

# Evaluating the Prognostic Value of the Modified H<sub>2</sub>FPEF Score in Patients With Heart Failure With Preserved Ejection Fraction

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## Abstract

**Background:** The H<sub>2</sub>FPEF score, a convenient tool developed for diagnosing heart failure with preserved ejection fraction (HFpEF), exhibited useful prognostic utility in HFpEF. However, the applicability and the prognostic value of the H<sub>2</sub>FPEF score in Chinese HFpEF patients have yet to be fully confirmed. The study aimed to evaluate the effect of modified H<sub>2</sub>FPEF score on the prognosis of Chinese HFpEF patients.

**Methods:** In this retrospective study, we calculated the H<sub>2</sub>FPEF scores by body mass index (BMI)  $\geq 25$  kg/m<sup>2</sup> and 30 kg/m<sup>2</sup> respectively, for 497 consecutive HFpEF patients in China. Subjects were divided into low- (0 - 3 points), intermediate- (4 - 6 points), and high-score (7 - 9 points) groups. The primary and secondary endpoints were heart failure (HF)-related events and acute coronary syndrome (ACS), respectively. Cox proportional hazard models were applied to calculate hazard ratios (HRs). Receiver operating characteristic (ROC) curves and areas under the curve (AUC) were used to evaluate the prediction of the H<sub>2</sub>FPEF score for adverse outcomes.

**Results:** Over a mean follow-up of 40.46  $\pm$  6.52 months, the primary and secondary endpoints occurred in 168 patients (33.8%) and 97 patients (19.5%), respectively. By the definition of obesity as BMI  $\geq 25$  kg/m<sup>2</sup>, a higher incidence of HF-related events and ACS was observed among those with a higher modified H<sub>2</sub>FPEF score. The modified H<sub>2</sub>FPEF significantly predicted HF-related events (AUC: 0.723; 95% confidence interval (CI): 0.676 - 0.770; P < 0.001) and ACS (AUC: 0.670; 95% CI: 0.608 - 0.731; P < 0.014) with higher power than the H<sub>2</sub>FPEF score calculated by BMI  $\geq 30$  kg/m<sup>2</sup>. The cutoff of the modified H<sub>2</sub>FPEF score was 6.5 for detecting HF-related events and ACS.

**Conclusions:** The modified H<sub>2</sub>FPEF score, using BMI  $\geq 25$  kg/m<sup>2</sup>

to define obesity, could more effectively predict the occurrence of subsequent cardiovascular events in Chinese HFpEF patients. The modified H<sub>2</sub>FPEF score above 6.5 is a risk factor for adverse cardiovascular events in HFpEF patients.

**Keywords:** Cardiovascular events; Heart failure with preserved ejection fraction; Heart failure; Acute coronary syndrome; Risk stratification

## Introduction

Heart failure with preserved ejection fraction (HFpEF), characterized by pathological increases in cardiac filling pressures at rest or with exertion, is a common clinical syndrome associated with high morbidity and mortality rates [1, 2]. HFpEF has progressed to be the dominant form of heart failure (HF) worldwide, accounting for approximately 50% of all hospital admissions for HF [3-5]. Meanwhile, the evidence suggests the prevalence of HFpEF is increasing at a rate of 1% per year [6-8]. Although HFpEF was historically called diastolic HF, it is now widely recognized that HFpEF is a systemic syndrome involving multiple pathophysiological abnormalities beyond left ventricular diastolic dysfunction [9-13]. Symptoms of HFpEF are non-specific, and diagnosis might be elusive, resulting in a diagnostic and therapeutic challenge. Exercise right heart catheterization is the current gold standard test for diagnosing HFpEF when HFpEF is suspected but left ventricular filling pressures at rest are normal. Nevertheless, exercising during right heart catheterization is not universally available [14, 15]. Under these circumstances, there was a great emphasis on finding simple and noninvasive indices of HFpEF diagnosis.

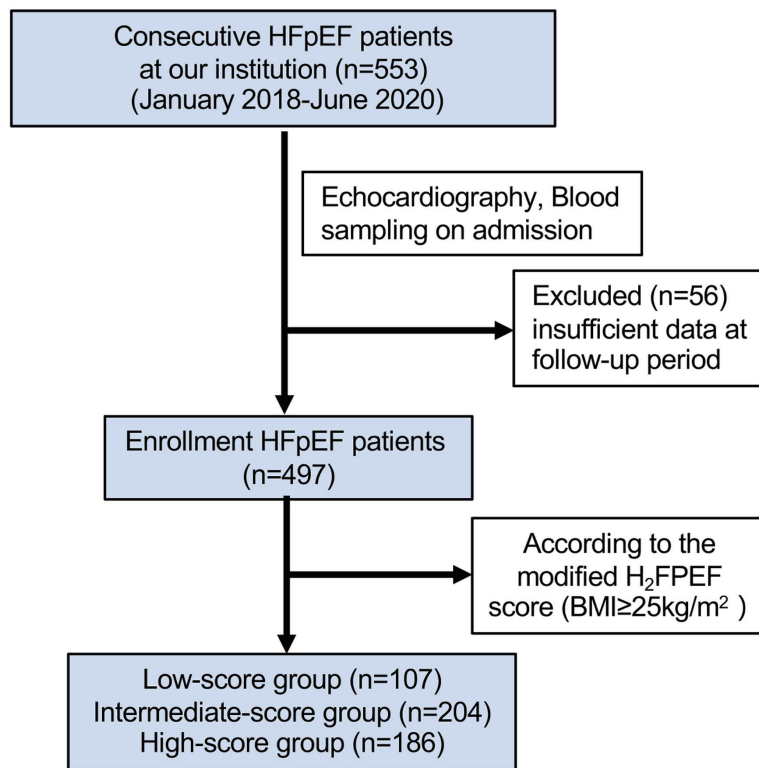
The H<sub>2</sub>FPEF score, a weighted score based on six variables that ranged from 0 to 9, was proposed by Reddi et al to diagnose symptomatic euolemic patients as HFpEF in 2018 [16]. In the H<sub>2</sub>FPEF score system, the set of predictive variables includes obesity, atrial fibrillation (AF), age > 60 years, treatment with  $\geq 2$  antihypertensives, echocardiographic E/e' ratio > 9, and echocardiographic pulmonary artery systolic pressure (PAP) > 35 mm Hg [16]. The H<sub>2</sub>FPEF score has been validated as a practical diagnostic tool for HFpEF [17, 18]. Furthermore, recent evidence supported that the H<sub>2</sub>FPEF score

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**Figure 1.** The flow chart for the investigation. HFpEF: heart failure with preserved ejection fraction.

was also a significant predictor for adverse cardiovascular events in HFpEF patients [19, 20]. Although several studies have tested the prognostic value of the H<sub>2</sub>FPEF score among HFpEF patients, whether the results could be widely applicable in Chinese HFpEF patients is not well validated. In this retrospective study, we aimed to examine the applicability of the H<sub>2</sub>FPEF score and the predictive value of the H<sub>2</sub>FPEF score among Chinese HFpEF patients in our institution.

## Materials and Methods

### Study subjects

We retrospectively assessed the HFpEF patients hospitalized at the Second Hospital of Hebei Medical University from January 1, 2018 to June 31, 2020. The diagnostic criteria were clinical symptoms or signs of HF with a left ventricular ejection fraction (LVEF)  $\geq 50\%$ , and elevated levels of natriuretic peptides (B-type natriuretic peptide (BNP)  $> 35$  ng/L or N-terminal pro B-type natriuretic peptide (NT-proBNP)  $> 125$  ng/L); and at least one of the following additional criteria: 1) relevant structural heart disease, including left ventricular (LV) hypertrophy and/or left atrial enlargement (left atrial volume index  $> 34$  mL/m<sup>2</sup>, left ventricular mass index (LVMI)  $\geq 115$  g/m<sup>2</sup> in men or  $\geq 95$  g/m<sup>2</sup> in women); 2) diastolic dysfunction (E/e' ratio  $\geq 13$  and/or e'  $< 9$  cm/s). The exclusion criteria included: 1) acute myocardial infarction (MI) within 1 month on admission; 2)

congenital heart disease; 3) primary cardiomyopathy; 4) severe valvular disease, 5) end-stage renal failure (estimated glomerular filtration rate (eGFR)  $< 30$  mL/min/1.73 m<sup>2</sup>); 6) acute exacerbation of the chronic obstructive pulmonary disease. A total of 553 consecutive patients ( $> 18$  years old) with HFpEF were hospitalized at our institution between January 1, 2018 and June 31, 2020; 56 patients were eliminated due to incomplete data during the follow-up phase. Finally, the remaining 497 HFpEF patients were enrolled in this study. All subjects provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committee of the Second Hospital of Hebei Medical University (approval number 2022-R677).

### H<sub>2</sub>FPEF score

Body mass index (BMI), treatment with  $\geq 2$  antihypertensives, presence of AF, PAP ( $> 35$  mm Hg), age ( $> 60$  years), and echocardiographic E/e' ratio ( $> 9$ ) were all used to calculate the H<sub>2</sub>FPEF score for each patient. In terms of the typical body shape of the Asian population, according to previous studies and the World Health Organization Asian classification suggested as obesity [21], we analyzed the data by defining obesity as BMI  $\geq 30$  kg/m<sup>2</sup> and  $\geq 25$  kg/m<sup>2</sup>, respectively. The H<sub>2</sub>FPEF score was available in all 497 patients with HFpEF. The study population was divided into three groups according to the H<sub>2</sub>FPEF score to evaluate the clinical features and echocardiographic parameters: the low-score group (0 - 3 points),

the intermediate-score group (4 - 6 points), and the high-score group (7 - 9 points). Figure 1 depicts the flow chart for the investigation.

### Clinical variables and echocardiography

The baseline demographic data, clinical characteristics, comorbidities, drug and intervention therapy, laboratory values, arrhythmias, and echocardiography findings were collected and recorded. Hypertension was defined as a recorded blood pressure  $\geq 140/90$  mm Hg or taking antihypertensive medications, as previously described. Diabetes was defined as a fasting blood glucose level of  $\geq 126$  mg/dL or current treatment for diabetes. Smoking status, including past and current smoking, was determined via an interview. Current smoker was defined as smoking status on admission.

Subjects were required to fast over 8 h before venous blood collection, and blood samples were usually obtained in the morning after admission. The BNP or NT-proBNP levels were analyzed by a commercially available assay (Abbott Japan, Matsudo, Japan) in the hospital clinical laboratory. The eGFR was calculated using the Japanese Society of Nephrology formula [22].

All subjects underwent echocardiography by experienced cardiac sonographers who were blind to this study. As described previously, LVEF was measured by modified Simpson's method. The ratio of early transmitral flow velocity to early diastolic mitral annular velocity ( $E/e'$ ) was assessed by tissue Doppler, and LVMI was measured by echocardiography (Philips IE33 system, Andover, MA, USA; Philips EPIQ 7C system, Andover, MA, USA) [23].

### Follow-up and endpoints

The observations were made by investigators who were blind to this study. The agreements for assessing outcomes were performed under the consensus of multiple evaluators. Patients were followed up at our outpatient clinics until June 31, 2021, or until an endpoint occurred. The primary and secondary endpoints were HF-related events (cardiovascular death and hospitalization for HF decompensation) and acute coronary syndrome (ACS) (nonfatal MI and unstable angina pectoris) at 42 months, respectively. Cardiovascular death was defined as death due to MI, congestive heart failure, or documented sudden death without non-cardiovascular causes. Hospitalization for HF decompensation was diagnosed if the patient had typical HF symptoms or objective signs of worsening HF that required intravenous drug administration when admission. ACS is caused by a critical obstruction of a coronary artery because of atherosclerotic coronary artery disease. Three specific conditions are included: ST-elevation MI (STEMI), non-ST elevation MI (NSTEMI), and unstable angina. Cardiovascular events were ascertained from a review of the medical records and confirmed by direct contact with the patients, their families, and their physicians. For patients with more than one cardiovascular event, only the first event was counted as an event, except for the cardiovascular death.

### Statistical analysis

Constant values were expressed as means  $\pm$  standard deviations ( $x \pm$  SDs), whereas non-normally distributed data were expressed as the median (interquartile range). Differences between the three groups were assessed by one-way analysis of variance (ANOVA) or the Kruskal-Wallis test for continuous variables and the Chi-squared test for categorical variables. Fisher's exact probability method was used for counting data with smaller sample sizes. The cumulative incidence and differences between groups of HF-related events or ACS events were determined by a Kaplan-Meier curve and the log-rank test, respectively. Univariate Cox proportional hazard regression was used to identify significant predictors of the outcomes. Significant predictors were then entered into multivariate analysis and variables that will cause internal correlations were excluded. The proportional hazards assumption was examined by using R. When the proportional hazards assumption does not hold, Cox regression models with time-varying coefficient were used. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. The factors of the BMI, prevalence of hypertension, prevalence of AF, age, and Doppler echocardiographic  $E/e'$  ratio were components of the H<sub>2</sub>FPEF score, and we thought these variables caused internal correlations with the H<sub>2</sub>FPEF score variable. Receiver operating characteristic (ROC) curves were constructed, and the areas under the curve (AUC) were calculated for the H<sub>2</sub>FPEF score to predict future HF-related events and ACS events. We defined the cutoff value of the H<sub>2</sub>FPEF score by utilizing the sensitivity, specificity, and likelihood ratio for future HF-related events and ACS events.

Statistical analyses were analyzed by the software Statistical Package for Social Sciences (SPSS) Version 24.0 (IBM Japan, Tokyo, Japan) and R program (Version 4.1.1 GUI 1.77; High Sierra build). A P-value  $< 0.05$  was considered statistically significant.

### Results

A total number of 497 patients with HFpEF were enrolled in this study. Overall, the patients had a mean age of  $69.05 \pm 10.47$  years, and 57.9% were female. The mean systolic and diastolic blood pressures were  $135.30 \pm 20.78$  and  $79.02 \pm 13.07$  mm Hg, respectively (Table 1). Over a mean follow-up of  $40.46 \pm 6.52$  months, the primary endpoint occurred in 168 patients (33.8%), among which 31 patients (6.2%) died of cardiovascular diseases and 148 patients (29.8%) were re-hospitalized due to heart failure. The secondary endpoint occurred in 97 patients (19.5%) (Table 2).

#### H<sub>2</sub>FPEF score calculated by BMI $\geq 30$ kg/m<sup>2</sup>

The average H<sub>2</sub>FPEF score was  $4.59 \pm 2.03$  when calculated by BMI  $\geq 30$  kg/m<sup>2</sup>. The patient numbers (percentage) of low- (1 - 3 points), intermediate- (4 - 6 points), and high-score (7 - 9 points) were 167 (33.6%), 230 (46.3%), and 100 (20.1%),

**Table 1.** Baseline Characteristics of HFpEF Patients According to the Modified H<sub>2</sub>FPEF Score

	All patients (n = 497)	Low-score group (0 - 3 points) (n = 107)	Intermediate-score group (4 - 6 points) (n = 204)	High-score group (7 - 9 points) (n = 186)	P
The modified H <sub>2</sub> FPEF score	5.48 ± 2.18	2.43 ± 0.79	4.95 ± 0.79 <sup>&amp;</sup>	7.81 ± 0.77 <sup>#*</sup>	< 0.001
Age (years)	69.05 ± 10.47	66.79 ± 13.10	69.15 ± 9.44 <sup>&amp;</sup>	70.25 ± 9.65 <sup>#</sup>	0.024
Female (%)	288 (57.9)	60 (56.1)	108 (52.9)	120 (64.5)	0.062
BMI (kg/m <sup>2</sup> )	25.99 ± 3.57	24.12 ± 3.04	25.44 ± 3.58	27.68 ± 3.08	< 0.001
SBP (mm Hg)	135.30 ± 20.78	133.07 ± 20.00	136.28 ± 21.52	135.52 ± 20.78	0.428
DBP (mm Hg)	79.02 ± 13.07	75.68 ± 11.05	78.84 ± 14.04 <sup>&amp;</sup>	81.15 ± 12.65 <sup>#*</sup>	0.002
Heart rate	82.85 ± 25.95	77.68 ± 25.70	81.15 ± 26.49	87.68 ± 24.81 <sup>#*</sup>	0.003
Smoking (%)	100 (20.1)	19 (17.8)	32 (15.7)	24 (12.9)	0.510
Hypertension (%)	358 (72.0)	61 (57.0)	151 (74.0)	146 (78.5)	< 0.001
Diabetes (%)	123 (24.7)	21 (19.6)	55 (27.0)	47 (25.3)	0.355
Atrial fibrillation (%)	271 (54.5)	1 (0.9)	84 (41.2)	186 (100.0)	< 0.001
Abnormal of thyroid function (%)	137 (27.6)	28 (26.2)	53 (26.0)	56 (30.1)	0.607
Ischemic heart disease (%)	258 (51.9)	54 (50.5)	102 (50.0)	102 (54.8)	0.599
Previous hospitalization for HF (%)	130 (26.2)	10 (9.3)	39 (19.1)	81 (43.5)	< 0.001
NYHA					
I (%)	1 (0.2)	-	-	1 (0.5)	-
II (%)	322 (64.8)	78 (72.9)	147 (72.1)	97 (52.5)	< 0.05
III (%)	147 (29.6)	25 (29.8)	46 (22.5)	76 (40.9)	< 0.05
IV (%)	27 (5.4)	4 (3.7)	11 (5.4)	12 (6.5)	< 0.05
Blood test					
BNP (pmol/L)	385.94 ± 336.24	407.48 ± 361.30	347.37 ± 286.62	411.74 ± 364.63	0.251
Cre (μmol/L)	77.04 ± 22.80	71.82 ± 20.78	77.68 ± 24.11	79.34 ± 22.07	0.021
eGFR (mL/min/1.73 m <sup>2</sup> )	77.96 ± 19.09	83.52 ± 18.02	78.01 ± 19.42 <sup>&amp;</sup>	74.70 ± 18.67 <sup>#</sup>	0.001
UA (μmol/L)	341.35 ± 103.14	318.58 ± 98.43	333.70 ± 103.18	362.85 ± 102.26 <sup>#*</sup>	0.001
ALT (U/L)	21.44 ± 18.36	20.05 ± 16.27	21.69 ± 17.59	21.98 ± 20.27	0.669
AST (U/L)	22.22 ± 13.20	23.07 ± 17.04	21.81 ± 12.62	22.18 ± 11.20	0.724
Hemoglobin (g/L)	130.94 ± 19.54	126.70 ± 20.09	131.45 ± 19.52 <sup>&amp;</sup>	132.83 ± 18.96 <sup>#</sup>	0.031
K <sup>+</sup> (mmol/L)	4.00 ± 0.47	3.99 ± 0.45	4.05 ± 0.46	3.95 ± 0.49	0.153
Na <sup>+</sup> (mmol/L)	142.50 ± 3.19	142.50 ± 3.25	142.30 ± 3.25	142.72 ± 3.10	0.438
Serum glucose (mmol/L)	5.46 ± 2.05	5.26 ± 1.47	5.63 ± 2.56	5.39 ± 1.67	0.261
HbA1c (%)	6.25 ± 1.17	6.14 ± 1.03	6.33 ± 1.26	6.23 ± 1.14	0.409
TC (mmol/L)	3.95 ± 0.96	3.89 ± 0.85	4.06 ± 1.02	3.87 ± 0.93	0.095
TG (mmol/L)	1.32 ± 0.72	1.30 ± 0.65	1.37 ± 0.88	1.28 ± 0.56	0.465
LDL-C (mmol/L)	2.44 ± 0.83	2.35 ± 0.74	2.54 ± 0.87	2.39 ± 0.83	0.087
HDL-C (mmol/L)	1.14 ± 0.28	1.19 ± 0.33	1.14 ± 0.27	1.12 ± 0.26	0.118
Echocardiography					
e' (cm/s)	5.48 ± 1.79	5.50 ± 2.03	5.48 ± 1.97	5.48 ± 1.38	0.997
LVMI (g/m)	112.46 ± 28.26	115.13 ± 33.49	111.16 ± 29.13	112.35 ± 23.70	0.501
LVED (mm)	46.18 ± 4.53	45.95 ± 4.69	45.97 ± 4.70	46.55 ± 4.23	0.370
LAD (mm)	37.86 ± 5.15	35.35 ± 4.76	37.12 ± 4.99 <sup>&amp;</sup>	40.13 ± 4.62 <sup>#*</sup>	< 0.001
RVD (mm)	22.21 ± 4.97	21.39 ± 2.66	22.63 ± 5.82	22.20 ± 4.93	0.112
IVST (mm)	10.15 ± 1.31	10.09 ± 1.41	10.06 ± 1.32	10.29 ± 1.24	0.202

**Table 1.** Baseline Characteristics of HFpEF Patients According to the Modified H<sub>2</sub>FPEF Score - (continued)

	All patients (n = 497)	Low-score group (0 - 3 points) (n = 107)	Intermediate-score group (4 - 6 points) (n = 204)	High-score group (7 - 9 points) (n = 186)	P
LVPW (mm)	10.10 ± 1.29	10.01 ± 1.46	10.02 ± 1.29	10.24 ± 1.19	0.178
RAD (mm)	47.64 ± 6.58	44.37 ± 5.07	46.90 ± 5.67 <sup>&amp;</sup>	50.32 ± 7.23 <sup>#*</sup>	< 0.001
LVEF (%)	62.00 ± 4.89	61.63 ± 5.48	62.20 ± 4.62	62.00 ± 4.83	0.629
E/e'	15.56 ± 7.23	13.50 ± 5.90	15.47 ± 7.63 <sup>&amp;</sup>	16.85 ± 7.22 <sup>#</sup>	0.001
PAP (mm Hg)	33.26 ± 8.99	29.29 ± 5.86	33.25 ± 9.41 <sup>&amp;</sup>	35.55 ± 9.24 <sup>#*</sup>	< 0.001
Drug therapy					
Beta-blocker (%)	298 (60.0)	60 (56.1)	123 (60.3)	115 (61.8)	0.621
ACEI/ARB (%)	173 (34.8)	32 (29.9)	81 (39.7)	60 (32.3)	0.148
Spirolactone (%)	212 (42.7)	19 (17.8)	95 (46.6)	98 (52.7)	< 0.001
Loop diuretic (%)	368 (74.0)	72 (67.3)	142 (69.6)	154 (82.8)	0.002
CCB (%)	160 (32.2)	37 (34.6)	65 (31.9)	58 (31.2)	0.828
Digoxin (%)	21 (3.8)	2 (1.9)	10 (4.9)	9 (4.8)	0.392
Antiplatelet drug (%)	286 (57.5)	63 (58.9)	127 (62.3)	96 (51.6)	0.100
Anticoagulant drug (%)	410 (82.5)	76 (71.0)	161 (78.9)	173 (93.0)	< 0.001
HMG-CoA reductase inhibitor	372 (74.8)	83 (77.6)	146 (71.6)	143 (76.9)	0.369
Intervention therapy					
PCI (%)	79 (15.9)	21 (19.6)	38 (18.6)	20 (10.8)	0.051
Radiofrequency ablation (%)	141 (28.4)	27 (25.2)	51 (25.0)	63 (33.9)	0.109
ICD (%)	72 (14.5)	19 (17.8)	32 (15.7)	21 (11.3)	0.260
CABG (%)	7 (1.4)	1 (0.9)	5 (2.5)	1 (0.5)	0.248

HFpEF: heart failure with preserved ejection fraction; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; NYHA: New York Heart Association; Cre: creatinine; eGFR: estimated glomerular filtration rate; UA: uric acid; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TC: cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein; LVMI: left ventricular mass index; LVED: left ventricular end diastolic; LAD: left atrial diameter; RAD: right atrial diameter; RVD: right ventricle diameter; IVST: interventricular septal thickness; LVPW: left ventricular posterior wall thickness; LVEF: left ventricular ejection fraction; E/e': mitral Doppler early velocity/mitral annular early velocity; PAP: pulmonary artery systolic pressure; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; MRA: mineralocorticoid receptor antagonists; CCB: calcium channel blockers; HMG-CoA: β-hydroxy β-methylglutaryl-CoA; PCI: percutaneous coronary intervention; ICD: implantable cardioverter defibrillators; CABG: coronary artery bypass graft. <sup>#</sup>Compared with low-score group, P < 0.05. <sup>\*</sup>Compared with intermediate-score group, P < 0.05. <sup>&</sup>Compared with low-score group, P < 0.05.

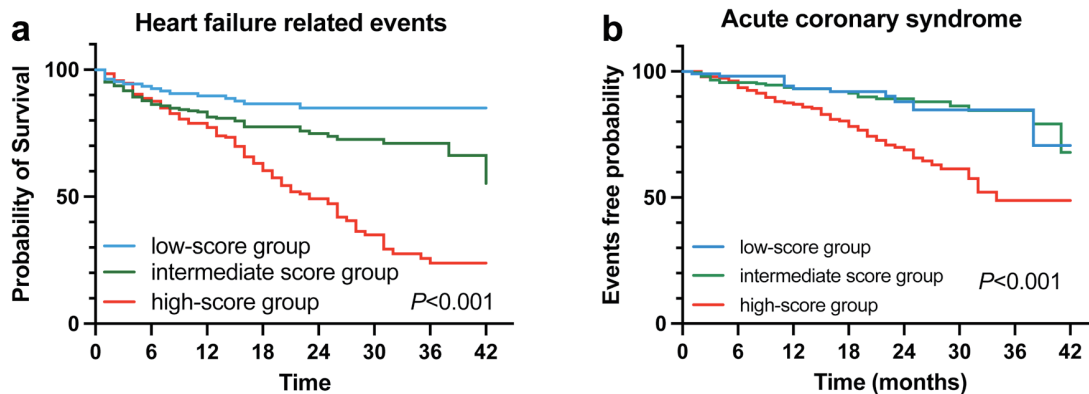
respectively (Supplementary Tables 1 and 2, www.cardiologyres.org). We found significantly higher rates of primary and secondary points in high-score group patients than those in the low-score group (P < 0.05) (Supplementary Table 3, www.cardiologyres.org). The Cox proportional hazards analysis indi-

cated that the H<sub>2</sub>FPEF score was associated with the primary point (HR: 1.065; 95% CI: 1.019 - 1.112; P < 0.001) but not the secondary point (HR: 1.054.370; 95% CI: 0.997 - 1.115; P = 0.066) (Supplementary Table 4, www.cardiologyres.org). ROC analysis showed the H<sub>2</sub>FPEF score had a predictive role

**Table 2.** Cardiovascular Events in the Study Groups According to the Modified H<sub>2</sub>FPEF Score

	All patients (n = 497)	Low-score group (n = 107)	Intermediate-score group (n = 204)	High-score group (n = 186)	P
HF-related events, n (%)	168 (33.8)	15 (14.0)	50 (24.5)	103 (55.4)	< 0.001
Cardiovascular death, n (%)	31 (6.2)	6 (5.6)	10 (4.9)	15 (8.1)	0.416
Hospitalization for HF decompensation, n (%)	148 (29.8)	13 (12.1)	45 (22.1)	90 (48.4)	< 0.001
Acute coronary syndrome events, n (%)	97 (19.5)	12 (11.2)	25 (12.3)	60 (32.2)	< 0.001
Non-fatal myocardial infarction, n (%)	15 (3.0)	5 (4.7)	4 (2.0)	6 (3.2)	0.405
Unstable angina pectoris, n (%)	82 (16.5)	7 (6.5)	21 (10.3)	54 (29.0)	< 0.001

HF: heart failure.



**Figure 2.** Kaplan-Meier analyses for primary (a) and secondary (b) endpoints according to the modified H<sub>2</sub>FPEF scores by BMI  $\geq 25$  kg/m<sup>2</sup>. BMI: body mass index.

for HF-related events (AUC: 0.666, 95% CI: 0.616 - 0.716;  $P < 0.001$ ) and ACS (AUC: 0.626, 95% CI: 0.563 - 0.689;  $P < 0.001$ ) (Supplementary Figure 1, www.cardiologyres.org).

### H<sub>2</sub>FPEF score calculated by BMI $\geq 25$ kg/m<sup>2</sup>

#### Clinical characteristics

According to the modified H<sub>2</sub>FPEF score calculated by BMI  $\geq 25$  kg/m<sup>2</sup>, the patient numbers (percentage) of low- (1 - 3 points), intermediate- (4 - 6 points), and high-score (7 - 9 points) were 107 (21.5%), 204 (41.0%), and 186 (37.4%), respectively (Table 1 and Supplementary Table 5, www.cardiologyres.org).

As compared to the low-score group, patients in the high-score group showed elevated age, BMI, heart rate, serum creatinine, uric acid (UA), hemoglobin levels, and declined eGFR, with higher prevalence of hypertension, AF and previous hospitalization for HF. Regarding the resting echocardiography, a higher E/e' ratio and PAP were observed in high-score group patients, with a larger left atrial diameter (LAD) and right atrial diameter (RAD). Meanwhile, compared to the patients with low H<sub>2</sub>FPEF scores, patients with high H<sub>2</sub>FPEF scores received more spironolactone, loop diuretic and anticoagulant drugs (Table 1).

Over the follow-up period, patients in the high-score group had higher rates of re-hospitalization ( $P < 0.001$ ) and ACS events ( $P < 0.001$ ) than those in the low-score group (Table 2, Supplementary Tables 6 and 7, www.cardiologyres.org).

#### Kaplan-Meier curves

The Kaplan-Meier analysis stratified by the modified H<sub>2</sub>FPEF score showed a significantly higher probability of primary endpoint in the patients with a high H<sub>2</sub>FPEF score at follow-up ( $P < 0.001$ ) (Fig. 2a). Additionally, the survival analysis indicated that the modified H<sub>2</sub>FPEF score successfully stratified the patients for HF re-hospitalization (Supplementary Figure

2B, www.cardiologyres.org, log-rank test  $P < 0.001$ ) but not for cardiovascular death (Supplementary Figure 2A, www.cardiologyres.org, log-rank test  $P = 0.177$ ). A significantly higher probability of the secondary endpoint was also observed in the high-score group ( $P < 0.001$ ) (Fig. 2b).

#### Cox proportional hazards analysis

Table 3 shows the modified H<sub>2</sub>FPEF score was a significant predictor of HF-related events (HR: 1.085; 95% CI: 1.038 - 1.134;  $P < 0.001$ ) and ACS events (HR: 1.072; 95% CI: 1.016 - 1.371;  $P = 0.011$ ). In addition, digoxin (HR: 2.383; 95% CI: 1.212 - 5.066;  $P = 0.024$ ) was independently associated with a higher risk of HF-related events.

#### ROC analysis

As shown in Figure 3, the AUC of the modified H<sub>2</sub>FPEF score for detecting HF-related events and ACS were 0.723 (95% CI: 0.676 - 0.770;  $P < 0.001$ ) and 0.670 (95% CI: 0.608 - 0.731;  $P < 0.001$ ). The modified H<sub>2</sub>FPEF score exhibited higher power compared to the H<sub>2</sub>FPEF score calculated by BMI  $\geq 30$  kg/m<sup>2</sup>. Using the cutoff value of 6.5, the sensitivity and specificity of the modified H<sub>2</sub>FPEF score for detecting HF-related events were 60.2% and 74.5%, respectively. The cutoff value of the modified H<sub>2</sub>FPEF score for the detection of ACS was 6.5 with 61.9% of sensitivity and 68.5% of specificity (Supplementary Tables 8 and 9, www.cardiologyres.org).

## Discussion

In this study, we retrospectively assessed the predictive value of the H<sub>2</sub>FPEF score among Chinese HFpEF patients. When obesity was defined by BMI  $\geq 25$  kg/m<sup>2</sup>, HFpEF patients with high modified H<sub>2</sub>FPEF scores had a significantly higher probability of HF-related events and ACS. The modified H<sub>2</sub>FPEF score was an independent predictor of future HF-related events and ACS with higher power than the H<sub>2</sub>FPEF score calculated

**Table 3.** Cox Proportional Hazards Analysis of Cardiovascular Events in HFpEF Patients

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
<b>HF-related events</b>				
The modified H <sub>2</sub> FPEF score	1.102 (1.059 - 1.147)	< 0.001	1.085 (1.038 - 1.134)	< 0.001
Female (%)	0.726 (0.529 - 0.996)	0.047		
IVST (mm)	1.125 (1.010 - 1.254)	0.032		
DBP (mm Hg)	0.998 (0.986 - 1.009)	0.689		
Heart rate	1.001 (0.996 - 1.007)	0.636		
Cre	1.002 (0.996 - 1.008)	0.491		
eGFR	0.992 (0.984 - 0.999)	0.029		
UA	1.001 (1.000 - 1.003)	0.090		
Hemoglobin (g/L)	0.996 (0.989 - 1.004)	0.340		
LAD (mm)	1.059 (1.029 - 1.091)	< 0.001		
RAD (mm)	1.021 (0.999 - 1.044)	0.068		
Spironolactone (%)	1.500 (1.108 - 2.030)	0.009		
Loop diuretic (%)	1.266 (0.882 - 1.818)	0.200		
Anticoagulant drug (%)	1.617 (1.033 - 2.531)	0.036		
Digoxin	2.270 (1.288 - 4.001)	0.005	2.383 (1.1212 - 5.066)	0.024
<b>Acute coronary syndrome events</b>				
The modified H <sub>2</sub> FPEF score	1.072 (1.016 - 1.131)	0.011	-	-
Female (%)	0.919 (0.611 - 1.382)	0.684		
DBP (mm Hg)	1.006 (0.992 - 1.021)	0.381		
Heart rate	0.995 (0.987 - 1.003)	0.227		
Cre	1.000 (0.991 - 1.008)	0.917		
eGFR	0.998 (0.988 - 1.008)	0.701		
UA	0.999 (0.997 - 1.001)	0.476		
Hemoglobin (g/L)	1.002 (0.992 - 1.012)	0.701		
LAD (mm)	1.0505 (0.996 - 1.044)	0.813		
RAD (mm)	1.002 (0.971 - 1.034)	0.918		
Spironolactone (%)	1.159 (0.777 - 1.727)	0.470		
Loop diuretic (%)	1.609 (0.963 - 2.686)	0.069		
Anticoagulant drug (%)	1.833 (0.977 - 3.438)	0.059		

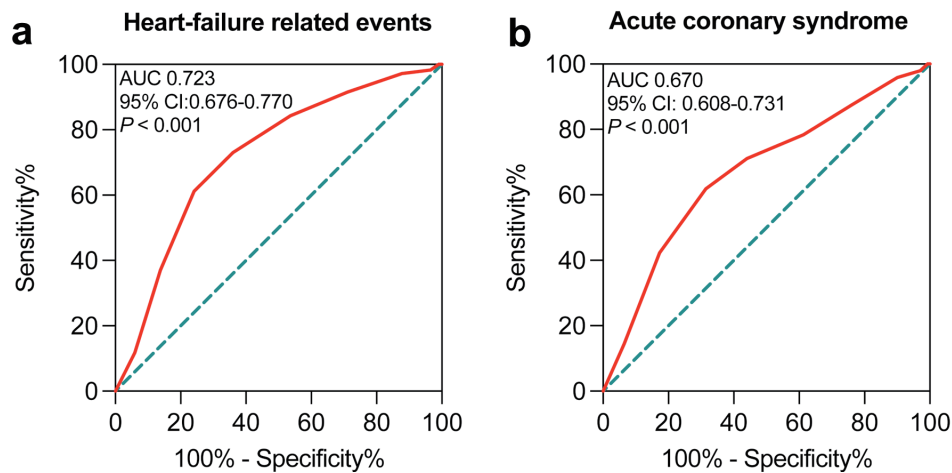
CI: confidence interval; HR: hazard ratio; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; BMI: body mass index; IVST: inter-ventricular septal thickness; DBP: diastolic blood pressure; Cre: creatinine; eGFR: estimated glomerular filtration rate; UA: uric acid; LAD: left atrial diameter; RAD: right atrial diameter.

by BMI  $\geq 30$  kg/m<sup>2</sup>. And the optimum cut-off value of H<sub>2</sub>FPEF was 6.5. In conclusion, the modified H<sub>2</sub>FPEF score was a predictive algorithm for adverse cardiovascular events in Chinese HFpEF patients.

Over the past three decades, the prevalence of HFpEF relative to total HF prevalence rose from 41% to 56%. Simultaneously, the prevalence of heart failure with reduced ejection fraction (HFrEF) and heart failure with midrange ejection fraction fell from 44% to 31% and 15% to 13%, respectively [5, 24]. This trend may have been influenced by increased awareness of HFpEF in recent decades [25]. The aging population

also contributes significantly to the increase in the number and proportion of HFpEF patients. Concomitant risk factors in modern life, such as obesity, diabetes mellitus, and chronic kidney disease, are partly responsible for the rise of HFpEF prevalence. The high frequency of comorbidities not only raises the chance of hospitalization and death but also leads to symptomatic deterioration, which results in decreased quality of life and functional capacity in patients. Early identification of at-risk patients and aggressive management are critical to preventing HFpEF and its progression.

The H<sub>2</sub>FPEF score, including six variables, is a practical



**Figure 3.** ROC curves for the modified H<sub>2</sub>FPEF scores by BMI  $\geq$  25 kg/m<sup>2</sup> to predict primary (a) and secondary (b) endpoints in HFpEF patients. BMI: body mass index; HFpEF: heart failure with preserved ejection fraction; ROC: receiver operating characteristic.

diagnostic tool and a prognostic algorithm for HFpEF. Obesity, a common risk factor for cardiovascular diseases, is defined as BMI  $\geq$  30 kg/m<sup>2</sup> in the initial H<sub>2</sub>FPEF score [16-18]. However, there is a debate regarding the best BMI classification for the Asian population because of their structural variations compared to the western population [21, 26]. In 2016, the Global BMI Mortality Collaboration conducted a meta-analysis of 239 prospective studies that showed that all-cause mortality in East Asians increased significantly with a BMI  $\geq$  25 kg/m<sup>2</sup> [27]. Therefore, different BMI criteria for obesity are needed for different races. Based on the fact that Asians have higher morbidity and mortality even with lower BMI and waist circumference (WC), the WHO Asia-Pacific region defined BMI  $\geq$  23 kg/m<sup>2</sup> as overweight and  $\geq$  25 kg/m<sup>2</sup> as obese [28]. Recently, some studies among the Asian population used a different cutoff of BMI to examine the role of H<sub>2</sub>FPEF score in HFpEF prognosis. Defined obesity as BMI  $\geq$  25 kg/m<sup>2</sup>, Sueta et al reported that the H<sub>2</sub>FPEF score was a potentially useful marker for predicting cardiovascular and HF-related events in Japanese HFpEF patients [17]. Nevertheless, Tao et al indicated that the H<sub>2</sub>FPEF score calculated by BMI  $\geq$  30 kg/m<sup>2</sup> had excellent predictive value for 1-year rehospitalization in Chinese HFpEF patients [29]. In this retrospective study, we found that the H<sub>2</sub>FPEF score with BMI  $\geq$  25 kg/m<sup>2</sup> exhibited a higher power for predicting adverse outcomes in Chinese HFpEF patients. Although the results needed to be evaluated in larger study cohorts, our findings highlighted the need for the application of population-specific and culturally appropriate metrics when assessing cardiovascular health.

In our study cohort, the Kaplan-Meier analysis indicated that a significantly higher probability of HF-related events was observed in the high-score group. However, the H<sub>2</sub>FPEF score was not correlated with cardiovascular mortality in the last episode of the follow-up. This may be due to the small sample size and relatively short follow-up period.

The Cox proportional hazards analysis showed that in addition to the modified H<sub>2</sub>FPEF score, digoxin treatment was related to adverse HF outcomes in HFpEF. Although numerous

clinical studies have found that HF patients treated with digoxin may have a higher risk with poor outcomes, digoxin therapy in HF remained controversial [30-32]. A multicenter study conducted among old patients (> 70 years) with HFpEF showed that digoxin treatment was associated with increased mortality and re-admission, particularly in those with lower heart rates [31]. However, a recent study reported that digoxin initiation prior to hospital discharge did not affect 30-day or 6-year outcomes in old hospitalized patients with HFpEF [33]. Another score-matched cohort of hospitalized HFpEF patients with AF who were not on digoxin at the time of hospitalization found that initiation of digoxin before hospital discharge was associated with a lower risk of HF re-admission but had no effect on mortality rate [34]. A potential explanation for the inconsistent results may lie in the study design and bias associated with the “time-dependent” initiation of digoxin. Patients may benefit from the early hemodynamic effects of digoxin. However, prevalent digoxin use is a marker of disease severity and is usually associated with a higher risk of adverse outcomes [35, 36].

The available data indicated that a high modified H<sub>2</sub>FPEF score was associated with ACS events in HFpEF patients. Although pretty common in HFpEF patients, the interaction of ACS and HFpEF has been underestimated [37, 38]. Compared to patients with only HFpEF, a more significant deterioration of LV function and a worse prognosis were observed in patients with HFpEF and coronary artery disease [39, 40]. Ischemic heart disease conferred an approximate 20% increase in the risk of major adverse renal and cardiovascular events for patients with HFpEF. On the other hand, a history of MI could be significantly linked to the risk of HFpEF. The prevalence of new-onset HF was reported to be 9.5% in ACS patients during a median follow-up of 63 months [41]. One of the possible explanations linking ACS and HFpEF is that they commonly coexist and share multiple risk factors [42]. Each parameter included in the H<sub>2</sub>FPEF score is known to be associated with the pathophysiology of HFpEF. It is reasonable that the H<sub>2</sub>FPEF score exhibited predictive value for future ACS events in HFpEF patients.

In this study, by using the definition of obesity as BMI  $\geq$



25 kg/m<sup>2</sup>, we suggested that the best cutoff value was 6.5 for the modified H<sub>2</sub>FPEF score predicting both HF-related events and ACS attacks in Chinese HFpEF patients. A retrospective and single-center study in Japan, with the same definition of obesity, reported the cutoff H<sub>2</sub>FPEF score was 5.5 for identifying cardiovascular and HF-related events [17]. Nevertheless, Suzuki et al suggested the cutoff value was 7 points for the H<sub>2</sub>FPEF score to predict future HF-related events in stable outpatients with one or more cardiovascular risk factors. The symptoms of patients in the latter study were relatively mild compared to the HFpEF patients, which may result in a higher H<sub>2</sub>FPEF score in predicting the adverse outcomes. In the future, additional detailed, prospective, multicenter studies are warranted to verify this precise usefulness.

Each component of the H<sub>2</sub>FPEF score is simple, and its calculation is easy with a low cost in clinical practice, providing a wide range of potential applications. If this score further predicts subsequent cardiovascular events in HFpEF patients, like the application of CHA<sub>2</sub>DS<sub>2</sub>-VASc score in the AF, it would represent a valuable indicator for cardiologists in the clinical situation. Furthermore, from recent studies, HFpEF was classified into three leading phenotype groups, which are primarily based on aging, cardiometabolic stress, and chronic hypertension [15, 43, 44]. These subgroups exhibited significant differences in survival and potential treatment response [45]. Identification of HFpEF subgroups may help select specific interventions that, in turn, will improve the likelihood of a positive treatment response. Thus, further studies that help to promote the identification of HFpEF subgroups and targeted treatment are needed.

### Study limitations

This study has several limitations. First, it was a single-center design with a relatively small Chinese population, which restricted the generalizability of the modified H<sub>2</sub>FPEF score. Second, the retrospective nature of these analyses creates a tremendous potential for bias. Prospective studies with a broader population are needed to validate the predictive utility of the modified H<sub>2</sub>FPEF score in real-time clinical trials. Third, although AF stood out as the most critical predictor of HFpEF in the H<sub>2</sub>FPEF score and concordantly received a 3-point score when positive, patients with high modified H<sub>2</sub>FPEF scores were all complicated with AF in our study, which may have caused a bias in the results. At last, we focused on different BMIs and did not consider other potentially relevant clinical variables or biomarkers that could enhance the prognostic accuracy. And it is unclear which factors contribute, and the extent of their contribution, to this classification and the prognosis of HFpEF. Thus, further pathophysiological and molecular physiological studies, including animal experiments, are warranted.

### Conclusions

Using BMI  $\geq$  25 kg/m<sup>2</sup> as the definition standard for obesity, the modified H<sub>2</sub>FPEF score can more effectively predict the occurrence of adverse cardiovascular events in Chinese HF-

pEF patients. The higher the score, the higher the risk of adverse cardiovascular events in HFpEF patients.

### Supplementary Material

**Figure 1.** Kaplan-Meier analyses for primary (A) and secondary (B) endpoints according to H<sub>2</sub>FPEF scores by BMI  $\geq$  30 kg/m<sup>2</sup>. Receiver operating characteristic (ROC) curves for H<sub>2</sub>FPEF scores by BMI  $\geq$  30 kg/m<sup>2</sup> to predict primary (C) and secondary (D) endpoints in HFpEF patients.

**Figure 2.** Kaplan-Meier analyses for cardiovascular death (A) and heart failure re-hospitalization (B) according to the modified H<sub>2</sub>FPEF scores (BMI  $\geq$  25 kg/m<sup>2</sup>). The 0-time point in the x-axis indicates discharge day of the qualifying heart failure hospitalization.

**Table 1.** Clinical characteristics according to H<sub>2</sub>FPEF score by BMI  $\geq$  30 kg/m<sup>2</sup>.

**Table 2.** Baseline characteristics of HFpEF patients according to the H<sub>2</sub>FPEF score by BMI  $\geq$  30 kg/m<sup>2</sup>.

**Table 3.** Cardiovascular events in the study groups according to the H<sub>2</sub>FPEF score by BMI  $\geq$  30 kg/m<sup>2</sup>.

**Table 4.** Cox proportional hazards analysis of cardiovascular events in HFpEF patient.

**Table 5.** Clinical characteristics according to the modified H<sub>2</sub>FPEF score.

**Table 6.** Comparison of the clinical characteristics between the groups with and without HF-related events in HFpEF patients.

**Table 7.** Comparison of the clinical characteristics between the groups with and without ACS in HFpEF patients.

**Table 8.** Sensitivity, specificity and likelihood ratio in the modified H<sub>2</sub>FPEF score for future HF-related events.

**Table 9.** Sensitivity, specificity and likelihood ratio in the modified H<sub>2</sub>FPEF score for future ACS.

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### Conflict of Interest

The authors have no conflict of interest to declare that are relevant to the content of this article.

### Informed Consent

All subjects provided written informed consent.

## Author Contributions

YQJ and LG performed the statistical analysis and drafted the manuscript. KKW was responsible for software and data visualization. YL, MXW, and XYG collected the data. JZ, XCY and BX revised the manuscript. JCL designed and supervised the study. All authors provided critical comments on the manuscript. All authors read and approved the final manuscript.

## Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

## Abbreviations

ACS: acute coronary syndrome; AF: atrial fibrillation; AUC: area under the curve; BMI: body mass index; BNP: B-type natriuretic peptide; CI: confidence interval; eGFR: estimated glomerular filtration rate; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; HR: hazard ratio; LAD: left atrial diameter; LV: left ventricular; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; MI: myocardial infarction; NSTEMI: non-ST elevation myocardial infarction; NT-proBNP: N-terminal pro B-type natriuretic peptide; PAP: pulmonary artery systolic pressure; RAD: right atrial diameter; ROC: receiver operating characteristic; SPSS: Statistical Package for Social Sciences; STEMI: ST elevation myocardial infarction; E/e': ratio of early transmitral flow velocity to early diastolic mitral annular velocity; UA: uric acid

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