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Generalizability of HFA-PEFF and H_2FPEF Diagnostic Algorithms and Associations With Heart Failure Indices and Proteomic Biomarkers: Insights From PROMIS-HFpEF

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ABSTRACT

Background: Diagnosing heart failure with preserved ejection fraction (HFpEF) remains challenging. We aimed to evaluate the generalizability of the HFA-PEFF (Heart Failure Association Pre-test assessment, Echocardiography & natriuretic peptide, Functional testing, Final etiology) and weighted H_2FPEF (Heavy, 2 or more Hypertensive drugs, atrial Fibrillation, Pulmonary hypertension, Elder age > 60, elevated Filling pressures) diagnostic algorithms and associations with HF severity, coronary microvascular dysfunction and proteomic biomarkers.

Methods and Results: Diagnostic likelihood of HFpEF was calculated in the prospective, multinational PROMIS-HFpEF (Prevalence of microvascular dysfunction in HFpEF) cohort using current European Society of Cardiology recommendations, HFA-PEFF and H_2FPEF algorithms. Associations between the 2 algorithms and left atrial function, Doppler-based coronary flow reserve, 6-minute walk test, quality of life, and proteomic biomarkers were investigated. Of 181 patients with an EF of ≥50%, 129 (71%) and 94 (52%) fulfilled criteria for high likelihood HFpEF as per HFA-PEFF and H_2FPEF, and 28% and 46% were classified as intermediate likelihood, requiring additional hemodynamic testing. High likelihood HFpEF patients were older with higher prevalence of atrial fibrillation and lower global longitudinal strain and left atrial reservoir strain ($P < .001$ for all variables). left atrial reservoir strain and global longitudinal strain were inversely associated with both HFA-PEFF and H_2FPEF scores (TauB = −0.35 and −0.46 and −0.21 and −0.31; $P < .001$ for all). There were no associations between scoring and 6-minute walk test, quality of life, and coronary flow reserve. Both scores were associated with biomarkers related to inflammation, oxidative stress, and fibrosis.

Conclusions: Although the HFA-PEFF and H_2FPEF scores were associated with measures of HF severity and biomarkers related to HFpEF, they demonstrated a modest and differential ability to identify HFpEF noninvasively, necessitating additional functional testing to confirm the diagnosis. (*J Cardiac Fail 2021;00:1−10*)

Key Words: Heart failure, HFpEF, HFA-PEFF, H2FPEF, diagnosis.

Heart failure (HF) with preserved ejection fraction (HFpEF) accounts for more than one-half of all HF admissions and imposes significant health burden worldwide.[1] Accurate diagnosis remains challenging and optimal selection for clinical trials and potential targeted therapy is difficult owing to the heterogeneity of this syndrome.

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In 2016, the European Society of Cardiology (ESC) recommended a diagnostic algorithm for HFpEF.[2] Since then, 2 scoring systems have been published to purportedly improve diagnosis in patients with suspected HF and an EF of ≥50%.The HFA-PEFF (Heart Failure Association Pretest assessment, Echocardiography & natriuretic peptide, Functional testing, Final etiology)[3] algorithm is a stepwise approach based on expert consensus spanning all levels of care from initial assessment till specialized tests to establish diagnosis in patients with suspected HFpEF. The weighted-criteria H_2FPEF[4] (Heavy, 2 or more Hypertensive drugs, atrial Fibrillation, Pulmonary hypertension, Elder age >60, elevated Filling pressures) score, derived from retrospective analysis of patients undergoing invasive exercise testing, proposes a composite score based primarily on clinical characteristics and echocardiography to establish a low, intermediate, and high likelihood of HFpEF.

Although both scores have subsequently been validated in populations with unexplained dyspnoea,[5–7] their ability to accurately represent HFpEF in more stringently selected populations is unknown. Given that patients classified as intermediate likelihood require additional invasive hemodynamic testing that entails relative technical complexity, costs, and risks (in a syndrome with no specific therapy), these diagnostic algorithms should, hypothetically, minimize the indeterminate classification in well-defined HFpEF cohorts. Further, studies exploring score the associations with the clinical, echocardiographic, and functional markers of HF severity are limited and do not include measures of coronary microvascular dysfunction (CMD), a proposed pathophysiological marker of HFpEF.

With this background, we aimed to (a) study the generalizability of these scoring models and (b) evaluate associations with measures of HF severity and CMD, biomarkers related to cardiovascular disease, functional capacity and quality of life in the multinational PROMIS-HFpEF (Prevalence of Microvascular Dysfunction in HFpEF) cohort.

Methods

Patient Population

PROMIS-HFpEF was designed as a prospective, multicenter, multinational observational study recruiting patients fulfilling strict criteria for HFpEF with the aim of assessing the prevalence of CMD measured by coronary flow reserve (CFR).[8] Details regarding selection criteria and study design have been previously reported.[9] Patients were included from 5 centers in 4 countries (Turku, Finland; Singapore; Stockholm, Sweden; Gothenburg, Sweden; and Chicago, USA). Inclusion criteria included symptomatic HF with New York Heart Association functional class II to IV, an EF of ≥40%, and one of the following: (i) prior hospitalization with evidence of left ventricular (LV) hypertrophy (LV mass index of >95 g/m^2 in women and >115 g/m^2 in men) or left atrial (LA) dilation (LA volume index of >34 mL/m^2), (ii) elevated natriuretic peptides (brain natriuretic peptide [BNP]; outpatient sinus rhythm of ≥75; atrial fibrillation of ≥200; hospitalized sinus rhythm of ≥125; atrial fibrillation of ≥350 ng/L; N-terminal pro-BNP [NT-proBNP]; outpatient sinus rhythm of ≥300; atrial fibrillation of ≥750; hospitalized sinus rhythm of ≥500; and atrial fibrillation of ≥1250 ng/L), (iii) E/e' of ratio ≥15, (iv) elevated invasive capillary wedge pressures at rest (>15 mm Hg) or with exercise (>25 mm Hg). In the present study, only patients with an EF of ≥50% were included in keeping with HFpEF definition in the 2016 ESC HF Guidelines,[2] and as used in the scoring models.[3,4] Patients with unrevascularized epicardial coronary disease were excluded in PROMIS-HFpEF as the primary aim was to assess CMD. All patients were assessed regarding medical history and underwent a physical examination, fasting blood and urine tests, 6-minute walk test, Kansas City Cardiomyopathy Questionnaire, and comprehensive transthoracic echocardiography which included LV global longitudinal strain (GLS) and LA reservoir strain analysis. CMD was assessed using transthoracic Doppler-derived CFR as per validated protocol.[10] The study complied with the Declaration of Helsinki and was approved by each institutional review board. All patients provided written informed consent.

Measurement of HFpEF Diagnostic Algorithms

Among patients included in the PROMIS-HFpEF as per specific criteria as mentioned elsewhere in this article, assessment of HFpEF was performed using the algorithm recommended by current 2016 ESC HF Guidelines,[2] in addition to calculating diagnostic likelihood by the HFA-PEFF[3] and H_2FPEF[4] models. The guideline-based algorithm classified patients as having HFpEF if they demonstrated elevated levels of NP (BNP of >35 pg/mL and/or NT-proBNP of >125 pg/mL) in addition to objective evidence of cardiac structural alterations as previously described.[2] Thus, it was possible to be included in PROMIS-HFpEF (by meeting biomarker or imaging criteria but not both, or by meeting invasive criteria but not biomarker or imaging criteria) without meeting all noninvasive ESC HF guideline criteria. Assessment of the HFA-PEFF[3] score in the PROMIS-HFpEF cohort was limited to step 2 of the algorithm, which identifies major and minor diagnostic criteria considering functional, structural, and biomarker domains. Step 3, which requires echocardiographic or invasive stress testing, was not available in PROMIS. Briefly, the functional domain considered age-specific cut-offs for myocardial early diastolic velocity (e'), ratio of peak mitral inflow velocity to average of septal and lateral e' (E/e'), tricuspid regurgitation velocity or pulmonary artery systolic pressure, and GLS. The morphologic domain considered rhythm-specific LA volume, wall thickness measures, and sex-specific measures of LV mass; and the biomarker domain considered rhythm-specific levels of BNP or NT-proBNP. Each domain provided a maximum of 2 points, with a maximum overall score of 6. Patients with a total score of 0 to 1 were classified as low, 2 to 4 as intermediate, and 5 or more as high likelihood for HFpEF. The H_2FPEF[4]

score was calculated using a weighted aggregate of 6 clinical and echocardiographic variables universally obtained during patient evaluation: obesity (body mass index of >30 kg/m^2) = 2 points, atrial fibrillation = 3 points, age >60 years = 1 point, hypertension treated with ≥2 antihypertensive drugs = 1 point and Doppler-based pulmonary artery systolic pressure of >35 mm Hg = 1 point. Patients with a score of 0 to 1 were classified as low, 2 to 5 as intermediate, and 6 to 9 as high likelihood for HFpEF.

Biomarker Assays

Fasting blood samples were taken from patients in a stable condition and euvolemic state, collected in chilled EDTA tubes, immediately centrifuged at 4°C and stored in aliquots at −70°C until analysis. Biomarker analysis was performed using high-throughput proximity extension assays (Olink Proseek Multiplex CVD II and III, and inflammation 96 × 96 kits).

Statistical Analysis

Proportions of PROMIS patients meeting HFpEF criteria according to the ESC Guidelines and the 2 scores are presented as percentages. Continuous patient data are presented as median and interquartile range (IQR) and categorical data as number and percentage. Comparisons between patients with high vs low or intermediate likelihood of HFpEF (HFA-PEFF score 0−4 vs 5−6 and or H_2FPEF score 0−5 vs 6−9) were performed using the Mann−Whitney *U* test or Fisher's exact test as appropriate. Score distribution was calculated in all patients and subgrouped based on sex. Associations between the 2 scoring models and respective scores and NT-proBNP, LA volume index, LA reservoir strain, CFR, 6-minute walk test, Kansas City Cardiomyopathy Questionnaire, and proteomic biomarkers were analyzed with Kendall's rank correlation coefficient and presented as TauB, accounting for ties. Tests were performed at 95% confidence intervals and, owing to multiple testing, Bonferroni-adjusted significance levels were applied. For analyses between patients with high- vs low or intermediate-likelihood of HFpEF a 2-sided *P* Value of <.001 (0.05/48) was applied, for correlation analyses between the 2 scoring models and measures of HF severity or functional capacity a *P* value of <.004 (0.05/14) and for the biomarker analyses a *P* value of .0002 (0.05/248 proteins). STATA version 14.2 (Stata Corp., College Station, TX) was used for analysis.

Results

Patient Characteristics and Score Distribution

Of the 202 patients that underwent successful CFR, 181 patients had an EF of ≥50% and were analyzed (Fig. 1). In total, 83% fulfilled HFpEF noninvasive criteria as per ESC guidelines.[2] Of the patients who did not fulfil criteria, one-third (11/30 [36%]) were included in PROMIS-HFpEF based on a prior history of increased filling pressures on invasive haemodynamic testing and the remainder by meeting biomarker or imaging but not both criteria.

The median for HFA-PEFF and H_2FPEF score were 5 (IQR 4−6) and 6 (IQR 4−7) points, respectively. A majority (129

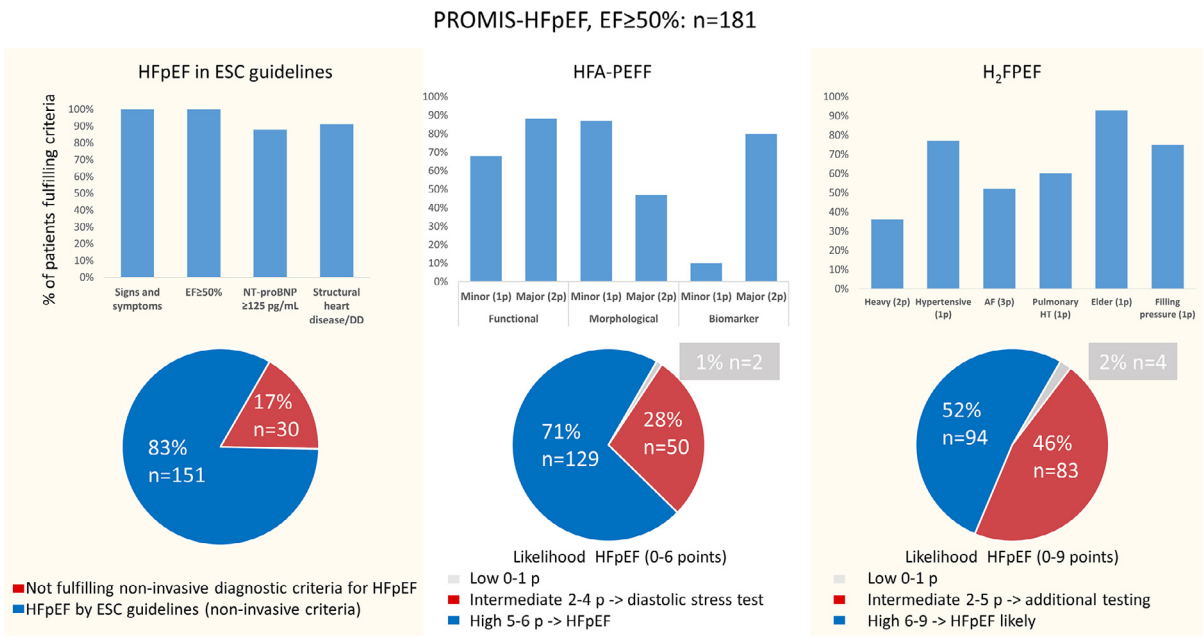

Fig. 1. HFpEF likelihood based on ESC guidelines, HFA-PEFF and H_2FPEF algorithms in PROMIS-HFpEF in addition to scoring distribution by domain/criteria. Of 202 individuals in PROMIS-HFpEF, 21 were excluded owing to an EF of <50% ($n = 18$) or EF missing ($n = 3$). AF, atrial fibrillation; BMI, body mass index; DD, diastolic dysfunction; EF, ejection fraction; ESC, European Society of Cardiology; GLS, global longitudinal strain; HFpEF, heart failure with preserved ejection fraction; LAVI, left atrial volume index; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro B-type natriuretic peptide; PASP, pulmonary artery systolic pressure; TRV, tricuspid regurgitation velocity.

patients [71%]) scored 5 or 6 on the HFA-PEFF score, indicating confirmed HFpEF without the need for additional invasive testing. However, only 52% of the patients (n = 94) demonstrated a corresponding H_2FPEF score of 6 to 9 points. In 45% of the patients (n = 81), both scores indicated high likelihood of HFpEF. When subgrouping by sex, 69 women (67%) vs 60 men (77%) (P = .22) scored as high likelihood by the HFA-PEFF. Corresponding data for H_2FPEF were 49 women (48%) vs 60 men (58%) (P = .185). A negligible few suggested low likelihood of HFpEF in this cohort using either scores (Figs. 1 and 2). There were regional differences in scoring with a median HFA-PEFF score of 5.5 (IQR 5−6) in patients from Finland (n = 34 [19%]), 5 (IQR 4−6) in patients from Singapore (n = 17 [9%]), 6 (IQR 5−6) in patients from Sweden (n = 82 [45%]), and 4 (IQR 3−5) in patients from the United States (n = 48 [27%]) (P < .001). Corresponding data for the H_2FPEF were for Finland 6 (IQR 5−8), Singapore 4 (IQR 4−7), Sweden 6 (IQR 4−7), and the United States 5 (IQR 3, 5−6) (P = .032). Baseline characteristics of the patients from the different countries are shown in Appendix Table 1.The prevalence of AF was lower in patients recruited in Singapore and the United States, whereas the patients from the United States had higher BMI and were younger.

Regarding score distribution within HFA-PEFF, a majority of patients scored 2 points in functional (n = 159 [88%]) and biomarker (n = 141 [78%]) domains. Fewer than one-half the patients fulfilled major criteria in the morphologic domain (n = 88 [49%]). When considering the H_2FPEF score, 66 patients (36%) received 2 points for a BMI of >30 kg/m^2, 140 (77%) 1 point for hypertension, 94 patients (52%) 3 points for AF, 108 patients (60%) 1 point for a pulmonary artery systolic pressure of >35 mm Hg, 171 patients (93%) 1 point for age >60 years, and 136 patients (75%) 1 point for an E/e' average of >9 (Fig. 1). Point distribution in the 2 scoring models, in addition to overlaps between and correlations between diagnostic algorithms are presented in Fig 2 a−d. Using the HFA-PEFF score, a progressive increase in patient proportion was observed with each additional point, but a normal distribution was observed in the H_2FPEF score. The 2 scores correlated weakly (TauB 0.29, P < .001).

A comparison between patients defined as having HFpEF as per the ESC noninvasive algorithm and those who required further testing, in addition to between low or intermediate-likelihood vs high-likelihood of having HFpEF based on the 2 models, are shown in Table 1. In general, patients with a lower score on the 2 models were younger and less likely to have AF. They had lower blood pressure and NT-proBNP readings as compared with those with high HFpEF probability. Echocardiographic data, CFR, and

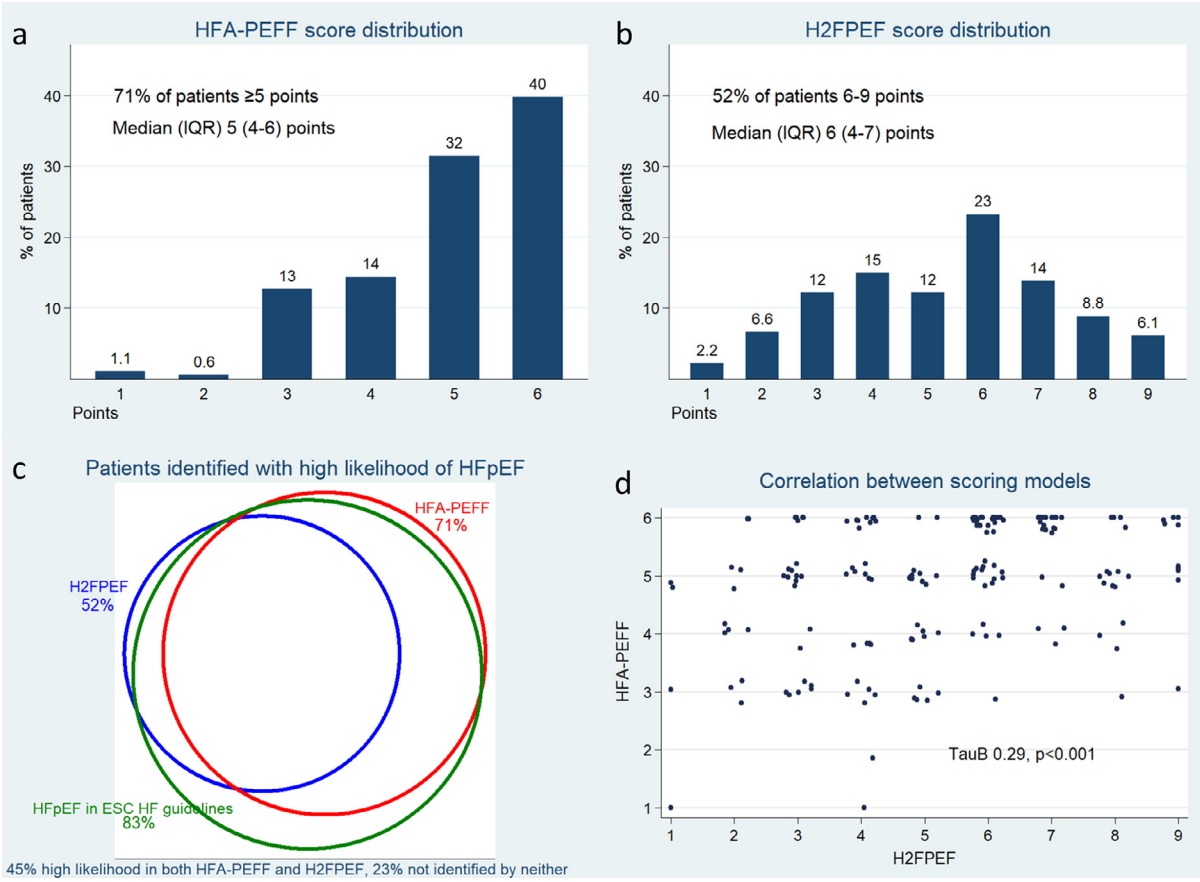

Fig. 2. (a−d) Score distribution by points in HFA-PEFF (a) and H_2FPEF (b) diagnostic scores. Venn diagram demonstrating high-likelihood HFpEF overlap between diagnostic algorithms. The circles in the diagram are resized to the relative proportion of individuals in each group (c). Correlation between the 2 scoring models (d). IQR, interquartile range. Other abbreviations as in Fig. 1.

Table 1. Baseline Characteristics for Patients With the Definite vs Indeterminate Diagnosis of HFpEF as Per ESC Guidelines and by Low- or Intermediate-Likelihood vs High-likelihood score in HFA-PEFF and H2FPEF, Respectively

	ESC HF Guidelines (Noninvasive Testing)		HFA-PEFF		H_2FPEF		Missing
	Further Tests Necessary ($n = 30$)	HFpEF ($n = 151$)	Low or Intermediate Likelihood 0−4 Points ($n = 52$)	High Likelihood 5−6 Points ($n = 129$)	Low or Intermediate Likelihood 0−5 Points ($n = 87$)	High Likelihood 6−9 Points ($n = 94$)	n (%)
Age (years)	67 (61−71)	76 (70−81)	69 (63−74)	77 (71−81)	71 (64−79)	76 (71−81)	0
Female sex	22 (73)	81 (54)	34 (65)	69 (54)	54 (62)	49 (52)	
Race							0
Asian	5 (17)	13 (9)	6 (12)	12(9)	11 (13)	7 (7)	
African American	3 (10)	3 (2)	4 (8)	2 (2)	5 (6)	1 (1)	
White	22 (73)	135 (89)	42 (81)	115 (89)	71 (82)	86 (91)	
Medical history							
Cardiovascular disease	10 (35)	61 (40)	18 (35)	53 (41)	33 (38)	38 (40)	1
Atrial fibrillation	0	94 (62)	15 (29)	79 (61)	9 (10)	85 (90)	0
Hypertension	25 (83)	129 (85)	44 (85)	110 (85)	74 (85)	80 (85)	
Diabetes	9 (30)	41 (27)	17 (33)	33 (26)	33 (38)	38 (40)	
NYHA class							
I/II	0/21 (70)	3 (2)/113 (75)	0/34 (65)	3 (2)/100 (78)	2 (2)/66 (76)	1 (1)/68 (72)	
III/IV	9 (30)/0	34 (23)/1 (1)	17 (33)/1 (2)	26 (20)/0	19 (22)/0	24 (26)/1 (1)	
Clinical assessment							
Heart rate (bpm)	68 (61−73)	67 (60−77)	69 (64−78)	66 (60−76)	66 (59−74)	68 (60−78)	0
BMI (kg/m^2)	28 (26−45)	28 (25−32)	32 (27−43)	27 (24−31)	28 (25−32)	29 (25−33)	0
SBP (mm Hg)	120 (106−140)	140 (130−155)	130 (116−141)	140 (130−158)	137 (120−155)	140 (129−152)	2 (1)
DBP (mm Hg)	67 (59−75)	78 (69−85)	69 (61−80)	78 (70−85)	70 (62−80)	80 (75−88)	2 (1)
Laboratory							
Hemoglobin (g/L)	125 (118−131)	131 (118−140)	130 (118−140)	128 (118−138)	128 (118−137)	129 (119−141)	3(2)
HbA1c (mmol/mol)	44 (38−55)	40 (37−48)	42 (38−55)	40 (37−48)	41 (37−48)	41 (38−50)	27 (15)
eGFR (mL/min/1.73 m^2)	66 (49−83)	59 (46−68)	62 (46−75)	59 (48−69)	65 (48−79)	56 (45−64)	2 (1)
NT-proBNP (pg/mL)	86 (40−117)	1050 (479−1770)	178 (82−479)	1140 (631−1839)	357 (118−775)	1462 (890−2030)	2 (1)

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; HbA1c, glycosylated hemoglobin; HFA-PEFF, Heart Failure Association Pre-test assessment, Echocardiography and natriuretic peptide, Functional testing, Final etiology diagnostic algorithm; H2FPEF, Heavy, 2 or more Hypertensive drugs, atrial Fibrillation, Pulmonary hypertension, Elder age >60, elevated Filling pressures; IQR, interquartile range; NT-proBNP, N-Terminal prohormone of brain natriuretic peptide; NYHA, New York heart association; SBP, systolic blood pressure.

P value for comparison between definite vs indeterminate diagnosis by ESC guidelines and low- or intermediate-likelihood vs high-likelihood HFpEF as per HFA-PEFF and H2PEF scores, respectively.

Values are median (interquartile range) or number (%).

Table 2. Echocardiographic and Doppler Data, Coronary Flow Reserve, Quality of Life, and Effort Tolerance for Patients With the Definite vs Indeterminate Diagnosis of HFpEF as per ESC Guidelines and by Low- or Intermediate-Likelihood vs High-Likelihood Score in HFA-PEFF and H2FPEF, respectively

	ESC HF Guidelines (Noninvasive Testing)			HFA-PEFF			H_2FPEF			Missing
	Further Tests Necessary ($n = 30$)	HFpEF ($n = 151$)	*P* Value	Low or Intermediate Likelihood 1−4 Points ($n = 52$)	High Likelihood 5−6 Points ($n = 129$)	*P* Value	Low or Intermediate Likelihood 1−5 Points ($n = 87$)	High Likelihood 6−9 Points ($n = 94$)	*P* Value	*n* (%)
Echocardiography										
LVEF (%)	64 (61−69)	60 (56−64)	<.001	63 (59−66)	60 (56−64)	.008	63 (58−66)	59 (55−63)	<.001	0
LV mass index (g/m^2)	82 (71−98)	105 (85−128)	<.001	83 (72−101)	108 (88−131)	<.001	95 (76−112)	110 (86−126)	.009	0
Septal wall thickness (cm)	1.2 (1.0−1.3)	1.3 (1.1−1.5)	<.001	1.1 (1.0−1.3)	1.3 (1.1−1.6)	<.001	1.2 (1.0−1.4)	1.3 (1.1−1.6)	.002	0
Relative wall thickness	0.5 (0.4−0.5)	0.5 (0.4−0.5)	.70	0.4 (0.4−0.5)	0.5 (0.4−0.5)	.30	0.4 (0.4−0.5)	0.5 (0.4−0.5)	.20	0
LAVI (mL/m^2)	25 (22−31)	38 (31−45)	<.001	29 (23−33)	40 (33−47)	<.001	31 (24−37)	41 (34−49)	<.001	0
Doppler										
E' septal (cm/s)	7.5 (6.9−8.3)	6.7 (5.4−8.4)	.019	7.8 (6.8−8.6)	6.4 (5.3−7.8)	<.001	7.0 (5.4−8.0)	6.7 (5.6−8.9)	.59	3 (2)
E' lateral (cm/s)	8.8 (8.0−9.8)	9.8 (7.7−11.9)	.082	9.6 (8.2−11.3)	9.4 (7.5−11.8)	.99	8.7 (6.8−10.1)	10.7 (8.8−12.8)	<.001	3 (2)
E/e' average (cm/s)	11.4 (9.4−12.5)	12.3 (9.1−15.8)	.15	11.0 (8.6−12.9)	12.7 (9.5−16.0)	.006	12.1 (9.2−14.8)	12.2 (9.0−15.9)	.49	3 (2)
TR velocity (m/s)	2.5 (2.4−3.0)	3.0 (2.7−3.4)	.001	2.7 (2.4−3.0)	3.0 (2.8−3.4)	<.001	2.7 (2.5−3.2)	3.1 (2.8−3.4)	<.001	28 (15)
PASP (mmHg)	33 (29−40)	43 (36−52)	.001	35 (31−42)	44 (37−53)	<.001	35 (30−48)	45 (39−53)	<.001	28 (15)
Mean CFR	2.2 (1.9−2.5)	2.1 (1.8−2.5)	.20	2.2 (1.9−2.6)	2.1 (1.8−2.4)	.050	2.1 (1.8−2.6)	2.1 (1.8−2.4)	.12	0
Strain imaging										
LV global longitudinal strain (%)	19 (18−21)	16 (14−18)	<.001	18 (16−19)	16 (14−19)	.002	18 (16−20)	16 (13−17)	<.001	2 (1)
LA reservoir strain (%)	24 (22−28)	13 (8−20)	<.001	23 (18−27)	12 (8−19)	<.001	23 (17−27)	10 (8−13)	<.001	2 (1)
QoL and effort tolerance										
KCCQ (score)	60 (32−78)	70 (50−82)	.073	59 (39−77)	71 (51−85)	.017	71 (52−86)	65 (48−77)	.064	4 (2)
6MWT (m)	333 (225−456)	341 (248−420)	.91	345 (227−435)	337 (256−415)	.84	3545 (256−426)	320 (240−415)	.14	8 (4)

Significance level set to .001 (0.05/48) to adjust for multiple testing.

Abbreviations: 6MWT, 6-minute walk test; CFR, coronary flow reserve; E', mitral annular early diastolic velocity; E, transmitral early diastolic velocity; EF, ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; LV, left ventricular; LAVI, left atrial volume index; MI, mass index; QoL, quality of life. Other abbreviations as in Table 1.

P Value for comparison between definite vs indeterminate diagnosis by European Society of Cardiology guidelines and low/intermediate vs high HFA-PEFF and H_2PEF score groups, respectively.

Values are median (interquartile range).

effort tolerance are presented in Table 2. Patients with a high likelihood of having HFpEF demonstrated a greater LA volume, a lower LV GLS, and LA reservoir strain using both scores. For the HFA-PEFF, the high HFpEF probability group displayed a higher LV mass and a tendency toward a lower EF. As for the H_2FPEF, the EF was lower in the high probability group but there was only a tendency toward a higher LV mass. There were no differences in CFR, quality of life, or 6-minute walk test between the high vs low likelihood groups.

Associations Between Scores and HF Severity Measures

Associations between higher score in HFA-PEFF or H_2FPEF and measures of HF severity, functional capacity or quality of life are presented in Appendix Table 2. LA reservoir strain (TauB = −0.35 and −0.46) and GLS (TauB = −0.21 and −0.32) displayed significant inverse associations with both HFA-PEFF and H_2FPEF scores, respectively. There were no significant associations between the scores and 6 MWT, Kansas City Cardiomyopathy Questionnaire, and CFR.

Associations with Proteomic Biomarkers

Biomarkers that were significantly associated with the HFA-PEFF and H_2FPEF scores are presented in Table 3. In addition to BNP and NT-proBNP, both scores demonstrated significant associations ($P < .0002$) with receptor for advanced glycation end products, insulin-like growth factor binding protein 7 (IGFBP7), and angiotensin-converting enzyme 2 ($P < 0.0002$ for all correlations). Beyond these, another 9 proteins correlated with the HFA-PEFF only whereof C-X-C motif chemokine ligand 16 (CXCL16) and Decorin, expressed inflammatory activation and low-density lipoprotein receptor, leptin, and IGFBP1 and 2 were related to hypercholesterolemia, oxidative stress, and the metabolic syndrome. Fewer proteins ($n = 6$) correlated with the H_2FPEF score, among them the anti-inflammatory hepatocyte growth factor, the hypotensive vasodilator adrenomedullin, and the inflammatory growth differentiating factor-15.

Discussion

In a relatively strictly defined HFpEF cohort such as the PROMIS-HFpEF, a high likelihood of HFpEF was present in only 71% of patients according to HFA-PEFF and 52% according to the H_2FPEF diagnostic score. Both scores were significantly associated with structural markers of HF severity, such as LA strain and GLS, biomarkers associated with HF, and were borderline significantly associated with CMD. Nevertheless, a major clinical implication is that, despite use of natriuretic peptides and functional and structural echocardiography criteria, additional or invasive testing would be needed to confirm diagnosis in 28% of patients using the HFA-PEFF and 46% using the H_2FPEF scores, respectively.

Scoring Performance

The HFA-PEFF and H_2FPEF scores were developed to overcome diagnostic difficulties in HFpEF, with the aim of identifying or excluding patients with a high and low probability of HFpEF, respectively, and refer those with intermediate vales to additional stress or invasive testing. Considering the additional costs, expertise, and relative technical complexity associated with these diagnostics, the hope was that these scores would improve the ability to arrive at a clear diagnosis with noninvasive clinical and echocardiographic variables available at rest. However, given that there is no specific therapy for HFpEF and that incremental information from invasive studies would unlikely change management, further testing would perhaps not be performed for clinical purposes. And because 28% to 46% of patients in PROMIS would require additional testing (and probably more patients in other less well-defined HFpEF cohorts), the clinical usefulness of these scores, in particular the H_2FPEF, may be limited. For inclusion in trials where confirmation of HFpEF is essential, the HFA-PEFF score may have usefulness, because it uses only

Table 3. Biomarkers Associated With Score in Both Algorithms and With HFA-PEFF and H2FPEF Respectively ($P < .0002$ for all)

Both scores	HFA-PEFF *TauB*	H_2FPEF *TauB*	HFA-PEFF	*TauB*	H_2FPEF	*TauB*
NTproBNP	0.51	0.35	FABP4	-0.27	GDF 15	0.23
BNP	0.52	0.29	VEGFD	0.31	HGF	0.21
RAGE	0.29	0.29	LDL receptor	-0.27	FGF23	0.25
IGFBP7	0.23	0.32	IGFBP1	0.27	ADM	0.22
ACE2	0.22	0.24	IGFBP2	0.29	SPON1	0.22
			MMP2	0.26	PRELP	0.21
			CXCL16	-0.22		
			LEP	-0.24		
			DCN	0.22		

Abbreviations: ACE2, angiotensin-converting enzyme 2; ADM, adrenomedullin; CXCL16, C-X-C motif chemokine ligand 16; DCN, Decorin; FAB4, fatty acid binding protein 4; FGF23, fibroblast growth factor; GDF15, growth differentiating factor-15; HGF, hepatocyte growth factor; IGFBP1, insulin-like growth factor binding protein 1; IGFBP2, insulin-like growth factor binding protein 2; IGFBP7, insulin-like growth factor binding protein 7; LDL receptor, low-density lipoprotein receptor; LEP, leptin; MMP2, matrix metalloproteinase 2; PRELP, proline/arginine-rich end leucine-rich repeat protein; RAGE, receptor for advanced glycation end products; SPON , spondin 1; VEGFD, vascular endothelial growth factor D. Other abbreviations as in Table 1.

Correlations presented as TauB (Kendall's rank correlation).

parameters that increase the likelihood of HFpEF. The H_2FPEF, in contrast, includes parameters that may instead confound the diagnosis of HFpEF. That is, older age, obesity, and AF are risk markers or risk factors for HFpEF, but they also increase the likelihood that symptoms may be explained by something other than HFpEF, and older age, and AF, although not obesity, also increase natriuretic peptide levels.

The HFA-PEFF adopts a stepwise, comprehensive evaluation spanning all levels of care and includes basic noninvasive to more specialized invasive diagnostic evaluation.[3] In our study, the HFA-PEFF algorithm classified slightly >70% of the enrolled patients as high likelihood HFpEF, limiting additional exercise or invasive testing to approximately a quarter of patients. This is comparable to the validation in the Maastricht−Chicago cohorts, where, overall, 36% of patients were identified as needing further testing.[11]

The H_2FPEF score was derived from a retrospective analysis of a single-center American cohort of patients with acute dyspnea referred for invasive hemodynamic exercise testing[4] and subsequently applied to trial subpopulations to assess regional heterogeneity and prognostic usefulness.[6,7] Similar to a recent validation effort,[12] the H_2FPEF model demonstrated a weak diagnostic performance in our cohort, with only 52% of patients classified as high likelihood of HFpEF. In comparison, an analysis from the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial (TOPCAT) demonstrated higher H_2FPEF median score in the Americas (median 6, IQR 4−7) and greater prevalence (74%) as compared with Russia/Georgia (median 5, IQR 3−5, 59%].[6] The low prevalence in our cohort may be attributed to a number of reasons. First, PROMIS-HFpEF patients had a relatively low BMI (median 28 kg/m^2, IQR 25−33 kg/m^2) as compared with the TOPCAT cohort (median 31 kg/m^2, IQR 27−36 kg/m^2).[4,6] Given that BMI and AF demonstrated the strongest association in the original H_2FPEF regression model and contribute with 2 and 3 points, respectively, to the differential point-based composite score, this finding may explain the lower identification power in our cohort. The prevalence of AF was nevertheless higher in PROMIS-HFpEF than in the derivation cohort (52 vs 32%), which ought to have the opposite effect on scoring performance.[6] Second, 15% of our patients demonstrated weak or absent tricuspid regurgitation signals directly contributing to calculation of Doppler-derived systolic pressures. Absent or weak tricuspid regurgitation signals have been reported in as high as 30% of study populations,[13] which may have a bearing on universal score usefulness in real-world clinical environments. Several of the proteins correlating with the HFA-PEFF score suggested an inflammatory activation and oxidative stress while the proteins associated with the H_2FPEF score were less specific. Finally, 5 of the 6 chosen criteria in the H_2FPEF score demonstrate low specificity for HFpEF, suggesting weakened predictive power when applied to cohorts with higher HFpEF prevalence, as suggested by del Buono and colleagues.[14]

The very small number of patients with a low likelihood of HFpEF, using both the HFA-PEFF (1%) and H_2FPEF (2%) scores, concurs with the strict selection of patients in our clinically well-defined cohort, which included invasive estimation of filling pressures in a subset. In comparison, the HFA-PEFF score identified as low likelihood 1.3% in the Maastricht cohort and 4.1% in the Chicago cohorts, with more obese patients impacting natriuretic peptide concentrations in the American cohort as a possible explanation for the difference in prevalence.[11]

Of note is that the results in the present analyses differs from the data presented in the original PROMIS-HFpEF report, since that analysis was based on the preliminary HFA-PEFF score, not accounting for the maximum of 2 points in each domain.[9] This analysis also highlights regional variations in scoring with higher scoring in patients included in Finland and Sweden, whereas the patients included in Singapore and the United States scored lower on both algorithms. This result may be explained by differences in the prevalence of AF and perhaps also regional differences in the prevalence of the younger obese HFpEF phenotype. In all, these findings stress the need of taking into account the heterogeneity of HFpEF when considering diagnostic algorithms.

Associations Between Score and Markers of HF Severity

Although the probability of higher HF_2PEF scores has earlier been associated with a larger LA size,[6] we demonstrate for the first time an association between both scores and LA reservoir strain, a novel echocardiographic marker earlier associated with both exercise intolerance and worse prognosis in HFpEF.[15,16] Although CMD is thought to be a key feature of HFpEF and is associated with various HF indices like NT-proBNP, LA function, and diastolic parameters, as well as both LV and RV systolic function,[9] there was no association between scoring and CFR. Given the modest performance of the scores, one can speculate that CFR may be a more reliable metric of HFpEF probability that requires further investigation.

Regarding proteomic biomarkers, both scores were associated with BNP/NT-proBNP and IGFBP7, all known to be associated with diastolic dysfunction and prognosis in HFpEF.[8,17] Still, the proteomic profiles differed in some aspects. Proteins associated with the HFA-PEFF score primarily expressed increased inflammatory activation and oxidative stress in form of IGFBP1, VEGFD, and leptin, which are known to be associated with HFpEF.[18,19] Inflammation was nevertheless present also in the H_2FPEF score reflected by growth differentiating factor-15. Moreover, the H2FPEF score protein profile also revealed a potential activation of a compensatory response through the vasodilator adrenomedullin, and the anti-inflammatory hepatocyte growth factor. In addition, FGF23, a predictor of decreased exercise capacity and iron deficiency in HFpEF,[20] was associated with H_2FPEF. This finding may indicate that the H_2FPEF score reflects systemic disease patterns associated with risk factors for HFpEF,

such as older age or overweight, and may be slightly less specific as a diagnostic HFpEF score.

Limitations

Although the PROMIS-HFpEF cohort can be considered a cohort of well-defined HFpEF with 89% of patients fulfilling the diagnosis by the ESC algorithm, all patients were not examined invasively. Further, patients with macrovascular coronary artery disease were excluded in the PROMIS-HFpEF cohort, although these may occur in clinical scenarios. In the present study, only patients with an EF of ≥50% were included to adopt the cohort to current HFpEF definitions. The absence of a control group may also be considered as a limitation of the study. The PROMIS-HFpEF cohort is a highly selected cohort and assessment of performance of the 2 scores in more general populations are desirable. In addition, the multicenter design of PROMIS-HFpEF can be considered a strength, but also highlights the need of further examining regional differences in the usefulness of the scoring models.

Conclusions

Although the HFA-PEFF and H_2FPEF scores were associated with measures of HF severity and biomarkers related to HFpEF, they demonstrated a modest and differential ability to identify HFpEF noninvasively, necessitating additional functional testing to confirm diagnosis in rather large subsets of patients.

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Supplementary materials

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