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Comparing the Diagnostic Performance of HFA-PEFF and H2FPEF Scoring Systems in Heart Failure with Preserved Ejection Fraction Patients: Insights from the APOLLON Registry

ABSTRACT

Background: Heart failure with preserved ejection fraction is a complex and heterogeneous clinical syndrome, poses significant diagnostic challenges. The HFA-PEFF [Heart Failure Association of ESC diagnostic algorithm, P (Pretest Assessment), E (Echocardiographic and Natriuretic Peptide score), F1 (Functional testing in Case of Uncertainty), F2 (Final Aetiology)] and H_2FPEF [Heavy (BMI>30 kg/m^2), Hypertensive (use of ≥2 antihypertensive medications), atrial Fibrillation (paroxysmal or persistent), Pulmonary hypertension (Doppler Echocardiographic estimated Pulmonary Artery Systolic Pressure >35 mm Hg), Elderly (age >60 years), Filling pressure (Doppler Echocardiographic E/e' >9)] scoring systems were developed to aid in diagnosing heart failure with preserved ejection fraction. This study aimed to assess the concordance and clinical accuracy of these scoring systems in the "A comPrehensive, ObservationaL registry of heart faiLure with mildly reduced and preserved ejection fractiON" cohort.

Methods: A comPrehensive, ObservationaL registry of heart faiLure with mildly reduced and preserved ejection fractiON study was conducted as a multicenter, cross-sectional, and observational study; to evaluate a group of Heart failure with mildly reduced ejection fraction and heart failure with preserved ejection fraction patients who were seen by cardiologists in 13 participating centers across 12 cities in Türkiye.

Results: The study enrolled 819 patients with heart failure with preserved ejection fraction, with high probability heart failure with preserved ejection fraction rates of 40% and 26% for HFA-PEFF and H_2FPEF scorings, respectively. The concordance between the 2 scoring systems was found to be low (Kendall's tau-b correlation coefficient of 0.242, $P < .001$). The diagnostic performance of both scoring systems was evaluated, revealing differences in their approach and ability to accurately identify heart failure with preserved ejection fraction patients.

Conclusion: The low concordance between the HFA-PEFF and H_2FPEF scoring systems underscores the ongoing challenge of accurately diagnosing and managing patients with heart failure with preserved ejection fraction. Clinicians should be aware of the strengths and limitations of each scoring system and use them in conjunction with other clinical and laboratory findings to arrive at an accurate diagnosis. Future research should focus on identifying additional diagnostic factors, developing more accurate and comprehensive diagnostic algorithms, and investigating alternative methods of diagnosis or stratification of patients based on different clinical characteristics.

Keywords: Heart failure with preserved ejection fraction, HFpEF, HFA-PEFF, H_2FPEF, diagnostic scoring systems

INTRODUCTION

Approximately half of the patients presenting signs and symptoms of heart failure (HF) have significant but not abnormal left ventricular ejection fraction (LVEF), referred to as HF with preserved ejection fraction (HFpEF). Accurate diagnosis of HF can be challenging due to the diverse manifestations of this syndrome. To aid selection and potential targeted therapy for clinical trials, a classification system was established by the 2016 European Society of Cardiology (ESC) HF Guidelines,[1] categorizing HF into 3 groups: HFpEF (LVEF ≥ 50%), HF with reduced

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LVEF (HFrEF, LVEF < 40%), and HF with mildly reduced ejection fraction (HFmrEF; LVEF: 40%-49%). The guidelines also introduced a diagnostic algorithm for HFpEF, which was adopted by the 2021 ESC HF guidelines.[2] Two novel scoring systems have been devised to attain a more accurate diagnosis of patients with HFpEF, namely, the HFA-PEFF [Heart Failure Association of ESC diagnostic algorithm, P (Pretest Assessment), E (Echocardiographic and Natriuretic Peptide score), F1 (Functional testing in Case of Uncertainty), F2 (Final Aetiology)] and H_2FPEF [Heavy (BMI>30 kg/m^2), Hypertensive (use of ≥2 antihypertensive medications), atrial Fibrillation (paroxysmal or persistent), Pulmonary hypertension (Doppler Echocardiographic estimated Pulmonary Artery Systolic Pressure >35 mm Hg), Elderly (age >60 years), Filling pressure (Doppler Echocardiographic E/e' >9)] scoring systems,[3] as defined here:

1. HFA-PEFF: A pretest evaluation by the HF Association, which includes echocardiography and natriuretic peptide testing, functional testing, and determination of the final etiology.[4]
2. H_2FPEF: A scoring system that takes into account several factors, including heavyweight, the use of 2 or more HT medications, atrial fibrillation (AF), pulmonary hypertension (HT), being over 60 years old, and elevated filling pressures.[5]

Both scores produce categorical results, helping determine the likelihood of HFpEF as low, moderate, or high based on clinical characteristics and echocardiography. Patients with an intermediate likelihood would need further invasive hemodynamic examinations that involve considerable technical intricacy, expenses, and hazards.[6] Importantly, since HFpEF is a syndrome without any unique therapy, it is important that these patients get diagnosed accurately. While the scoring systems have been validated in cohorts[4,5] experiencing unexplained dyspnea, their capability of precisely diagnosing HFpEF in a more delicately targeted group has not been entirely comprehended. To uncover the clinical and epidemiological characteristics of HFmrEF and HFpEF in Türkiye, the APOLLON (A comPrehensive, ObservationaL registry of heart faiLure with mildly reduced and preserved ejection fractiON) study[7] was conducted, which is a multicenter, cross-sectional, and observational study. This subanalysis of the study aimed to assess the applicability and clinical precision of the H_2FPEF and HFA-PEFF scoring systems in individuals with HFpEF, utilizing the national APOLLON cohort.

HIGHLIGHTS

- The study shows a low concordance between HFA-PEFF and H_2FPEF scoring systems for diagnosing heart failure with preserved ejection fraction (HFpEF), indicating their insufficiency for accurate diagnosis.
- A thorough, individualized diagnostic evaluation, along with clinical and laboratory findings, is crucial for assessing patients with suspected HFpEF.
- The study highlights the need for identifying additional diagnostic factors, developing more accurate and comprehensive algorithms, and exploring alternative methods for diagnosis or stratification of HFpEF patients.

METHODS

Study Design

The plan and justification behind the APOLLON trial (ClinicalTrials.gov identifier NCT03026114) have been elaborated in detail elsewhere.[7] Furthermore, the results of the primary investigation have been elaborated elsewhere.[8-10]

To summarize, the APOLLON registry included a group of HFmrEF and HFpEF patients who were seen by cardiologists in 13 participating centers across 12 cities in Türkiye (İstanbul, Ankara, Eskişehir, Kayseri, Kırıkkale, Muğla, Kahramanmaraş, Zonguldak, Çorum, Şanlıurfa, Adıyaman, and Kars). Following the ethics committee approval, enrollment for the study commenced on March 31, 2018, and concluded on May 20, 2018, with a total of 1065 patients with HF signs and/or symptoms who visited the outpatient cardiology clinics being enrolled. The study enrolled individuals (age ≥ 18 years) who presented with HF symptoms, had an LVEF ≥ 40%, and had N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels ≥ 125 pg/mL. Patients with LVEF < 40% and who have cor pulmonale, history of myocardial infarction, recent (within the last 90 days) stroke or coronary artery bypass surgery and pacemaker implantation or percutaneous coronary intervention within last month, presence of primary valvular heart disease in need of intervention or surgery or presence of prosthetic valves, patients with hypertrophic obstructive or infiltrative cardiomyopathy, pericardial constriction, congenital heart diseases, and pregnant patients were excluded from the study.

According to recent guidelines, HFmrEF criteria defined as LVEF between 41% and 49% with HF signs or symptoms, and patients who have signs or symptoms of HF with LVEF ≥50% and evidence of cardiac structural or functional abnormalities indicates LV diastolic dysfunction or raised filling pressures with raised natriuretic peptides were defined as HFpEF.[2] Among the 1065 patients, 819 enrolled patients were HFpEF and were included in the subgroup analysis. In this subgroup analysis, data from the APOLLON trial were computed to evaluate diagnostic algorithms and scoring models for HFpEF.

Patient's Clinical, Laboratory, and Echocardiographic assessment

The detailed medical histories of the patients and their physical examinations were evaluated and laboratory assessment, electrocardiography, and transthoracic echocardiographic evaluation of the patients were performed at the time of admission. Patient's age, weight, comorbidities, all medical and interventional treatments and medications that patients receive and treatments of HF, information on smoking status, alcohol use, educational status, and the participant's place of residence (whether rural or urban), and their hospitalization history in the past year was collected by questionnaire method. Complete blood counts, biochemistry test, anemia panel, and natriuretic peptides (NT-proBNP)

as specified in the HF guidelines, were taken at the admission. The Modification of Diet in Renal Disease equation (12) was utilized to calculate the estimated glomerular filtration rate (eGFR), and eGFR <60 mL/min/1.73 m^2 was defined as renal failure. Transthoracic echocardiographic evaluation of the patients was performed at admission. LVEF was measured using the modified Simpson's method in apical 4- and 2-chamber views. Diastolic parameters including septal and lateral wall *E* and *e'* (cm/s), left atrial volume index (LAVI) (mL/m^2), left atrial mass index (LVMI), and left atrial enlargement were evaluated. All data were collected in a single visit. Patients were evaluated as "HFpEF" or "HFmrEF" according to their LVEF and patients with HFpEF were included in the analysis.

Heart Failure with Preserved Ejection Fraction Probability According to HFA-PEFF and H_2FPEFF Scorings

Patients included in the APOLLON cohort were evaluated for the likelihood of HF according to the HFA-PEFF[4] and H_2FPEF[5] scoring systems recommended in 2016 and 2021 ESC HF guidelines.[2]

The HFA-PEFF score consists of 4 stages as previously described.[4] The first stage consists of a Pretest Assessment, which consists of HF symptoms and findings, natriuretic peptides, risk factors, standard echocardiography, comorbidities, 6-minute walk test, or exercise test evaluation. If the first step is significant in terms of HF, then step 2 should be done. Step 2 describes the diagnostic workup, which contains comprehensive echocardiographic evaluation and natriuretic peptide measurement if not measured in the first step. After this stage, it results in as low, intermediate, and high probability HFpEF according to the HFA-PEFF scoring. HFA-PEFF scoring includes functional, morphological, and biomarker consisting of 3 main domains. A functional evaluation includes age-specific myocardial early diastolic velocity (*e'*), the ratio of mitral inflow velocity to septal and lateral *e'* (*E*/*e'*), systolic pulmonary artery pressure (PAPs) measured over tricuspid regurgitation (TR) velocity, and global longitudinal strain. Morphological evaluation encompasses several parameters including left atrial volume index (LAVI), sex-specific left ventricular mass index (LVMI), relative wall thickness, and additionally left ventricular (LV) wall thickness in minor criteria. The biochemical aspect examines levels of brain natriuretic peptide or NT-proBNP. Each major criterion is assigned 2 points, while meeting minor criteria results in 1 point classification. The likelihood of HFpEF is classified as follows: a total of 0 to 1 point is considered low, 2 to 4 points are classified as intermediate, and 5 or more points indicate a high likelihood. In low probability, HFpEF will be excluded, in high probability HFpEF is confirmed. For individuals with intermediate probability, additional tests are recommended in the scoring system. In the APOLLON study, the HFA-PEFF score was calculated by echocardiographic septal *e'*, average *E*/*e'*, TR velocity, PAPs, LAVI, LVMI, functional and morphological measurements, and natriuretic peptides levels. GLS assessment and invasive measurements were not performed.

The H_2FPEF scoring is calculated by scoring 6 clinical variables and evaluating them on the HFpEF probability scale.[5] In this scoring, BMI > 30 kg/m^2 is 2 points, 2 or more antihypertensive drugs are 1 point, paroxysmal or persistent AF is 3 points, Doppler echocardiographic estimated PAPs > 35 mm Hg is 1 point, age > 60 years is 1 point, Doppler echocardiographic *E*/*e'* > 9 is 1 point. Patients with a score of 1 and below were classified as low, 2 to 5 as intermediate, and 6 to 9 as high likelihood for HFpEF.

Statistical Analyses

The Shapiro–Wilk normality test was used to assess the distribution of the variables and they were distributed non-normally. Mann–Whitney *U*-test and the χ^2 test were used to compare continuous and categorical variables, respectively. Categorical and continuous variables were described as frequencies (percentages) and median (interquartile range), respectively. Kendall's rank correlation coefficient was used to analyze associations between the scoring systems, presented as TauB while accounting for ties. A $P < .05$ was considered significant. All analyses were performed using the Statistical Package for the Social Sciences Statistics, version 22.0, software (SPSS Inc., Chicago, Ill, USA).

RESULTS

Our research found that both the median HFA-PEFF and H_2FPEF scores were 4 points. In terms of HFA-PEFF scores, 40% of patients were in the high probability group, 57% were in the intermediate probability group, and 3% were in the low probability group. For H_2FPEF scores, 26% of patients were in the high probability HFpEF group, 60% were in the intermediate group, and 14% were in the low probability group.

Regarding the HFA-PEFF score, we found that the proportions of patients with minor and major criteria in the functional domain were similar (35.9% vs. 30.9%). In contrast, the proportions of patients with major scores in the morphological and biomarker domains were higher. A total of 57.9% of the patients met the morphological major criteria, and 34.9% met the morphological minor criteria. In the biomarker domain, 67.6% of the patients had major criteria, and 23% met with minor criteria.

Based on the H_2FPEF scoring system, over half of the patients were found to be hypertensive, elderly, and had higher LV filling pressure. The study population consisted of 38.0% patients with BMI higher than 30 kg/m^2, 60% with HT, 38.2% with AF, 23.8% with pulmonary HT, 74.8% aged over 60 years, and 51.3% with elevated LV filling pressures (Figure 1). It was observed that the proportion of patients scoring 0-5 on the H2FPEF score was similar; however, there was a gradual decline in the rates of patients scoring higher than 6 points (as shown in Figure 2). Subsequently, Figure 3 depicts the reclassification of patients into low, intermediate, and high likelihood categories based on the conversion of the H_2FPEF score to the HFA-PEFF score and vice versa. In both scoring systems, patients' demographics and comorbidities were assessed under the categories of low or medium likelihood and high likelihood of HFpEF diagnosis. In both high likelihoods of HFpEF groups, the average age was higher, and a lower proportion of females were found in the HFA-PEFF group while a higher proportion was observed in the H_2FPEF

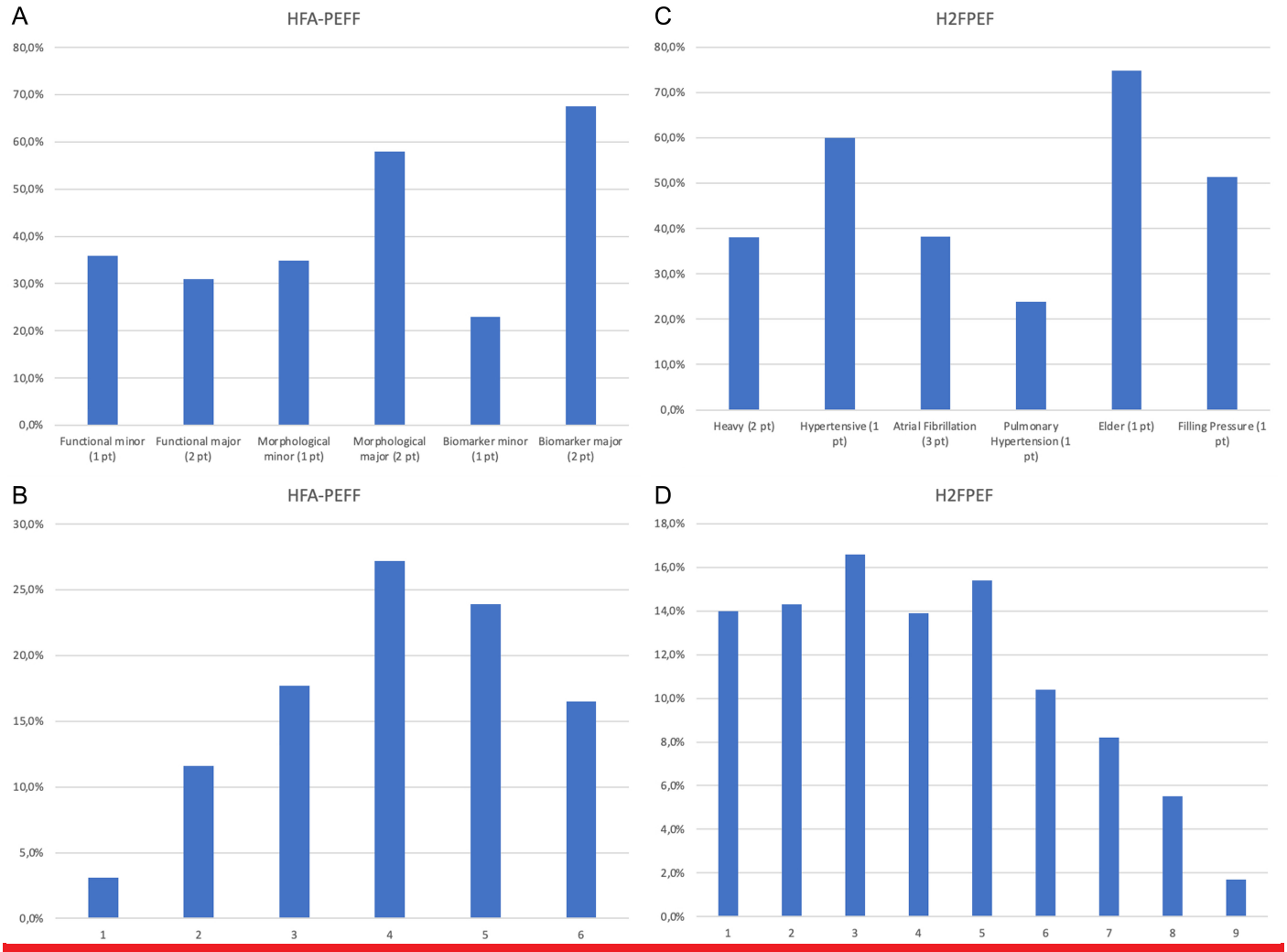

Figure 1. The frequency distribution of HFA-PEFF score domains (A) and likelihood points (B) in the APOLLON trial, as well as the frequency distribution of clinical variables and likelihood points (D) of the H_2FPEF score in the APOLLON registry.

scoring group. Table 1 summarizes the discrepancies between the groups in terms of New York Heart Association classification, BMI, heart rate, hospitalization within the last year, AF, HT, chronic kidney disease, and coronary artery disease.

Table 2 shows that natriuretic peptide levels were higher in the "high likelihood of HFpEF" groups compared to the "low or intermediate likelihood of HFpEF" in both scoring systems. We observed no differences in the eGFR values between groups, but hemoglobin levels were significantly lower in both the high likelihood groups.

Regarding the Doppler echocardiographic examination, the septal *e'* mean was comparable across the groups, but the *E*/*e'* ratios were significantly higher in the high likelihood groups. Additionally, there were differences noted between the groups in terms of LAVI, LA enlargement, and PAPs values. Although there was a difference in LVMI in the HFA-PEFF group, there was no significant difference in H2FPEF scoring between the groups. The findings of the 2-dimensional transthoracic echocardiographic and Doppler data are summarized in Table 3.

To further evaluate the concordance between HFA-PEFF and H_2FPEF scores, a Kendall's tau-b similarity ratio was conducted. The correlation coefficient value was 0.242 ($P < .001$).

DISCUSSION

The finding that the concordance between the HFA-PEFF and H_2FPEF scoring systems for diagnosing HFpEF is low (Kendall's tau-b correlation coefficient of 0.242, $P < .001$) has important implications for the clinical management of patients with suspected HFpEF. While both scoring systems have shown promise in diagnosing HFpEF, the low concordance between them suggests that they may not be interchangeable. Similar results and low concordance were also revealed in the subgroup analysis of PROMIS-HFpEF including 181 patients.[3]

Heart failure with preserved ejection fraction is a complex and heterogeneous clinical syndrome that can be challenging to diagnose. Accurate diagnosis is important because it guides appropriate management, including targeted

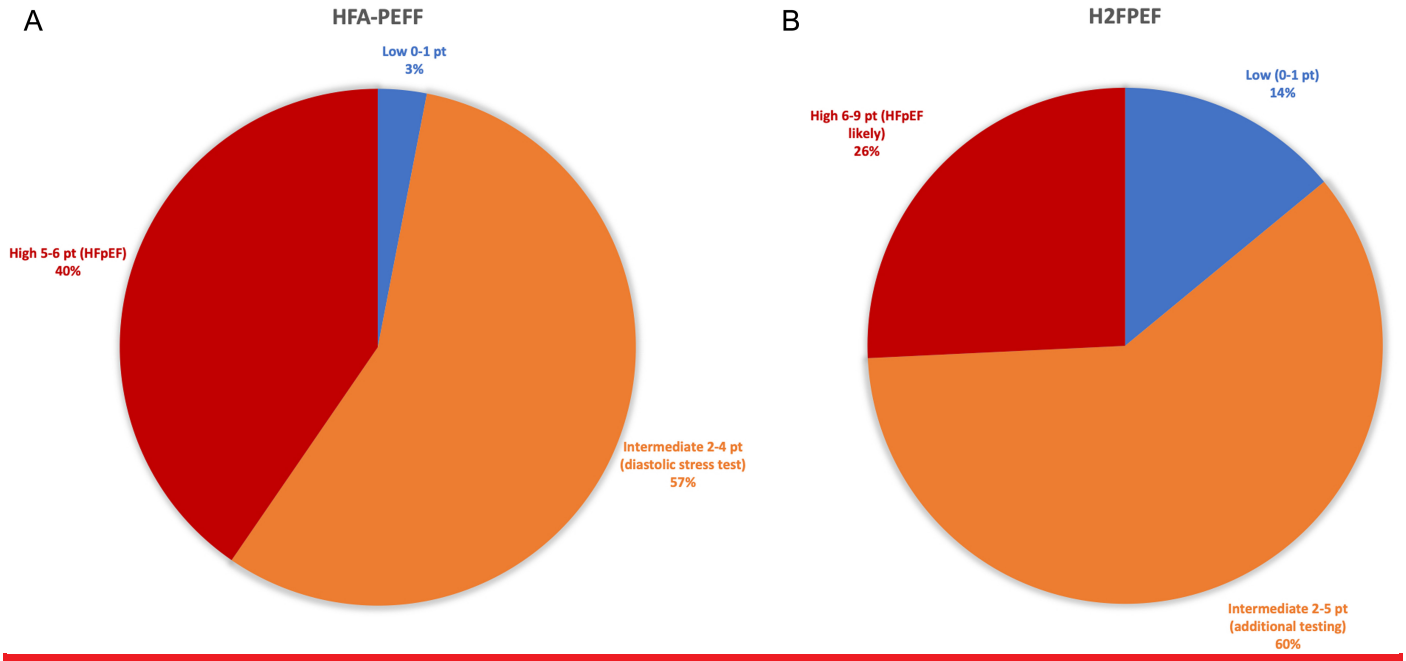

Figure 2. The categorical outcomes of the HFA-PEFF (A) and H2FPEF (B) scores, representing the likelihood of HFpEF in the APOLLON registry. HFpEF, heart failure with preserved ejection fraction.

therapy and enrollment in clinical trials. The 2 scoring systems, HFA-PEFF and H_2FPEF, were developed to aid in the diagnosis of HFpEF by considering a range of clinical, echocardiographic, and laboratory parameters.[11] However, the low concordance between these 2 scoring systems suggests that they may identify and prioritize diagnostic factors differently. Prior research has revealed that low concurrence exists in confirming the diagnosis of HFpEF among these scoring systems. Nevertheless, agreement may be present when assessing similar parameters in identical patients.[12] While this study lacks a direct comparison between the 2 scoring systems, there seem to be no obstacles in utilizing both in clinical practice.

According to a recent study the H_2FPEF score is a better diagnostic tool than the HFA-PEFF score for diagnosing HFpEF (area under the curve: 0.89 vs. 0.82, respectively, $P = .004$) in Japanese patients.[13] Additionally, in a recent multicenter international study, the H_2FPEF algorithm was found to outperform the HFA-PEFF score in accuracy and provide

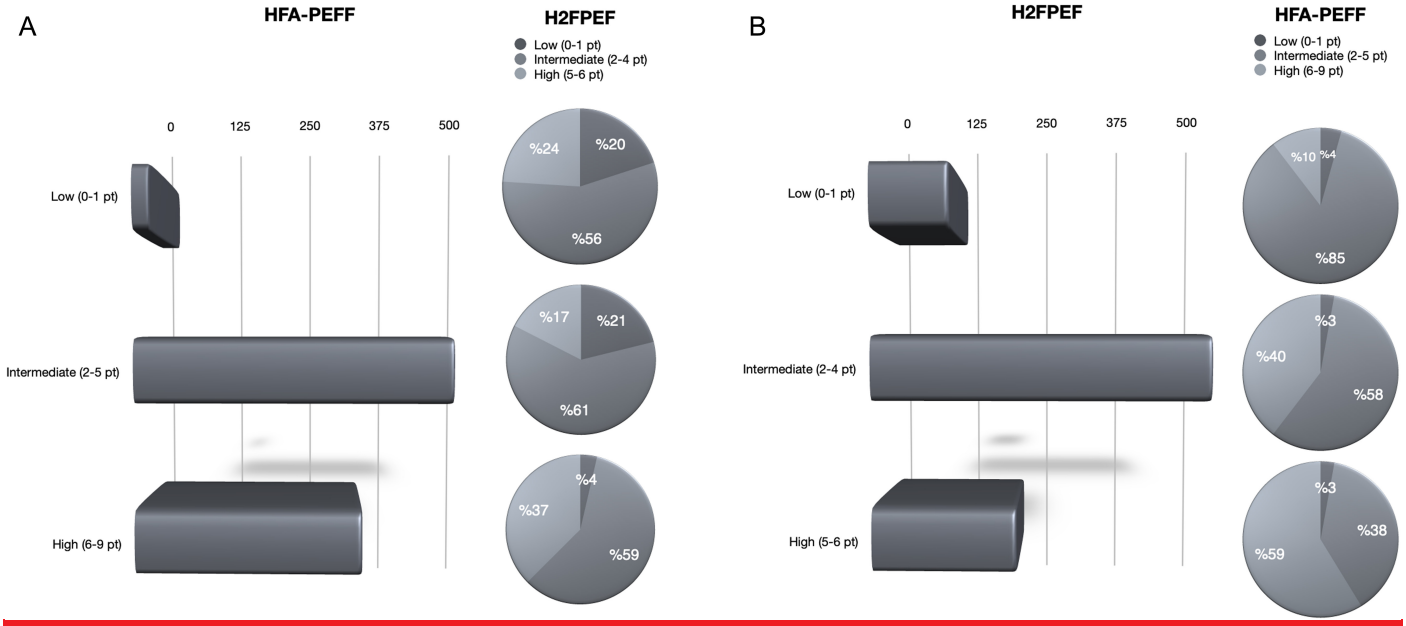

Figure 3. Reclassification of patients into likelihood categories (low, intermediate, and high) from the HFA-PEFF to H_2FPEF score (A) and vice versa (B).

Table 1. Patient Demographics, Characteristics, and Comorbidities

	HFA-PEFF			H2FPEF		
	Low or Intermediate Likelihood 1-4 Points (n = 488)	High Likelihood 5-6 Points (n = 331)	*P*	Low or Intermediate Likelihood 1-5 Points (n = 608)	High Likelihood 6-9 Points (n = 211)	*P*
Age (years)	66.0 (60.0-73.0)	71.0 (64.0-78.0)	<.001	66.0 (59.0-73.0)	71.5 (65.0-78.0)	<.001
Female sex, n (%)	252 (51.6)	221 (46.7)	<.001	322 (53.0)	151 (71.6)	<.001
Smoking, n (%)	85 (17.4)	44 (13.3)	.112	117 (19.2)	12 (5.7)	<.001
Alcohol use, n (%)	24 (4.9)	5 (1.5)	.01	27 (4.4)	2 (0.9)	.018
Educational status, n (%)			.039			<.001
Illiterate	136 (27.9)	100 (30.2)		141 (23.2)	95 (45.0)	
Primary	215 (44.1)	157 (47.4)		282 (46.4)	90 (42.7)	
Secondary	55 (11.3)	41 (12.4)		82 (13.5)	14 (6.6)	
High	54 (11.1)	27 (82)		70 (11.5)	11 (5.2)	
University	2 (5.7)	6 (1.8)		33 (5.4)	1 (0.5)	
Place of residence, n (%)			.896			.081
Rural	151 (30.9)	101 (30.5)		177 (29.1)	75 (35.5)	
Urban	337 (69.1)	230 (6.5)		431 (70.9)	136 (64.5)	
NYHA, n (%)			<.001			<.001
I	138 (28,3)	37 (11.2)		154 (25.3)	21 (10.0)	
II	284 (58.2)	173 (52.3)		336 (55.3)	121 (57.3)	
III	58 (11.9)	103 (31.1)		103 (16.9)	58 (27.5)	
IV	8 (1.6)	18 (5.4)		15 (2.5)	11 (5.2)	
Body mass index, kg/m^2	28.7 (26.0-32.3)	29.1 (25.0-32.5)	.781	28.1 (25.6-31.6)	30.9 (26.1-34.2)	<.001
SBP, mm Hg	130.0 (120.0-145.0)	130.0 (120.0-145.0)	.728	130.0 (120.0-145.0)	130.0 (120.0-146.0)	.642
DBP, mm Hg	80.0 (70.0-88.0)	80.0 (70.0-90.0)	.268	80.0 (70.0-88.0)	80.0 (70.0-90.0)	.106
Heart rate, bpm	78.0 (70.0-90.0)	84.0 (74.0-95.0)	.008	78.0 (70.0-90.0)	89.0 (76.0-105.3)	<.001
Hospitalization for HF in the last year (n) (%)	57 (11.7)	95 (28.7)	<.001	84 (13.8)	68 (32.2)	<.001
Atrial fibrillation (n) (%)	168 (34.4)	145 (43.8)	.007	111 (18.3)	202 (95.7)	<.001
Hypertension (n) (%)	367 (75.2)	256 (77.3)	.482	444 (73.0)	179 (84.8)	.001
Diabetes (n) (%)	133 (27.3)	111 (33.5)	.054	187 (30.8)	57 (27.0)	.306
Chronic kidney disease (n) (%)	42 (8.6)	46 (13.9)	.016	63 (71.6)	25 (11.8)	.548
Obstructive sleep apnea (n) (%)	35 (7.2)	20 (6.0)	.526	43 (7.1)	12 (5.7)	.489
CAD (n) (%)	186 (38.1)	85 (25.7)	<.001	23 (38.0)	40 (19.0)	<.001

bpm, beats per minute; CAD, coronary artery disease; DBP, diastolic blood pressure; HF, heart failure; NYHA, New York Heart Association classification; SBP, systolic blood pressure.

superior discriminatory ability, despite requiring fewer input variables in patients with unexplained dyspnea.[14] In another recent study from Japan, it was shown that H_2FPEF score was superior to accurately discriminate between HFpEF and healthy individuals based on peak ergometry exercise performance.[15] These findings suggest that the H_2FPEF score may be a more helpful tool for clinicians when evaluating patients with unexplained dyspnea for HFpEF diagnosis, but still more evidence is needed to establish the superiority of one over the other.

One possible explanation for the low concordance is that the 2 scoring systems were developed using different populations, with different underlying characteristics and comorbidities.[16] For example, the HFA-PEFF score includes a focus on natriuretic peptide levels, while the H_2FPEF score prioritizes age and comorbidities such as HT and AF. These differences may lead to different diagnostic priorities in patients with suspected HFpEF, depending on the patient's individual clinical profile.[17]

Another potential explanation is that the diagnostic accuracy of both scoring systems may be limited by the complexity and heterogeneity of HFpEF. While these scoring systems attempt to capture important clinical and diagnostic factors, there may be other unmeasured or poorly understood factors that are equally or more important for accurate diagnosis.[18,19] For example, differences in diastolic function, exercise capacity, or inflammation may be important in some patients but not fully captured by either scoring system.[20]

Table 2. Laboratory Parameters

	HFA-PEFF			H_2FPEF		
	Low or Intermediate Likelihood 1-4 Points (n = 488)	High Likelihood 5-6 Points (n = 311)	*P*	Low or Intermediate Likelihood 1-5 Points (n = 608)	High Likelihood 6-9 Points (n = 211)	*P*
NT-proBNP, pg/mL	278.0 (176.0-552.5)	916.0 (458.8-1587.0)	<.001	338.0 (187.0-716.8)	954.0 (422.7-1692.5)	<.001
Fasting blood glucose, mg/dL	102.0 (93.0-122.0)	105.0 (92.5-139.5)	.565	104.0 (94.0-130.0)	101.0 (91.8-123.3)	.095
Serum creatinine, mg/dL	0.82 (0.7-1.0)	0.8 (0.7-1.0)	.307	0.83 (0.7-1.0)	0.8 (0.7-1.0)	.775
Serum sodium, mmol/L	140.0 (139.0-142.0)	141.0 (139.0-143.0)	.065	140.0 (138-142)	141.0 (139.0-142.0)	.032
Serum potassium, mmol/L	4.5 (4.2-4.8)	4.5 (4.2-4.9)	.190	4.5 (4.2-4.8)	4.5 (4.2-4.9)	.052
Uric acid, mg/dL	5.5 (4.7-6.6)	5.6 (4.7-6.8)	.007	5.5 (4.6-6.6)	5.7 (4.8-6.8)	.037
Hemoglobin, g/dL	13.2 (12.3-14.6)	12.5 (11.6-13.5)	<.001	13.1 (12.0-14.2)	12.9 (11.7-13.7)	.044
Leukocyte, x 10^3 µL	7.7 (6.5-9.0)	7.9 (6.7-9.3)	.887	7.9 (6.5-9.2)	7.7 (6.7-8.9)	.614
C-reactive protein, mg/dL	3.2 (1.4-7.0)	4.0 (2.3-9.0)	.058	3.5 (1.7-7.7)	3.7 (2.0- 7.6)	.508
Ferritin, ng/dL	55.0 (29.6-95.6)	49.0 (26.5-85.5)	.128	52.0 (29.0-93.1)	54.9 (26.0-88.0)	.752
TSH, mIU/mL	1.5 (1.0-2.4)	1.4 (0.9-2.1)	.382	1.5 (1.0-2.3)	1.4 (0.9—2.1)	.255

TSH, thyroid-stimulating hormone.

Overall, the finding of low concordance between HFA-PEFF and H_2FPEF scores highlights the ongoing challenge of accurately diagnosing and managing patients with HFpEF. Further research is needed to identify additional diagnostic factors and to develop more accurate and comprehensive diagnostic algorithms. In the meantime, clinicians should continue to use a combination of clinical judgment, diagnostic testing, and targeted therapy to manage patients with suspected or confirmed HFpEF.[19] It is possible that a combination of multiple scoring systems or a new scoring system that incorporates additional clinical and laboratory parameters may be needed to accurately diagnose HFpEF. Furthermore, the low concordance between the HFA-PEFF and H_2FPEF scoring systems suggests that clinicians should be cautious when relying on a single scoring system to diagnose HFpEF and should instead use a comprehensive approach that incorporates multiple diagnostic parameters.[21]

Therefore, for clinicians, this finding underscores the importance of careful and individualized diagnostic evaluation when assessing patients with suspected HFpEF. Although both scoring systems are designed to aid in the diagnosis of HFpEF, they may not always agree on the diagnosis. Clinicians should therefore be aware of the strengths and limitations of each system and use them in conjunction with other clinical and laboratory findings to arrive at an accurate diagnosis. Also, for researchers, this finding highlights the challenge of accurately diagnosing and studying HFpEF. Accurate diagnosis is crucial for selecting patients appropriately for clinical trials due to the heterogeneity of this syndrome. However, the low concordance between the HFA-PEFF and H_2FPEF scoring systems suggests that a standardized diagnostic approach may not be feasible. Future research should consider alternative diagnostic methods or patient stratification based on different clinical characteristics. Previous studies compared various clinical tools, such as natriuretic peptide levels, electrocardiography, and echocardiography, to diagnose HFpEF. However, these studies found that none of these tools could accurately diagnose HFpEF in all patients, indicating the difficulty in diagnosing this syndrome with accuracy.

In the 2016[1] and 2021[2] ESC HF guidelines, the classification of HFpEF, HFrEF, and HFmrEF was proposed. To diagnose patients with suspected HFpEF accurately, the HFA-PEFF and H_2FPEF scoring systems were introduced. These scores suggest categorical outcomes, categorized primarily by clinical features and echocardiography results, to determine the low, moderate, and high probability of HFpEF. Patients with intermediate likelihood require further invasive hemodynamic examinations that pose considerable technical intricacy, expenses, and hazards, especially for HFpEF, which lacks a specific therapy. While both scores have been validated in cohorts experiencing unexplained dyspnea, it is unclear whether they can accurately diagnose HFpEF in more complicated populations.

The APOLLON study evaluated the clinical accuracy and generalizability of HFA-PEFF and H_2FPEF scoring models in patients with HFpEF in the national APOLLON cohort in Türkiye. In this study, 819 patients with HFpEF were enrolled, with high probability HFpEF rates of 40% and 26% reported for HFA-PEFF and H_2FPEF scoring models, respectively. However, 57% and 60% of the groups were identified as intermediate and requiring further investigation, respectively. Although a lower percentage of such cases is desirable, existing evidence shows that invasive tests are critical in HF clinics, particularly when a detailed examination is necessary for the diagnosis of HFpEF. The results are consistent with the findings of Parcha et al,[22] who recently demonstrated that both scoring systems exhibit low sensitivity but high specificity in diagnosing HFpEF. The H_2FPEF score had a higher specificity but a lower sensitivity than the HFA-PEFF score. These findings suggest that both scores may be useful in ruling out HFpEF but not in ruling it in. Similarly, Sanders-van Wijk et al[23] recently demonstrated that the 2 scoring systems largely disagree in classifying patients with

Table 3. Two-Dimensional Transthoracic Echocardiographic and Doppler Data

	HFA-PEFF			H_2FPEF		
	Low or Intermediate Likelihood 1-4 Points (n = 488)	High Likelihood 5-6 Points (n = 331)	*P*	Low or Intermediate Likelihood 1-5 Points (n = 608)	High Likelihood 6-9 Points (n = 211)	*P*
LVEF, %	60.0 (55.0-65.0)	60.0 (55.0-62.0)	.312	60.0 (55.0-63.8)	60.0 (55.0-65.0)	.508
e', cm/s	7.3 (6.4-8.1)	7.1 (6.0-8.0)	.152	7.1 (6.0-8.0)	7.5 (6.5-8.1)	.066
E/e'	8.2 (7.0-10.5)	11.2 (9.0-15)	<.001	9.0 (7.1-12.0)	11.0 (9.0-13.0)	<.001
LV diastolic dysfunction, n (%)			<.001			<.001
None	58 (11.9)	46 (13.9)		70 (11.5)	34 (16.1)	
Grade 1	195 (40.0)	30 (9.1)		198 (32.6)	27 (12.8)	
Grade 2	179 (36.7)	132 (39.9)		216 (35.5)	95 (45.0)	
Grade 3	56 (11.5)	123 (37.2)		124 (20.4)	55 (26.1)	
LVED dimension, mm	47.0 (44.0-51.0)	48.0 (45.0-51.0)	.148	48.0 (44.0-51.0)	48.0 (44.0-51.0)	.662
LVES dimension, mm	31.0 (28.0-35.0)	32.0 829.0-36.0)	.115	31.0 (28.0-35.0)	32.0 (29.0-37.0)	.296
IVS dimension, mm	11.0 (10.0-12.0)	11.0 (10.0-13.0)	.01	11.0 (10.0-12.0)	11.0 (10.0-12.0)	.119
LVPW dimension, mm	10.0 (10.0-11.0)	11.0 (10.0-12.0)	<.001	11.0 (10.0-12.0)	10.0 (10.0-11.0)	.664
LAVI, mL/m^2	31.0 (27.0-36.0)	40.0 (35.0-47.5)	<.001	33.0 (28.0-38.0)	39.5 (32.0-48.3)	<.001
LA enlargement (n) (%)	147 (30.1)	245 (74.0)	<.001	250 (41.1)	142 (67.3)	<.001
LVMI, g/m^2	102.0 (87.1-119.5)	111.8 (90.8-130.9)	<.001	105.1 (88.2-125.5)	104.0 (89.1-122.8)	.804
PAPs, mm Hg	23.0 (15.0-30.0)	35.0 (24.5-40.0)	<.001	24.5 (15.0-32.0)	35.0 (27.0-40.0)	<.001
Mitral regurgitation, n (%)			<.001			<.001
None	211 (43.2)	59 (17.8)		241 (39.6)	29 (13.7)	
Mild	230 (47.1)	175 (52.9)		288 (47.4)	117 (55.5)	
Moderate	47 (9.6)	94 (28.4)		76 (12.5)	65 (30.8)	
Severe	0 (0)	3 (0.9)		3 (0.5)	0 (0)	
Mitral stenosis, n (%)			.561			.334
None	4700 (96.3)	318 (96.1)		588 (96.7)	200 (94.8)	
Mild	13 (2.7)	7 (2.1)		12 (2.0)	8 (3.8)	
Moderate	5 (1.0)	6 (1.8)		8 (1.3)	3 (1.4)	
Aortic regurgitation, n (%)			<.001			<.001
None	398 (81.6)	228 (68.9)		485 (79.8)	141 (66.8)	
Mild	82 (16.8)	86 (26.0)		102 (16.8)	66 (31.3)	
Moderate	8 (1.6)	17 (5.1)		21 (3.5)	4 (1.9)	
Aortic stenosis, n (%)			.004			
None	482 (98.8)	314 (94.9)		595 (97.9)	201 (95.3)	.042
Mild	4 (0.8)	11 (3.3)		9 (1.5)	6 (2.8)	
Moderate	2 (0.4)	6 (1.8)		4 (0.7)	4 (1.9)	
Tricuspid regurgitation, n (%)			<.001			<.001
None	227 (46.5)	73 (22.1)		261 (42.9)	39 (18.5)	
Mild	211 (43.2)	124 (37.5)		255 (41.9)	80 (37.9)	
Moderate	45 (9.1)	113 (34.1)		78 (12.8)	80 (37.9)	
Severe	5 (1.0)	21 (6.3)		14 (2.3)	12 (5.7)	

IVS, interventricular septum; LA, left atrium; LV, left ventricle; LVED, left ventricle end diastolic; LVEF, left ventricle ejection fraction; LVES, left ventricle end systolic; LVMI, left ventricle mass index; LVPW, left ventricle posterior wall; PAPs, systolic pulmonary artery pressure.

suspected HFpEF. Therefore, further investigations may be necessary to establish a diagnosis in intermediate likelihood cases. The H_2FPEF score was derived from a single-center, retrospective analysis of patients with acute dyspnea etiology referred for invasive hemodynamic exercise testing. It has also been mentioned in previous studies that the criteria with low specificity to HFpEF in the H_2FPEF score reduced the predictive power.[24] We might say that the H_2FPEF score is a correlation study that indicates a potential HFpEF diagnosis. Patients with lower BMI, single antihypertensive use or sinus rhythm may be excluded/included in the low likelihood HFpEF. However, the HFA-PEFF score provides more

comprehensive steps in diagnosing and excluding the HFpEF. This includes measuring natriuretic peptides, using invasive methods when necessary, and determining specific etiology.

Study Limitations

Since our study was cross-sectional and without follow-up, we were unable to observe its impact on prognosis. Additionally, GLS echocardiographic evaluations were not performed due to limited availability across centers; however, alternative echocardiographic parameters were analyzed. If GLS measurement is not feasible in clinical practice, these alternative parameters remain viable. Alternatively, cardiac magnetic resonance can be used if echocardiographic measurements like LAVI or LVMI, or wall thickness, are not achievable. The APOLLON study evaluated outpatients who met the ESC HF criteria through clinical and echocardiographic assessments, without invasive testing. Lastly, due to its design, the study did not assess the cost-effectiveness of implementing these scores in clinical practice.

CONCLUSION

Our study highlights the discrepancies between the HFA-PEFF and H_2FPEF scoring systems in diagnosing HFpEF and underscores the significance of precise and personalized diagnostic assessments of patients with suspected HFpEF. Clinicians must be vigilant of the respective strengths and limitations of each scoring system and utilize them in conjunction with other clinical and laboratory findings to arrive at an accurate diagnosis. Future research endeavors should concentrate on identifying additional diagnostic factors, developing more accurate and comprehensive diagnostic algorithms, as well as exploring alternative methods for patient stratification based on varying clinical attributes.

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