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Prognostic value of the HFA-PEFF and H(2) FPEF scores for clinical outcomes in patients with coronary artery disease and preserved ejection fraction

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ABSTRACT

Background: Coronary artery disease (CAD) is a significant risk factor for heart failure with preserved ejection fraction (HFpEF). While the HFA-PEFF and H2FPEF scoring systems were developed to aid in the diagnosis of HFpEF, their predictive performance in patients with CAD remains underexplored.
Methods: This single-center retrospective cohort study included patients who underwent drug-eluting stent implantation between January 2018 and October 2022. The study's primary endpoint was a composite outcome of all-cause mortality and heart failure hospitalization during follow-up. Kaplan-Meier survival curves were used to evaluate time to adverse events, and differences between groups were analyzed using the log-rank test. Cox proportional hazards regression was applied to assess the independent predictive value of the HFA-PEFF and H2FPEF scores for adverse outcomes.
Results: The HFA-PEFF score categorized 65.7 % of patients as intermediate, 25.1 % as high, and 9.2 % as low probability for HFpEF. The H2FPEF score placed 77.3 % in the intermediate group, 19.3 % in the low, and 3.4 % in the high-probability group. The median follow-up period was 29 months. Adjusted Cox proportional hazard regression revealed the HFA-PEFF score was significantly associated with the composite endpoint of all-cause mortality and heart failure hospitalization (HR: 1.33, 95 % CI:1.07–1.65). Each point increase in the HFA-PEFF score raised heart failure hospitalization risk by 26 % (HR:1.26, 95 % CI: 1.05–1.51). In contrast, the H2FPEF score did not show a significant association with adverse events.
Conclusions: The HFA-PEFF score demonstrated superior prognostic value for predicting adverse outcomes in CAD patients with preserved ejection fraction compared to the H2FPEF score.

1. Introduction

Coronary artery disease (CAD) remains the leading health burden in both developed and developing countries [1]. Left ventricular ejection fraction (LVEF) plays a pivotal role in the prognosis and management of CAD. Patients with preserved LVEF, while seemingly at lower risk compared to those with reduced LVEF [2,3], are not exempt from adverse outcomes. The ARIC study demonstrated that CAD without baseline LVEF decline was associated with a high risk of heart failure [4]. Moreover, studies have shown that these patients face an increased risk of MI, stroke, mortality, and revascularization [5,6]. Thus, accurate risk stratification in patients with CAD and preserved LVEF is essential for improving clinical outcomes.

Myocardial ischemia and fibrosis frequently result in diastolic dysfunction in patients with CAD [7]. CAD is a recognized etiological factor in the development of heart failure with preserved ejection fraction (HFpEF), with autopsy data revealing that over 60 % of HFpEF patients had coexisting CAD [8]. Studies have demonstrated that in patients with CAD, parameters reflecting diastolic function—including invasive assessments and echocardiographic findings—can aid in risk stratification [9,10]. Furthermore, CAD patients with concomitant HFpEF were at high risk for cardiovascular death [11]. This highlights

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[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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the importance for accurate identification of diastolic dysfunction and the potential for HFpEF in patients with CAD.

The HFA-PEFF score and the H2FPEF score were introduced to facilitate the diagnosis of HFpEF. The HFA-PEFF score integrates clinical, echocardiographic, and biomarker data to assess the likelihood of HFpEF [12], whereas the H2FPEF score offers a simpler approach by focusing on easily accessible clinical variables [13], enhancing its applicability in routine practice. Both scoring systems not only facilitated the diagnosis of HFpEF but also showed promise in predicting adverse outcomes, such as heart failure hospitalization and mortality [14–16].

Despite their growing use, the application of these scores in CAD populations remains limited. Whether the HFA-PEFF and H2FPEF scores can reliably predict outcomes in CAD patients remains unclear. This study aims to assess and compare the prognostic value of the HFA-PEFF and H2FPEF scores in predicting adverse outcomes among CAD patients with preserved ejection fraction.

2. Methods

2.1. Study population and data collection

As previously described, this single-center, retrospective cohort study was conducted in the Department of Cardiology at the First People's Hospital of Foshan [17]. Patients who underwent drug-eluting stent implantation between January 2018 and October 2022 were consecutively screened. Exclusion criteria included: (1) a diagnosis of acute ST-elevation myocardial infarction or non-ST-elevation myocardial infarction, (2) LVEF < 50 %, (3) missing body mass index (BMI) and N-terminal pro-brain natriuretic peptide (NT-proBNP) data, and (4) insufficient key echocardiographic data for calculating the H2FPEF and HFA-PEFF scores. The detailed process of subject enrollment and screening is outlined in Fig. 1. This study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the First People's Hospital of Foshan, which waived the requirement for informed consent due to its retrospective design.

2.2. Clinical, laboratory, and echocardiographic data

Demographic characteristics, comorbidities, physical examination results, laboratory findings, and treatment details were obtained from electronic medical records. BMI was derived by dividing body weight in kilograms by the square of height in meters. NT-proBNP levels were determined using the electrochemiluminescence (ECLIA) monoclonal technique (Roche Diagnostics).

Echocardiographic assessments were performed by trained physicians following the detailed guidelines established by the American Society of Echocardiography [18]. Measurements, including left ventricular end-diastolic diameter (LVEDD), interventricular septum thickness (IVS), and posterior wall thickness (PWT) were taken from parasternal long-axis views. LVEF was calculated using Simpson's method. Relative wall thickness was computed as (2*PWT/LVEDD). Left ventricular mass (LVM) was estimated through the formula: $LVM = 0.8 * 1.04 * [(LVEDD + IVS + PWT)^3 - LVEDD^3] + 0.6$. LVM and left atrial volume (LAV) were indexed to body surface area (LVMI and LAVI, respectively). Early diastolic velocity (e') at the mitral annulus was derived via tissue Doppler imaging at septal wall sites in the apical four-chamber view. Mitral inflow velocity was assessed using pulsed-wave Doppler in the same view. Pulmonary arterial systolic pressure (PASP) was calculated based on the peak velocity of the tricuspid regurgitation jet, alongside an estimation of right atrial pressure.

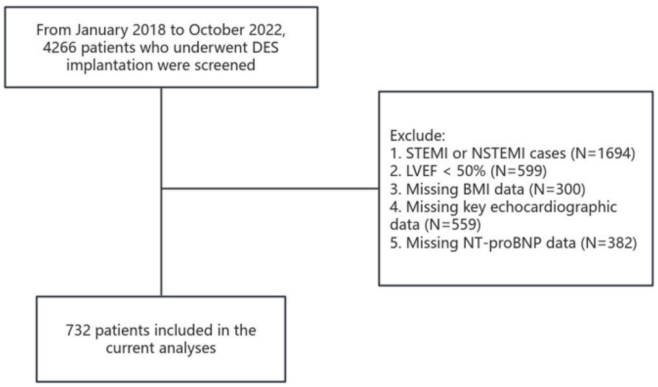

Fig. 1. The overview of the selection of study participants.

2.3. HFA-PEFF and H2FPEF score calculation

The HFA-PEFF score was derived based on echocardiographic findings (including functional and morphological echocardiographic variables) and laboratory data (NT-proBNP). The score ranged from 0 to 6, with values of 0–1 indicating low likelihood, 2–4 indicating intermediate likelihood, and 5–6 indicating high likelihood of HFpEF(12). Global longitudinal strain (GLS), one of the functional scores, was not available in this study.

The H2FPEF score was calculated using six clinical and echocardiographic parameters: obesity (BMI > 30 kg/m2), age > 60 years, atrial fibrillation, hypertension (treated with two or more antihypertensive drugs), PASP > 35 mmHg, and E/e′ ratio > 9. The score ranged from 0 to 9. Patients were ranked as having a low, intermediate, and high probability of HFpEF when their score was 0–1,2–5 and > 5, respectively [13].

2.4. Follow-up and outcomes

Follow-up was conducted through medical record reviews, patient interviews, and phone calls to patients or their families. If an adverse event occurred, a medical record was reviewed to verify the event. The primary endpoint of this study was the incidence of composite outcomes of all-cause mortality and heart failure hospitalization during follow-up. The secondary endpoint was the incidence of heart failure hospitalization.

2.5. Statistical analysis

Descriptive statistics were used to summarize baseline patient characteristics. Continuous variables were expressed as mean ± standard deviation or median (interquartile range) depending on their distribution, and compared using Student's *t*-test or Mann–Whitney *U* test as appropriate. Categorical variables were reported as counts and percentages, with comparisons made using the chi-square test or Fisher's exact test.

For survival analysis, Kaplan-Meier curves were constructed to evaluate the time to adverse events, with differences between groups compared using the log-rank test. Cox proportional hazard regression was employed to assess the independent predictive ability of the HFA-PEFF and H2FPEF scores for adverse outcomes. Variables found to be statistically significant in univariable analysis ($p < 0.1$) or considered clinically important were included in the multivariable Cox regression model. However, variables already accounted for in the HFA-PEFF or H2FPEF scores were not included to avoid redundancy. For the HFA-PEFF score, the model was adjusted for age, gender, New York Heart Association (NYHA) class II-IV, diabetes mellitus, BMI, hemoglobin, albumin, uric acid, estimated glomerular filtration rate (eGFR), and LVEF. For the H2FPEF score, the model was adjusted for gender, NYHA class II-IV, diabetes mellitus, hemoglobin, albumin, uric acid, eGFR, LVEF, and NT-proBNP. Additionally, discharge medications were incorporated into both models to assess robustness. Hazard ratios (HR) with 95 % confidence intervals (CI) were calculated, and a p-value of <

0.05 was considered statistically significant. All statistical analyses were performed using the R Programming Language (version 4.2.1).

3. Results

3.1. Baseline characteristics

Baseline characteristics of the study population stratified by HFA-PEFF and H2FPEF groups are summarized in Tables 1 and 2. Patients in the high HFA-PEFF score group were older, had lower proportions of males, and had higher systolic blood pressure. A greater proportion of patients in the high-score group were classified as NYHA class II-IV. In terms of comorbidities, hypertension, diabetes, atrial fibrillation, and chronic kidney disease were more prevalent in the high-score group. Laboratory findings revealed that patients in the high HFA-PEFF score group had significantly lower hemoglobin, albumin, high-density

Table 1
Clinical characteristics, laboratory and echocardiographic findings and medications of the study population stratified by the HFA-PEFF groups (low vs. intermediate vs. high).

Variables	Total (n = 732)	LowHFA-PEFF score (n = 67)	Intermediate HFA-PEFF score (n = 481)	High HFA-PEFF score (n = 184)	*p*-value
Clinical characteristics					
Age (years)	66.00 (58.00, 72.00)	56.00 (48.50,64.00)	65.00 (58.00,71.00)	69.00 (63.00,75.00)	0<.001
Male sex, n (%)	529 (72.27)	58 (86.57)	360 (74.84)	111 (60.33)	0<.001
BMI (kg/m^2)	24.68 ± 3.18	24.32 ± 2.71	24.87 ± 3.05	24.34 ± 3.61	0.095
Obesity, n(%)	36 (4.92)	2 (2.99)	28 (5.82)	6 (3.26)	0.293
SBP (mmHg)	137.07 ± 18.82	129.73 ± 17.01	136.68 ± 18.11	140.78 ± 20.39	0<.001
DBP (mmHg)	79.00 (71.00, 88.00)	77.00 (71.00,84.00)	79.00 (71.00,88.00)	79.00 (69.00,89.00)	0.347
HR (bpm)	73.00 (66.00, 82.00)	72.00 (64.50,81.00)	74.00 (67.00,82.00)	74.00 (66.75,81.25)	0.649
Smoking, n (%)	258 (35.25)	24 (35.82)	163 (33.89)	71 (38.59)	0.522
Drinking, n (%)	171 (23.36)	12 (17.91)	116 (24.12)	43 (23.37)	0.531
NYHA class II-IV, n (%)	314 (42.90)	24 (35.82)	192 (39.92)	98 (53.26)	0.004
Hypertension, n (%)	469 (64.07)	27 (40.30)	303 (62.99)	139 (75.54)	0<.001
Diabetes, n (%)	217 (29.64)	7 (10.45)	144 (29.94)	66 (35.87)	0<.001
Dyslipidaemia, n (%)	238 (32.51)	33 (49.25)	153 (31.81)	52 (28.26)	0.006
Hyperuricemia, n (%)	205 (28.01)	23 (34.33)	130 (27.03)	52 (28.26)	0.458
Atrial fibrillation, n (%)	23 (3.14)	0 (0.00)	12 (2.49)	11 (5.98)	0.021
History of stroke, n (%)	70 (9.56)	5 (7.46)	46 (9.56)	19 (10.33)	0.792
CKD, n(%)	74 (10.14)	1 (1.52)	40 (8.32)	33 (18.03)	0<.001
SYNTAX score	14.00 (9.00, 19.00)	15.00 (8.50,20.00)	14.00 (9.00,19.00)	15.00 (10.00,19.00)	0.518
Laboratory findings					
Haemoglobin (g/L)	135.00 (123.00, 145.00)	142.00 (131.50,151.50)	136.00 (125.00,146.00)	127.00 (116.00,138.00)	0<.001
Albumin (g/L)	40.10 (38.10, 42.30)	40.80 (39.10,42.60)	40.35 (38.30,42.50)	39.00 (37.25,41.45)	0<.001
Uric acid (μmol/L)	409.54 ± 110.24	407.73 ± 113.92	407.99 ± 110.90	414.24 ± 107.66	0.807
eGFR (mL/min/1.73 m^2)	89.62 ± 24.67	94.79 ± 19.21	91.94 ± 24.31	81.65 ± 25.69	0<.001
Total cholesterol (mmol/L)	4.17 (3.43, 4.97)	4.44 (3.50,5.32)	4.19 (3.47,4.95)	4.04 (3.32,4.99)	0.250
Triglyceride (mmol/L)	1.52 (1.07, 2.17)	1.42 (1.07,1.79)	1.52 (1.06,2.24)	1.50 (1.10,2.12)	0.366
Low density lipoprotein (mmol/L)	2.39 (1.79, 3.12)	2.67 (1.77,3.36)	2.41 (1.81,3.02)	2.23 (1.77,3.13)	0.320
High density lipoprotein (mmol/L)	1.01 (0.89, 1.16)	1.10 (0.94,1.27)	1.02 (0.89,1.17)	1.00 (0.86,1.14)	0.010
Fasting blood glucose (mmol/L)	4.96 (4.61, 5.71)	4.75 (4.50,5.06)	5.00 (4.62,5.71)	5.04 (4.65,5.83)	0.044
NT-proBNP (ng/L)	115.15 (49.30, 259.50)	47.00 (28.50,68.05)	81.00 (43.00,147.10)	526.35 (301.18,1286.25)	0<.001
Echocardiographic findings					
IVS (mm)	11.00 (10.00, 13.00)	10.00 (9.00,11.00)	11.00 (10.00,12.00)	12.00 (11.00,14.00)	0<.001
LVEDD (mm)	44.00 (41.00, 48.00)	46.00 (41.50,48.00)	44.00 (41.00,47.00)	44.00 (41.00,49.00)	0.512
PWT (mm)	10.00 (9.00, 11.00)	9.00 (9.00,10.00)	10.00 (9.00,11.00)	10.00 (9.00,12.00)	0<.001
LAVI (mm)	19.85 (15.27, 25.08)	17.25 (13.68,21.14)	19.47 (15.17,24.17)	23.75 (16.74,29.01)	0<.001
LVEF	66.00 (61.00, 70.00)	67.00 (62.00,70.00)	66.00 (61.00,70.00)	65.00 (60.00,70.00)	0.223
PASP (mmHg)	28.00 (23.00, 33.00)	26.00 (22.00,30.50)	28.00 (23.00,33.00)	28.00 (23.00,34.25)	0.021
Septal e' (cm/s)	6.00 (5.00, 7.21)	8.70 (8.00,10.40)	6.00 (5.00,7.06)	5.00 (4.00,6.00)	0<.001
E/e' ratio	11.20 (9.20, 13.50)	7.90 (6.85,8.83)	11.00 (9.40,13.10)	12.85 (10.88,15.70)	0<.001
LVMI (g/m^2)	97.51 (83.11, 113.59)	90.33 (71.99,97.38)	95.88 (82.74,108.21)	115.38 (92.46,128.92)	0<.001
RWT	0.48 (0.43, 0.54)	0.41 (0.39,0.48)	0.48 (0.43,0.53)	0.52 (0.46,0.57)	0<.001
Medications at discharge					
Aspirin, n (%)	708 (96.72)	67 (100.00)	468 (97.30)	173 (94.02)	0.030
ADP antagonist, n (%)	723 (98.77)	66 (98.51)	477 (99.17)	180 (97.83)	0.286
ACEi/ARBs, n (%)	419 (57.24)	22 (32.84)	274 (56.96)	123 (66.85)	0<.001
Statins, n (%)	714 (97.54)	67 (100.00)	471 (97.92)	176 (95.65)	0.130
Beta-blockers, n (%)	520 (71.04)	40 (59.70)	335 (69.65)	145 (78.80)	0.007
SGLT2, n(%)	79 (10.79)	2 (2.99)	57 (11.85)	20 (10.87)	0.091
Furosemide, n (%)	40 (5.46)	1 (1.49)	17 (3.53)	22 (11.96)	0<.001
Spirolactone, n(%)	34 (4.64)	0 (0.00)	9 (1.87)	25 (13.59)	0<.001
Digoxin, n(%)	9 (1.23)	0 (0.00)	2 (0.42)	7 (3.80)	0.003
Outcomes					
Death, n(%)	25 (3.42)	0 (0.00)	13 (2.71)	12 (6.52)	0.014
HF hospitalization, n(%)	100 (13.66)	4 (5.97)	51 (10.60)	45 (24.46)	<0.001

ACEi: Angiotensin-Converting Enzyme Inhibitors; ARB: angiotensin receptor blockers; BMI: body mass index; CKD: chronic kidney disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HF: heart failure; HR: heart rate; IVS: interventricular septum thickness; LAVI: left atrial volume index; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; LVPWT: left ventricular posterior wall thickness; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; PASP: pulmonary arterial systolic pressure; RWT: relative wall thickness; SBP: systolic blood pressure.

Table 2
Clinical characteristics, laboratory and echocardiographic findings and medications of the study population stratified by the H_2FPEF groups (low vs. intermediate vs. high).

Variables	Total (n = 732)	Low H_2FPEF score (n = 141)	Intermediate H_2FPEF score (n = 566)	High H_2FPEF score (n = 25)	*p*-value
Clinical characteristics					
Age (years)	66.00 (58.00, 72.00)	55.00 (48.00,59.00)	67.00 (62.00,73.00)	72.00 (67.00,73.00)	0<.001
Male sex, n (%)	529 (72.27)	124 (87.94)	388 (68.55)	17 (68.00)	0<.001
BMI (kg/m^2)	24.68 ± 3.18	24.69 ± 2.39	24.64 ± 3.30	25.72 ± 4.02	0.247
Obesity, n(%)	36 (4.92)	0 (0.00)	32 (5.65)	4 (16.00)	0<.001
SBP (mmHg)	137.07 ± 18.82	129.52 ± 16.39	138.64 ± 19.01	144.12 ± 16.26	0<.001
DBP (mmHg)	79.00 (71.00, 88.00)	79.00 (72.00,90.00)	79.00 (71.00,88.00)	81.00 (75.00,89.00)	0.465
HR (bpm)	73.00 (66.00, 82.00)	74.00 (66.00,82.00)	73.00 (67.00,82.00)	73.00 (67.00,76.00)	0.824
Smoking, n (%)	258 (35.25)	50 (35.46)	200 (35.34)	8 (32.00)	0.942
Drinking, n (%)	171 (23.36)	31 (21.99)	135 (23.85)	5 (20.00)	0.826
NYHA class II-IV, n (%)	314 (42.90)	56 (39.72)	245 (43.29)	13 (52.00)	0.481
Hypertension, n (%)	469 (64.07)	24 (17.02)	421 (74.38)	24 (96.00)	0<.001
Diabetes, n (%)	217 (29.64)	30 (21.28)	178 (31.45)	9 (36.00)	0.047
Dyslipidaemia, n (%)	238 (32.51)	56 (39.72)	175 (30.92)	7 (28.00)	0.121
Hyperuricemia, n (%)	205 (28.01)	43 (30.50)	157 (27.74)	5 (20.00)	0.536
Atrial fibrillation, n (%)	23 (3.14)	0 (0.00)	8 (1.41)	15 (60.00)	0<.001
History of stroke, n (%)	70 (9.56)	10 (7.09)	57 (10.07)	3 (12.00)	0.513
CKD, n(%)	74 (10.14)	5 (3.57)	65 (11.50)	4 (16.00)	0.013
SYNTAX score	14.00 (9.00, 19.00)	13.00 (8.00,19.00)	15.00 (9.00,19.00)	18.00 (14.00,22.00)	0.074
Laboratory findings					
Haemoglobin (g/L)	135.00 (123.00, 145.00)	140.00 (128.00,151.50)	133.00 (121.00,143.00)	132.00 (120.00,140.00)	0<.001
Albumin (g/L)	40.10 (38.10, 42.30)	40.80 (39.00,42.95)	39.90 (37.82,42.18)	39.80 (37.00,41.30)	0.002
Uric acid (μmol/L)	409.54 ± 110.24	415.97 ± 102.75	407.58 ± 111.76	419.65 ± 117.54	0.667
eGFR (mL/min/1.73 m^2)	89.62 ± 24.67	96.01 ± 22.53	88.17 ± 25.02	86.64 ± 23.16	0.003
Total cholesterol (mmol/L)	4.17 (3.43, 4.97)	4.36 (3.70,5.00)	4.12 (3.40,4.97)	4.29 (3.56,4.78)	0.337
Triglyceride (mmol/L)	1.52 (1.07, 2.17)	1.52 (1.08,2.17)	1.52 (1.07,2.18)	1.45 (0.82,2.12)	0.739
Low density lipoprotein (mmol/L)	2.39 (1.79, 3.12)	2.60 (1.91,3.24)	2.35 (1.77,3.02)	2.35 (1.89,3.02)	0.103
High density lipoprotein (mmol/L)	1.01 (0.89, 1.16)	0.98 (0.86,1.11)	1.03 (0.90,1.17)	1.06 (0.93,1.17)	0.076
Fasting blood glucose (mmol/L)	4.96 (4.61, 5.71)	4.81 (4.45,5.26)	5.00 (4.64,5.74)	5.24 (4.69,7.10)	0.018
NT-proBNP (ng/L)	115.15 (49.30, 259.50)	63.60 (32.00,151.90)	124.30 (57.65,283.00)	284.40 (123.80,947.90)	0<.001
Echocardiographic findings					
IVS (mm)	11.00 (10.00, 13.00)	11.00 (10.00,11.00)	11.00 (10.00,13.00)	11.00 (10.00,13.00)	0<.001
LVEDD (mm)	44.00 (41.00, 48.00)	45.00 (42.00,48.00)	44.00 (41.00,48.00)	45.00 (42.00,49.00)	0.101
PWT (mm)	10.00 (9.00, 11.00)	10.00 (9.00,10.00)	10.00 (9.00,11.00)	10.00 (9.00,11.00)	0<.001
LAVI (mm)	19.85 (15.27, 25.08)	18.17 (14.29,21.38)	20.33 (15.58,25.53)	25.80 (20.54,33.03)	0<.001
LVEF	66.00 (61.00, 70.00)	66.00 (61.00,69.00)	66.00 (61.00,70.00)	65.00 (60.00,69.00)	0.706
PASP (mmHg)	28.00 (23.00, 33.00)	24.00 (21.00,28.00)	29.00 (23.25,34.00)	37.00 (29.00,42.00)	0<.001
Septal e' (cm/s)	6.00 (5.00, 7.21)	7.25 (6.00,8.99)	5.90 (4.80,7.00)	5.36 (4.90,6.50)	0<.001
E/e' ratio	11.20 (9.20, 13.50)	8.50 (7.30,10.40)	11.60 (9.90,14.03)	13.20 (11.50,15.00)	0<.001
LVMI (g/m^2)	97.51 (83.11, 113.59)	89.36 (77.57,103.36)	99.36 (84.61,116.03)	100.26 (82.74,119.44)	0<.001
RWT	0.48 (0.43, 0.54)	0.46 (0.40,0.50)	0.49 (0.43,0.55)	0.48 (0.43,0.53)	0<.001
Medications at discharge					
Aspirin, n (%)	708 (96.72)	139 (98.58)	553 (97.70)	16 (64.00)	0<.001
ADP antagonist, n (%)	723 (98.77)	139 (98.58)	560 (98.94)	24 (96.00)	0.252
ACEi/ARBs, n (%)	419 (57.24)	40 (28.37)	363 (64.13)	16 (64.00)	0<.001
Statins, n (%)	714 (97.54)	139 (98.58)	551 (97.35)	24 (96.00)	0.432
Beta-blockers, n (%)	520 (71.04)	88 (62.41)	413 (72.97)	19 (76.00)	0.040
SGLT2, n(%)	79 (10.79)	15 (10.64)	61 (10.78)	3 (12.00)	0.979
Furosemide, n (%)	40 (5.46)	6 (4.26)	30 (5.30)	4 (16.00)	0.055
Spirolactone, n(%)	34 (4.64)	3 (2.13)	27 (4.77)	4 (16.00)	0.009
Digoxin, n(%)	9 (1.23)	2 (1.42)	6 (1.06)	1 (4.00)	0.252
Outcomes					
Death, n(%)	25 (3.42)	1 (0.71)	24 (4.24)	0 (0.00)	0.097
HF hospitalization, n(%)	100 (13.66)	15 (10.64)	82 (14.49)	3 (12.00)	0.477

ACEi: Angiotensin-Converting Enzyme Inhibitors; ARB: angiotensin receptor blockers; BMI: body mass index; CKD: chronic kidney disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HF: heart failure; HR: heart rate; IVS: interventricular septum thickness; LAVI: left atrial volume index; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; LVPWT: left ventricular posterior wall thickness; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; PASP: pulmonary arterial systolic pressure; RWT: relative wall thickness; SBP: systolic blood pressure.

lipoprotein, and eGFR, and markedly elevated levels of NT-proBNP. Echocardiographic parameters showed that the high-score group had a significantly increased E/e'ratio, LAVI, LVMI, and PASP. Regarding medications at discharge, cardiovascular medications use was higher in the high-score group, except for aspirin use, which was used less, and no significant differences were found for ADP antagonist and statin. Conversely, there were no significant differences in NYHA class, dyslipidemia, high-density lipoprotein, or use of furosemide and digoxin among the HF2PEF groups, while other characteristics mirrored those of the HFA-PEFF groups.

After a median follow-up of 29 [19, 50] months, the study observed 25 deaths and 100 heart failure hospitalizations. Table 3 compares the characteristics between patients with and without events. Those who experienced events tended to be older, were less likely to be male, and had a lower BMI. They were also more likely to have diabetes and chronic kidney disease, exhibited lower hemoglobin levels, and had

Table 3
Clinical characteristics, laboratory, echocardiographic findings and medications between patients with and without event.

Variables	Total (n = 732)	Without events (n = 609)	With events (n = 123)	*p*-value
Clinical characteristics				
Age (years)	66.00 (58.00, 72.00)	65.00 (57.00, 71.00)	69.00 (62.50, 74.50)	0<.001
Male sex, n (%)	529 (72.27)	450 (73.89)	79 (64.23)	0.029
BMI (kg/m2)	24.68 ± 3.18	24.80 ± 3.14	24.13 ± 3.32	0.032
Obesity, n(%)	36 (4.92)	31 (5.09)	5 (4.07)	0.631
SBP (mmHg)	137.07 ± 18.82	136.88 ± 18.63	138.02 ± 19.78	0.539
DBP (mmHg)	79.00 (71.00, 88.00)	79.00 (71.00, 89.00)	78.50 (68.25, 86.00)	0.136
HR (bpm)	73.00 (66.00, 82.00)	73.00 (66.00, 81.00)	73.00 (67.00, 82.00)	0.628
Smoking, n (%)	258 (35.25)	214 (35.14)	44 (35.77)	0.893
Drinking, n (%)	171 (23.36)	141 (23.15)	30 (24.39)	0.767
NYHA class II-IV, n (%)	314 (42.90)	256 (42.04)	58 (47.15)	0.295
Hypertension, n (%)	469 (64.07)	383 (62.89)	86 (69.92)	0.138
Diabetes, n (%)	217 (29.64)	169 (27.75)	48 (39.02)	0.013
Dyslipidaemia, n (%)	238 (32.51)	202 (33.17)	36 (29.27)	0.400
Hyperuricemia, n (%)	205 (28.01)	169 (27.75)	36 (29.27)	0.732
Atrial fibrillation, n (%)	23 (3.14)	18 (2.96)	5 (4.07)	0.719
History of stroke, n (%)	70 (9.56)	60 (9.85)	10 (8.13)	0.554
CKD, n(%)	74 (10.14)	53 (8.72)	21 (17.21)	0.005
SYNTAX score	14.00 (9.00, 19.00)	14.00 (9.00, 19.00)	15.00 (9.00, 20.00)	0.446
Laboratory findings				
Haemoglobin (g/L)	135.00 (123.00, 145.00)	136.00 (124.00, 145.00)	130.50 (119.00, 140.00)	0.002
Albumin (g/L)	40.10 (38.10, 42.30)	40.20 (38.20, 42.20)	39.50 (37.50, 42.50)	0.121
Uric acid (μmol/L)	409.54 ± 110.24	406.68 ± 108.56	423.29 ± 117.50	0.132
eGFR (mL/min/1.73 m2)	89.62 ± 24.67	91.10 ± 24.75	82.23 ± 22.98	0<.001
Total cholesterol (mmol/L)	4.17 (3.43, 4.97)	4.19 (3.42, 5.01)	4.14 (3.50, 4.89)	0.516
Triglyceride (mmol/L)	1.52 (1.07, 2.17)	1.52 (1.08, 2.15)	1.50 (1.07, 2.29)	0.911
Low density lipoprotein (mmol/L)	2.39 (1.79, 3.12)	2.41 (1.79, 3.12)	2.29 (1.77, 3.00)	0.337
High density lipoprotein (mmol/L)	1.01 (0.89, 1.16)	1.01 (0.89, 1.16)	1.03 (0.91, 1.18)	0.669
Fasting blood glucose (mmol/L)	4.96 (4.61, 5.71)	4.95 (4.60, 5.70)	4.96 (4.66, 5.77)	0.438
NT-proBNP (ng/L)	115.15 (49.30, 259.50)	98.00 (47.00, 223.60)	222.30 (80.65, 554.20)	0<.001
Echocardiographic findings				
IVS (mm)	11.00 (10.00, 13.00)	11.00 (10.00, 13.00)	12.00 (10.00, 13.00)	0.002
LVEDD (mm)	44.00 (41.00, 48.00)	45.00 (41.00, 48.00)	43.00 (40.00, 46.00)	0.007
PWT (mm)	10.00 (9.00, 11.00)	10.00 (9.00, 11.00)	10.00 (9.00, 11.00)	0.599
LAVI (mm)	19.85 (15.27, 25.08)	19.92 (15.31, 25.05)	19.68 (15.19, 25.55)	0.900
LVEF	66.00 (61.00, 70.00)	66.00 (62.00, 70.00)	62.00 (57.50, 68.50)	0<.001
PASP (mmHg)	28.00 (23.00, 33.00)	27.00 (23.00, 33.00)	28.00 (23.00, 33.50)	0.493
Septal e' (cm/s)	6.00 (5.00, 7.21)	6.00 (5.00, 7.45)	5.32 (4.00, 6.00)	0<.001
E/e' ratio	11.20 (9.20, 13.50)	11.00 (9.10, 13.40)	11.70 (9.85, 14.05)	0.046
LVMI (g/m2)	97.51 (83.11, 113.59)	97.65 (82.74, 113.46)	97.31 (85.18, 114.95)	0.368
RWT	0.48 (0.43, 0.54)	0.48 (0.42, 0.54)	0.50 (0.43, 0.57)	0.002
Medication at discharge				
Aspirin, n (%)	708 (96.72)	589 (96.72)	119 (96.75)	1.000
ADP antagonist, n (%)	723 (98.77)	600 (98.52)	123 (100.00)	0.364
ACEi/ARBs, n (%)	419 (57.24)	343 (56.32)	76 (61.79)	0.264
Statins, n (%)	714 (97.54)	593 (97.37)	121 (98.37)	0.738
Beta-blockers, n (%)	520 (71.04)	430 (70.61)	90 (73.17)	0.568
SGLT2, n(%)	79 (10.79)	63 (10.34)	16 (13.01)	0.385
Furosemide, n (%)	40 (5.46)	30 (4.93)	10 (8.13)	0.154
Spirolactone, n(%)	34 (4.64)	25 (4.11)	9 (7.32)	0.123
Digoxin, n(%)	9 (1.23)	7 (1.15)	2 (1.63)	1.000
HFpEF Scores				
H2FPEF	3.00 (2.00, 3.00)	2.00 (2.00, 3.00)	3.00 (2.00, 3.00)	0.004
HFAPEF	3.00 (3.00, 5.00)	3.00 (2.00, 4.00)	4.00 (3.00, 5.00)	0<.001

ACEi: Angiotensin-Converting Enzyme Inhibitors; ARB: angiotensin receptor blockers; BMI: body mass index; CKD: chronic kidney disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HF: heart failure; HR: heart rate; IVS: interventricular septum thickness; LAVI: left atrial volume index; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; LVPWT: left ventricular posterior wall thickness; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; PASP: pulmonary arterial systolic pressure; RWT: relative wall thickness; SBP: systolic blood pressure.

higher NT-proBNP values. Echocardiographic findings revealed that patients with events had lower LVEF, reduced septal e', and an elevated E/e' ratio. Notably, both scoring systems were significantly higher in the group with events.

3.2. Distribution of HFA-PEFF and H2PEFF scores

Fig. 2 illustrates the distribution patterns of the two scoring systems among the study participants. Most patients were concentrated around mid-range scores in both systems, with fewer individuals at the extremely high or low ends. However, the HFA-PEFF score distribution was skewed toward higher values, while the H2FPEF score tended to cluster toward lower values.

When stratified by standardized cut-off points, the intermediate probability group comprised the largest proportion of patients for both systems, with percentages exceeding those in the low and high categories. The HFA-PEFF score classified 65.7 % of patients as intermediate, 25.1 % as high, and 9.2 % as low probability for HFpEF, identifying a higher proportion of patients in the high-probability category. In contrast, the H2FPEF score placed 77.3 % in the intermediate group, 19.3 % in the low, and only 3.4 % in the high-probability category, showing minimal representation in the high-probability group.

3.3. Outcome

Fig. 3 illustrates the association between HFA-PEFF score groups and clinical outcomes, encompassing the composite endpoints of all-cause mortality and heart failure hospitalization, as well as individual

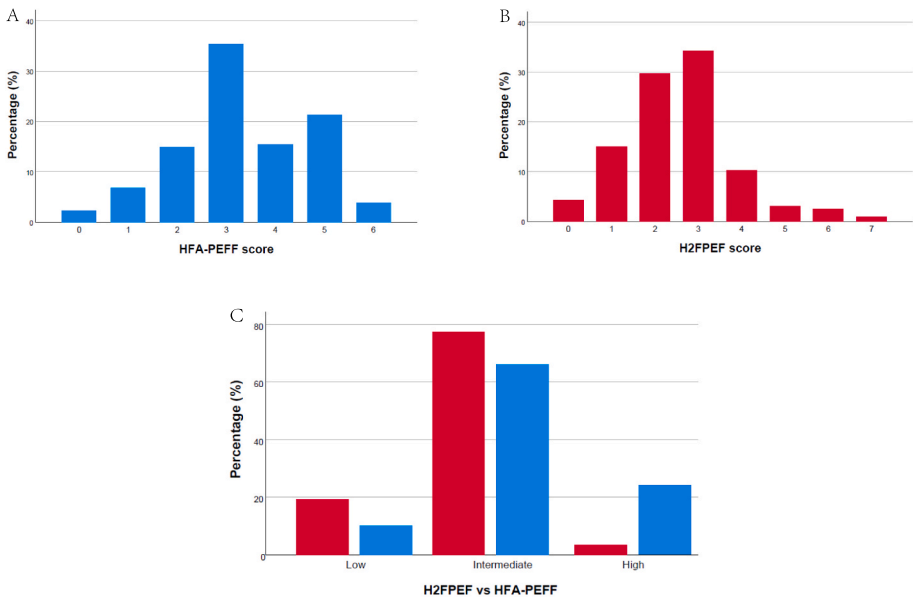

Fig. 2. (A) Distribution of the HFA-PEFF scores across the study participants. (B) Distribution of the H2FPEF scores across the study participants. (C) Distribution of the low, intermediate and high H2FPEF and HFA-PEFF groups across the study participants.

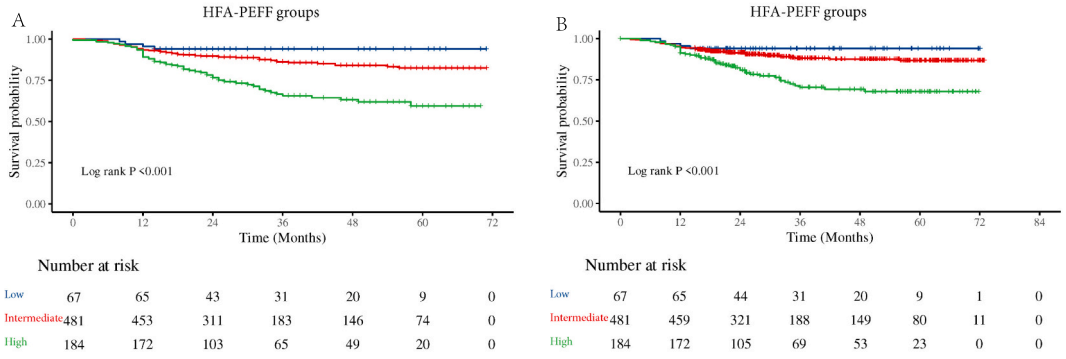

Fig. 3. (A) Freedom from all-cause mortality and heart failure hospitalization according to the HFA-PEFF groups. (B) Freedom from heart failure hospitalization according to the HFA-PEFF groups.

occurrences of heart failure hospitalization. Both curves showed a significant difference in event-free survival across the score groups, with patients in the low-score group exhibiting the highest event-free survival throughout the follow-up period. In contrast, patients in the high-score group experienced the steepest decline in survival probability ($p < 0.001$), indicating that higher HFA-PEFF scores were consistently associated with worse outcomes.

In contrast, no statistically significant differences in survival were observed across the H2FPEF score groups with respect to the composite endpoints of all-cause mortality and heart failure hospitalization ($p = 0.176$), or in instances of heart failure hospitalization alone ($p = 0.564$) (Fig. 4). Even after excluding patients in the high-score group due to their small sample size, the survival difference between the low and intermediate H2FPEF groups remained non-significant (Supplementary

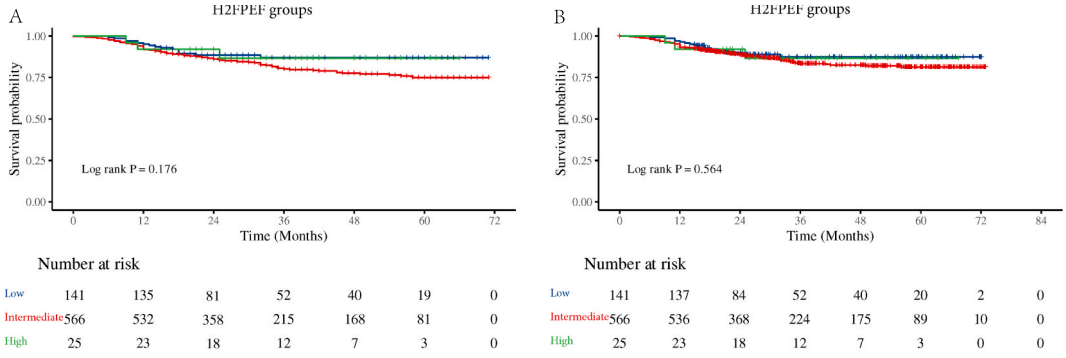

Fig. 4. (A) Freedom from all-cause mortality and heart failure hospitalization according to the H2FPEF groups. (B) Freedom from heart failure hospitalization according to the H2FPEF groups.

Fig. 1).

The HFA-PEFF score demonstrated a robust and independent correlation with the composite endpoints of all-cause mortality and heart failure hospitalization (Table 4). Patients with higher scores were associated with an increased risk of this outcome in the unadjusted model (HR: 1.59, 95 % CI: 1.31–1.91). After adjusting for clinical covariates, including age, sex, NYHA classification, comorbidities, and cardiac function parameters (Model 1), the associations remained statistically significant (HR: 1.33, 95 % CI: 1.07–1.65). Further adjustment for discharge medications (Model 2) confirmed the robustness of these associations (HR: 1.33, 95 % CI: 1.07–1.65). Similarly, higher HFA-PEFF scores consistently predicted an increased risk of heart failure hospitalization, and this relationship was stable even after adjustments for clinical variables (HR: 1.23, 95 % CI: 1.03–1.47) and discharge medications (HR: 1.26, 95 % CI: 1.05–1.51).

In contrast, the H2FPEF score demonstrated a weaker predictive value (Table 5). Although initially associated with the composite endpoints of all-cause mortality and heart failure hospitalization in the unadjusted model (HR: 1.14, 95 % CI: 1.01–1.29), this association lost significance after adjusting clinical covariates and discharge medications. No significant associations were found between the H2FPEF score and the incidence of heart failure hospitalization in any model, suggesting that the H2FPEF score may have limited prognostic utility in predicting adverse outcomes in this cohort.

4. Discussion

In this study, we found two distinct patterns in the predictive value of the HFA-PEFF and H2FPEF scores in patients with CAD and preserved ejection fraction. First, both scoring systems classified the majority of patients into the intermediate probability group for HFpEF. However, the HFA-PEFF score identified a larger proportion of patients as high probability for HFpEF, whereas the H2FPEF score classified more patients into the low probability group. Second, the HFA-PEFF score was significantly associated with adverse outcomes, including all-cause mortality and heart failure hospitalization. In contrast, the H2FPEF score showed no significant relationship with these outcomes in this population.

CAD is recognized as a major contributor to the development of HFpEF [19]. One study indicated that over half of HFPEF patients had angiographically confirmed CAD [20]. Additionally, many CAD patients may have underlying microvascular disease [21]. Even in cases where patients with CAD undergo complete revascularization, coronary microvascular dysfunction continues to play a significant role in the progression of HFPEF [22,23]. This may be due to impaired myocardial perfusion leading to ischemia and cardiomyocyte injury, which results in decreased cardiac functional reserve and myocardial fibrosis [24,25]. Furthermore, CAD often coexists with comorbidities such as hypertension, diabetes, and obesity, which further exacerbate left ventricular stiffness and impaired relaxation [26].

Routine assessment of diastolic function in CAD patients is of great value, as it helps to identify early signs of HFpEF, even before overt clinical heart failure symptoms appear [4]. Echocardiographic measures of diastolic dysfunction, such as E/e' ratio and LAVI, are commonly used to evaluate left ventricular relaxation and filling pressures in CAD patients. Studies have demonstrated that diastolic function evaluated by echocardiographic examination is associated with mortality in patients undergoing coronary angiography [10]. Left ventricular end-diastolic pressure (LVEDP) serves as an important indicator of diastolic function, and guidelines recommend its measurement to confirm the diagnosis of HFPEF [27]. In a cohort of acute coronary syndrome patients undergoing percutaneous coronary intervention, elevated LVEDP was observed in more than one-third of cases, and LVEDP was independently linked to mortality [9]. Additionally, the time constant of pressure decline in the left ventricle (Tau) has been used as an index of diastolic relaxation, reporting a similar prevalence of left ventricular diastolic dysfunction in patients with CAD. Importantly, Tau was independently associated with an increased risk for cardiac death or cardiovascular hospitalization [28]. This highlights the critical need for accurate identification and management of diastolic function in patients with CAD.

Due to the complexity of HFpEF, diagnosing this condition poses a challenge in clinical practice. To address this, the HFA-PEFF score and H2FPEF score were developed as a comprehensive diagnostic tool for HFpEF. Both score systems have been validated across various populations, including community cohorts, hospitalized patients, and individuals with specific heart diseases [29–31]. However, their efficacy in detecting HFpEF patients varied. The H2FPEF score demonstrated significantly greater accuracy than the HFA-PEFF score in diagnosing HFpEF among patients hospitalized with acute decompensated heart failure [29]. Conversely, in patients with cardiac amyloidosis, the HFA-PEFF score exhibited higher diagnostic utility for HFpEF [31]. Furthermore, several studies suggested that both algorithms often produced discordant classification in a significant fraction of patients [30,32]. In our study, the HFA-PEFF score identified more patients as having a high probability of HFpEF compared to the H2FPEF score. It is important to note that both scoring systems demonstrated lower than expected sensitivity for diagnosing HFPEF [33]. Consequently, when ruling out HFPEF in patients with low or intermediate scores, individual clinical considerations should be carefully integrated into the decision-making process [34].

The mortality rate observed in our study is substantially lower than the 14.1 %–29 % range reported in previous studies [35,36]. Several factors may explain this favorable outcome.

First, our patients exhibited a lower baseline risk profile, with fewer high-risk comorbidities— such as diabetes mellitus, chronic kidney disease, and atrial fibrillation, which are known risk factors for coronary artery disease [37]. Second, the cohort consisted of patients with relatively mild disease severity at baseline, as evidenced by lower average SYNTAX scores, whereas earlier studies often included patients who had undergone CABG or had prior PCI or CABG, suggesting more advanced disease. Third, differences in study design and inclusion criteria likely

Table 4
Cox regression model for HFA-PEFF score to predict adverse outcomes.

Outcomes	Unadjusted		Model 1		Model 2	
	HR(95 % CI)	*p*-value	HR(95 % CI)	*p*-value	HR(95 % CI)	*p*-value
Death and HF	1.59 (1.31 ~ 1.91)	<0.001	1.33 (1.07 ~ 1.65)	0.009	1.33 (1.07 ~ 1.65)	0.011
HF	1.50 (1.28 ~ 1.76)	0<.001	1.23 (1.03 ~ 1.47)	0.022	1.26 (1.05 ~ 1.51)	0.014

Model 1: adjusted for age, gender, NYHA II-IV, DM, BMI, HB, albumin, uric acid, eGFR, LVEF.
Model 2: adjusted for model 1 plus medications at discharge.

Table 5
Cox regression model for H2FPEF score to predict adverse outcomes.

Outcomes	Unadjusted		Model 1		Model 2	
	HR(95 % CI)	*p*-value	HR(95 % CI)	*p*-value	HR(95 % CI)	*p*-value
Death and HF	1.14 (1.01 ~ 1.29)	0.047	1.01 (0.87 ~ 1.17)	0.861	1.07 (0.90 ~ 1.26)	0.452
HF	1.08 (0.93 ~ 1.25)	0.311	0.94 (0.80 ~ 1.12)	0.493	0.98 (0.81 ~ 1.19)	0.855

Model 1: adjusted for gender, NYHA II-IV, DM, HB, albumin, uric acid, eGFR, LVEF, NT-proBNP.
Model 2: adjusted for model 1 plus medications at discharge.

contributed to the variation in mortality rates. For example, our study excluded STEMI and non-STEMI patients, which may have resulted in better outcomes. Fourth, the higher usage of statins, antiplatelet agents, and renin-angiotensin system inhibitors in our cohort may have further improved outcomes. In fact, another study with patient characteristics similar to ours reported a five-year mortality rate of 7.5 %, which aligns with our findings [38].

The prognostic capabilities of these scores to predict adverse outcomes have been reported differently. One study indicated that high H2FPEF and HFA-PEFF scores carried equivalent risks of heart failure hospitalization or death [30]. In contrast, another study demonstrated that the HFA-PEFF score possessed an independent prognostic value for all-cause mortality, whereas the H2FPEF score did not [31]. Nonetheless, additional studies suggested that the H2FPEF score may also hold prognostic value [39,40]. In our study, the HFA-PEFF score demonstrated a stronger predictive value for adverse outcomes compared to the H2FPEF score, including all-cause mortality and heart failure hospitalization.

The enhanced predictive ability of the HFA-PEFF score is likely due to its more comprehensive inclusion of echocardiographic parameters and NT-proBNP testing, which reflect diastolic dysfunction and systemic congestion. For instance, the HFA-PEFF score differentiated NYHA class and diuretic use across its categories more effectively than the H2FPEF score, underlining its clinical relevance. The predictive power of the HFA-PEFF score largely benefits from NT-proBNP, as its biomarker subscore achieves a similar AUC to the total score [41]. Although atrial fibrillation is not directly included in the score, its prevalence increased with higher HFA-PEFF grades, likely due to underlying structural heart changes that predispose patients to arrhythmias [42]. This suggests that the HFA-PEFF score indirectly captures the impact of atrial fibrillation on outcomes, further enhancing its prognostic utility. Furthermore, the score also correlated with traditional risk factors such as advancing age and higher rates of hypertension and diabetes, reinforcing its value in patient stratification.

The H2FPEF score, though more straightforward and practical for routine use, primarily focuses on clinical variables that represent the classical phenotype of HFpEF. Notably, obesity and atrial fibrillation carry the highest weights in this scoring system (2 and 3 points, respectively), with other factors assigned 1 point each. However, in this cohort, the prevalence of atrial fibrillation and obesity was low. As a result, many patients scored zero for these two criteria, making it difficult to reach the high-risk threshold, potentially classifying most as low- or intermediate-risk and reducing the score's prognostic effectiveness. In a study on HFpEF due to cardiac amyloidosis, some patients were categorized as low-probability by the H2FPEF score despite having poor outcomes [31]. While prior studies have demonstrated the prognostic value of this score, those investigations typically involved patients who were more obese and had a higher prevalence of atrial fibrillation compared to our cohort [39,40]. Additionally, the H2FPEF score does not incorporate NT-proBNP testing, which was recognized as a marker for mortality and heart failure hospitalization [43]. Although a graded association between NT-proBNP levels and the H2FPEF score was observed, the smaller differences in NT-proBNP levels across H2FPEF categories compared to HFA-PEFF scores might partly explain the weaker prognostic impact of the H2FPEF score. Unlike prior studies focused on patients with established heart failure, our cohort mainly consisted of NYHA class I patients with relatively low NT-proBNP levels and normal cardiac structure, reflecting early-stage disease. Since the H2FPEF score is based on relatively traditional and simple clinical variables, its applicability in our cohort may be limited. In a group of suspected HFpEF patients, the HFA-PEFF score classified 54 % as high probability for HFpEF, whereas only 5 % met the high-probability threshold under the H2FPEF score, suggesting it often assigns an "uncertain" middle-range score, and may miss high-risk subclinical cases [44].

5. Limitations

Despite these findings, there are several limitations to consider. First, this was a retrospective study, which may introduce bias in data collection and analysis. Second, our study population consisted primarily of patients undergoing drug-eluting stent implantation, which may not be representative of all CAD patients. Third, GLS, a minor parameter in the HFA-PEFF score, was unavailable in our study cohort, potentially leading to an underestimation of HFpEF prevalence. However, a validation study of the HFA-PEFF score indicated that incorporating GLS < 16 as a criterion resulted in the reclassification of very few individuals [45]. Nonetheless, our approach aligns with how clinicians would address similar gaps in information when utilizing the HFA-PEFF score. Finally, we do not have information about the type of heart failure hospitalization during follow-up. Although it has been reported that the incidence of HFrEF and HFpEF in patients with CAD were similar [46], this lack of distinction in the type of heart failure hospitalization during follow-up limits our ability to explore potential differences in predictive performance for heart failure with reduced ejection fraction (HFrEF) versus HFpEF.

6. Conclusion

In conclusion, our study supported the use of the HFA-PEFF score as a more effective tool for predicting adverse outcomes in CAD patients with preserved ejection fraction compared to the H2FPEF score. Further prospective studies are warranted to confirm these findings and refine the use of these scoring systems in CAD populations.

Authors' contributions

Dr. Xuefeng Wu contributed to the data acquisition, analysis and drafted the manuscript. Dr. Jianming Li contributed to data organization and processing. Professor Zhaoyan Xu and Yingqing Feng obtained funding and provided administrative support. All the authors have read and approved the final version of the manuscript.

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CRediT authorship contribution statement

Xuefeng Wu: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Jianming Li:** Validation, Software. **Zhaoyan Xu:** Writing – review & editing, Supervision, Funding acquisition. **Yingqing Feng:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Xuefeng Wu reports administrative support was provided by the Science and Technology Innovation Project of Foshan Science and Technology Bureau. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2025.101655.

Data availability

The data are shared on request. Please contact the corresponding author directly to request for data sharing.

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