Review Article

Diagnostic Scores in Heart Failure with Preserved Ejection Fraction

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Abstract

The diagnosis of heart failure with preserved ejection fraction (HFpEF) can be challenging and diagnostic scores have been proposed to help in the diagnostic process. This article reviews these scores to provide insights on their role and interpretation in clinical practice. To date, two scores have been validated for the diagnosis of HFpEF. The H2FPEF includes clinical – obesity, hypertension, atrial fibrillation, age – and echocardiographic data – pulmonary hypertension and E/e' ratio. The HFA-PEFF uses multiple echocardiographic parameters on structural and functional cardiac abnormalities and includes natriuretic peptide blood levels. The accuracy of the H2FPEF score appear to be superior to the HFA-PEFF score in identifying patients with elevated pulmonary capillary wedge pressure at rest or during exercise, but the gold-standard definition of HFpEF is still a matter of debate. A high rating in either of the two scores has a high positive predictive value, and the scores are most useful when HFpEF is clinically suspected, but the diagnosis is uncertain.

Introduction

The diagnosis of heart failure with preserved ejection fraction (HFpEF) can be challenging. In the universal definition of heart failure (HF), HF is a syndrome with signs/symptoms caused by cardiac structural/functional abnormalities, corroborated by either elevated natriuretic peptides or objective evidence of systemic/pulmonary congestion by imaging method or hemodynamic measurement.[1] In a patient with overt congestion and left ventricular ejection fraction (LVEF) ≥ 50%, it is usually easy to diagnose HFpEF. Nevertheless, the diagnosis becomes difficult when signs/symptoms are not typical, such as in outpatients with exertional dyspnea, particularly in the presence of comorbidities. In the last years, two approaches have been proposed and validated for the diagnosis of HFpEF, which may help the clinician to make decisions in equivocal cases. This article reviews these approaches to provide insights on their role and interpretation in clinical practice.

Keywords

Diastolic Heart Failure; Diagnosis; Patients.

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The H2FPEF score

The H2FPEF score was developed by Reddy at al.[2] at the Mayo Clinic, Rochester, USA. The authors used data from 414 consecutive patients undergoing a supine cycle ergometry exercise test with hemodynamic catheterization to investigate dyspnea of unknown origin.[2] They defined HFpEF as elevated pulmonary capillary wedge pressure (PCWP) at rest (≥15 mm Hg) or during exercise (≥25 mmHg). Patients without evidence of cardiac cause for dyspnea after exhaustive clinical evaluation and with normal pressures at rest and during exercise were classified as having non-cardiac dyspnea.

From the results, they built a score using six parameters: obesity, hypertension, atrial fibrillation, age, pulmonary hypertension and elevated filling pressures – the last two measured by echocardiogram (Table 1).[2] Each parameter is given a score according to the presence of the respective criteria. The final H2FPEF score is calculated by the sum of points, indicating low probability (< 2 points), intermediate probability (2-5 points) or high probability (> 5 points) of HFpEF.

The HFA-PEFF score

A consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology proposed a four-step diagnostic algorithm for HFpEF: step 1 (P) – pre-test assessment; step 2 (E) – echocardiographic and natriuretic peptide HFpEF score; Step 3 (F1) – Functional testing; and Step 4 (F2) – Final etiology. On Step 2 (E), the authors proposed the HFA-PEFF score, which was based on

Table 1 – H2FPEF score items[2]

	Parameter	Characteristic	Points
H_2	**H**eavy	BMI > 30 kg/m²	2
	Hypertension	≥ 2 antihypertensive medications	1
F	Atrial **F**ibrillation	Persistent or paroxysmal	3
P	**P**ulmonary hypertension	PASP > 35 mmHg*	1
E	**E**lderly	Age > 60 years	1
F	**F**illing Pressures	E/e'>9*	1
H2FPEF score			Sum (0-9)
Interpretation		0-1: Low probability (unlikely HFpEF) 2-5: Intermediate probability 6-9: High probability (likely HFpEF)	

*BMI: body mass index; PASP: pulmonary artery systolic pressure; HFpEF: heart failure with preserved ejection fraction. *Measured by echocardiogram.*

echocardiographic and natriuretic peptide measurements. The echocardiographic criteria reflect consensus recommendations for the diagnosis of left ventricular diastolic dysfunction with specific cutoff points.[3,4] The HFA-PEFF score has three domains: functional, morphological and biomarker (Table 2). For each domain, a maximum of two points can be scored – two points if any major criterium is met; one point if one minor criterium and no major criterium is met; and no point if no criteria (major or minor) are met. The HFA-PEFF score results from the sum of the points in each domain, which guides the next step in the algorithm. A score less than 2 points indicates that HFpEF is unlikely, and an alternative diagnosis should be considered, while a score above four points is considered diagnostic for HFpEF. Patients with intermediate score (2-4 points) need further evaluation, and a diastolic stress test is proposed as a next step (step 3, functional testing).[3]

Performance of H2FPEF and HFA-PEFF scores for the diagnosis of HFpEF

The performance of diagnostic tests can be evaluated by their sensitivity, specificity, positive and negative predictive values, along with their discrimination and calibration performances. Model discrimination is related to its ability to distinguish between individuals with and without the disease and is measured by the area under the ROC curve (AUC). Model calibration reflects how closely the predicted probabilities agree with the actual outcomes. To estimate the performance of a diagnostic score in clinical practice, they should be externally validated – *i.e.* discrimination and calibration should be measured in a sample that was not used to build the score.

Both H2FPEF and HFA-PEFF scores have been externally validated in different populations, such as patients with unexplained dyspnea or those recently hospitalized for HF. Overall, they showed good discrimination with an AUC consistently estimated as above 0.80 (Table 3). They also showed good model calibration, with predicted probabilities that were similar to observed ones (Hosmer-Lemeshow goodness-of-fit test p values above 0.05).

Comparison between the H2FPEF and HFA-PEFF scores

The HFA-PEFF score requires the measurement of natriuretic peptides and a large number of echocardiographic parameters compared with the H2FPEF score (Table 4). This narrows the use of the HFA-PEFF score to settings where the resources needed to calculate it are available.

Also, these scores disagree with each other in clinical practice, which can further complicate their use. Almost two fifths (28 to 41%) of patients have discordant estimates of the probability of HFPEF from H2FPEF and HFA-PEFF scores.[5-7] Studies have compared the accuracy of the two scores, with divergent findings. While two studies showed superior discriminating power with the H2FPEF score, other two showed they were similar, and one study showed superior AUC with the HFA-PEFF score (Table 3). These discrepancies likely result from methodological differences, sample size, lack of appropriate control group and criteria for defining HFpEF as "gold standard" (see below).

When the hemodynamic definition of HFPEF was used – *i.e.* increased PCWP at rest or during exercise, the H2FPEF seemed to perform better, while the HFA-PEFF had higher false negative rates. For instance, 25% of patients with low H2FPEF scores (0-1 points), but 56% of those with low HFA-PEFF scores had HFpEF by the hemodynamic definition.[6] On the other hand, when both scores were high, 94% had HFpEF.

Table 2 – HFA-PEFF score items[3]

Domain	Major criteria (2 points)	Minor criteria (1 point)	Score (Max 2 points per domain)
Functional	Septal e' < 7 Lateral e' < 10 Average E/e' ratio ≥ 15 TR velocity > 2.8 m/s (PASP > 35 mmHg)	Average E/e'ratio 9-14 GLS < 16%	
Morphological	LAVI > 34 mL/m^2 ou LVMI > 149/122 g/m^2 (m/w) and RWT > 0.42	LAVI 29 - 34 mL/m^2 LVMI > 115/95 g/m^2 (m/w) RWT > 0,42 LVWT ≥ 12 mm	
Biomarker (Sinus Rhythm)	NT-proBNP > 220 pg/mL BNP > 80 pg/mL	NT-proBNP 125 - 220 pg/mL BNP 35 - 80 pg/mL	
Biomarker (Atrial fibrillation)	NT-proBNP > 660 pg/mL BNP > 240 pg/mL	NT-proBNP 365 - 660 pg/mL BNP 105 - 240 pg/mL	
HFA-PEFF score			Sum (0-6)
Interpretation			0-1: Low probability (unlikely HFpEF) 2-4: Intermediate probability 5-6: High probability (HFpEF diagnosis)

TR: tricuspid regurgitation; PASP: pulmonar artery systolic pressure; LAVI: left atrial volume index; LVMI: left ventricular mass index; m: men; w: women; RWT: relative wall thickness; LVWT: left ventricular wall thickness; GLS: global longitudinal strain; BNP: B-type natriuretic peptide; NT-proBNP: N-terminal B-type natriuretic peptide; HFpEF: heart failure with preserved ejection fraction.

Table 3 – Diagnostic scores for heart failure and preserved ejection fraction

Author, year of publication	Country	Population	N	Accuracy (AUC [95% Confidence Interval])	Definitive "Gold Standard" HFpEF diagnosis
Reddy et al. 2018[2]*	United States	Patients with unexplained dyspnea	100	H2FPEF: 0.886 [0.789-0.941]	Elevated PCWP at rest (≥ 15 mmHg) or during exercise (≥ 25 mmHg)
Sepehrvand et al. 2019[8]	Canada	Patients at-risk for HF with LVEF ≥ 50%, known HFpEF and age- and sex-matched healthy controls	424	H2FPEF: 0.80 (0.75–0.84)	Clinical consensus from two HF specialists.
Aizpurua et al. 2020[9]	Netherlands and United States	Outpatients with suspected HFpEF	270	HFA-PEFF: 0.90 (0.84–0.96)	Clinical consensus from two HF specialists.
Ouwerkerk et al. 2020[10]	Singapore	Asian adults with clinical diagnosis of HFpEF vs hypertensive controls§	506	H2FPEF: 0.822 [0.788-0.857] HFA-PEFF: 0.821 [0.784-0.821]	Clinical HF diagnosis from a HF specialist.
Wijk et al., 2020[5]	Netherlands	Outpatients with suspected HFpEF	363	H2FPEF: 0.77 [0.71-0.83] HFA-PEFF: 0.88 [0.82-0.93] ‡	Clinical consensus from two HF specialists.
Tada et al., 2021[11]	Japan	Patients recently hospitalized for HFPEF vs non-HFPEF patients referred to echo for dyspnea	372	H2FPEF: 0.89 [0.86-0.93] HFA-PEFF: 0.82 [0.78-0.86]‡	Clinical diagnosis of acute HF according to Framingham criteria by two experienced cardiologists.
Parcha et al., 2021[12]	Multiple countries	HFpEF patients included in the TOPCAT and RELAX trials vs age-sex-race matched participants with unexplained dyspnea from ARIC cohort	934	H2FPEF: 0.838 HFA-PEFF: 0.800	Inclusion in HFPEF trials.
Churchill et al., 2021[13]	United States	Patients with unexplained dyspnea	156	H2FPEF: 0.74 [0.66-0.81] HFA-PEFF: 0.73 [0.65-0.81]	Elevated PCWP at rest (≥ 15 mmHg) or during exercise (≥ 25 mmHg) coupled with a PCWP/cardiac output slope > 2.0 mmHg. $L^{-1}.min^{-1}$
Reddy et al., 2022[6]	United States, the Netherlands, Denmark, and Australia	Patients with unexplained dyspnea	485	H2FPEF: 0.845 [0.810-0.875] HFA-PEFF: 0.710 [0.659-0.756]†	Elevated PCWP at rest (≥ 15 mmHg) or during exercise (≥ 25 mmHg)

*PCWP: pulmonary capillary wedge pressure; ARIC: Atherosclerosis Risk in Communities; LVEF: left ventricular ejection fraction; HFpEF: heart failure with preserved ejection fraction; HF: heart failure. *From the testing data subset for external validation in the original publication. † p for AUC comparison between the two scores < 0.001. ‡ p for AUC comparison between the two scores < 0.01. § The study reported validation for two cohorts, but only one is being reported here*

Table 4 – Characteristics of the H2FPEF and HFA-PEFF scores

Characteristic	H2FPEF score	HFA-PEFF score
Gold standard HF definition in the score derivation	Invasive hemodynamic test	Expert consensus recommendation
Number of parameters	6	13
Echocardiographic variables	2	9
Inclusion of natriuretic peptides	No	Yes

HF: heart failure.

Lack of gold standard definition for the diagnosis of HFpEF

The main issue on validating the diagnostic scores is the lack of a "gold standard" for the diagnosis of HFpEF. Because HF is a syndrome, the diagnosis relies on a combination of signs, symptoms and multiple complementary exams. While this argues for an expert consensus to define HFpEF, this is also subject to subjectivity and high inter-observer variability, particularly in equivocal cases where scores are expected to be used. On the other hand, defining HFpEF by increased filling pressures at rest or during the exercise is more appealing, since invasive measurements are highly reproducible, and it is strongly related to mechanisms underlying the pathophysiology of HFpEF.[6] In this regard, the hemodynamic exercise testing has been proposed as the gold standard method for the diagnosis of HFPEF, although it has not been widely accepted.

H2FPEF and HFA-PEFF scores in the prognosis of HFpEF

Although the H2FPEF and HFA-PEFF scores have been developed for the diagnosis of HFpEF, they are also associated with HF-related events. The ability to predict HF hospitalization, which is supposedly pathognomonic of HF (due to overt congestion), could indicate whether the score is detecting cases that will progress to an unequivocal diagnosis of HF. In the Atherosclerosis Risk in Communities cohort, both scores were directly associated with increased risk of HF hospitalization or mortality in individuals with unexplained dyspnea.[7] Noteworthy, the event rates in those with elevated H2FPEF and/or HFA-PEFF were similar to those with previously diagnosed HFpEF. This suggests that these scores helped to identify patients with either undiagnosed HFpEF or at higher risk of developing clinical HF.

In patients with stablished HFpEF, both scores were also related to the prognosis, with patients with high scores having increased risk of HF-related events (Table 5).

Final comments and how the scores should be used

The main indication for the use of diagnostic scores in HFpEF is the uncertainty in the diagnosis. The scores have been well validated for patients with unexplained dyspnea and suspected HF. Therefore, they should not be applied to asymptomatic patients, with symptoms clearly due to an alternative cause or when the diagnosis of HF is unequivocal.

In practice, we can interpret a high score of either instrument (H2FPEF > 5 or HFA-PEFF > 4) as highly suggestive of HFPEF, while a low score in both instruments (H2FPEF and HFA-PEFF > 2) virtually rule out HFpEF. Nevertheless, the low scoring in one algorithm only is more likely to be a false negative result, particularly for the HFA-PEFF. For instance, a patient with low HFA-PEFF score and high clinical suspicious of HFpEF would warrant further investigation.

Table 5 – Association between scores for HFPEF and prognosis

Author, year of publication	Design	Sample	N	Score criteria (vs comparator)	Results*
Myhre et al. 2019[14]	Cohort (from a clinical trial)	HFpEF patients in the TOPCAT trial	362	H2FPEF per 1-point increase	HR: 1.12 (1.02–1.23) for the composite of CV mortality, HF hospitalization or aborted cardiac arrest
Selvaraj et al., 2020[7]	Cohort	Unexplained dyspnea	641	H2FPEF ≥ 5 (vs asymptomatic individuals) HFA-PEFF ≥ 4 (vs asymptomatic individuals)	HR: 2.38 (1.80–3.16); HR: 2.67 (2.11–3.38) for the composite of all-cause mortality and HF hospitalization
Sotomi et al. 2021[15]	Cohort	Hospitalized HFpEF patients	804	HFA-PEFF 6 (vs 2 to 5) at discharge	Adj HR: 1.45 (1.10 – 1.90) for HF re-hospitalization and all-cause death
Verbrugge et al. 2021[16]	Cohort	Hospitalized HFpEF patients	443	HFA-PEFF - every 1-point increase HF2FPEF – every 10%-probability-increase	Adj HR: 1.19 (1.04 – 1.38) and 1.17 (1.05 – 1.33) for HF re-hospitalization and all-cause death
Sun et al. 2021[17]	Cohort	Hospitalized HFpEF patients	358	HFA-PEFF ≥ 5 (vs ≤ 2)	Adj HR: 5.29 (1.24–22.59) for all-cause death
Sun et al., 2021[18]	Retrospective cohort	Hospitalized HFpEF patients	476	H2FPEF ≥ 6 (vs <2)	Adj HR: 6.35 (1.48–27.22) for all-cause mortality Adj HR: 2.06 (1.35–3.14) for re-hospitalization
Hwang et al., 2021[19]	Retrospective cohort	Hospitalized HFpEF patients	1105	H2FPEF ≥ 6 (vs <2)	Adj HR: 1.29 (1.06–1.59) for the composite of all-cause mortality and HF re-hospitalization
Suzuki et al. 2010[20]	Cohort	Patients with at least one cardiovascular risk factor	356	H2FPEF per 1-point increase	Adj HR: 1.91 (1.46–2.50) for the composite of cardiovascular mortality and HF hospitalization
Seoudy et al. 2022[21]	Cohort	Post-TAVI with preserved EF	570	H2FPEF ≥ 6 (vs <5)	Adj HR: 2.70 (1.70–4.28) for the composite of all-cause mortality and HF hospitalization
Egashira et al. 2022[22]	Cohort	Hospitalized HFpEF patients	502	HFA-PEF ≥ 5 (vs 2 to 4)	Adj HR: 1.66 (1.11 – 2.50) for HF re-hospitalization

** Data presented as hazard ratio (95% confidence interval). HR: Hazard ratio; HFPEF: heart failure with preserved ejection fraction; TAVI: transcatheter aortic valve implantation; EF: ejection fraction; HF: heart failure.*

Compared with the HFA-PEFF score, the H2FPEF score uses a simpler approach and seems to be more accurate in detecting HFpEF defined by the hemodynamic criteria. Although this might suggest a preference for the H2FPEF score, the diagnosis of HFPEF lacks a gold standard to validate against. The definition of HFPEF has evolved and results of recent positive clinical trials in this population may guide the development of more definitive diagnostic criteria that will help finding patients who will benefit from interventions that change their prognosis.

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Conception and design of the research, Acquisition of data, Analysis and interpretation of the data and Writing of the manuscript: Fernandes-Silva MM.

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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