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ORIGINAL RESEARCH ARTICLE

Predictive value of H_2FPEF score in patients with heart failure with preserved ejection fraction

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Abstract

Aims The H_2FPEF score is a convenient risk stratification tool for diagnosing heart failure with preserved ejection fraction (HFpEF). This study examined the value of the H_2FPEF score for predicting all-cause mortality and rehospitalization in HFpEF patients.

Methods and results This was a retrospective cohort study of patients diagnosed with HFpEF by echocardiography at a single tertiary centre between 1 January 2015 and 30 April 2018. According to the H_2FPEF score, the subjects were divided into low (0–1 points), intermediate (2–5 points), and high (6–9 points) score groups. The primary outcomes were all-cause mortality and rehospitalization. A total of 476 patients (mean age: 70.5 ± 8.4 years, 60.7% female) were included. Of these, 47 (9.9%), 262 (55.0%), and 167 (35.1%) were classified into the low, intermediate, and high score groups, respectively. Over a mean follow-up of 27.5 months, 63 patients (13.2%) died, and 311 patients (65.3%) were rehospitalized. The mortality rates were 3 (6.4%), 29 (11.1%), and 31 (18.6%), and the number of patients with rehospitalization was 28 (59.6%), 159 (60.7%), and 124 (74.3%) for the low, intermediate, and high score groups, respectively. Multivariate Cox regression identified H_2FPEF score as an independent predictor of all-cause mortality (hazard ratio [HR]: 1.46, 95% CI: 1.23–1.73, $P < 0.0001$) and rehospitalization (HR: 1.15, 95% CI: 1.08–1.22, $P < 0.0001$). Receiver operating characteristic (ROC) analysis demonstrated the H_2FPEF score can effectively predict all-cause mortality (AUC 0.67, 95% CI: 0.60–0.73, $P < 0.0001$) and rehospitalization (AUC 0.59, 95% CI: 0.54–0.65, $P = 0.001$) after adjusting for age and NYHA class. With a cut-off value of 5.5, the sensitivity and specificity were 68.3% and 55.4% for all-cause mortality and 50.5% and 66.7% for rehospitalization.

Conclusions The H_2FPEF score can be used to predict prognosis in HFpEF patients. Higher scores are associated with higher all-cause mortality and rehospitalization.

Keywords Heart failure with preserved ejection fraction; H_2FPEF score; All-cause mortality; Rehospitalization; Risk stratification

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Introduction

Heart failure (HF) represents the terminal stage of various cardiovascular diseases. In the latest European Society of Cardiology (ESC) guidelines, HF was divided into HF with reduced ejection fraction (HFrEF), HF with mid-range ejection fraction (HFmrEF), and HFpEF based on left ventricular ejection fraction (LVEF).[1,2] HFpEF is a clinical syndrome characterized by abnormal diastolic function, decreased compliance, and increased stiffness. The main mechanisms include left atrial hypertension, pulmonary hypertension (PH), plasma volume expansion, systemic microvascular inflammation, cardiometabolic functional abnormalities, and cellular (titin)/extracellular (fibrosis) structural abnormalities.[3,4] In addition, common characteristics of patients with HFpEF include advancing age, a higher body mass index (BMI), female gender, and atrial fibrillation (AF) but lower frequency of ischemic heart disease (IHD).[5] Over the past few decades, the prevalence of HFpEF increased from 41% to 56%, whereas the prevalence of HFrEF and HFmrEF decreased from 44%

to 31% and from 15% to 13%, respectively.[6] Currently, HFpEF has become the dominant form of HF worldwide, accounting for approximately 50% of all hospital admissions for HF.[7] At present, there are no definitive treatments that have been proven to improve prognosis and no measures available to evaluate the prognosis of HFpEF.

The H_2FPEF score was proposed by Reddi *et al*. for the diagnosis of HFpEF in 2018.[8] This score comprised BMI >30 kg/m^2, two or more antihypertensive medications, paroxysmal or persistent AF, pulmonary arterial systolic pressure >35 mmHg by echocardiography, age >60 years, E/e' >9 by Doppler echocardiography. For this score, six dichotomized variables remained associated with HFpEF and were assigned a score proportional to the strength of their respective associations. These scores were summed to yield the global H_2FPEF score ranging from 0 to 9. The scoring criteria and interpretations were as follows: 0 or 1, exclude HFpEF; 2–5, further examination is needed to confirm the diagnosis; and 6–9, high probability of HFpEF diagnosis. However, whether it can be used to predict prognosis has not been explored in detail. Therefore, this study examined whether H_2FPEF score can be used to predict adverse outcomes in HFpEF patients.

Methods

Study population and groups

All procedures were conducted in accordance with the Declaration of Helsinki. The study was approved by the institutional review board of Dalian Medical University, and informed consent has been obtained from the subjects. A total of 856 consecutive patients with HFpEF were hospitalized at the First Affiliated Hospital of Dalian Medical University between 1 January 2015 and 31 April 2018; 380 patients were excluded due to missing echocardiographic data (n = 125), loss to follow-up (n = 110), or meeting other exclusion criteria (n = 145). We calculated the H_2FPEF score for the remaining patients and divided the cohort into three groups according to H_2FPEF score: low score group (H_2FPEF score 0–1 points), intermediate score group (2–5 points), and high score group (6–9 points).

Clinical definitions

HFpEF was diagnosed according to the 2016 ESC guidelines for the diagnosis and treatment of acute and chronic HF. The diagnostic criteria were clinical symptoms or signs of HF, LVEF $\geq$50%, elevated levels of natriuretic peptides (B-type natriuretic peptide >35 pg/mL or N-terminal pro B-type natriuretic peptide >125 pg/mL), and at least one of the following additional criteria: (i) relevant structural heart disease (left ventricular hypertrophy or left atrial enlargement) and (ii) diastolic dysfunction. The exclusion criteria were severe valvular disease, end-stage renal failure (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2), or systemic inflammatory disease.

Clinical data

Details of clinical characteristics, co-morbidities, drug therapy, laboratory values, arrhythmias, and echocardiography findings of the subjects were collected and recorded. Subjects were required to fast more than 8 h before venous blood collection, and blood samples were usually obtained the morning after admission. All subjects underwent dynamic electrocardiography to record the occurrence of various arrhythmias. Echocardiography was performed under stable condition before discharge by experienced cardiologists who had no knowledge of the study.

Follow-up

Observations were performed by investigators who were blinded to the study information. Most of the enrolled patients were required to return to the outpatient clinic every month. Nevertheless, if the patients did not appear at their scheduled clinic, they were to be interviewed by telephone annually. The cut-off was 30 April 2018 or the occurrence of death or rehospitalization. Mean follow-up duration was 27.5 months, and the main endpoints were all-cause mortality and worsening of HF resulting in rehospitalization. Rehospitalization for decompensated HF was defined as when patients were admitted with typical symptoms of HF and objective evidence of worsening HF that required intravenous treatment.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences, Version 24.0 (SPSS Inc., Chicago, IL). Qualitative variables were expressed as percentages (%), and Fisher's exact test and χ^2 test were used for comparison between groups as appropriate. Data with a non-normal distribution were expressed as the median (interquartile range). The Kruskal–Wallis test was used for multi-group comparisons. Normally distributed data were expressed as means ± standard deviations (x ± s), and ANOVA was used for between-group comparison. Kaplan–Meier analysis was used to describe the cumulative incidence of adverse events, and the log-rank test was used to compare differences. Univariate Cox proportional hazard regression was used to identify significant predictors of the primary outcomes. Significant predictors were entered into multivariate analysis. Hazard

ratios (HRs) with 95% confidence intervals (CIs) were presented. All values were two-tailed, and *P*-values <0.05 were considered statistically significant.

Results

Baseline characteristics

The study flow chart is shown in *Figure 1*. A total of 476 patients with HFpEF were enrolled in the study; the percentages of the low, intermediate, and high score groups were 47 (9.9), 262 (55.0), and 167 (35.1), respectively. The basic clinical characteristics are shown in *Table 1*. Overall, compared with the low and intermediate H_2FPEF score groups, patients in the high score group were older, more likely to have a history of AF/atrial flutter, less likely to have myocardial infarction (MI), and more likely to take medications, including angiotensin-converting enzyme inhibitors (ACEI), calcium channel blockers, diuretics, and digoxin. However, patients in the intermediate score group had a heavier burden of hypertension and type 2 diabetes mellitus (T2DM), greater prevalence of New York Heart Association (NYHA) classes 3 and 4, and higher values of systolic blood pressure.

In terms of laboratory tests, patients in the high score group had higher serum sodium and uric acid (UA) levels but lower triglyceride levels compared with those in the low and intermediate score groups. Regarding electrophysiological findings, the incidence of AF was significantly higher in the high score group than in the low and intermediate score groups. There were statistically significant differences in the incidence of premature atrial contraction and atrial tachycardia among the three groups ($P < 0.05$). Regarding echocardiographic findings, the high score group had higher right ventricular outflow tract thickness, right ventricular diameter,

Figure 1 Flow chart of the study protocol.

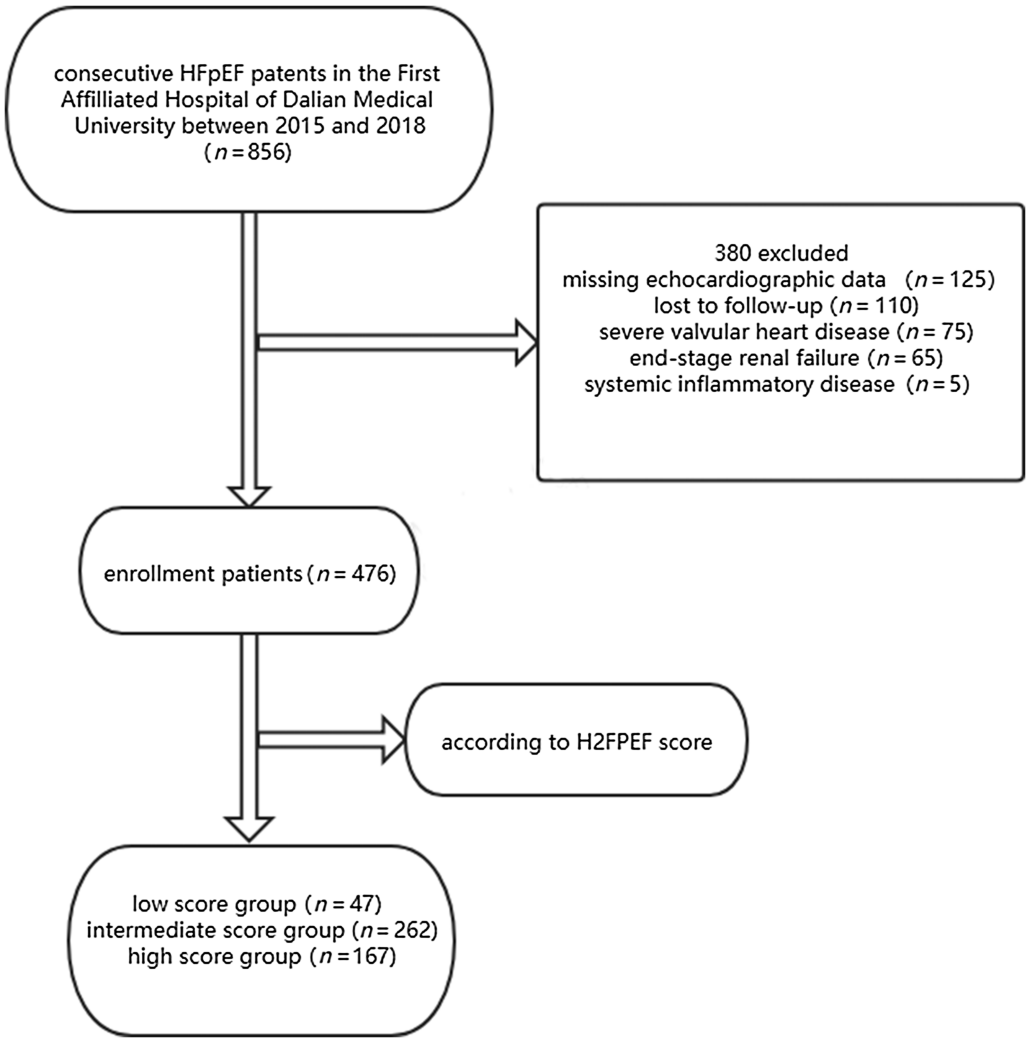


Table 1 Baseline characteristics of HFpEF patients stratified by the H_2FPEF score

	0–1 points	2–5 points	6-9points	*P* value
Case (*n*, %)	47 (9.9)	262 (55.0)	167 (35.1)	—
Age (years)	66.3 ± 10.4$^{\Psi\dagger}$	70.3 ± 8.9	72.1 ± 6.2	<0.001
Female (*n*, %)	24 (57.4)	159 (60.7)	106 (63.4)	0.306
NYHA				
II (*n*, %)	14 (16.1)$^{\Psi\dagger}$	50 (57.5)	23 (26.4)	0.036
III (*n*, %)	21 (7.6)	150 (54.2)	106 (38.3)	0.063
IV (*n*, %)	12 (10.8)	61 (55.0)	38 (34.2)	0.916
BMI	23.8 ± 2.57$^{\Psi\dagger}$	26.6 ± 3.91*†	28.1 ± 4.48*$^{\Psi}$	<0.001
Systolic (mmHg)	134.9 ± 24.86	145.5 ± 26.59*†	138.9 ± 22.81	0.004
Diastolic (mmHg)	75.5 ± 14.95	81.3 ± 17.01	70.2 ± 13.44	0.064
Atrial fibrillation/flutter (*n*, %)	0 (0.0)$^{\Psi\dagger}$	87 (33.2)*†	162 (97.0)*$^{\Psi}$	<0.001
Hypertension (*n*, %)	26 (55.3)$^{\Psi\dagger}$	216 (82.4)	135 (80.8)	<0.001
Diabetes (*n*, %)	15 (31.9)$^{\Psi\dagger}$	137 (52.3)	83 (49.7)	0.036
MI (*n*, %)	20 (42.6)	63 (24.0)*†	29 (17.4)	0.001
PCI (*n*, %)	8 (17.0)	30 (11.5)	20 (12.0)	0.558
Pacemakers (*n*, %)	1 (2.1)	11 (4.2)	4 (2.4)	0.531
Drug therapy				
Loop diuretics (*n*, %)	22 (46.8)	167 (63.7)*†	120 (71.9)	0.005
Beta-blockers	27 (58.7)	182 (69.5)	137 (82.0)*$^{\Psi}$	0.010
ACEI (*n*, %)	7 (14.9)$^{\Psi\dagger}$	73 (27.9)	56 (33.5)	0.041
ARB (*n*, %)	1 (2.1)$^{\Psi\dagger}$	89 (34.0)	54 (32.3)	<0.001
Spironolactone (*n*, %)	18 (39.1)	134 (51.1)	100 (59.9)*	0.022
CCB (*n*, %)	3 (6.4)	99 (37.8)*†	75 (44.9)	<0.001
Digoxin (*n*, %)	0 (0.0)$^{\Psi\dagger}$	19 (7.3)*†	24 (14.4)*$^{\Psi}$	0.038
Statin (*n*, %)	26 (55.3)	169 (64.5)	99 (59.3)	0.351
Antiplatelet drug (*n*, %)	24 (51.1)$\psi^{\dagger}$	135 (51.5)	58 (34.7)	0.002
Laboratory values				
Haemoglobin (g/L)	12.4 ± 22	12.4 ± 26	12.8 ± 24	0.183
BNP (pg/mL)	221 (92, 493)	254 (107, 571)	286 (171, 513)	0.227
hs-TnI (μg/L)	0.04 (0.01, 0.13)†	0.02 (0.01, 0.05)	0.02 (0.01, 0.03)	0.035
D-Dimer (μg/mL)	630 (218, 1128)	565 (268, 1225)	560 (245, 1140)	0.835
Glu (mmol/L)	6.7 ± 2.5	7.0 ± 3.2	6.4 ± 2.5	0.075
Urea (mmol/L)	7.2 (5.7, 8.5)	7.8 (5.9, 11.5)	7.4 (6.0, 10.5)	0.216
Cre (mmol/L)	72 (58, 92)	82 (66, 111)	79 (63, 106)	0.080
UA (mmol/L)	0.369 (0.289, 0.451)†	0.426 (0.334, 0.526)	0.443 (0.353, 0.532)	0.018
TC (mmol/L)	4.5 ± 1.19	4.5 ± 1.31	4.3 ± 1.03	0.211
TG (mmol/L)	1.4 ± 0.9	1.6 ± 0.9†	1.3 ± 0.6	0.006
HDL-C (mmol/L)	1.1 ± 0.3	1.2 ± 0.4	1.1 ± 0.3	0.233
LDL-C (mmol/L)	2.6 ± 0.9	2.6 ± 0.9	2.4 ± 0.8	0.299
Na (mmol/L)	140 ± 5$^{\Psi\dagger}$	141 ± 4	142 ± 4	0.006
K (mmol/L)	3.9 ± 0.5	4.1 ± 0.6*†	3.9 ± 0.5	0.003
Echocardiography findings				
Right ventricular diameter (mm)	19.2 ± 3.2	18.4 ± 2.9†	19.3 ± 2.6	0.004
Thickness of right anterior ventricular wall (mm)	5.1 ± 0.6	5.0 ± 0.1	5.0 ± 0.4	0.220
Thickness of right ventricular outflow tract (mm)	27.4 ± 3.4	27.6 ± 4.3	28.9 ± 3.6*$^{\Psi}$	0.004
Interventricular septal thickness (mm)	11.2 ± 2.2	11.5 ± 1.8	11.2 ± 1.5	0.419
Aortic diameter (mm)	25.6 ± 3.1	25.1 ± 3.3	25.3 ± 2.9	0.636
Left atrial diameter (mm)	38.9 ± 5.8$^{\Psi\dagger}$	41.5 ± 6.6*†	44.9 ± 6.3*$^{\Psi}$	<0.001
Left ventricular end diastolic diameter (mm)	46.9 ± 7.1	47.3 ± 5.7	48.1 ± 5.4	0.265
Inner diameter of pulmonary artery (mm)	22.3 ± 3.5	22.5 ± 3.0	23.3 ± 2.7*$^{\Psi}$	0.010
Thickness of the posterior wall of the left ventricle (mm)	10.7 ± 2.2	10.5 ± 1.5	10.6 ± 1.2	0.785
E peak	81.6 ± 44.4	90.2 ± 36.2	110.1 ± 29.6*$^{\Psi}$	<0.001
EDT	177.3 ± 49.6	190.1 ± 53.6†	177.1 ± 48.7	0.038
E/e′	8.0 ± 3.1$^{\Psi\dagger}$	12.1 ± 6.6	12.9 ± 4.4	0.001
LVEF (*n*, %)	55.8 ± 2.7$^{\Psi}$	56.9 ± 2.8	56.6 ± 2.5	0.035

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CCB, calcium channel blockers; Cr, creatinine; EDT, E peak deceleration time; E/e′, mitral Doppler early velocity/mitral annular early velocity; Glu, glucose; HDL-C, high-density lipoprotein cholesterol; hs-TNI, high-sensitivity troponin; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; TC, cholesterol; TG, triglyceride; UA, uric acid.
*In the measurement data compared with 0–1 group $P < 0.05$.
$^{\Psi}$In the measurement data compared with 2–5 group $P < 0.05$.
†In the measurement data compared with 6–9 group $P < 0.05$.
*In the counting data compared with 0–1 group $P < 0.017$.
$^{\Psi}$In the counting data compared with 2–5 group $P < 0.017$.
†In the counting data compared with 6–9 group $P < 0.017$.

left atrial meridian, pulmonary artery diameter, E peak and early diastolic velocity (E/e') compared with the remaining two groups; peak deceleration time (EDT) was significant shorter in the high score group than in the intermediate score group.

Adverse events on follow-up

Over a mean follow-up of 27.5 ± 11.3 months, 63 patients died (13.2%) and 311 (65.3%) were rehospitalized. The mortality rates were 3 (6.4%), 29 (11.1%), and 31 (18.6%), and the number of patients with rehospitalization was 28 (59.6%), 159 (60.7%), and 124 (74.3%) for the low, intermediate, and high score groups, respectively. The mortality rate of the three groups significantly differed at 24 and 36 months following discharge (*Figure 2*), whereas for rehospitalization, a significant difference was observed 24 months but not 36 months after discharge (*Figure 3*).

Multivariate Cox regression showed that diabetes (HR: 4.2, 95% CI: 2.03–8.6, $P < 0.0001$), BNP (HR: 1.001, 95% CI: 1.000–1.001, $P < 0.0001$), H_2FPEF score (HR: 1.5, 95% CI: 1.23–1.723, $P < 0.0001$), and BMI (HR: 0.87, 95% CI: 0.81–0.95, $P = 0.001$) were significant predictors of all-cause mortality (*Table 2*). Compared with the low score group, the high score group showed a significantly higher risk of all-cause mortality (HR: 6.35, 95% CI: 1.48–27.22, $P = 0.013$), but the intermediate group did not (HR: 2.36, 95% CI: 0.55–10.15, $P = 0.247$). Furthermore, multivariate Cox regression demonstrated that angina (HR: 2.47, 95% CI: 1.74–3.51, $P < 0.0001$) and H_2FPEF score (HR: 1.15, 95% CI: 1.08–1.22, $P < 0.0001$) were significant predictors of rehospitalizations (*Table 3*). As with all-cause mortality, compared with low score group, the high score group showed a significantly higher risk of rehospitalization (HR: 2.06, 95% CI: 1.35–3.14, $P = 0.001$), but the intermediate group did not (HR: 1.42, 95% CI: 0.95–2.12, $P = 0.092$).

Receiver operating characteristics analysis was used to evaluate the availability of H_2FPEF score to predict all-cause mortality and rehospitalization in HFpEF patients (*Figure 4*). The areas under the curve (AUC) of the H_2FPEF score for the prediction of adverse outcomes were 0.67 (95% CI: 0.60–0.73, $P < 0.0001$) and 0.59 (95% CI: 0.54–0.65, $P = 0.001$) after adjusting for age and NYHA class,

Figure 2 Mortality between the three groups at 12, 24, 36, and more than 36 months.

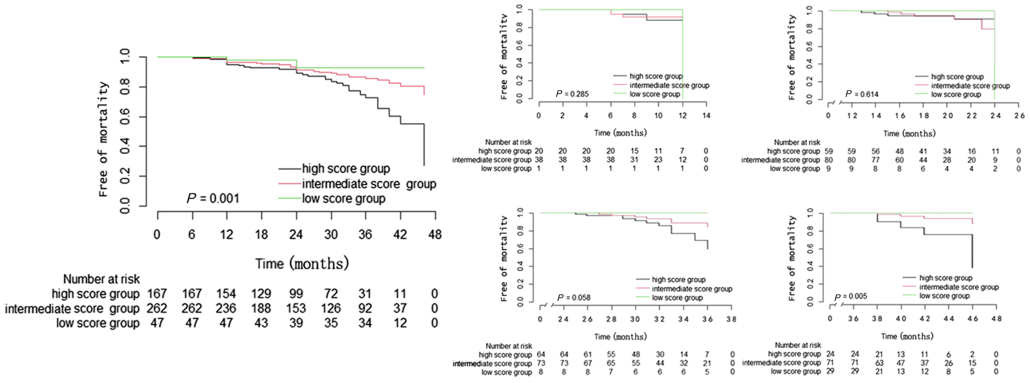


Figure 3 Rehospitalization between the three groups at 12, 24, 36 and more than 36 months.

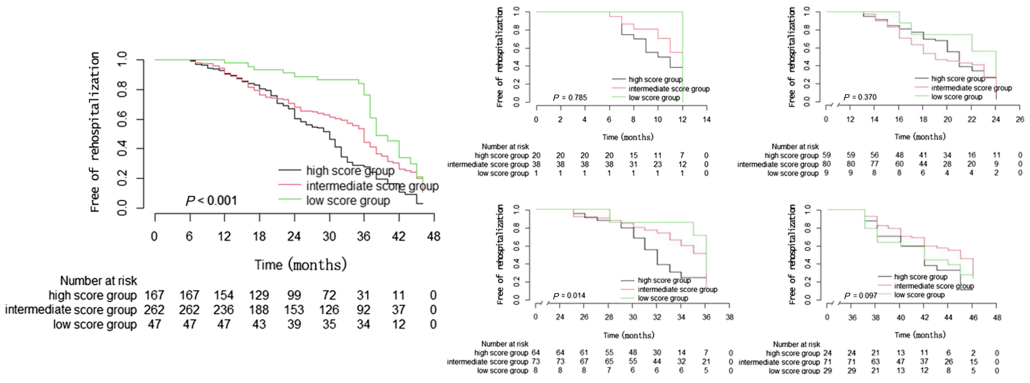


Table 2 Cox regression for all-cause mortality in HFpEF patients

	Univariate analysis			Multivariate analysis		
	RR	95% CI	*P*-value	RR	95% CI	*P*-value
Age	1.074	1.031–1.119	0.001	1.049	0.997–1.104	0.064
BMI	0.909	0.852–0.970	0.004	0.874	0.808–0.946	0.001
NYHA class			0.010			0.512
III/II	3.128	1.111–8.804	0.031	2.036	0.604–6.862	0.251
IV/II	6.290	2.178–18.167	0.00	2.029	0.548–7.512	0.289
PCI	2.236	1.184–4.233	0.013	1.768	0.786–3.973	0.168
Diabetes	2.233	1.321–3.775	0.003	4.188	2.028–8.648	0.000
Atrial fibrillation/flutter	1.881	1.124–3.150	0.016	0.594	0.175–2.011	0.402
PH	3.434	2.069–5.698	0.000	0.969	0.439–2.141	0.938
LA	1.079	1.043–1.117	0.000	1.029	0.982–1.078	0.228
EF	1.024	0.936–1.120	0.602	0.962	0.868–1.066	0.458
BNP	1.000	1.000–1.001	0.000	1.001	1.000–1.001	0.000
hs-TNI	0.987	0.921–1.057	0.704	0.985	0.742–1.235	0.739
Cre	1.002	1.001–1.004	0.010	1.002	0.999–1.005	0.131
Na	0.947	0.962–0.985	0.000	0.996	0.980–1.011	0.581
Diuretic	2.106	1.178–3.776	0.012	1.069	0.503–2.271	0.862
H_2FPEF score	1.224	1.087–1.377	0.010	1.457	1.228–1.729	0.000
Groups			0.003			0.000
Intermediate versus low	2.535	0.771–8.334	0.125	2.364	0.551–10.147	0.247
High versus low	5.140	1.560–16.941	0.007	6.351	1.482–27.221	0.013

BMI, body mass index; BNP, B-type natriuretic peptide; Cre, creatinine; EF, ejection fraction; hs-TNI, high-sensitivity troponin; LA, left atrial diameter; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PH, pulmonary hypertension.

Table 3 Cox regression for rehospitalization in HFpEF patients

	Univariate analysis			Multivariate analysis		
	RR	95% CI	*P*-value	RR	95% CI	*P*-value
Ages	1.025	1.010–1.041	0.010	1.007	0.989–1.025	0.443
NYHA class			0.027			0.080
III/II	1.211	0.895–1.639	0.215	0.950	0.680–1.325	0.761
IV/II	1.588	1.122–2.247	0.009	1.340	0.913–1.968	0.135
Angina	2.824	2.084–3.828	0.000	2.467	1.736–3.506	0.000
Atrial fibrillation/flutter	1.530	1.220–1.918	0.000	1.014	0.657–1.564	0.950
PH	1.908	1.491–2.441	0.000	1.262	0.937–1.701	0.126
LA	1.022	1.005–1.040	0.014	0.997	0.975–1.019	0.768
EF	1.017	0.977–1.059	0.409	1.003	0.958–1.050	0.910
BNP	1.000	1.000–1.000	0.266	1.000	1.000–1.000	0.987
hs-TNI	1.001	0.994–1.008	0.763	1.003	0.997–1.010	0.282
Diuretic	1.485	1.169–1.887	0.001	1.135	0.852–1.512	0.387
ACEI	1.287	1.004–1.648	0.046	1.162	0.879–1.536	0.292
β-Blockers	1.434	1.113–1.847	0.005	1.259	0.943–1.680	0.118
H_2FPEF score	1.224	1.087–1.377	0.010	1.148	1.078–1.223	0.000
Groups			0.000			0.001
Intermediate versus low	1.586	1.061–2.372	0.025	1.416	0.945–2.123	0.092
High versus low	2.513	1.659–3.804	0.000	2.056	1.346–3.142	0.001

ACEI, angiotensin-converting enzyme inhibitor; BNP, B-type natriuretic peptide; EF, ejection fraction; hs-TNI, high-sensitivity troponin; LA, left atrial diameter; NYHA, New York Heart Association; PH, pulmonary hypertension.

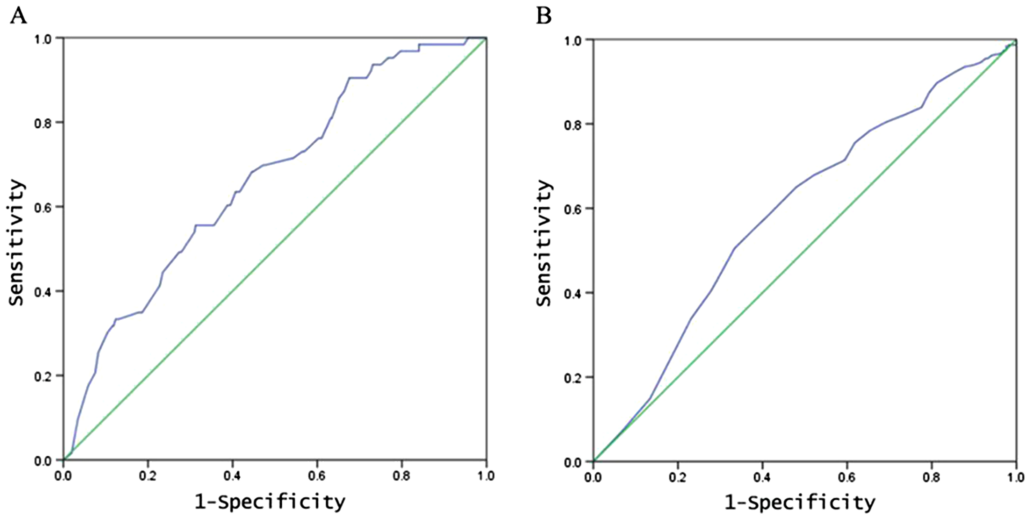
respectively. The sensitivity and specificity of H_2FPEF score at the cut-off of 5.5 were 68.3% and 55.4% and 50.5% and 66.7%, respectively.

Discussion

The main findings of this study are as follows: (i) H_2FPEF score was not only a convenient diagnostic tool for HFpEF but can also effectively predict prognosis in HFpEF. (ii) H_2FPEF score was an independent predictor of all-cause mortality and re-hospitalization on multivariate Cox regression. (iii) A higher H_2FPEF score was significantly associated with worse outcomes in HFpEF patients. (iv) The optimum cut-off values of H_2FPEF were 5.5 for both all-cause mortality and rehospitalization.

Indeed, HF is often complicated by various co-morbidities that adversely affect prognosis.[9–13] Therefore, targeting co-morbidities has been increasingly advocated as being

Figure 4 Receiver operating characteristic (ROC) curves for H_2FPEF scores to predict all-cause mortality and rehospitalization in HFpEF patients. (A) All-cause mortality after adjustment of age and NYHA class. (B) Rehospitalization after adjustment of age and NYHA class.



relevant to HF care.[14] According to the ESC Heart Failure Pilot Survey, 74% of patients with HF had at least one co-morbidity, and HF patients commonly have multiple co-morbidities.[15] In this study, HFpEF patients also had a high burden of co-morbidities (hypertension [79%], diabetes [49%], MI [23.5%], and AF/atrial flutter [52%]). Surprisingly, these co-morbidities showed no significant association with endpoints after adjustment except for diabetes. With the H_2FPEF score, the presence of persistent or paroxysmal AF is assigned 3 points, whereas other variables are 1 or 2 points, indicating that AF stands out as the most important predictor of HFpEF. Because HFpEF and AF share common epidemiology, pathophysiology, pathogenesis, and risk factors,[16] the two diseases commonly coexist[17]; AF increases the risk of stroke, hospitalization for HF, and mortality.[18] The incidence of AF in HFpEF patients enrolled in this study on follow-up was 52%, with a statistically higher incidence in the high score group compared with the low and intermediate score groups. However, AF was not positively correlated with any-cause mortality and rehospitalization after adjustment. This may be due to the small sample size and relatively short follow-up period, and thus, we cannot rule out a correlation between AF and endpoints in HFpEF patients.

Two studies have previously examined the relationship between H_2FPEF score and adverse outcomes. According to Tao *et al*., the H_2FPEF score had excellent predictive value for 1-year rehospitalization of patients with HFpEF.[19] Our study also revealed the relationship between H_2FPEF score and rehospitalization; however, the differences among the three groups appeared until 24 months after discharge. This discrepancy between the two studies may be attributed to different baseline characteristics of the cohort of the previous study, namely, older age, fewer females, a higher frequency of hypertension and AF, and worse cardiac function. These characteristics would predispose to the patients to higher rates of HF-related hospitalizations. As to the reason why there were no statistical differences in rehospitalization at the last episode of the follow-up, this is likely attributable to death as a competing event to rehospitalization. In Sueta *et al*., patients with higher H_2FPEF score had significantly higher probability of adverse cardiovascular events and HF-related events.[20] Our study also identified the H_2FPEF score as an independent predictor of all-cause mortality and rehospitalization and demonstrated significantly higher incidence of the main endpoint among subjects with a higher H_2FPEF score.

The results of the PARAGON-HF trial were presented during the ESC Congress 2019,[21] bringing cardiologists face to face with the reality that there was no available convincing evidence-proven strategy that delivers definitive benefits for HFpEF patients. One way to resolve this might be returning to an aetiology-oriented treatment approach and abandoning the one-size-fits-all way of thinking. Recently, Ge *et al*. introduced a clinical phenotypic classification of HFpEF,[22] which included the following: (i) vascular-related HFpEF; (ii) cardiomyopathy-related HFpEF; (iii) right heart- and pulmonary-related HFpEF; (iv) valvular- and rhythm-related HFpEF; and (v) extracardiac disease-related HFpEF. This phenotypic coding helps introduce a better understanding of the risk factors, aetiology, pathophysiology, and clinical course of HFpEF and contributes to guiding targeted treatment, as is the case for HFrEF.[23] In the near future, treatment targeted to aetiology and co-morbidities may be the best choice in treatment of HFpEF patients.

Limitations of this study

Nevertheless, we must note that this study has several limitations. Firstly, this was a retrospective study, which inevitably resulted in selection bias and recall bias. Secondly, this was a single-centre study with relatively few subjects; therefore, a larger multicentre clinical study is needed. Thirdly, it was still unclear as to which factors contribute, and the extent of their contribution, to prognosis in HFpEF patients. In this regard, preclinical animal experiments will contribute to our understanding regarding the pathophysiological mechanisms of HFpEF. Finally, data on LA strain, 3D echocardiography, and invasive catheterization were only available in a small number of patients and could not be explored as potential prognostic factors. These should be evaluated prospectively for the HFpEF population in the future.

Conclusions

The H_2FPEF score can be used to predict prognosis in HFpEF patients. Higher scores are associated with higher all-cause mortality and rehospitalization.

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Conflict of interest

None declared.

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Author contributions

Yuxi Sun was responsible for collecting clinical data and writing the paper. Niuniu Wang assisted Sun in collecting data and conducting telephone follow-up. Xiao Li helped Niuniu Wang with the follow-up, Yanli Zhang and Jie Yang were responsible for the statistical analysis, and Ying Liu and Gary Tse were responsible for revising the paper and determining the research direction. All authors were involved in the drafting or revision of the manuscript.

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