

Prognostic significance of the HFA-PEFF score in patients with heart failure with preserved ejection fraction

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Abstract

Aims The HFA-PEFF score is a part of the stepwise diagnostic algorithm of heart failure with preserved ejection fraction (HFpEF). We aimed to evaluate the prognostic significance of the HFA-PEFF score on the clinical outcomes in patients with HFpEF.

Methods and results The Prospective mUlticenter oBServational stUdy of patienTs with Heart Failure with preserved Ejection Fraction (PURSUIT-HFpEF) study is a prospective, multicentre, observational study in which collaborating hospitals in Osaka record clinical, echocardiographic, and outcome data of patients with acute decompensated heart failure with preserved left ventricular ejection fraction ($\geq 50\%$) [UMIN-CTR ID: UMIN000021831]. Acute decompensated heart failure was diagnosed on the basis of the following criteria: (i) clinical symptoms and signs according to the Framingham Heart Study criteria; and (ii) serum N-terminal pro-B-type natriuretic peptide level of ≥ 400 pg/mL or brain natriuretic peptide level of ≥ 100 pg/mL. The HFA-PEFF score has functional, morphological, and biomarker domains. We evaluated the prognostic significance of the HFA-PEFF score (calculated based on the data at hospital discharge) on post-discharge clinical outcomes in this cohort. The primary endpoint of the present study was a composite of all-cause death and heart failure readmission. Between June 2016 and December 2019, 871 patients were enrolled from 26 hospitals (mean follow-up duration 399 ± 349 days). A total of 804 patients were finally analysed after excluding patients with scores of 0 ($N = 5$) and 1 ($N = 15$) from 824 patients with available HFA-PEFF score based on the echocardiographic and laboratory data at discharge. According to the laboratory and echocardiographic data at the time of discharge, 487 patients (59.1%) were diagnosed as HFpEF (HFA-PEFF score ≥ 5) while 317 patients (38.5%) had intermediate score. Kaplan–Meier analysis divided by the HFA-PEFF score [low, score 2–5 ($N = 494$) vs. high, score 6 ($N = 310$)] indicated that the HFA-PEFF score successfully stratified the patients for the primary endpoint (log-rank test $P < 0.001$). Cox proportional hazard model showed that the HFA-PEFF score was significantly associated with the primary endpoint (high score with reference to low score, adjusted hazard ratio 1.446, 95% confidence interval [1.099–1.902], $P = 0.008$).

Conclusion The HFA-PEFF score at discharge was significantly associated with the post-discharge clinical outcomes in acute decompensated heart failure patients with preserved ejection fraction. This study suggested clinical usefulness of the HFA-PEFF score not only as a diagnostic tool but also a practical prognostic tool.

Keywords HFpEF; HFA-PEFF score

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Introduction

The comprehensive diagnostic algorithm for heart failure with preserved ejection fraction (HFpEF) was recently introduced by the Heart Failure Association (HFA) of the European Society of Cardiology.¹ Because understanding of the pathophysiology of HFpEF has advanced and diagnostic options have evolved, these data have been integrated into the new comprehensive diagnostic algorithm for suspected HFpEF. This algorithm consists of four steps: Step 1, pre-test assessment; Step 2, echocardiographic and natriuretic peptide HFpEF diagnostic score; Step 3, functional testing; and Step 4, final aetiology. The HFA-PEFF score is a scoring system in the Step 2 evaluating echocardiographic parameters and laboratory tests (natriuretic peptide). Its clinical utility was recently tested by Barandiaran Aizpurua *et al.* The HFA-PEFF score was successfully validated in two independent prospective cohorts.² The score consists of three domains; functional, morphological, and biomarker domains. These domains are all closely related with the left ventricular filling pressure.^{3–5} Therefore, the HFA-PEFF score indicates the severity of the HFpEF itself. Although the HFA-PEFF score is originally a part of diagnostic algorithm, it is hypothesized that the scoring system can be useful for prediction of subsequent clinical outcomes. We aimed to evaluate the prognostic significance of the HFA-PEFF score on the clinical outcomes in patients with HFpEF in a large prospective multicentre registry.

Methods

Study subjects

The Prospective multicentre observational study of patients with Heart Failure with preserved Ejection Fraction (PURSUIT-HFpEF) study is a prospective, multicentre, observational study in which collaborating hospitals in Osaka record clinical, echocardiographic, and outcome data of patients with acute decompensated heart failure with preserved left ventricular ejection fraction (left ventricular ejection fraction $\geq 50\%$) [UMIN-CTR ID: UMIN000021831].⁶ Consecutive patients with acute decompensated heart failure and preserved ejection fraction were prospectively registered and agreed to be followed up for collection of outcome data. Acute decompensated heart failure was diagnosed on the basis of the following criteria: (i) clinical symptoms and signs according to the Framingham Heart Study criteria⁷; and (ii) serum N-terminal pro-B-type natriuretic peptide level of ≥ 400 pg/mL or brain natriuretic peptide level of ≥ 100 pg/mL. All patients provided written informed consent for participation in this study. The study protocol was approved by the ethics committee of each participating hospital. This study conformed to the ethical guidelines outlined in the Declaration of Helsinki.

Data collection

Details of the data collection were previously described elsewhere.^{8,9} In brief, basic patient characteristics, echocardiography, laboratory tests, and medications were obtained on admission, at discharge, and at each annual follow-up time point. Because the present analysis focused on the prognostic impact of the HFA-PEFF score on clinical outcomes after discharge, we used laboratory data and echocardiography data mainly at the time of discharge (after treatment of acute decompensated heart failure AND in stable condition).

Study endpoints

The primary endpoint of the present study was a composite of all-cause death and heart failure readmission. The secondary endpoints were each individual components of the primary endpoint. In the present study, patient follow-up started from the time point of discharge. All patients were followed up in each hospital after discharge. Survival data were obtained by dedicated coordinators and investigators by direct contact with patients and their physicians at the hospital or in an outpatient setting or by a telephone interview with their families or by mail. In the present analysis, we analysed all available clinical follow-up data up to the end of 2019.

HFA-PEFF score calculation

The HFA-PEFF score is originally a part of the HFA-PEFF diagnostic algorithm.¹ The second step of the diagnostic algorithm is calculation of the HFA-PEFF score, which has functional, morphological, and biomarker domains. Details of the criteria are described elsewhere.¹ The global longitudinal strain data in the functional domain were not available in the PURSUIT-HFpEF registry. We calculated the HFA-PEFF score even if not all parameters are obtained, as the consensus document recommended.¹ When all three domains were missing, we did not calculate the HFA-PEFF score and left as missing in this study. When at least one domain was available, we did calculate the HFA-PEFF score assuming the missing data as zero. In the original HFA-PEFF diagnostic algorithm,¹ a total score ≥ 5 points is considered to be diagnostic 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 functional and aetiology evaluation. Of note, in this study, we calculated the score based on the clinical and echocardiographic data at hospital discharge (not before diagnosis of heart failure) and evaluated its prognostic significance.

Statistical analysis

Categorical variables are expressed as counts (percentages) and compared with χ^2 test or Fisher exact test. Continuous variables are expressed as mean (standard deviation) or median [interquartile range] and compared using Student *t*-test, Mann–Whitney U test, ANOVA, or Kruskal–Wallis test as appropriate. The primary endpoint and secondary endpoint of all-cause death were assessed according to the HFA-PEFF score in a time-to-first-event fashion with the Kaplan–Meier method and compared with the log-rank test. The secondary endpoint of heart failure readmission was assessed with cumulative incidence function approach and Gray's test, considering all-cause death as a competing risk. Patients with the HFA-PEFF scores of missing ($N = 47$), 0 ($N = 5$), and 1 ($N = 15$) were excluded from the analysis due to the small sample size. In the survival analysis, patients were stratified into two groups [low, score 2–5 ($N = 494$) vs. high, score 6 ($N = 310$)]. Receiver operating characteristics analysis showed that the best cutoff value of the HFA-PEFF score for predicting the clinical event was 6 (sensitivity 0.469, specificity 0.650) with the area under the curve of 0.577 [95% confidence interval 0.536–0.618]. On the basis of this cutoff value, we stratified the patients into scores of 2–5 [low] vs. 6 [high]. As an exploratory analysis, we also stratified patients into scores of 2–4 (intermediate) vs. 5–6 (high) based on the original HFA-PEFF algorithm. Cox proportional hazard models were constructed to evaluate the association between the HFA-PEFF score and the primary endpoint and the secondary endpoint of all-cause death without and with adjustment for following variables: age, sex, hypertension, diabetes mellitus, dyslipidaemia, coronary artery disease, history of percutaneous coronary intervention or coronary artery bypass graft, chronic kidney disease, haemoglobin level, frailty scale, malignancy, and medications (angiotensin-converting-enzyme inhibitor, angiotensin II receptor blocker, beta blocker, calcium channel blocker, vasodilators, diuretics, mineralocorticoid receptor antagonists, digitalis, antiarrhythmic drug, anticoagulants, and antiplatelets). The Fine and Gray model was used for the secondary endpoint of heart failure readmission in the same way considering all-cause death as a competing risk. The proportional hazards assumption of HFA-PEFF score for the primary endpoint was confirmed by Schoenfeld residuals ($P = 0.470$). Discriminative performance and predictive performance of the HFA-PEFF score were evaluated with C-statistics and Hosmer–Lemeshow test for the univariate binary logistic regression model. As a sensitivity analysis, we performed the same analyses with an imputed dataset. We used the Multivariate Imputation by Chained Equations (MICE) method. The MICE approach is an established imputation method for creating multiple complete datasets in which missing values are replaced with estimates from a specified regression model using the observed data. We created 10 datasets with 20 iterations using the MICE package in R and

used one randomly selected dataset. A probability value of less than 0.05 was considered statistically significant. All analyses were undertaken using SPSS 26.0 (IBM Corporation, Armonk, NY) or R software (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

Study subjects

Between June 2016 and December 2019, 871 patients were enrolled from 26 hospitals. Mean follow-up duration was 399 ± 349 days. We could calculate the HFA-PEFF score for 824 patients (94.6%). According to the laboratory and echocardiographic data at the time of discharge, 487 patients (59.1%) were diagnosed as HFpEF (HFA-PEFF score ≥ 5) while 317 patients (38.5%) had intermediate score. Patients' characteristics are tabulated in *Table 1*. Patients with higher HFA-PEFF score were older and had higher systolic blood pressure, lower estimated glomerular filtration rate, and a lower prevalence of atrial fibrillation than those with lower HFA-PEFF score. Body mass index did not differ between the HFA-PEFF score subgroups. Medication at discharge is summarized in *Table 2*. Use of angiotensin-converting-enzyme inhibitor or angiotensin II receptor blocker, calcium channel blocker, diuretics, and digitalis were significantly different amongst the different HFA-PEFF scores. Distribution of the HFA-PEFF score is illustrated in *Figure 1*. Each individual domain of the HFA-PEFF score is summarized in *Figure 2*. A total of 236 patients performed invasive hemodynamic assessment during hospitalization (*Table S1*). Right ventricular end-diastolic pressure was significantly higher in patients with a HFA-PEFF score of 6 than the others except for scores of 0–2.

Clinical significance of the HFA-PEFF score

In the overall cohort (871 patients), the primary endpoint (a composite of all-cause death and heart failure readmission) occurred in 265 patients (30.4%). The all-cause mortality was 14.0% (122 patients), whereas the rate of heart failure readmission was 20.2% (176 patients).

A total of 804 patients were finally analysed after excluding patients with scores of 0 ($N = 5$) and 1 ($N = 15$) from the 824 patients with available HFA-PEFF score. The survival analysis stratified by the HFA-PEFF score [low, score 2–5 ($N = 494$) vs. high, score 6 ($N = 310$)] indicated that the HFA-PEFF score successfully stratified the patients for the primary endpoint (*Figure 3A*, log-rank test $P = 0.000266$) and both secondary endpoints, all-cause death (*Figure 3B*, $P = 0.000333$) and heart failure readmission (*Figure 3C*, $P = 0.0142$). Results of the other stratification (intermediate, score 2–4 vs. high, score 5, 6) are shown in *Figure S1*. The

Table 1 Baseline characteristics stratified by HFA-PEFF score

Characteristic	Overall	HFA-PEFF score			
		0	1	2	3
Number	871	5	15	63	88
Age (years)	82.0 [76.5, 87.0] 389 (44.7)	80.0 [76.0, 84.0] 0 (0.0)	79.0 [76.5, 85.0] 11 (73.3)	80.0 [75.0, 84.0] 34 (54.0)	81.5 [77.75, 86.0] 52 (59.1)
Male gender	23.70	23.30	24.70	23.50	23.55
Body mass index	[20.80, 26.80] 147.0	[20.28, 26.48] 138.0	[22.75, 26.05] 126.0	[20.70, 27.60] 145.0	[20.83, 26.78] 142.50
Systolic blood pressure (mmHg)	[128.0, 170.0] 80.0	[109.0, 142.0] 90.0	[121.0, 144.50] 81.0	[123.0, 162.50] 78.0	[126.75, 164.50] 80.50
Diastolic blood pressure (mmHg)	[66.0, 93.50] 82.0	[90.0, 93.0] 97.0	[62.50, 93.50] 82.0	[70.50, 91.50] 88.0	[64.0, 97.0] 81.0
Heart rate (bpm)	[66.0, 100.0] 5.0	[91.0, 103.0] 5.0	[72.0, 100.50] 4.0	[73.0, 109.50] 5.0	[63.75, 101.0] 5.0
CHA ₂ DS ₂ VASc score	[4.0, 6.0] 11.30	[4.0, 5.0] 11.40	[4.0, 5.0] 12.60	[4.0, 5.0] 12.10	[4.0, 5.0] 12.0
Haemoglobin (g/dL)	[10.0, 12.70] 41.60	[9.30, 13.20] 31.30	[11.50, 14.60] 46.20	[10.80, 13.17] 50.50	[10.80, 13.40] 49.90
eGFR (mL/min/1.73 m ²)	[29.92, 54.40] 5.90	[16.52, 45.20] 6.60	[34.10, 54.65] 5.80	[35.90, 61.30] 5.90	[36.95, 60.15] 6.00
HbA1c (%)	[5.60, 6.50] 1090.0	[5.60, 7.10] NA	[5.70, 6.05] 201.95	[5.60, 6.27] 333.0	[5.70, 6.50] 498.50
NT-proBNP (pg/mL)	[481.0, 2550.0]	[220.27, 269.62]	[133.25, 232.75]	[236.0, 1025.50]	[275.25, 1180.0]
NYHA class					
NYHA I	309 (36.1)	11 (25.6)	4 (26.7)	29 (47.5)	44 (51.2)
NYHA II	475 (55.4)	21 (48.8)	10 (66.7)	26 (42.6)	34 (39.5)
NYHA III	60 (7.0)	3 (7.0)	1 (6.7)	5 (8.2)	7 (8.1)
NYHA IV	13 (1.5)	8 (18.6)	0 (0.0)	1 (1.6)	1 (1.2)
Patient history					
Hypertension	736 (84.8)	40 (87.0)	12 (80.0)	48 (76.2)	73 (83.0)
Dyslipidaemia	356 (41.2)	12 (26.1)	4 (26.7)	25 (41.0)	26 (29.5)
Diabetes mellitus	287 (33.3)	12 (26.1)	2 (13.3)	19 (30.6)	31 (36.0)
Smoking					
Current smoker	87 (10.2)	1 (2.1)	1 (6.7)	7 (11.3)	9 (10.3)
Past smoker	232 (27.1)	14 (29.8)	4 (26.7)	21 (33.9)	29 (33.3)
Atrial fibrillation	440 (50.5)	23 (48.9)	10 (66.7)	36 (57.1)	59 (67.0)
Bleeding	40 (4.7)	3 (6.7)	2 (13.3)	2 (3.3)	0 (0.0)
Coronary artery disease	150 (17.5)	6 (14.0)	1 (6.7)	9 (14.5)	16 (18.2)
Myocardial infarction	65 (7.6)	3 (7.0)	1 (6.7)	5 (8.2)	7 (8.0)
Coronary artery bypass graft	31 (3.6)	3 (6.5)	0 (0.0)	1 (1.6)	4 (4.5)
Percutaneous coronary intervention	119 (13.8)	4 (8.7)	1 (6.7)	7 (11.3)	13 (14.9)
Peripheral artery disease	48 (5.7)	1 (2.3)	2 (14.3)	1 (1.7)	2 (2.3)
Chronic kidney disease	341 (39.5)	20 (44.4)	4 (26.7)	15 (24.6)	25 (28.7)
Liver dysfunction	56 (6.5)	1 (2.2)	1 (6.7)	4 (6.7)	6 (6.9)
Malignant tumour	100 (11.7)	11 (23.9)	2 (13.3)	8 (13.1)	13 (14.8)
Prior hospitalization for heart failure	213 (25.1)	15 (33.3)	4 (26.7)	13 (21.3)	16 (18.6)
Hypertrophic cardiomyopathy	32 (3.8)	3 (6.8)	0 (0.0)	0 (0.0)	3 (3.4)
Pace-maker implantation	68 (7.8)	3 (6.4)	1 (6.7)	2 (3.2)	9 (10.2)
Stroke	121 (14.1)	5 (11.1)	2 (13.3)	11 (18.0)	14 (15.9)

(Continues)

Table 1 (Continued)

Characteristic	HFA-PEFF score			P value
	4	5	6	
Number	166	177	310	
Age (years)	82.0 [76.0, 86.0]	81.0 [76.0, 87.0]	83.0 [77.0, 88.0]	0.007
Male gender	69 (41.6)	76 (42.9)	125 (40.5)	0.003
Body mass index	23.0 [20.52, 26.67]	24.10 [20.70, 27.95]	23.80 [21.20, 26.65]	0.874
Systolic blood pressure (mmHg)	149.50 [130.25, 166.0]	150.0 [132.0, 171.0]	148.50 [129.0, 176.75]	0.037
Diastolic blood pressure (mmHg)	79.50 [69.0, 91.0]	82.0 [70.0, 94.0]	77.0 [65.0, 94.75]	0.800
Heart rate (bpm)	87.0 [67.0, 101.75]	79.0 [66.0, 102.0]	80.0 [66.0, 98.0]	0.144
CHA ₂ DS ₂ VASc score	5.0 [4.0, 6.0]	5.0 [4.0, 6.0]	5.0 [4.0, 6.0]	0.438
Haemoglobin (g/dL)	11.35 [10.20, 12.60]	11.50 [9.90, 13.10]	10.90 [9.50, 12.20]	<0.001
eGFR (mL/min/1.73 m ²)	45.35 [32.75, 55.30]	41.70 [32.35, 55.00]	37.00 [24.00, 49.40]	<0.001
HbA1c (%)	5.90 [5.60, 6.50]	6.10 [5.60, 6.70]	5.90 [5.60, 6.50]	0.395
NT-proBNP (pg/mL)	728.0 [375.0, 1658.0]	1126.0 [530.0, 2060.0]	1715.0 [822.75, 3722.50]	<0.001
NYHA class				<0.001
NYHA I	71 (43.6)	64 (36.2)	82 (26.7)	
NYHA II	79 (48.5)	104 (58.8)	200 (65.1)	
NYHA III	12 (7.4)	7 (4.0)	25 (8.1)	
NYHA IV	1 (0.6)	2 (1.1)	0 (0.0)	
Patient history				
Hypertension	140 (84.3)	154 (87.5)	266 (86.1)	0.325
Dyslipidaemia	69 (41.8)	75 (42.6)	143 (46.4)	0.047
Diabetes mellitus	50 (30.3)	67 (38.3)	105 (34.1)	0.391
Smoking				0.713
Current smoker	19 (11.7)	15 (8.6)	35 (11.6)	<0.001
Past smoker	38 (23.3)	46 (26.2)	79 (26.2)	0.162
Atrial fibrillation	93 (56.0)	91 (51.4)	124 (40.0)	0.622
Bleeding	7 (4.3)	10 (5.7)	15 (5.0)	0.830
Coronary artery disease	25 (15.2)	28 (16.1)	64 (20.9)	0.418
Myocardial infarction	10 (6.1)	10 (5.7)	29 (9.6)	0.259
Coronary artery bypass graft	2 (1.2)	6 (3.4)	15 (4.9)	0.419
Percutaneous coronary intervention	17 (10.2)	23 (13.1)	53 (17.2)	0.002
Peripheral artery disease	8 (4.9)	13 (7.5)	21 (7.1)	0.901
Chronic kidney disease	58 (35.2)	78 (44.1)	141 (45.8)	0.194
Liver dysfunction	10 (6.0)	10 (5.6)	24 (7.8)	0.285
Malignant tumour	17 (10.6)	20 (11.4)	29 (9.5)	0.558
Prior hospitalization for heart failure	33 (20.5)	43 (24.7)	87 (28.7)	0.838
Hypertrophic cardiomyopathy	6 (3.7)	5 (2.8)	15 (5.0)	0.1
Pace-maker implantation	14 (8.4)	13 (7.3)	26 (8.4)	0.898
Stroke	26 (15.8)	25 (14.2)	37 (12.1)	1.3

eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; NA, not available.

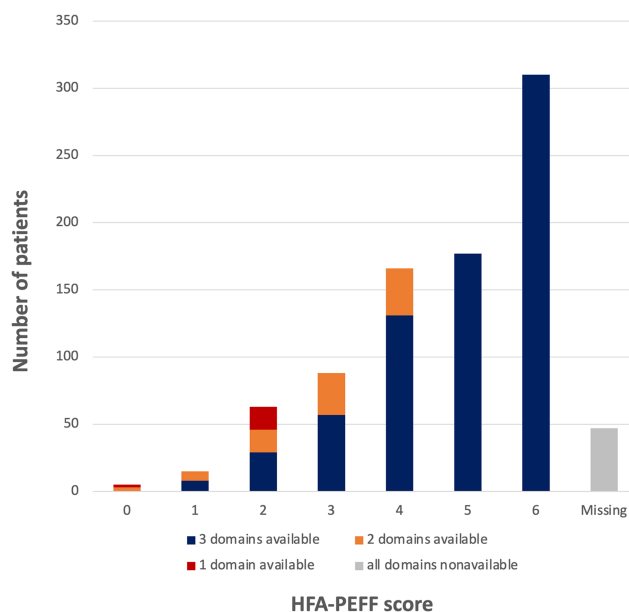
Data are expressed as median [interquartile range], or number (percentage).

Table 2 Medication at discharge

Medication	HFA-PEFF score							Missing (%)	P value
	0	1	2	3	4	5	6		
Overall	5	15	63	88	166	177	310	0.8	0.001
Number	47	14	47	14	47	14	47		
Angiotensin-converting-enzyme inhibitor or Angiotensin II receptor blocker	3 (60.0)	7 (46.7)	28 (44.4)	51 (58.6)	98 (59.0)	95 (53.7)	173 (55.8)	0.9	0.464
Beta blocker	0 (0.0)	4 (26.7)	23 (36.5)	42 (48.3)	74 (44.6)	91 (51.4)	170 (54.8)	0.9	<0.001
Calcium channel blocker	0 (0.0)	2 (13.3)	4 (6.3)	8 (9.2)	15 (9.0)	14 (7.9)	32 (10.3)	0.9	0.934
Vasodilators	4 (80.0)	12 (80.0)	43 (68.3)	75 (85.2)	126 (75.9)	147 (83.1)	265 (85.5)	0.8	0.003
Diuretics	3 (60.0)	4 (26.7)	18 (28.6)	34 (38.6)	64 (38.6)	64 (36.2)	129 (41.6)	0.8	0.323
Mineralocorticoid receptor antagonists	1 (20.0)	0 (0.0)	2 (3.2)	3 (3.4)	12 (7.2)	3 (1.7)	7 (2.3)	0.9	0.037
Digitalis	2 (40.0)	2 (13.3)	8 (12.7)	9 (10.3)	15 (9.0)	10 (5.6)	24 (7.7)	0.9	0.074
Antiarrhythmic drug	5 (100.0)	10 (66.7)	40 (63.5)	62 (70.5)	107 (64.5)	101 (57.1)	161 (51.9)	0.8	0.008
Anticoagulants	2 (40.0)	4 (26.7)	14 (22.2)	24 (27.6)	46 (27.7)	65 (36.7)	99 (31.9)	0.9	0.185
Antiplatelets	0 (0.0)	0 (0.0)	3 (4.8)	3 (3.4)	4 (2.4)	11 (6.2)	20 (6.5)	1.0	0.487
Sodium-glucose transport protein 2 inhibitor	2 (40.0)	5 (33.3)	21 (33.3)	21 (24.1)	53 (31.9)	65 (36.7)	110 (35.5)	0.9	0.624
Statin	12 (30.0)	289 (33.5)							

Data are expressed as number (percentage).

Figure 1 Distribution of the HFA-PEFF score in the PURSUIT-HFpEF registry. Bar graphs indicate the distribution of the HFA-PEFF score. When all three domains were missing, we did NOT calculate the HFA-PEFF score and left as missing in this study. When at least one domain was available, we did calculate the HFA-PEFF score assuming the missing data as zero. Number of available domains is colour-coded as follows: Blue = three domains available; Orange = two domains available; Red = only one domain available; Grey = all domains non-available.

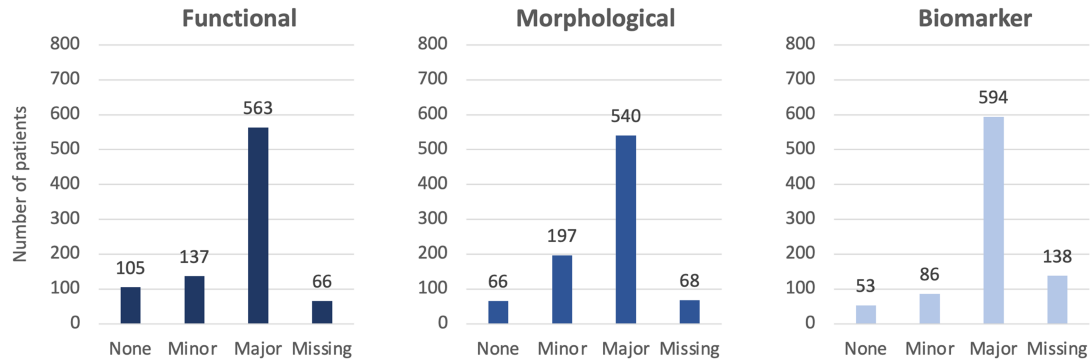


former cutoff point more specifically identified high risk patients than the latter one. Prognostic significance of the HFA-PEFF score is tabulated in *Table 3*. The Cox proportional hazard model showed that the HFA-PEFF score was significantly associated with the primary endpoint (high score with reference to low score, adjusted hazard ratio 1.446, 95% confidence interval [1.099–1.902], $P = 0.008$). The C-statistic of the HFA-PEFF score was 0.577 [95% confidence interval 0.536–0.618], indicating poor discriminative performance of the score. A P value of Hosmer–Lemeshow test was 0.716 for the univariate binary logistic regression model, indicating good model calibration. Sensitivity analyses with the imputed dataset ($N = 871$) showed consistent results (*Figures S2 and S3* and *Table S2*).

Discussion

Main findings of the present study can be summarized as follows: (i) in our prospective multicentre HFpEF registry, 59.1% of the overall cohort was diagnosed as HFpEF based on the laboratory and echocardiographic data at discharge while the others were not; (ii) The HFA-PEFF score was significantly associated with the post-discharge clinical outcome

Figure 2 Distribution of the individual domains in the HFA-PEFF score. Bar graphs indicate the distribution of the individual domains (functional, morphological, and biomarker) in the PURSUIT-HFpEF registry. Data are expressed as number/denominator (percentage) in the table below. *Major criterion: septal $e' < 7$ cm/s or lateral $e' < 10$ cm/s [subjects aged < 75 years]; septal $e' < 5$ cm/s or lateral $e' < 7$ cm/s [subjects aged ≥ 75 years]. †Major criterion: >34 mL/m² in SR; >40 mL/m² in AF. Minor criterion: 29–34 mL/m² in SR; 34–40 mL/m² in AF. Abbreviations: AF, atrial fibrillation; m, men; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LAVI, left atrium volume index; LVMI, left ventricle mass index; RWT, relative wall thickness; SR, sinus rhythm; TR, tricuspid valve regurgitation; w, women.



	Functional domain	Prevalence	Data missing	Morphological domain	Prevalence	Data missing	Biomarker domain*	Prevalence	Data missing
Major Criteria (2 points)	*septal $e' < 7$ cm/s	382/781 (48.9)	90	†LAVI > 34 mL/m ²	521/700 (74.4)	171	NT-proBNP > 220 pg/mL (SR), 660 pg/mL (AF)	594/733 (81.0)	138
	*lateral $e' < 10$ cm/s	387/738 (52.4)	133	LVMI $\geq 149/122$ g/m ² (m/w) and RWT > 0.42	154/797 (19.3)	74			
	average $E/e' \geq 15$	249/733 (34.0)	138						
	TR velocity > 2.8 m/s	216/739 (29.2)	132						
Minor Criteria (1 point)	average $E/e' 9-14$	352/733 (48.0)	138	†LAVI 29-34 mL/m ²	88/700 (12.6)	171	NT-proBNP 125-220 pg/mL (SR), 365-660 pg/mL (AF)	86/733 (11.7)	138
	global longitudinal strain $< 16\%$	Not available	LVMI $> 115/95$ g/m ² (m/w)	384/797 (48.2)	74				
			RWT > 0.42	424/804 (52.7)	67				
			LV wall thickness ≥ 12 mm	202/808 (25.0)	63				

Figure 3 Survival analysis for the primary and secondary endpoints. We performed Kaplan–Meier analysis stratified by HFA-PEFF score (low 2–5 vs. high 6) in the PURSUIT-HFpEF registry for the primary endpoint (A) and secondary endpoint of all-cause death (B). Cumulative incidence curves are presented for the secondary endpoint of heart failure readmission considering all-cause death as a competing risk (C). Abbreviation: HF, heart failure.

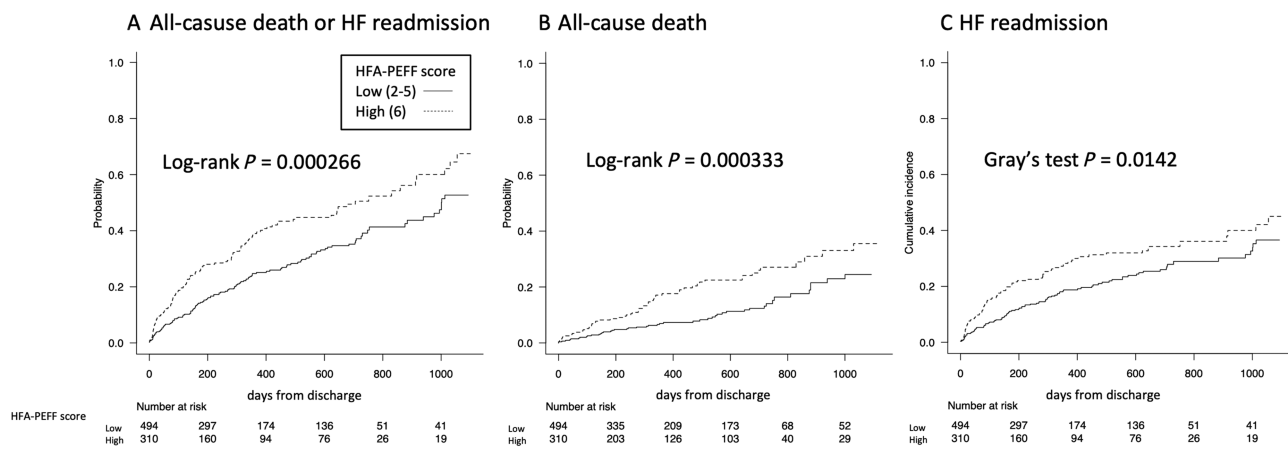


Table 3 Prognostic significance of the HFA-PEFF score

Variable				Hazard ratio [95% confidence interval]	P value
HFA-PEFF score (as continuous value)	Primary endpoint	All-cause death or heart failure readmission	Adjusted	1.178 [1.043–1.330]	0.008
			Crude	1.209 [1.083–1.349]	0.001
	Secondary endpoint	All-cause death	Adjusted	1.199 [0.985–1.460]	0.070
			Crude	1.239 [1.041–1.475]	0.016
		Heart failure readmission ^a	Adjusted	1.155 [1.006–1.327]	0.042
			Crude	1.208 [1.062–1.374]	0.004
HFA-PEFF score (High 6 with reference to low 2–5)	Primary endpoint	All-cause death or heart failure readmission	Adjusted	1.446 [1.099–1.902]	0.008
			Crude	1.598 [1.239–2.060]	<0.001
	Secondary endpoint	All-cause death	Adjusted	1.690 [1.091–2.619]	0.019
			Crude	2.019 [1.364–2.987]	<0.001
		Heart failure readmission ^a	Adjusted	1.334 [0.966–1.840]	0.080
			Crude	1.461 [1.080–1.975]	0.014

A total of 804 patients were analysed after excluding patients with scores of 0 ($N = 5$) and 1 ($N = 15$) from the 824 patients with available HFA-PEFF score. Cox proportional hazard models were constructed to evaluate the association between the HFA-PEFF score and the primary endpoint and all-cause death without and with adjustment for following variables: age, sex, hypertension, diabetes mellitus, dyslipidaemia, coronary artery disease, history of percutaneous coronary intervention or coronary artery bypass graft, chronic kidney disease, haemoglobin level, frailty scale, malignancy, and medications (angiotensin-converting-enzyme inhibitor, angiotensin II receptor blocker, beta blocker, calcium channel blocker, vasodilators, diuretics, mineralocorticoid receptor antagonists, digitalis, antiarrhythmic drug, anticoagulants, and antiplatelets). Impact of the HFA-PEFF score was assessed as continuous value (upper row) and categorical value [high (6) with reference to low (2–5)] (lower row).

^aThe Fine and Gray model was used for heart failure readmission in the same way considering all-cause death as a competing risk.

(a composite of all-cause death and heart failure readmission) in HFpEF patients.

Diagnosis of HFpEF in ‘HFpEF registry’

All patients in the PURSUIT-HFpEF registry should have fulfilled the criteria of the Framingham Heart Study and the laboratory test (N-terminal pro-B-type natriuretic peptide level of ≥ 400 pg/mL brain natriuretic peptide level of ≥ 100 pg/mL) at the time of heart failure admission. Nevertheless, at the time of discharge, only 59.1% of the overall cohort was diagnosed as HFpEF. The number looks so small, but it is quite similar to the numbers in the US and the European cohorts as Barandiaran Aizpurua *et al.* reported.² The remaining approximately 40% of patients would represent the diagnostic difficulty of HFpEF in a stable condition. These patients may be diagnosed as HFpEF if functional or etiological assessments were performed. These findings may insist on the importance of the last two steps of the diagnostic algorithm when we evaluate the patients in a stable condition. The main limitation of the PURSUIT-HFpEF study and other HFpEF studies is the lack of a ‘gold standard’ for the diagnosis of HFpEF, although several diagnostic algorithms are recommended to date.^{1,2,10} Establishment of precise diagnostic scheme remains to be one of the important scientific topics in this field.

Prognosis of HFpEF

As presented in *Figure 3*, the HFA-PEFF score successfully stratified the patients’ risk for all-cause death and heart

failure readmission. Several multivariable prognostic risk scores have been developed: Get With the Guidelines–Heart Failure risk score for in-hospital mortality; Seattle Heart Failure Model for 1-year, 2-year, and 3-year mortality; Meta-analysis Global Group in Chronic Heart Failure risk score for 3 years of mortality and so on.^{11–16} A systematic review examining 64 prognostic models along with a meta-analysis and meta-regression study of 117 prognostic models revealed only a moderate accuracy of models predicting mortality, whereas models designed to predict the combined endpoint of death or hospitalization, or only hospitalization, had an even poorer discriminative ability.^{17–19} Because the HFpEF is a common disease in elderly, hospitalization for heart failure may have rather stronger impact on their quality of life than all-cause death. The present analysis demonstrated that the HFA-PEFF score was significantly associated with the primary composite endpoint, which was driven by both all-cause death and heart failure readmission. Hence, clinical significance as a prognostic tool of the HFA-PEFF score should be more highlighted.

As shown in *Table 2*, drug usage was significantly different in the subgroups. Therefore, we included these drug data in the prediction models. However, albeit statistically significant differences, it seems difficult to find clinically relevant trends of drug use in the subgroups. In general, the current drug therapy does not affect the prognosis of HFpEF patients. Therefore, this methodology might be a matter of debate. In addition, in Japan, angiotensin–neprilysin inhibitor (ARNI) was available from August 2020. As we described in the method section, the dataset that we used in the present study included all available clinical data up to the end of 2019. Since ARNI was used in no patients in this cohort, we cannot assess the influence of ARNI in the present cohort.²⁰ We might be

able to create our own risk prediction model from the current cohort. However, the sample size is not large enough to develop a reliable model. The PURSUIT-HFpEF registry is still ongoing and planned to enrol up to 1500 patients. Risk prediction model development including the HFA-PEFF score and more up-to-date drugs will be the next scientific topic after completion of the present registry.

Clinical implication

While the HFA-PEFF score is originally a diagnostic tool for HFpEF, this study suggested usefulness of the HFA-PEFF score not only as a diagnostic tool but also as a prognostic tool. The consensus document on the diagnosis of HFpEF recommends us to calculate the HFA-PEFF score even if not all parameters are obtained.¹ This may facilitate its clinical utility as a diagnostic tool. However, for the risk assessment after discharge (as a prognostic tool), it would be desirable to obtain all the parameters and calculate the score as precisely as possible in order not to underestimate the patient risk. The present results insist the importance of the accurate diagnosis of HFpEF and the estimation of its severity. The domains in the HFA-PEFF score are all non-invasive and easily evaluable in our daily clinical practice. It can be applicable even for atrial fibrillation. It would be, therefore, helpful for decision-making of the post-discharge treatment to precisely estimate the patients' risk using this score. Of note, the cutoff value as a risk prediction tool is different from that of the original HFA-PEFF score. Receiver operating characteristics analysis indicated that the best cutoff value is 6 as a prediction tool for subsequent clinical events, whereas in the original diagnostic HFA-PEFF score, scores of 5 and 6 are defined as HFpEF. Although in the limited cohort, significantly higher right ventricular end-diastolic pressure in patients with score of 6 than the others shown by invasive hemodynamic assessment (*Table S1*) further support this cutoff point as a prediction tool.

As we described above, the reliable risk prediction model for HFpEF is still to be established in the future investigation. Nevertheless, the HFA-PEFF score can be used as a practical prognostic tool for the time being. Applicability of the findings to the other populations should be carefully evaluated. The median age of the current cohort was 82 years, and the median body mass index was 23.7. Obesity is one of the typical features of HFpEF in Western populations.²¹ However, this Asian cohort showed substantially low body mass index, which is unique and suggests importance of racial difference in HFpEF. The lower prevalence of atrial fibrillation in the high HFA-PEFF score groups might partially be due to the higher cutoff values of biological domains in atrial fibrillation than in sinus rhythm, but again possibly imply the racial difference. The current findings have confirmed the prognostic importance of the HFA-PEFF score at least in East-Asian

population. However, these substantially unique features of our cohort in comparison with Western populations or even other Asian populations would impair the generalizability of the findings.^{22–24} The findings should be reinvestigated and reconfirmed in further studies in other countries.

Limitations

Several limitations should be acknowledged. First, a certain amount of the patients did not have complete data for the all three domains in the HFA-PEFF score (*Figure 1*). Missing data in the HFA-PEFF score reduced statistical power and caused selection bias. Even in parameters in the major criteria, there were missing data with a maximum proportion of 19.6% (171/871) in LAVI (*Figure 2*). Global longitudinal strain data, the minor criteria in the functional domain of the HFA-PEFF score, were not available in the PURSUIT-HFpEF registry. However, it was reported that added global longitudinal strain reclassified only 0.7% from a low to an intermediate likelihood-category in the US cohort,² suggesting that the influence of the strain data is limited. Because the study protocol basically recommended investigators to evaluate all the parameters in the domains except for the global longitudinal strain, it is highly probable that the missing data imply patient's severe illness. Therefore, our assumption (translation of the missing data to score 0) might have caused underestimation of the patients' risk. Not only the missing data but also scores of 0, 1, 2 did not mean low-risk group but did presumably mean high-risk population. *Figure 1* clearly shows the unreliability of the low score in this population. Although we excluded the patients with scores of missing, 0 and 1 from the main analysis in order to eliminate the statistical noise as much as possible, this methodology might have resulted in underestimation of the prognostic performance of the HFA-PEFF score. Nevertheless, our analysis with the imputed dataset also showed consistent results and therefore supports robustness of the findings. Second, we assessed but do not present the HFA-PEFF score on hospital admission. Lack of the data of LAVI on admission caused serious underestimation of the score. Because the score on admission was misleading, we did not evaluate the serial change of the score during hospitalization. Third, we did not assess the impact of the functional and etiological assessments (the last two steps of the algorithm) which could increase the prognostic significance of the score. Because the inclusion criteria of the present prospective registry were the diagnosis of acute decompensated heart failure, all patients have been diagnosed as HFpEF on hospital admission. Therefore, further functional testing and etiological tests that the HFA-PEFF diagnostic tool recommends were not basically performed. Even after the diagnosis of HFpEF, some examinations to assess the specific underlying aetiology would be

required. Some investigators performed cardiovascular magnetic resonance, cardiac biopsies, computed tomography, scintigraphy, and genetic testing. However, these examinations were not mandatory but optional in the present registry. We could not use these data systematically for the analysis. Lastly, the H₂FPEF score (body mass index > 30 kg/m², ≥2 antihypertensive medicines, paroxysmal, or persistent atrial fibrillation, Doppler echocardiographic estimated pulmonary artery systolic pressure >35 mmHg, Doppler echocardiographic E/e' > 9) was also recently introduced to our clinical practice as a diagnostic tool for HFpEF.¹⁰ We did not evaluate its prognostic significance in the present study. Especially, the cut-off value of body mass index of 30 might not be applicable for Asian population and would need to be fine-tuned. This will be the next scientific topic.

Conclusions

The HFA-PEFF score at discharge was significantly associated with the post-discharge clinical outcomes in acute decompensated heart failure patients with preserved ejection fraction. This study suggested the clinical usefulness of the HFA-PEFF score not only as a diagnostic tool but also a practical prognostic tool.

Conflict of interest

S. Hikoso received grants from Roche Diagnostics, FUJIFILM Toyama Chemical, Actelion Pharmaceuticals; personal fees from Daiichi Sankyo Company, Astellas Pharma, Bayer, Pfizer Pharmaceuticals, Boehringer Ingelheim Japan, Kowa Company, and Ono Pharmaceutical. D. Nakatani received

honoraria from Roche Diagnostics. Y. Sakata received personal fees from Otsuka Pharmaceutical, Ono Pharmaceutical, Daiichi Sankyo Company, Mitsubishi Tanabe Pharma Corporation, AstraZeneca K.K. and Actelion Pharmaceuticals, and received grants from Roche Diagnostic, FUJIFILM Toyama Chemical, Bristol-Myers Squibb, Co, Biosense Webster, Inc., Abbott Medical Japan, Otsuka Pharmaceutical, Daiichi Sankyo Company, Mitsubishi Tanabe Pharma Corporation, Astellas Pharma, Kowa Company, Boehringer Ingelheim Japan, and Biotronik. The other authors have nothing to disclose.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Survival analysis for the primary and secondary endpoints (original stratification of the HFA-PEFF score).

Figure S2. Survival analysis for the primary and secondary endpoints (imputed dataset).

Figure S3. Survival analysis for the primary and secondary endpoints (imputed dataset: original stratification of the HFA-PEFF score).

Table S1. Invasive hemodynamic evaluation (right heart catheterization).

Table S2. Prognostic significance of the HFA-PEFF score (imputed dataset).

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