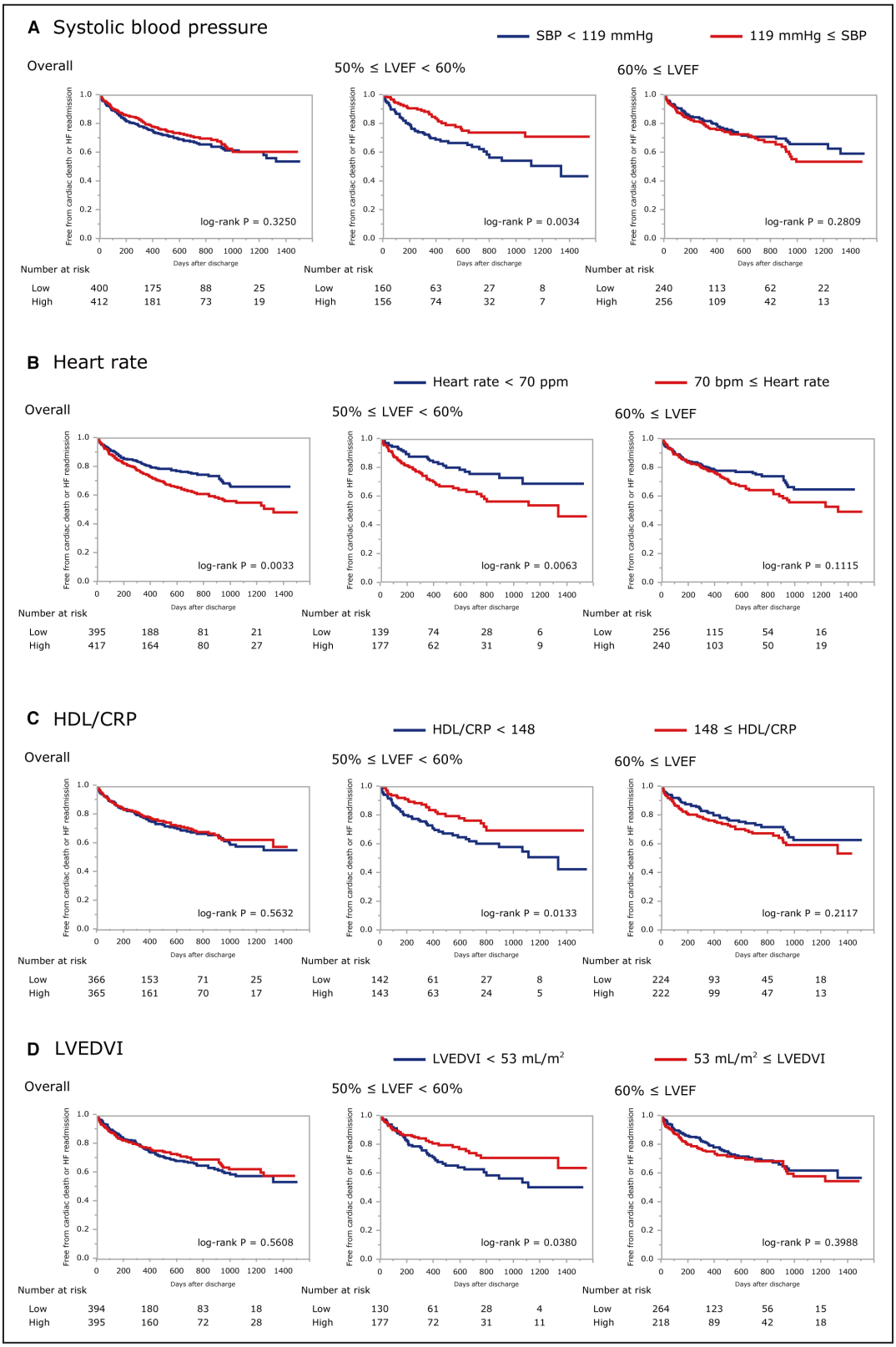

Figure 3. Kaplan-Meier curves by potential specific prognostic factors for patients with 50% ≤ LVEF <60%.

Patients are divided with the median values of systolic blood pressure (**A**), heart rate (**B**), HDL/CRP ratio (**C**) and LVEDVI (**D**). CRP indicates C-reactive protein; HDL, high-density lipoprotein; HF, heart failure; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; and SBP, systolic blood pressure.

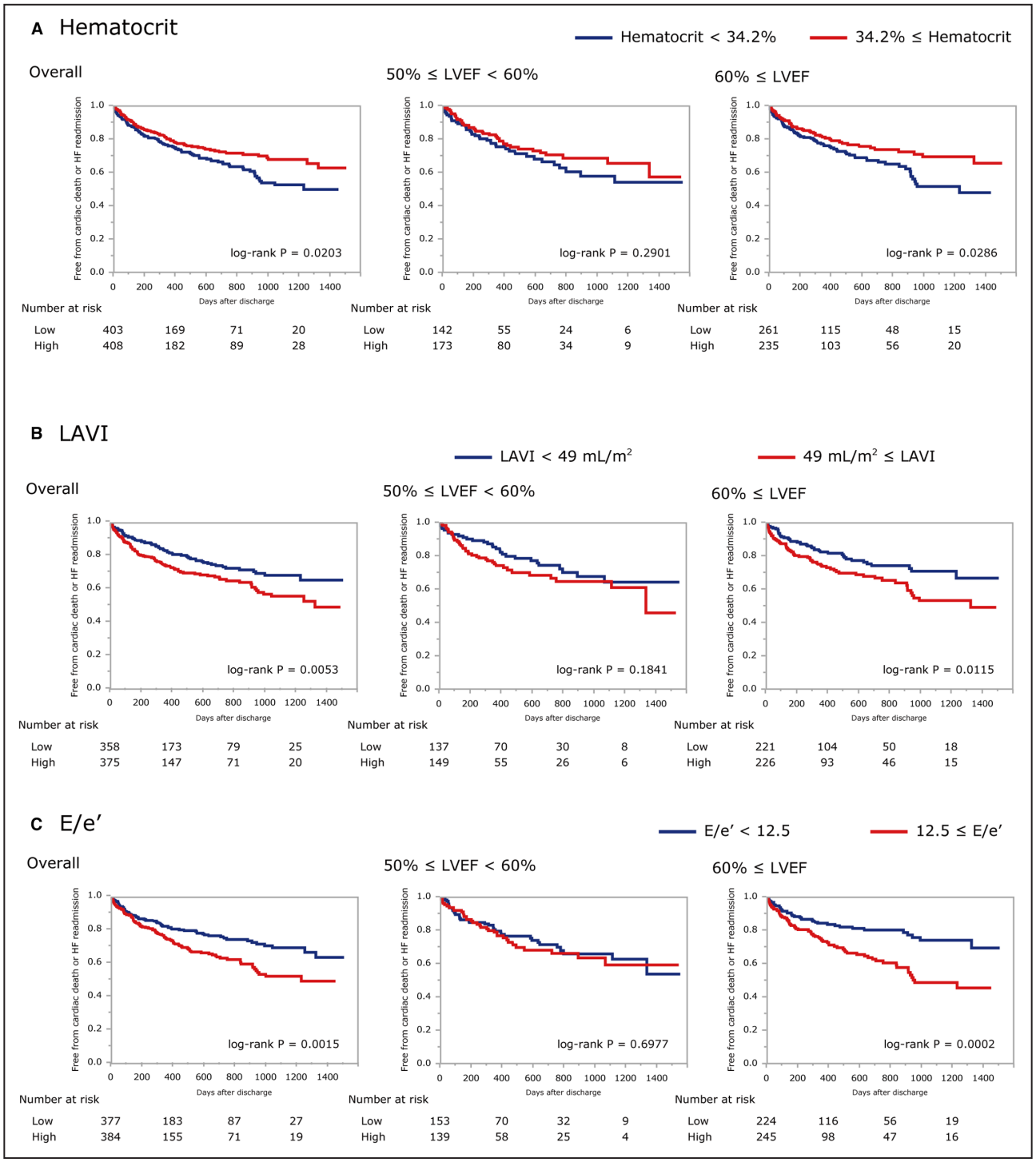

Figure 4. Kaplan-Meier curves by potential specific prognostic factors for patients with 60% ≤ LVEF.
Patients are divided with the median values of hematocrit (**A**), LAVI (**B**) and E/e' (**C**). E/e', ratio of peak early mitral inflow velocity to velocity of mitral annulus early diastolic motion e'; HF, heart failure; LAVI, left atrial volume index; and LVEF, left ventricular ejection fraction.

different between patients with HFpEF whose LVEF was below or above 60%. Furthermore, we also found more interestingly that prognostic outcomes showed no differences between these 2 groups, and that although systolic blood pressure, HDL/CRP ratio, and LV volume were characteristic prognostic factors in patients with LVEF below 60%, E/e' was uniquely highlighted in patients with LVEF above 60%. Whereas it might still be difficult to explain what caused the different therapeutic effects on patients with HFpEF with

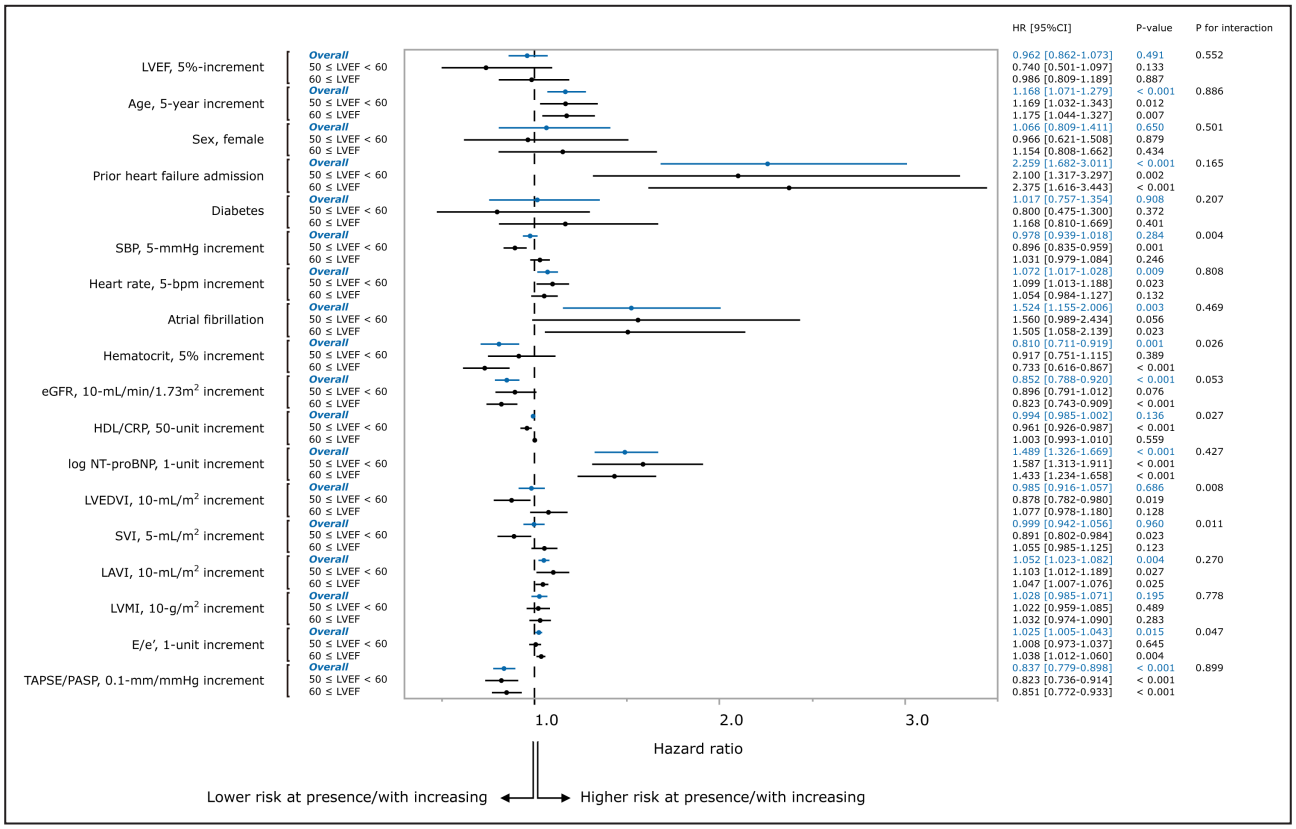

Figure 5. Predictors of composite outcome assessed by univariable Cox regression.
Forest plot depicting univariable HRs for the composite outcome (time to cardiac mortality or heart failure rehospitalization). CRP indicates C-reactive protein; eGFR, estimated glomerular filtration rate; E/e′, ratio of peak early mitral inflow velocity to velocity of mitral annulus early diastolic motion e′; HF, heart failure; HR, hazard ratio; LAVI, left atrial volume index; log NT-proBNP, log-transformed N-terminal pro–B-type natriuretic peptide; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; PASP, pulmonary arterial systolic pressure; SBP, systolic blood pressure; SVI, stroke volume index; and TAPSE, tricuspid annular plane systolic excursion.

higher and lower LVEF in PARAGON-HF study and EMPEROR-Preserved study, these findings indicate that key pathophysiological factors differed quite substantially between the 2 populations.

No Significant Prognostic Differences Between Lower and Higher LVEF Patients With HFpEF

As shown in the I-PRESERVE (Irbesartan in Heart Failure with Preserved Systolic Function) trial, LVEF is a strong predictor of outcomes in HFpEF.[20] The TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial) also showed that lower LVEF predicted major outcomes, and that spironolactone had a favorable treatment effect,[22] as well as that systolic dysfunction had prognostic importance using LV longitudinal strain.[23] These previous studies were based on their respective inclusion criteria and an HFpEF definition of LVEF ≥45%. Although the adverse event risk of patients with $LVEF_{50–60}$ did not significantly differ from that of patients with $LVEF_{60–}$ in our present study, this may be partly attributable to our different inclusion criteria of LVEF ≥50% compared with these previous studies.

Lower LVEF Patients With HFpEF Have Some Aspects of HFrEF

Patient characteristics assessment revealed that patients with $LVEF_{50–60}$ presented larger LVEDVI than patients with $LVEF_{60–}$, whereas their LVMI and SVI were not statistically different. Patients with $LVEF_{50–60}$ showed a slightly larger LV volume than a healthy Japanese population on 3-dimensional echocardiography (mean LVEDVI in men and in women was 50±12 and 46±9 mL/m^2, respectively).[24] Lower LVEF patients showed a larger LV size even among patients with HFpEF, which was consistent with prior findings from comparisons of the TOPCAT, CHARM (Candesartan Cilexetil in Heart Failure Assessment of Reduction in Mortality and Morbidity), CHARMES (Echocardiographic Substudy), and PARAMOUNT (Prospective Comparison of ARNI With ARB on Management of Heart Failure With

Table 3. Multivariable Cox Regression Hazard Models for the Composite End Point of Cardiac Death or Heart Failure Readmission

	Overall: HR [95% CI]	*P* value	50% ≤ LVEF <60%: HR [95% CI]	*P* value	60% ≤ LVEF: HR [95% CI]	*P* value	*P* for interaction
SBP, 5-mm Hg increments	0.994 [0.952–1.037]	0.789	0.925 [0.862–0.992]	0.028	1.045 [0.988–1.105]	0.120	0.124
Hematocrit, 5% increments	0.936 [0.808–1.084]	0.372	1.104 [0.889–1.355]	0.365	0.827 [0.672–1.018]	0.069	0.061
HDL/CRP, 50-unit increments	0.993 [0.983–1.001]	0.094	0.975 [0.944–0.995]	0.007	0.999 [0.989–1.007]	0.830	0.212
LVEDVI, 10-mL/m^2 increments	1.000 [0.921–1.080]	0.996	0.870 [0.759–0.997]	0.037	1.087 [0.981–1.195]	0.110	0.011
E/e′, 1-unit increments	1.015 [0.993–1.035]	0.175	0.999 [0.963–1.028]	0.954	1.034 [1.003–1.062]	0.034	0.125

Cox regression tests were adjusted by age, sex, heart rate, atrial fibrillation, estimated glomerular filtration rate, log-transformed N-terminal pro-B-type natriuretic peptide, and prior heart failure history. CRP indicates C-reactive protein; E/e′, ratio of peak early mitral inflow velocity to velocity of mitral annulus early diastolic motion e′; HDL, high-density lipoprotein; HR, hazard ratio; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; and SBP, systolic blood pressure.

Preserved Ejection Fraction) trials.[25] The increased LV volume in patients with $LVEF_{50–60}$ possibly reflects compensatory mechanisms for potential LV systolic dysfunction, as observed in the HFrEF phenotype.[26]

Key Clinical Factors Among Lower LVEF Patients With HFpEF

A multivariable Cox regression model showed that systolic blood pressure, LVEDVI, and HDL/CRP ratio were particular prognostic factors among patients with $LVEF_{50–60}$ (Table 3).

Lower blood pressure was associated with higher adverse event risks in this study. This association has been reported not only in HFrEF[27–29] but also in HFpEF.[30] It was speculated that lower blood pressure in HFpEF might reflect a more advanced disease state and lower cardiac output. The major difference between HFrEF and HFpEF lies in the fact that the loss of contractile function is accompanied by proportional LV enlargement in HFrEF, versus only slight LV dilatation in HFpEF.[31] LV dilatation in HFrEF compensates for the loss of contractile function. On this basis, the association between lower LVEDVI and worse outcome among patients with $LVEF_{50–60}$ may reflect inadequate compensation for the loss of systolic function. The pathogenesis of contractile dysfunction in patients with HFpEF is possibly related to inflammation.[32] From the PURSUIT-HFpEF registry, Yano et al evaluated the HDL/CRP ratio as an anti-inflammatory marker and showed that the ratio on admission was an independent predictor for all-cause mortality and cardiac death in patients with HFpEF.[8] We found that the ratio at discharge, in a more stable status, was a distinctive prognostic factor among lower LVEF patients with HFpEF. Empagliflozin potentially restores cardiac microvascular endothelial function via the modulation of inflammatory mediators.[33] Another sodium-glucose cotransporter 2 inhibitor, dapagliflozin, is reported to mediate the proposed athero-protective effects of elevated HDL and to ameliorate thrombin-platelet-mediated inflammation.[34] We found that a possible inflammatory marker of HDL/CRP ratio had significant prognostic importance among lower LVEF patients with HFpEF.

The prognostic importance of systolic blood pressure, HDL/CRP ratio, and LVEDVI in patients with $LVEF_{50–60}$ with HFpEF might suggest that the pathophysiology closely links to the potential contractile dysfunction and eccentric remodeling, which partly overlap with HFrEF.

Key Clinical Factors in Higher LVEF Patients With HFpEF

Although E/e′ ratio was similar in the $LVEF_{50–60}$ and $LVEF_{60–}$ groups, we found that it was a distinctive prognostic factor among patients with $LVEF_{60–}$ but not among patients with $LVEF_{50–60}$ on not only univariable but also multivariable Cox regression models with adjustment for age, sex, heart rate, AF, eGFR, NT-proBNP, and HF history (Table 3). E/e′ has been reported to be a prognostic factor for patients with HFpEF,[35,36] but precisely what E/e′ reflects warrants careful interpretation. E/e′ ratio is used to estimate LV filling pressure and diastolic function, but diagnostic accuracy is limited among patients with HFpEF because of the difficulty in reliably measuring LV chamber stiffness.[37] The Euro-Filling study revealed that the positive and negative predictive values of an average E/e′ ratio ≥14 in detecting abnormal invasive LV filling pressure were modest, at only 56% and 62%, respectively.[38] It is noteworthy that E/e′ ratio was more definitive in the prognosis of our patients with $LVEF_{60–}$ than LVMI and LAVI, which also closely relate to diastolic function. This finding in turn emphasizes the particular importance of E/e′ among higher LVEF patients with HFpEF. Our findings indicate that patients with $LVEF_{60–}$ have some pathogenesis

that is closely related to E/e′. These results warrant further investigation to clarify what E/e′ reflects in clinical settings.

Although many systemic background variables, including comorbidities and laboratory markers, showed no significant differences between our $LVEF_{50–60}$ and $LVEF_{60–}$ groups, patients with $LVEF_{60–}$ presented with lower hematocrit, as was also seen in a previous study.[39] The negative result of multivariable Cox regression analysis among patients with $LVEF_{60–}$ showed that the prognostic value of anemia might represent confounding by other factors. However, it is noteworthy that a low hematocrit level was significantly associated with a poor prognosis on univariable Cox regression testing. Because anemia is reported to be an important prognostic factor among patients with HFpEF[40] and to be even more common in patients with HF with higher LVEF,[41] hemoglobin concentration should be enough focused.

The prognostic importance of E/e′ in patients with $LVEF_{60–}$ with HFpEF might suggest that diastolic dysfunction is deeply involved in the pathophysiology. Given the importance of hemoglobin concentration, systemic problems might also comprise the pathophysiology.

Nonnegligible Factors Among Patients With HFpEF Regardless of LVEF Category

LVEF is one profile factor in patients with HF. A consensus statement noted that, in addition to LVEF, cardiac structural and functional information is also important in guiding appropriate management for patients with HFpEF.[4] As shown in our univariable Cox regression testing (Figure 5), heart rate, AF, LAVI, and TAPSE/PASP ratio as well as NT-proBNP were shown to warrant attention overall in patients with HFpEF, suggesting that the fundamental pathophysiology that causes these architectural and functional alterations should not be ignored. Increased wall stress is a common key factor for both of HFrEF and HFpEF, and affects cardiac myocyte morphology, ventricular volume, and wall thickness.[42] Moreover, systolic dysfunction is not unique to HFrEF, and diastolic dysfunction is not unique to HFpEF, meaning that all forms of HF are hybrids involving both abnormalities in varying proportion.[43] We showed here that LVEF could stratify patients with HFpEF into pathophysiologically differing subgroups.

LVEF is also known to be closely related to LV geometry, including intrasarcomeric cytoskeleton, extrasarcomeric cytoskeleton, and extracellular matrix.[44] Concentric LV hypertrophy is frequently observed in patients with HFpEF, and increased wall thickness amplifies systolic thickening, compensates for the decrease in myocardial fiber shortening, and preserves LVEF.[45] Although the distributions of LV remodeling category did not significantly differ between the $LVEF_{50–60}$ and $LVEF_{60–}$ groups (P=0.558; Table 1), it should be noted that geometric aspects must be also considered when evaluating actual cardiac function among patients with HFpEF.

Limitations

Several limitations of this study should be noted. First, we analyzed 812 enrolled patients after excluding 162 without LVEF data, which could have introduced unavoidable selection bias. Second, the patient population was exclusively East Asian with quite an advanced age (median of 83 years), and the generalizability of our findings should therefore be considered carefully. Additionally, all patients were hospitalized with acute decompensated HF, and thus differed from participants in the EMPEROR-Preserved and PARAGON-HF trials, which should also be considered carefully when comparing results. Third, because we registered patients with HFpEF based on data at admission, we were unable to avoid including HF with patients with recovered LVEF. Fourth, despite the central interest in LVEF, we did not observe global longitudinal strain, which could provide more detailed evaluation for cardiac function including the systolic–diastolic coupling[46] among patients with HFpEF, because the strain was unfortunately not commonly measured in the participating centers. Cardiac sonographers were not blinded to clinical information, which may have caused measurement bias. Moreover, measurements were done by sonographers and were not evaluated by an imaging core laboratory. Fifth, the limited number of follow-up completion among event-free patients in this study must be noticed. Because the prognostic follow-up period was planned to be as long as 5 years after discharge in the PURSUIT-HFpEF registry, most of the event-free patients were still under follow-up. Of the 608 event-free patients, only 2 completed the 5-year follow-up. Finally, further investigations including a purpose for verification are required to confirm the results of this study and to support a deeper understanding of the meaning of LVEF among patients with HFpEF.

CONCLUSIONS

We showed in a multicenter observational cohort study that prognostic factors distinctly differ between patients with HFpEF with 50% ≤ LVEF <60% versus those with 60% ≤ LVEF. These findings suggest that there are underlying pathophysiologic differences between these subgroups, upon which therapeutic strategies should be arranged.

ARTICLE INFORMATION

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Supplemental Material

Data S1
Table S1
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Data S1. Details of the PURSUIT-HFpEF Registry

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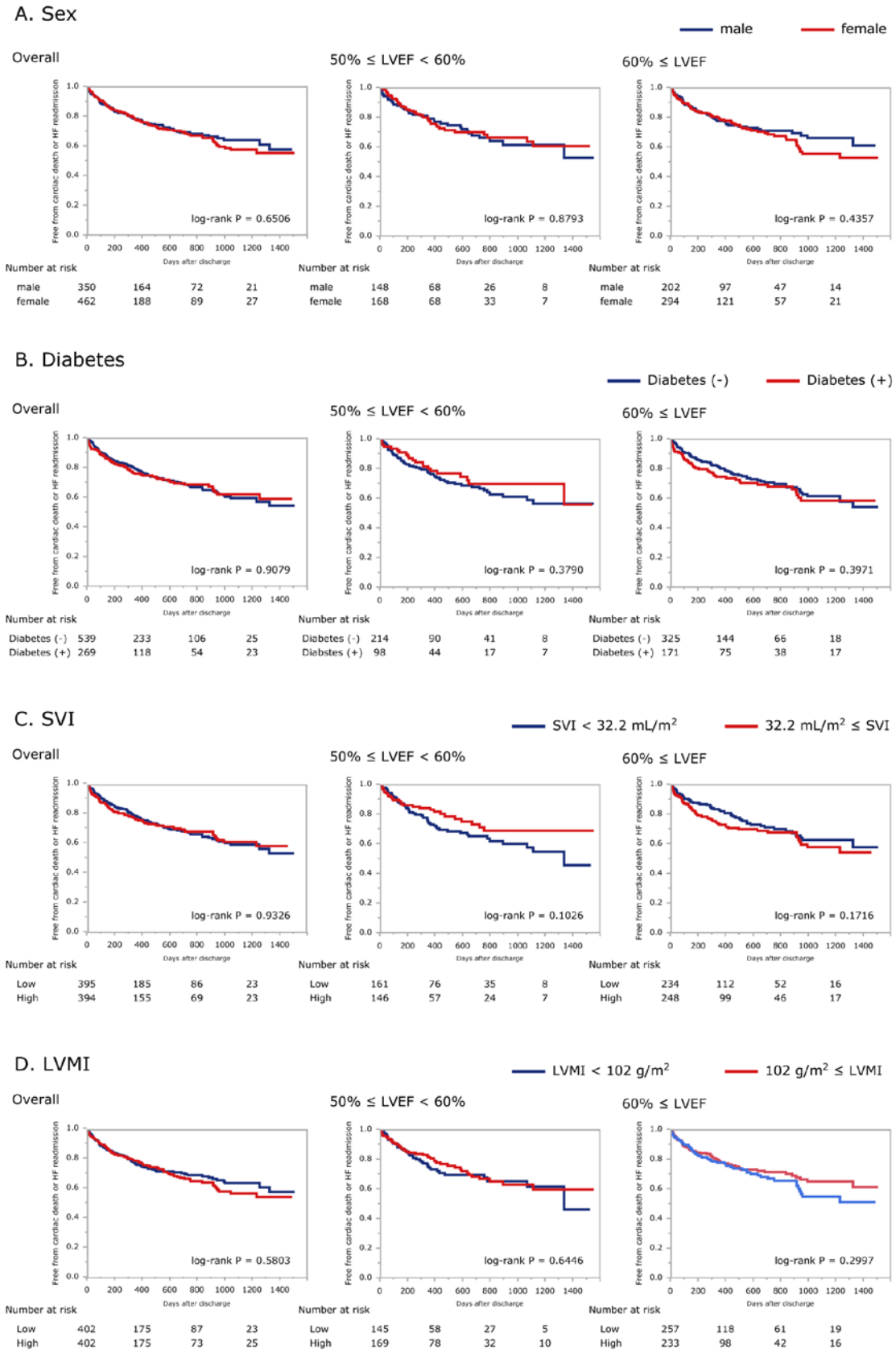
Table S1. Potential triggers for heart failure worsening

	Overall (n = 812)	50% ≤ LVEF < 60% (n = 316)	60% ≤ LVEF (n = 496)	P
Excessive sodium/water intake	220 (27)	86 (27)	134 (27)	0.950
Poor medication compliance	51 (6)	24 (8)	27 (5)	0.218
Over working	72 (9)	34 (11)	38 (8)	0.130
Infection	148 (18)	59 (19)	89 (18)	0.794
Arrhythmia	237 (29)	89 (28)	148 (30)	0.609
Cardiac ischemia	26 (3)	15 (5)	11 (2)	0.046
Uncontrolled hypertension	127 (16)	46 (15)	81 (16)	0.498
Others	103 (13)	35 (11)	68 (14)	0.272
Unknown	97 (12)	33 (10)	64 (13)	0.292

Values are given as n (%). Abbreviations: LVEF, left ventricular ejection fraction

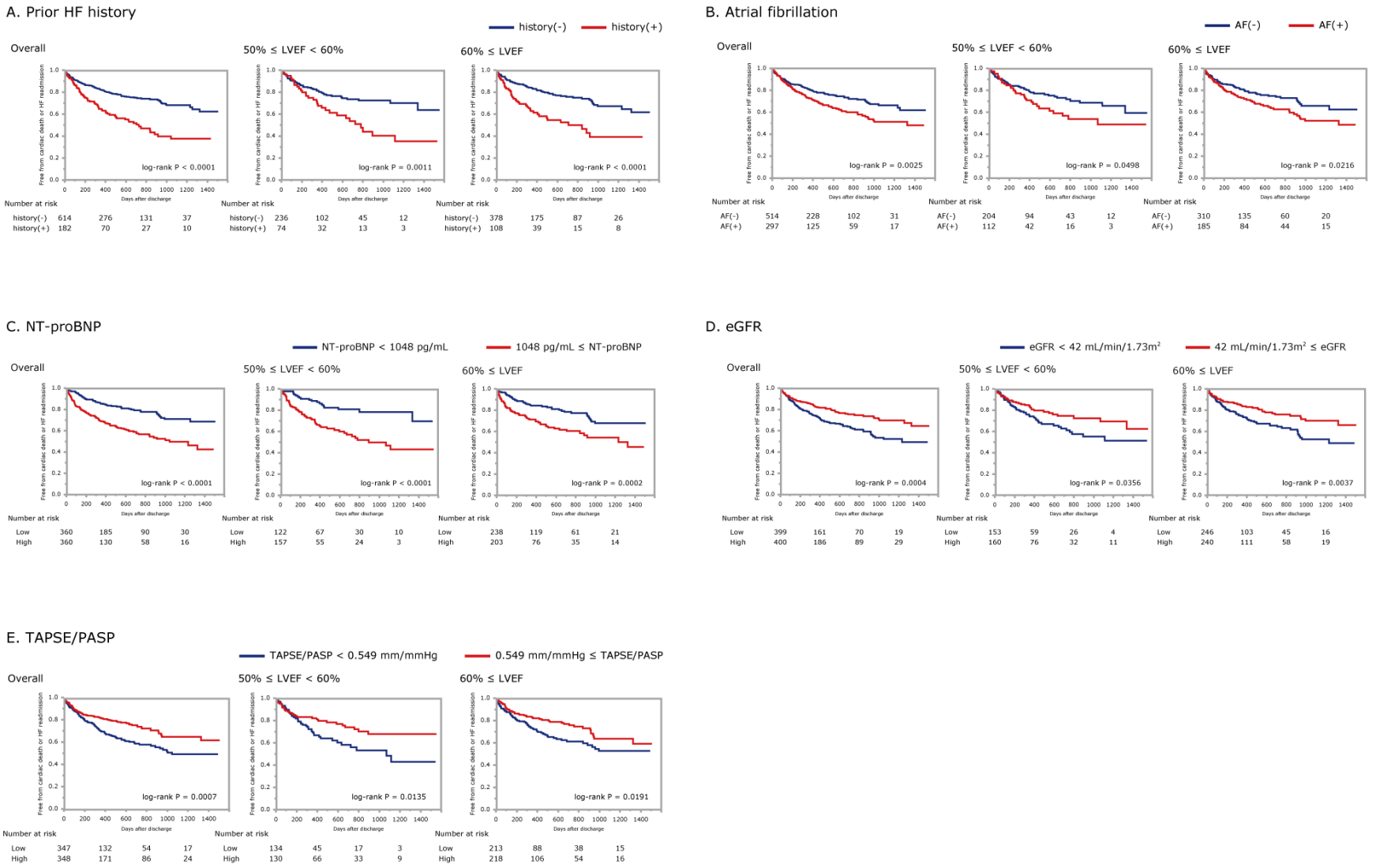
Between-group comparisons were performed using Pearson's chi-squared test.

Figure S1. Kaplan-Meier curves by non-related prognostic factors



Abbreviations: HF, heart failure; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; SVI, stroke volume index

Figure S2. Kaplan-Meier curves by potential prognostic factors for patients with whole LVEF spectrum



Abbreviations: eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PASP, pulmonary arterial systolic pressure; TAPSE, tricuspid annular plane systolic excursion