International Journal of Cardiology 342 (2021) 43–48

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Performance of the H_2FPEF and the HFA-PEFF scores for the diagnosis of heart failure with preserved ejection fraction in Japanese patients: A report from the Japanese multicenter registry

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ARTICLE INFO

Keywords:
Decision support techniques
Heart failure with preserved ejection fraction
Diagnosis
Echocardiography

ABSTRACT

Background: Diagnosing heart failure with preserved ejection fraction (HFpEF) is challenging. Although the H_2FPEF score and HFA-PEFF algorithm have been proposed for diagnosing HFpEF, previous validation studies were conducted in stable chronic heart failure (HF). Moreover, information on their applicability in the Asian population is limited. We sought to investigate these scores' diagnostic performance for HFpEF in Japanese patients recently hospitalized due to acute decompensated HF.

Methods: We examined patients with HFpEF recently hospitalized with acute decompensated HF from a nationwide HFpEF-specific multicenter registry (HFpEF group) and control patients who underwent echocardiography to investigate the cause of dyspnea in our hospital (Non-HFpEF group).

Results: The studied population included 372 patients (194 HFpEF group and 178 Non-HFpEF group; HFpEF prevalence, 52%). A high H_2FPEF score (6–9 points) could diagnose HFpEF with a high specificity of 97% and a positive predictive value (PPV) of 94%, and a low H_2FPEF score (0–1 point) could rule out HFpEF with a high sensitivity of 97% and a negative predictive value (NPV) of 93%. HFpEF could be diagnosed with a high HFA-PEFF score (5–6 points) (specificity, 84%; PPV, 82%) or ruled out with a low HFA-PEFF score (0–1 point) (sensitivity, 99%; NPV, 89%). The H_2FPEF score was significantly superior to the HFA-PEFF score in diagnostic accuracy (area under the curve: 0.89 vs. 0.82, respectively, $p = 0.004$).

Conclusions: The H_2FPEF and the HFA-PEFF scores had acceptable diagnostic accuracy in diagnosing HFpEF in Japanese patients.

1. Introduction

Approximately half of the patients with heart failure (HF) have preserved left ventricular (LV) ejection fraction, and this proportion has increased over time [1]. The standard diagnosis of HF with preserved ejection fraction (HFpEF) is based on the following: 1) symptoms of HF, 2) preserved LV ejection fraction (LVEF, >50%), and 3) presence of LV diastolic dysfunction confirmed by echocardiography or cardiac catheterization [2]. Additionally, an elevated brain natriuretic peptide (BNP) level is useful in diagnosing HFpEF [3]. However, there are limits to the diagnostic accuracy of individual parameters, and what cut-off values should be applied and how they should be combined remain unclear.

Recently, two diagnostic algorithms for HFpEF have been developed and are currently available: the H_2FPEF score [4] and the HFA-PEFF algorithm [5]. The H_2FPEF score consists of six clinical and

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https://doi.org/10.1016/j.ijcard.2021.08.001
Received 22 June 2021; Received in revised form 27 July 2021; Accepted 2 August 2021
Available online 5 August 2021
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echocardiographic variables, and the total score is calculated. The HFA-PEFF algorithm is a multistep approach. In the first step, the possibility of HFpEF is suspected based on symptoms and signs of HF and clinical examination. In the second step, the HFA-PEFF score is calculated by sub-scores (functional, morphological, and biomarker) obtained by echocardiography and BNP. Both scores are classified as having a low, intermediate, or high likelihood of HFpEF depending on the total score.

The external validity of the H_2FPEF score [6] and the HFA-PEFF score [7] has been tested and may be generally applicable. Nonetheless, since these validation studies were conducted on patients with stable chronic HF, the diagnostic accuracy for HFpEF lacked robustness. Furthermore, these validation cohorts mostly consisted of the Western population, although only a few studies have reported on the validity of these scores in the Asian population [8,9]. In Western countries, patients with HFpEF are predominantly obese/overweight and have hypertension, diabetes mellitus, chronic obstructive pulmonary disease, and renal failure [10–12]. Meanwhile, being elderly with atrial fibrillation (AF), metabolic, and diabetic with low body mass index (BMI) is more common in Asian patients with HFpEF [13,14]. Therefore, the characteristics and phenotypes of HFpEF would differ between the Western and Asian populations.

Accordingly, this study aimed to investigate the diagnostic performance of the H_2FPEF and HFA-PEFF scores in Japanese patients with HFpEF who had recently developed acute decompensated HF.

2. Methods

2.1. Study design and population

2.1.1. HFpEF group

Data from the Japanese Heart Failure Syndrome with Preserved Ejection Fraction registry (JASPER), obtained between November 2012 and March 2015, were analyzed. Details of the JASPER registry have been described elsewhere [14]. Briefly, the study is a multicenter, observational, prospective cohort that included consecutive patients aged ≥20 years requiring hospitalization with a diagnosis of acute decompensated HF according to the Framingham criteria [15] by at least two experienced cardiologists, with preserved LV systolic function defined as LVEF ≥50% by the modified Simpson method or LV fractional shortening ≥25% by echocardiography. Patients with acute coronary syndrome, receiving hemodialysis, or with a history of heart transplantation or severe valvular heart disease were excluded. From the 535 patients enrolled in the JASPER registry, those without echocardiography data at discharge and with incalculable H_2FPEF or HFA-PEFF scores were excluded. Ultimately, 194 patients were eligible for the HFpEF group (Supplementary Fig. S1). This study was approved by the Institutional Review Board of each site and registered under the Japanese UMIN Clinical Trials Registration (UMIN000010601).

2.1.2. Non-HFpEF group

A total of 322 consecutive patients who underwent echocardiography to investigate the cause of dyspnea in the Hokkaido University Hospital between November 2012 and December 2020 were analyzed. Of the 322 patients, those with a history/presence of HF or missing BNP data were excluded by board-certified cardiologists based on the current HF guidelines [16,17]. Ultimately, 178 patients were eligible for the Non-HFpEF group (Supplementary Fig. S1). This part of the study was approved by the Institutional Review Board of the Hokkaido University Hospital (No. 020–0424).

2.2. Calculation of diagnostic scores for HFpEF

2.2.1. H_2FPEF score

The H_2FPEF score consists of six clinical and echocardiographic variables. The presence of paroxysmal or persistent AF is worth 3 points, BMI > 30 kg/m^2 is worth 2 points, and all other criteria (age ≥ 60 years, treatment with ≥2 antihypertensives, echocardiographic E/e´ ratio > 9, and echocardiographic pulmonary artery systolic pressure (PASP) >35 mmHg) are worth 1 point each. The total score was classified as low likelihood score (0–1 point), intermediate likelihood score (2–5 points), and high likelihood score (6–9 points), based on the previously reported cut-off criteria [4].

2.2.2. HFA-PEFF score

All patients met the pre-test assessment suggested in the first step of the HFA-PEFF algorithm. In the second step of the algorithm, the total score for each sub-score (2 points each for functional, morphological, and biomarker) was calculated. The total score was classified as low likelihood score (0–1 point), intermediate likelihood score (2–4 points), and high likelihood score (5–6 points), according to the cut-off criteria previously described [5]. Global longitudinal strain (GLS), one of the functional scores, was not available in this study. The third step (echocardiography or invasive hemodynamic exercise stress test) and fourth step (further investigations of the final etiology of HFpEF) suggested by the HFA-PEFF score were not performed in this study.

2.3. Statistical analyses

Continuous variables are presented as mean ± SD when normally distributed, and as median and interquartile range when non-normally distributed. Unpaired *t*-test or Mann-Whitney *U* test were conducted for continuous variables and by chi-squared test or Fisher's exact test for dichotomous variables, when appropriate, to compare the differences between groups. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the scores were calculated using two approaches: (i) "rule-out" approach (both the intermediate and high score categories as "positive"), and (ii) "rule-in" approach (only the high score category as "positive"). Moreover, the predictive values were calculated considering the prevalence of the disease. Receiver operating characteristic (ROC) curves and area under the curve (AUC) were computed to compare the diagnostic accuracy of the H_2FPEF and HFA-PEFF scores. All tests were two-tailed, and a value of $p < 0.05$ was considered significant. All analysis was performed using the Stata MP64 version 16 (StataCorp, College Station, TX).

3. Results

The studied population included 372 patients (194 HFpEF group and 178 Non-HFpEF group; HFpEF prevalence, 52%). The baseline characteristics of both groups are shown in Table 1. The distributions of the H_2FPEF and the HFA-PEFF scores were significantly different between both groups ($p < 0.001$) (Fig. 1A and B). Breakdown of variables for the H_2FPEF and the HFA-PEFF scores are shown in Supplementary Tables S1 and S2, respectively.

3.1. Diagnostic performance of the H_2FPEF score

The H_2FPEF score classified 86/372 (23%) of all patients into the high likelihood category, 84/372 (23%) into the low likelihood category, and 202/372 (54%) into the intermediate category (Fig. 2A). A high H_2FPEF score (6–9 points) could diagnose HFpEF with high specificity of 97% and PPV of 94%, and a low H_2FPEF score (0–1 point) could rule out HFpEF with high sensitivity of 97% and NPV of 93% (Supplementary Table S3 and Fig. 2A). The sensitivity, specificity, PPV, and NPV for each score obtained from the diagnostic score for HFpEF are shown in Supplementary Table S4. In the H_2FPEF score, specificity was maintained up to the cut-off value of ≥4 points.

3.2. Diagnostic performance of the HFA-PEFF score

The HFA-PEFF score classified 155/372 (42%) of all patients into the high likelihood category, only 19/372 (5%) into the low likelihood

category, and 198/372 (53%) into the intermediate category (Fig. 2B). HFpEF could be diagnosed with a high HFA-PEFF score (5–6 points; specificity, 84%; PPV, 82%) and ruled out with a low HFA-PEFF score (0–1 point; sensitivity, 99%; NPV, 89%) (Supplementary Table S3, Fig. 2B).

3.3. Diagnostic accuracy of each score

The diagnostic accuracy based on the AUC of the ROC curve was 0.89 (0.86–0.93) for the total H_2FPEF score and 0.82 (0.78–0.86) for the total HFA-PEFF score, with the H_2FPEF score having superior diagnostic accuracy (Fig. 3A). In the HFA-PEFF sub-score, the functional score showed little diagnostic value, while the morphological and biomarker scores showed moderate diagnostic value (Fig. 3B).

4. Discussion

The major findings of this study were as follows: 1) using the H_2FPEF score, the "rule-in" approach could diagnose HFpEF with high specificity (97%), and the "rule-out" approach could exclude HFpEF with high sensitivity (97%); 2) using the HFA-PEFF score, the "rule-in" approach was only able to diagnose HFpEF with a specificity of 84%, and the "rule-out" approach could exclude HFpEF with high sensitivity (99%); and 3) the H_2FPEF score was significantly superior to the HFA-PEFF score in terms of diagnostic accuracy.

The HFA-PEFF score showed excellent diagnostic performance (AUC, 0.90) in an external validation study [7], which was in contrast to that in the present study. This difference may be attributed to the relatively low diagnostic accuracy of each sub-score, especially the functional score in the present study (AUC, 0.54) (Fig. 3B). Previous reports have shown similarly low diagnostic accuracy (AUC, 0.56) for functional scores [7], indicating that there may be room for improvement in the current score assessment. Here, 84% of all patients were classified into the "major" criteria, which may be predominantly due to the inclusion of PASP >35 mmHg criteria in the functional score. In fact, among the patients classified into PASP >35 mmHg, 31/100 (31%) belonged to the Non-HFpEF group (Supplementary Table S2). This may be a limitation of the score in assessing the possibility of HFpEF in patients with dyspnea. Meanwhile, the morphological score in our study had a slightly worse diagnostic accuracy than that in a previous report [7]. A breakdown of the morphological score showed that 55% of our patients were classified as having a left atrial volume index (LAVI) >34 mL/m^2 (Supplementary Table S2). An LAVI >34 mL/m^2 is suitable for discriminating the boundary between a normal and an enlarged left atrium in terms of prognostic risk [18,19]. The median LAVI of the HFpEF groups in the previous study was 46 mL/m^2 in the Maastricht cohort and 31 mL/m^2 in the Northwestern (Chicago) cohort [7], whereas the LAVI in the present study was larger at 57 mL/m^2. Since LAVI is calculated by dividing the left atrial volume by body surface area (BSA), the LAVI can be larger in patients with a low BSA. In the previous study, the BSA values of the HF group were 2.12 ± 0.29 m^2 in the United States and 1.91 ± 0.23 m^2 in France [20], while it was 1.52 ± 0.21 m^2 in the present study. Therefore, Japanese patients with HFpEF have a relatively larger LAVI than Western patients and are prone to overestimation of the morphological score in the HFA-PEFF score. Because the BSA of patients with HF in other Asian countries is also lower than that of Western patients [20], the application of our findings may expand to other Asian countries. Furthermore, the biomarker score showed a diagnostic accuracy close to the total score, which is consistent with evidence that BNP has superior value in ruling out HF [21].

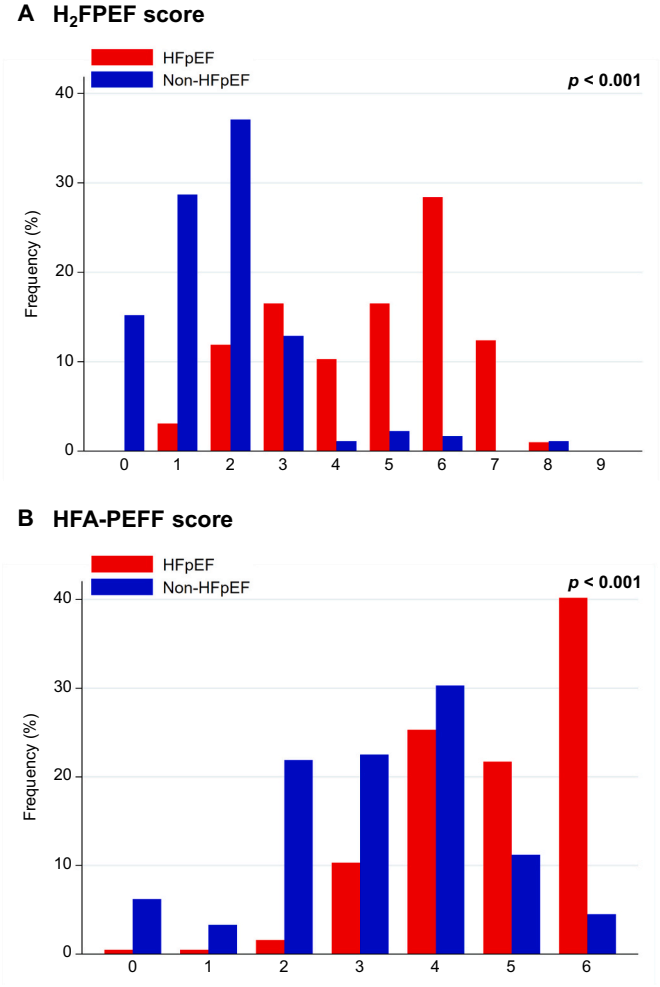


Fig. 1. The distribution of the diagnostic scores for HFpEF.
HFpEF = heart failure with preserved ejection fraction.

Here, a high H_2FPEF score and a low H_2FPEF score had excellent PPV and NPV, respectively. The diagnostic accuracy of the H_2FPEF score was comparable to that of the validation cohort (AUC, 0.88) [4]. One reason may be that the H_2FPEF score was set with loading on the presence of AF. Most patients with AF (117/122; 96%) were in the HFpEF group (Supplementary Table S1), indicating that the high prevalence of AF contributes to the diagnosis of HFpEF in our cohort. Indeed, Japanese HF patients predominantly have elderly / AF morbidity among those in the Asian countries [13]. In contrast, only 25/322 (7%) of all patients were classified into the BMI > 30 kg/m^2 category (Fig. 2A and Supplementary Table S1). In the United States and European countries, obesity is one of the most common phenotypes of HFpEF [10,22,23], and a load of 2 points is assigned in the H_2FPEF score. However, in the Japanese population, HFpEF complicated by obesity is rare, and being underweight is relatively common [14,24]. Moreover, a small number of patients (9/194; 5%) obtained 2 points for the BMI > 30 kg/m^2 category in our HFpEF patients (Supplementary Table S1), resulting in only two patients with the H_2FPEF score of 8–9 points.

Our current investigation has several clinical implications. In Japanese patients, the H_2FPEF score can be used to confirm or exclude HFpEF with high accuracy, which is consistent with previous validation studies on the Western population. Furthermore, the HFA-PEFF score is a complex algorithm involving multiple cut-off values, while the H_2FPEF score is simple, allowing easy calculation of scores at bedside and rapid screening. Nevertheless, approximately 54% of all patients had an intermediate H_2FPEF score in the present study. In such patients, exercise-induced echocardiography or invasive cardiac hemodynamic measurements would be recommended for the final diagnosis. In the original validation study, the cut-off value for rule-in was set to 6 [4]. However, we found that reasonable specificity was maintained even when the cut-off value was lowered to 4. If this is adapted, the number of patients with H_2FPEF scores classified as intermediate category will decrease, and

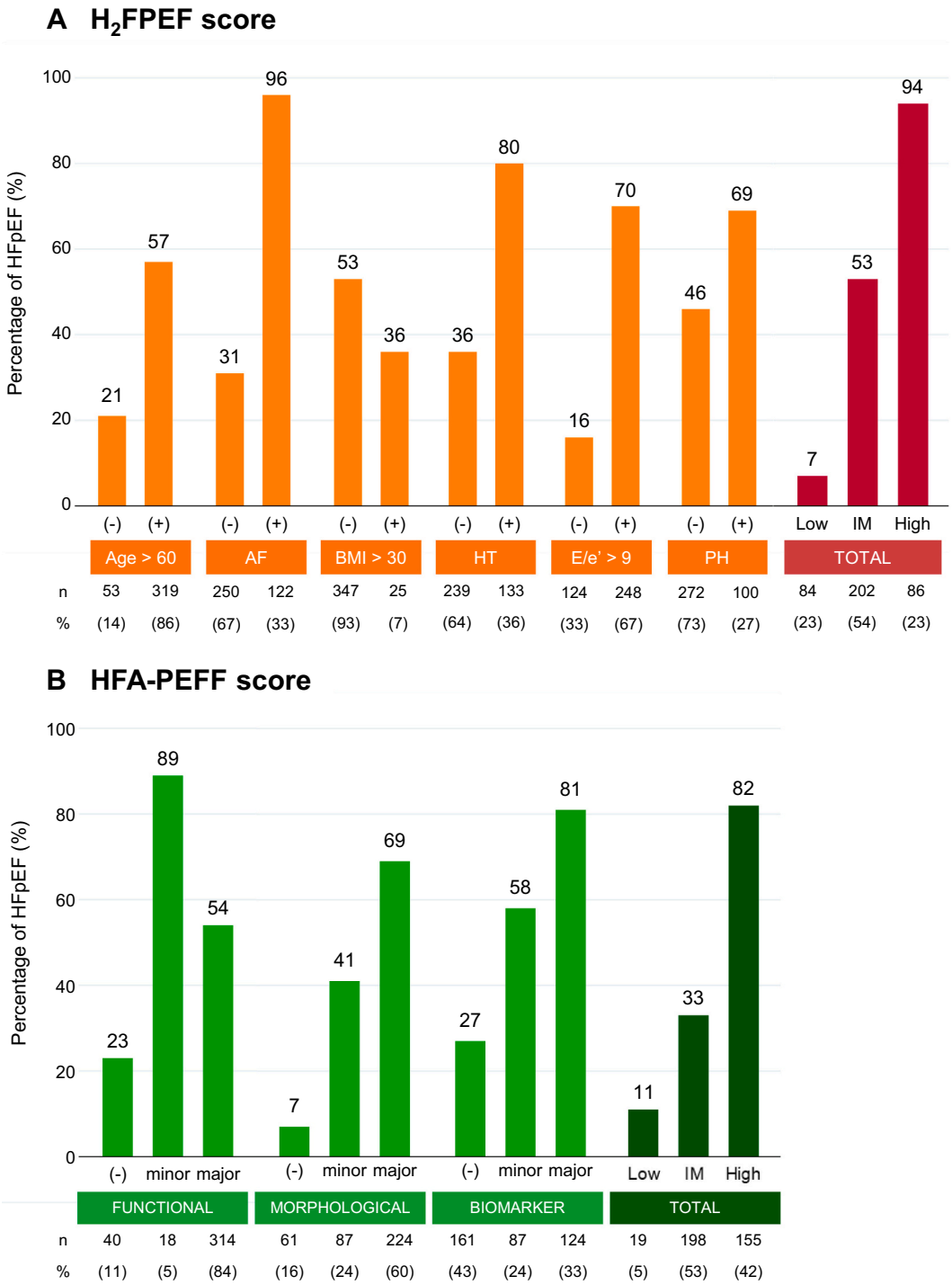


Fig. 2. Percentage of HFpEF for sub-scores and total score categories.
AF = atrial fibrillation; BMI = body mass index; HFpEF = heart failure with preserved ejection fraction; HT = hypertension; IM = intermediate; PH = pulmonary hypertension.

they may be correctly reclassified into the high score group without invasive diagnostic testing.

4.1. Strength and limitations

The strength of our study is the robustness in diagnosing HFpEF because the entire cohort was recently hospitalized due to acute decompensated HF, despite we did not perform invasive hemodynamic assessment. Although a study comparing HFpEF scores with invasive hemodynamic assessment has been reported [25], the cohorts of chronic HFpEF in the previous validation studies are often questioned as to whether patients are correctly diagnosed with HFpEF. There are several potential limitations of the present study which should be acknowledged. First, the sample size was relatively small, thereby limiting the ability to generalize the findings and the statistical power for detecting differences in negative data. Therefore, larger-scale prospective studies

Table 1
Baseline characteristics.

Variables	HFpEF group (n = 194)	Non-HFpEF group (n = 178)	p-Value
Age (years)	77 ± 10	66 ± 14	<0.001
Male, n (%)	92 (47)	81 (46)	0.71
Body mass index, kg/m^2	22.3 ± 4.4	23.8 ± 4.6	0.002
Body surface area, m^2	1.52 ± 0.21	1.60 ± 0.20	<0.001
NYHA class III or IV, n (%)	15 (8)	N/A	–
Heart rate, beats/min	66 ± 11	72 ± 13	<0.001
Systolic blood pressure, mmHg	115 ± 17	128 ± 21	<0.001
Past history, n (%)			
Hypertension	159 (82)	61 (34)	<0.001
Diabetes mellitus	77 (40)	32 (18)	<0.001
Hyperlipidemia	81 (42)	50 (28)	0.005
Stroke	41 (21)	4 (2)	<0.001
COPD	12 (6)	15 (8)	0.41
Atrial fibrillation	117 (60)	5 (3)	<0.001
Heart failure	64 (33)	0 (0)	<0.001
Medications, n (%)			
ACE inhibitors / ARBs	114 (59)	43 (24)	<0.001
Beta-blockers	128 (66)	12 (7)	<0.001
Calcium channel blocker	107 (55)	43 (24)	<0.001
MRAs	68 (35)	6 (3)	<0.001
Loop diuretics	156 (80)	9 (5)	<0.001
Statin	60 (31)	34 (19)	0.009
Laboratory data			
Hemoglobin, g/dL	11.6 ± 2.0	12.7 ± 1.9	<0.001
Sodium, mEq/L	139.0 ± 3.4	139.5 ± 2.6	0.132
Potassium, mEq/L	4.4 ± 0.5	4.2 ± 0.5	0.001
BUN, mg/dL	26 (19–37)	16 (12–20)	<0.001
Creatinine, mg/dL	1.1 (0.8–1.5)	0.8 (0.6–1.0)	<0.001
Albumin, g/dL	3.7 ± 0.4	3.9 ± 0.5	<0.001
BNP, pg/mL	169 (83–323)	23 (11–48)	<0.001
Echocardiographic parameters			
LVEF, %	61 ± 9	66 ± 6	<0.001
LVDD, mm	47 ± 7	44 ± 5	<0.001
LVPWD, mm	11 ± 2	8 ± 1	<0.001
LVIVSD, mm	11 ± 4	8 ± 1	<0.001
LAVI, mL/m^2	57 (43–73)	31 (23–39)	<0.001
LVMI, g/m^2	122 ± 44	79 ± 20	<0.001
E wave, cm/s	81 (64–107)	62 (53–76)	<0.001
e' (septum), cm/s	5.1 (3.8–6.5)	6.2 (5.0–8.0)	<0.001
DcT, ms	222 ± 78	223 ± 51	0.98
E/e'	17 (12–22)	8 (7–10)	<0.001
PASP, mmHg	33 ± 11	30 ± 10	0.003
IVCD, mm	16 ± 6	12 ± 3	<0.001

Values are mean ± standard deviation, median (interquartile range) or percentages. ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker; BNP = brain natriuretic peptide; BUN = blood urea nitrogen; COPD = chronic obstructive pulmonary disease; DcT = deceleration time of early-diastolic flow; HFpEF = heart failure with preserved ejection fraction; IVCD = inferior vena cava diameter; LAVI = left atrial volume index; LVDD = LV diastolic diameter; LVEF = left ventricular (LV) ejection fraction; LVIVSD = LV intraventricular septum diameter; LVMI = LV mass index; LVPWD = LV posterior wall diameter; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; PASP = pulmonary artery systolic pressure.

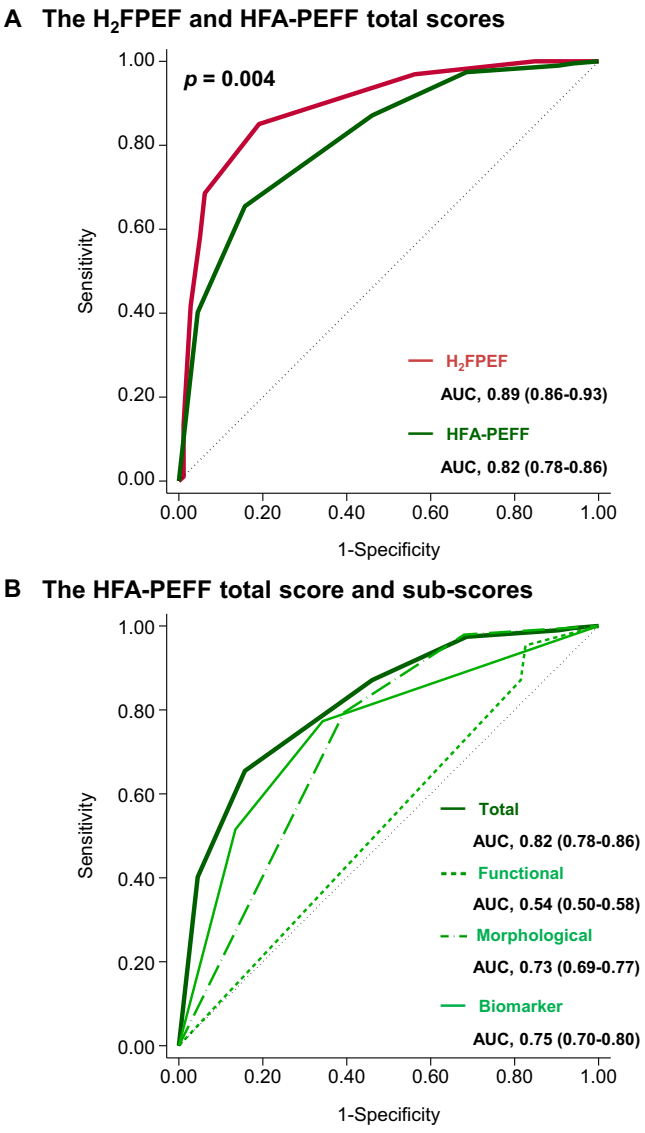


Fig. 3. Receiver operating characteristic curves of the diagnostic scores for HFpEF.
HFpEF = heart failure with preserved ejection fraction.

are warranted to confirm the validity of the diagnostic scores for HFpEF in the Japanese population. Second, our study had unavoidable selection bias since we excluded patients who had no echocardiographic data at discharge or those without the data for calculating HFpEF diagnostic scores, although variables other than the echocardiographic findings were comparable between the excluded population and the study population (Supplementary Table S5). Third, our current analysis using the cohorts in this study could be somewhat artificial since the HFpEF and Non-HFpEF groups were composed of patients with a prior diagnosis of HF and those without HF, respectively. Therefore, prospective studies are warranted to assess the validity of these scores in patients with unexplained dyspnea. Fourth, approximately 17% of the patients in the Non-HFpEF group had a PASP of >35 mmHg. Moreover, invasive hemodynamic assessment and exercise testing were not performed in Non-HFpEF group. Given that the patients underwent echocardiography for dyspnea, the presence of pulmonary heart disease or subclinical HF cannot be excluded, although the median BNP was low at 23 pg/mL. Fifth, 64 patients (33%) in the HFpEF group had a history of HF, and therefore many patients belonged to the high-risk category. Sixth, although this study showed the accuracy of "rule-out" and "rule-in" in each HFpEF diagnostic score, we did not evaluate the intermediate group with additional tests such as hemodynamic assessment. In this study, more than 50% of patients for both HFpEF diagnostic scores were classified in the intermediate-risk category, indicating that hemodynamic assessment is necessary for the intermediate-risk category in actual clinical practice. Seventh, this study was conducted primarily in Japanese patients, and the results may not be applicable to the entire Asian population. In fact, it has been reported that the characteristics and phenotypes of HFpEF are different among Asian countries [13]. Finally, GLS was not available in this study. If the GLS criteria were met, 40 patients (11%) with a functional score of zero could be upgraded to the "minor" criteria in the HFA-PEFF score. Indeed, seven patients (1.9%) could be changed from a low- to an intermediate-risk category and one patient (0.3%) could be changed from an intermediate to a high-risk category. In addition, there were no significant differences in c-

statistics for the HFA-PEFF scores regardless of the availability of GLS (GLS−; 0.817 [0.776 to 0.859], GLS+; 0.819 [0.778 to 0.860], $p = 0.67$).

5. Conclusions

The H_2FPEF and the HFA-PEFF scores had acceptable specificity and sensitivity for the diagnosis and exclusion of HFpEF. These scores may be useful for diagnosing HFpEF in Japanese patients.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2021.08.001.

Funding

This work was supported by a grant from the Japan Cardiovascular Research Foundation (T.A., 24-4-2), a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (JSPS KAKENHI) (T.N., 18K08122) and a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (JSPS KAKENHI) (T. A., 20H03670).

Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

Acknowledgments

The authors are grateful for the contributions of all the investigators, clinical research coordinators, and data managers involved in the JASPER registry.

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