



RESEARCH ARTICLE

ASSESSING THE PREDICTIVE PERFORMANCE OF HFA-PEFF AND H₂FPEF SCORES IN PATIENTS WITH SUSPECTED HEART FAILURE AND PRESERVED EJECTION FRACTION

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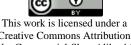
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ABSTRACT

Two scoring systems, HFA-PEFF and H₂FPEF, have been developed for the diagnosis of heart failure with preserved ejection fraction (HFpEF) and have also demonstrated prognostic value in individuals with exertional dyspnea. A total of 69 patients suspected of having HFpEF, based on clinical symptoms and transthoracic echocardiography (TTE), were included and monitored for 12-18 month. Both HFA-PEFF and H₂FPEF scores were calculated upon enrolment, and patients were classified as having intermediate or low risk based on these scores. During the monitoring period, 27 patients (39% of the cohort) experienced cardiac decompensation. Receiver operating characteristic (ROC) analysis showed that both scoring systems can predict cardiac decompensation in patients with suspected HFpEF, with an area under the curve (AUC) of 0.730 for the HFA-PEFF score and 0.720 for the H₂FPEF score. Univariate logistic regression analysis revealed that patients with an HFA-PEFF score of \geq 3.5 had an Odds Ratio (OR) of 7.60 (p = 0.002) for cardiac decompensation, while those with an H₂FPEF score of ≥ 3.5 had an OR of 6.87 (p = 0.002) for cardiac decompensation. In the multivariate analysis, both scores remained predictive, with ORs of 5.07 for HFA-PEFF and 4.65 for H₂FPEF for cardiac decompensation. The confusion matrices showed accuracies of approximately 67.74% for HFA-PEFF and 64% for H₂FPEF in predicting the cardiac decompensation. When both scores were combined, their accuracy was also 67.74%. In conclusion, both the HFA-PEFF and H2FPEF scoring systems demonstrated moderate predictive value in assessing the risk of cardiac decompensation in patients suspected of HFpEF, maintaining their significance in multivariate analysis.



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Keywords: heart failure, HFA-PEFF, H₂FPEF

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is a syndrome responsible for 50% of HF cases, with an increasing incidence and prevalence due to the aging of the population (1-3). The mortality and morbidity rates are relatively similar between patients with HFpEF and those with heart failure with reduced ejection fraction (4).

The early diagnosis of HFpEF presents a significant challenge, primarily due to overlapping symptoms with other conditions and the fact that pathological changes often manifest only during exertion (5-9). Accurate heart failure diagnosis necessitates the presence of clinical signs and symptoms, a preserved left ventricular ejection fraction (LVEF), and evidence of elevated diastolic

pressures, which may be measured at rest or during exertion (6,8).

During the last years, two scoring systems HFA-PEFF and H₂FPEF have been developed to help identifying patients in an early stage of HFpEF. (6,10)

HFA-PEFF The score is a consensus recommendation by the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) designed to enhance the diagnostic accuracy of HFpEF. It includes major and minor criteria across three domains: functional [E/e', e', tricuspid regurgitation (TR) velocity, global longitudinal strain (GLS)], morphological [left atrial volume index (LAVI) and parameters reflecting left ventricular hypertrophy], and biomarkers [N-terminal pro-B-type natriuretic peptide (NT-proBNP)]. (6) The H₂FPEF score is based only on 4 clinical factors (age, body mass index (BMI), atrial fibrillation (AF), and hypertension) and 2 echocardiographic variables [E/e' and pulmonary artery systolic pressure (PASP)] and was developed to estimate the likelihood of HFpEF in patients presenting with unexplained dyspnea. (10) An HFA-PEFF score ≥ 5 or an H₂FPEF score ≥6 is considered diagnostic for HFpEF. Patients with scores < 2 are at low risk for HF. For an HFA-PEFF score between 2-4 and an H₂FPEF score between 2 -5, patients are considered at intermediate risk of HFpEF and further investigations are required (invasive hemodynamic evaluation at rest ideally and with exercise, echocardiography) (6,10).

Both HFA-PEFF and H₂FPEF scores have been externally validated and they showed good discrimination with an Area Under the Curve (AUC) of 0.9 for HFA-PEFF score, and an AUC of 0.8 for H₂FPEF score (11,12).

The applicability of the HFA-PEFF and H₂FPEF scoring systems was first assessed in the general population by Selvaraj et al., utilizing data from the ARIC cohort (13). Although these scores were originally designed for diagnosing HFpEF, the study also highlighted their prognostic value in individuals with unexplained dyspnea and patients with known HFpEF. Participants with unexplained dyspnea who scored higher on both algorithms demonstrated an increased risk of heart failure hospitalization or mortality. Notably, those with scores exceeding the diagnostic thresholds had event rates comparable to those with established HFpEF. These findings indicate that both scores effectively identify patients at risk of developing heart failure, as well as those with undiagnosed heart failure. Additionally, patients with a confirmed diagnosis of HFpEF and higher scores were associated with an elevated risk of heart failure-related events (13).

The primary objective of our study was to investigate the accuracy of the HFA-PEFF and H₂FPEF scores in predicting cardiac decompensations in patients with suspected HFpEF. Additionally, the study aimed to conduct a descriptive statistical analysis of the patient cohort to provide a comprehensive overview of the demographic and clinical characteristics associated with these patients.

MATERIAL AND METHODS

We conducted a prospective, observational, non-randomized study between 2018-2020 and 2022-2024, involving patients suspected of having HFpEF, based on clinical symptoms and transthoracic echocardiography (TTE). Inclusion criteria were patients over 18 years old with exertional dyspnea who exhibited an indeterminate or normal pattern after diastolic dysfunction assessment according to ASE/EACVI guidelines (9) and had a normal left ventricular ejection fraction (LVEF ≥50%). Exclusion criteria included the following: prior diagnosis of HF, NT-proBNP ≥125 pg/mL, significant valvular disease (defined as at least moderate to severe regurgitation or mild stenosis), significant coronary artery disease, arrhythmia other than sinus rhythm (SR) at the time of study enrollment, recent pulmonary embolism, known aortic dissection or aneurysm >50 mm, severe chronic kidney disease [glomerular filtration rate (GFR) <30 mL/min/1.73 m²], or other conditions contributing to dyspnea [including at least moderate respiratory conditions or significant anemia with hemoglobin (Hb) <10 g/dL].

A complete TTE, focused on diastolic dysfunction (DD) evaluation in accordance with ASE/EACVI guidelines, was performed on all subjects upon enrollment. The following parameters with the corresponding cut-off values were assessed: average E/e' > 14, septal e' velocity < 7 cm/s or lateral e' velocity < 10 cm/s, TR velocity > 2.8 m/s, and LAVI > 34 mL/m² (9). Patients with an indeterminate-normal pattern (50% of parameters abnormal or <50% of parameters abnormal) were included.

The Vivid E 95 ultrasound system was used in all cases (GE Vingmed Ultrasound, Horten, Norway). All data were stored digitally and analyzed using EchoPAC software, version 112 (GE Vingmed Ultrasound). Echocardiographic parameters were measured according to the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging by two cardiologists (14).

The patient's age, weight, height, and medical history (including comorbidities and medications) were

recorded. Complete blood tests, as recommended in the HF guidelines, including NT-proBNP, and an electrocardiogram were performed at enrollment.

Both HFA-PEFF and H_2 FPEF scores were calculated for all patients and subsequently classified as having intermediate (2-4 for the HFA-PEFF score, 2-5 for the H_2 FPEF score) or low risk (<2 for both scores) based on these scores.

Patients were monitored for 12-18 months, and episodes of cardiac decompensation were recorded if they occurred.

Cardiac decompensation was defined as the occurrence of any of the following events: worsening HF symptoms requiring medications adjustment (including loop diuretics), with confirmation of HFpEF; hospitalization for HF; new-onset atrial fibrillation or flutter (EHRA II–IV classification); or cardiovascular death.

The study was conducted in accordance with the principles of the Declaration of Helsinki and the local ethics committee. All patients provided informed consent prior to participation in the study.

Statistical analysis

Fisher's exact test was used for categorical variables with small sample sizes, while the Welch Two Sample t-test was applied to compare means between two independent groups with unequal variances. Pearson's Chi-squared test was used to assess the association between categorical variables, and the Mann-Whitney U test was employed to compare the distributions of continuous variables between two independent groups when the normality assumption was not met.

The significance threshold (α) was established at 0.05, with p-values below this value considered statistically significant.

The Receiver Operating Characteristic (ROC) analysis was conducted for each score independently, followed by a comparison of the two ROC curves employing the DeLong test (Figure 1 and 2).

The cut-off values derived from the ROC analysis were utilized to stratify patients into two distinct groups for each score. These stratifications were then incorporated as predictor variables in both univariate and multivariate binary logistic regression models. To evaluate the predictive capability of each score, the study cohort was partitioned into two subsets. The first subset, comprising 35 patients, was employed for model development (training set), while the second subset, consisting of 34 patients, was used for model validation, specifically to classify the presence or absence of cardiac decompensation. A probability threshold of 0.5 was applied for classification. Furthermore, predictive the

performance of a composite model incorporating both scores was also evaluated.

For statistical analysis, R software, version 4.4.1, was used (Copyright (C) 2024 The R Foundation for Statistical Computing, R Core Team, 2024). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org.

RESULTS

The study group included 69 patients suspected of HFpEF, with a median age of 57 years (mean \pm standard deviation of 57 \pm 15 years), 65% males, with dyspnea (NYHA class I- III) and the following risk factors: obesity (38.8%), hypertension (73.9%), history of atrial fibrillation (11.5%) and diabetes (13%).

Twenty-seven patients, representing 39% of the total cohort, experienced cardiac decompensation, 10 patients (14.4%) exhibited worsening symptoms with a confirmed diagnosis of HFpEF, 10 patients (14.4%) required hospitalization for HFpEF, and 7 patients (10%) had atrial fibrillation/ flutter. No death was recorded.

The results of the descriptive and comparative statistical analysis of the group with cardiac decompensation versus the group without cardiac decompensation are presented in Table1.

The ROC analysis showed an AUC of 0.730 for the HFA-PEFF score, with 90.5% specificity and 44% sensitivity for a cut-off value of 3.5; and an AUC of 0.720 for the H_2 FPEF score, with 88.1% specificity and 48% sensitivity for a cut-off value of 3.5. The DeLong test revealed no statistically significant differences between the two scores (Z = 0.13, p = 0.88, 95% CI = -0.12 to 0.14).

Univariate logistic regression analysis revealed that patients with an HFA-PEFF score of \geq 3.5 had an odds ratio (OR) of 7.60 (p = 0.002) for cardiac decompensation, while those with an H₂FPEF score of \geq 3.5 had an OR of 6.87 (p = 0.002) for cardiac decompensation. (Table 2)

To assess the predictive capabilities of each score, the study cohort was divided into two subsets: 35 patients for model development (training set) and 34 patients for validation. A probability threshold of 0.5 was used for classification. The confusion matrices showed an accuracy of 67.74% for the HFA-PEFF score and 64.70% for the H₂FPEF score (Tables 4 and 5).

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HyPEPEF score, Median (IQR)	Variable	Overall, N = 69	Without decompesation	With decompesation	p-value ¹
Age, γr, Smean (SD) 57 (15) 52 (15) 65 (10) <0.0 Sex, n (%) <0.0 Female 24 (35) 5 (12) 19 (70) Male 45 (65) 37 (88) 8 (30) BMIM, kg/m, Mean (SD) 27.6 (4.7) 26.5 (4.9) 29.2 (4.0) 0.0 Comorbidities Hypertension, n (%) 28 (67) 26 (96) 0.0 No 15 (22) 14 (33) 1 (4) Diabetes, n (%) 28 (67) 26 (96) 0.3 Yes 9 (13) 4 (10) 5 (19) 0.3 No 60 (87) 36 (90) 22 (81) 1.0 History of atrial fibrillation (%) 1 (2) 7 (26) 7 (26) Yes 8 (12) 1 (2) 7 (26) 7 (26) No 61 (88) 41 (98) 20 (74) 1.2 Laboratories NT-proBNP, pg/ml (Mean (SD) 76 (33) 66 (34) 9 (125) <0.0	HFAPEFF score, Median (IQR)	3.00 (1.00)	2.50 (1.75)	3.00 (1.50)	< 0.001
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Antiplatelet therapies, n (%) 0.55 Yes 35 (51) 20 (48) 15 (56)	Yes	22 (32)	10 (24)		
Yes 35 (51) 20 (48) 15 (56)	No	47 (68)	32 (76)	15 (56)	
	Antiplatelet therapies, n (%)				0.52
24 (40)	Yes	35 (51)	20 (48)	15 (56)	
NO 34 (49) 22 (52) 12 (44)	No	34 (49)	22 (52)	12 (44)	
Statin, n (%) 0.0	Statin, n (%)				0.079
Yes 45 (65) 24 (57) 21 (78)	Yes	45 (65)	24 (57)	21 (78)	
No 24 (35) 18 (43) 6 (22)	No	24 (35)	18 (43)	6 (22)	

Table 1 - Descriptive and comparative statistical analysis of the group with cardiac decompensation versus the group without cardiac decompensation.

¹ Welch Two Sample t-test; Fisher's exact test; Pearson's Chi-squared test, Mann-Whitney U test. Data given as number (%),

mean±standard deviation, Body mass index (BMI),N-terminal pro B type natriuretic peptide (NT-proBNP), left ventricle ejection fraction (LVEF), left atrial volume index (LAVI), global longitudinal strain (GLS), left ventricle mass index (LVMI), Pulmonary artery systolic pressure (PASP), angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRA).

Predictor	N	Cardiac decompensation N	OR (95% CI) ¹	p-value
Category HFA-PEFF score				
< 3.5	53	15	_	
>= 3.5	16	12	7.60 (2.26 to 30.8)	0.002
Category H₂FPEF score		•		
< 3.5	51	14	_	
>= 3.5	18	13	6.87 (2.17 to 24.9)	0.002

Table 2 - Univariate logistic regression analysis

¹ OR = Odds Ratio, CI = Confidence Interval

Predictor	N	Cardiac decompensation N	OR (95% CI) ¹	p-value	VIF ¹
Category H₂FPEF score					1.0
< 3.5	51	14	_		
>= 3.5	18	13	4.65 (1.32 to 17.9)	0.019	
Category HFA-PEFF score					1.0
< 3.5	53	15	_		
>= 3.5	16	12	5.07 (1.35 to 21.8)	0.019	

Table 3 - Multivariable Binary Logistic Regression

¹ OR = Odds Ratio, CI = Confidence Interval, VIF = Variance Inflation Factor

	Without/ Real	With /Real
Without/ Model	18	2
With/ Model	9	5

Table 4 - Confusion matrix for HFA-PEFF score (with/without decompensation)

	Without/ Real	With /Real
Without/ Model	18	2
With/ Model	10	4

Table 5 - Confusion matrix for H₂FPEF score (with/without decompensation)

In the multivariable binary logistic regression analysis, both scoring systems remained significant predictors, with odds ratios (ORs) of 4.65 for cardiac decompensation for the H₂FPEF score and 5.07 for the HFA-PEFF score (Table 3).

The predictive performance of the multiple model was also tested, using a procedure similar to the previous ones (Table 6).

	Without/ Real	With /Real
Without/ Model	18	2
With/ Model	10	4

Table 6 - Confusion matrix for the multiple model (with/without decompensation)

DISCUSSIONS

Our study demonstrated that both the HFA-PEFF and H₂FPEF scores effectively predicted cardiac decompensation in a population suspected of having HFpEF, especially among individuals classified as intermediate to low risk for both scores. The evaluation of these scoring systems employed a robust statistical approach, including ROC analysis, the De Long test for AUC comparison, confusion matrices for accuracy assessment, univariate logistic regression to determine

odds ratios, and multivariate analysis to confirm their predictive relevance. Collectively, these methods showed that both scoring systems hold significant predictive value for identifying patients at risk of cardiac decompensation.

The assessment of the patient demographics indicated that, patients with cardiac decompensation were older (65 vs 52, p < 0.001), had a higher BMI (29.2 vs 26.5, p = 0.017), were predominantly female (p < 0.001), and presented higher values for NT-pro-BNP levels (p < 0.001). This outcome was anticipated, as age, female sex, and obesity are recognized risk factors for HFpEF (15). Furthermore, both age and obesity are components of the H₂FPEF score (10). These findings are consistent with those of the study by Selvaraj et al., which demonstrated that the use of both scoring systems facilitated the identification of patient groups with dyspnea who are at increased risk for adverse events, particularly among women and obese individuals, even in the absence of a definitive HF diagnosis (13). Additionally, NT-proBNP, which is included in the HFA-PEFF score, is known to predict risk and is associated with disease progression in HFpEF (16).

Patients with cardiac decompensation also exhibited a higher prevalence of comorbid conditions associated with HFpEF, such as hypertension (p= 0.004) and a history of atrial fibrillation (p=0.005), although no significant difference was observed for diabetes (p=0.32) (17,18). It is noteworthy that hypertension and atrial fibrillation are included in the H_2 FPEF score (10).

Key echocardiographic parameters essential for diagnosing HFpEF, specifically LAVI (33 ml/m² vs 29 ml/m^2 , p=0.025) and the E/e' ratio (9.16 vs 7.76, p= 0.010) were significantly elevated in our study among patients with cardiac decompensation. Additionally, GLS was significantly reduced in these patients (-17.85 vs -19.78, p= 0.008). GLS is widely recognized as the most reliable and sensitive parameter for the early detection of myocardial contractility impairment in individuals with HFpEF, also having prognostic value in this population (6, 14, 19). However, no statistically significant differences were found between the two groups in terms of LVEF (56.5% vs 58%, p= 0.18), LVMI $(86 \text{ g/m}^2\text{vs } 89 \text{ g/m}^2, p=0.56), \text{ or PASP } (20 \text{ mmHg vs } 17)$ mmHg, p= 0.2). The absence of a statistically significant difference between the two groups regarding LVMI and PASP is likely due to the early stage of cardiac impairment in the patients who experienced cardiac decompensation.

The use of loop diuretics was significantly higher among patients with cardiac decompensation, with 15% of these patients including this medication in

their treatment regimen, compared to none of the non-decompensated patients, indicating that these patients were more severely affected but received appropriate management. On the other hand, no significant differences were observed in the use of Indapamide (p= 0.073), mineralocorticoid receptor antagonists (MRA) (p=0.3), and angiotensin-converting enzyme (ACE) inhibitors / angiotensin II receptor blockers (ARBs) (p=0.39), which are commonly used in hypertension management. Furthermore. blockers (p = 0.007) and calcium channel blockers (p = 0.049) were more frequently prescribed to patients with cardiac decompensation, while no significant differences were found for statins (p = 0.079) and antiplatelet therapy (p = 0.52).

In our study, the AUC values obtained from ROC analysis indicated that both scoring systems can effectively differentiate between patients at risk of cardiac decompensation and those with greater stability within the population of patients with suspected HFpEF. The AUC values were 0.73 for the HFA-PEFF score and 0.72 for the H₂FPEF score. Our results closely align with findings from previous studies that evaluated the predictive capabilities of the two scores in patients with HFpEF (20,21). Specifically, the research by SunY et al. demonstrated that the HFA-PEFF score effectively predicts all-cause mortality in HFpEF patients, reporting an AUC of 0.726 (95% CI: 0.651-0.800, P = 0.000) (20). Similarly, Sueta et al. found that the H₂FPEF score significantly predicted cardiovascular events, achieving an AUC of 0.626 (95% CI: 0.557-0.693; P < 0.001), as well as heart failurerelated events with an AUC of 0.680 (95% CI: 0.600-0.759; P < 0.001) in HFpEF patients (21).

Conversely, other studies assessing the diagnostic capabilities of the two scores for HFpEF typically reported enhanced performance, with AUC values ranging from 0.8 to 0.9 for the HFA-PEFF score and from 0.77 to 0.89 for the H₂FPEF score. (10-12,22-25) Notably, the study by Churchill et al. reported lower AUC values of 0.73 for the HFA-PEFF and 0.74 for the H₂FPEF scores, highlighting the variability in the diagnostic effectiveness of these scoring systems across different populations (26).

Several of the previously mentioned clinical studies, observed a notable discordance in estimating heart failure probabilities between the two scores, with discrepancies ranging from 28% to 41% (13, 24, 25). Moreover, differing results regarding the diagnostic accuracy of the two scores were identified. Although the HFA-PEFF score is more complex, it has been shown to have lower diagnostic accuracy for HFpEF compared to the simpler H₂FPEF score (22, 25). In our research, the De Long test conducted for the

ROC analysis showed no statistically significant difference between the two scores (Z = 0.13, p = 0.88, 95% CI = -0.12 to 0.14) regarding their accuracy in predicting cardiac decompensation among patients suspected of having HFpEF.

Importantly, both scores exhibited high specificity values in our study, with a specificity of 0.905 for the HFA-PEFF score and 0.881 for the H₂FPEF score at a cut-off value of 3.5. This underscores their effectiveness in accurately identifying true negative cases, helping to exclude patients not experiencing cardiac decompensation.

However, the relatively low sensitivity values—0.44 for HFA-PEFF and 0.48 for H₂FPEF—highlight a significant limitation: these scoring systems may not fully capture all positive cases, raising concerns about potential false negatives. One possible explanation for the reduced sensitivity observed in our study could be the relatively high cut-off value (3.50), which may have limited the ability of both scores to detect all patients with cardiac decompensation. This issue of reduced sensitivity, especially for the HFA-PEFF score, has been observed also in previous studies, which evaluated the diagnostic efficacy of the two scores for HFpEF (11,24,25).

Univariate logistic regression analysis revealed that patients with an HFA-PEFF score of ≥ 3.5 had a significantly increased risk of cardiac decompensation, with an Odds Ratio (OR) of 7.60 (p = 0.002), indicating a 7.60-fold greater likelihood of cardiac decompensation compared to those with lower scores. Similarly, an H₂FPEF score of ≥ 3.5 was associated with an OR of 6.87 (p = 0.002).

Both scoring systems remained predictive also, after the multivariable binary logistic regression analysis, although with slightly reduced OR. Specifically, independent of the H_2 FPEF category, patients with an HFA-PEFF score of ≥ 3.5 had an OR of 5.07 for cardiac decompensation, while patients with an H_2 FPEF score of ≥ 3.5 , regardless of the HFA-PEFF category, had an OR of 4.65.

The confusion matrices showed moderate accuracy values of 67.74% for the HFA-PEFF score and 64.70% for the H_2 FPEF score in predicting cardiac decompensation. The HFA-PEFF score demonstrated the highest predictive value, with a sensitivity of approximately 71.4% and a specificity of around 66.7%. In contrast, the H_2 FPEF score exhibited lower sensitivity at 66.7% and specificity at 64.3%. These results differ from those of previous studies, as we mentioned before, which reported greater diagnostic accuracy for the H_2 FPEF score, particularly when invasive diagnostic methods for HFpEF were used (22,25).

The combined model, which integrated both scoring systems, achieved an accuracy of 67.74%, with sensitivity and specificity values similar to those of the HFA-PEFF score. This suggests that combining the scores may offer limited added benefit in improving predictive accuracy.

CONCLUSIONS

Both the HFA-PEFF and H₂FPEF scores demonstrated significant predictive value in identifying patients at risk of cardiac decompensation among those suspected of having HFpEF. The ROC analysis and DeLong test revealed no statistically significant difference between the two scores' accuracy. All statistical tests confirmed the predictive capability of both scores. A key aspect of our research was assessing the prognostic value of these scores in a population suspected of HFpEF, particularly among individuals classified as intermediate to low risk. This context may explain the moderate predictive value observed, likely due to the relatively low-risk population. Overall, these findings support the use of these scoring systems in clinical practice for risk stratification in patients suspected of HFpEF.

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