H_2FPEF score predicts 1-year rehospitalisation of patients with heart failure with preserved ejection fraction

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ABSTRACT

Background Heart failure with preserved ejection fraction (HFpEF) has received widespread attention in recent years. There is currently a lack of valuable predictors for the prognosis of this disease. Here, we aimed to identify a non-invasive scoring system that can effectively predict 1-year rehospitalisation for patients with HFpEF.

Methods We included 151 consecutive patients with HFpEF in a prospective cohort study and investigated the association between H_2FPEF score and 1-year readmission for heart failure using multivariate Cox regression analysis.

Results Our findings indicated that obesity, age >70 years, treatment with ≥2 antihypertensives, echocardiographic E/e' ratio >9 and pulmonary artery pressure >35 mm Hg were independent predictors of 1-year readmission. Three models (support vector machine, decision tree in R and Cox regression analysis) proved that H_2FPEF score could effectively predict 1-year readmission for patients with HFpEF (area under the curve, 0.910, 0.899 and 0.771, respectively; p<0.001).

Conclusion Our study demonstrates that the H_2FPEF score has excellent predictive value for 1-year rehospitalisation of patients with HFpEF.

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is a form of heart failure (HF) in which the left ventricular ejection fraction (LVEF) is normal. Patients with HFpEF account for approximately 50% of all hospital admissions for HF, while the remaining 50% of patients have HF with reduced ejection fraction (HFrEF).[1] Symptoms, hospitalisation rates and mortality among patients with HFpEF are similar to those among patients with HFrEF.[2] Left ventricular (LV) diastolic dysfunction, abnormalities in right ventricular (RV) function, chronotropic incompetence, abnormal systemic and pulmonary vasodilation and endothelial dysfunction are the main mechanisms underlying HFpEF.[3] The prognosis of patients with HFpEF should be evaluated as early as possible to identify high-risk patients so that optimised treatment can be initiated. Patients with exertional dyspnoea, however, present a diagnostic challenge in the absence of radiographic or biomarker evidence. The diagnosis of these patients depends on right-sided heart catheterisation but, because of its invasiveness and high cost, the clinical application of this technique is limited.[4]

The study by Reddy *et al* proposed using the H_2FPEF score, which is based on obesity, atrial fibrillation (AF), age, treatment with ≥2 antihypertensives, echocardiographic E/e' ratio and pulmonary artery systolic pressure, to discriminate HFpEF from non-cardiac causes of dyspnoea.[5] This scoring system is mainly used for the diagnosis of HFpEF. In the present investigation, we performed a prospective cohort study to assess the prognostic value of H_2FPEF score in patients with HFpEF.

METHODS

Study subjects

A total of 151 consecutive patients with HFpEF, who were admitted to the Second Affiliated Hospital of Soochow University from April 2016 to November 2018, were enrolled in the study. The diagnosis of HFpEF was based on manifestations of dyspnoea, fatigue, fluid retention, LVEF≥50%, elevation of B-type natriuretic peptide and LV diastolic dysfunction.[6] Exclusion criteria included congenital heart disease, significant valvular heart disease (greater than mild stenosis or moderate regurgitation), acute myocardial infarction, primary cardiomyopathy and glomerular filtration rate <30 mL $min^{-1}\times1.73\,m^{-2}$. Demographic, clinical and biochemical data included in this study were obtained from medical records and all study participants provided written informed consent.

Clinical evaluation

General information about the patients with HFpEF was collected at admission. AF was assessed using clinical history and an ECG. Diabetes mellitus was defined as treatment with antidiabetic medications, fasting plasma glucose ≥7 mmol/L or haemoglobin A1c≥65 mg/L. The number of antihypertensive medications taken by each patient was determined. N-terminal pro-B-type natriuretic peptide, haemoglobin, creatinine, uric acid, thyroid function and other indicators were measured on admission. All echocardiographic measurements were performed by experienced technicians who were blinded to the clinical conditions.

H_2FPEF score

The H_2FPEF score, which has a value between 0 and 9, is a composite of clinical data. Body mass index (BMI) >30 kg/m^2 contributes two points to the score, AF contributes three points to the score,

Table 1 Baseline characteristics

Characteristics	Non-readmission (n=76)	Readmission (n=75)	P value
Age (years)	73.87±9.07	78.77±7.11	0.056
Female (%)	46.1	46.7	0.940
Body mass index (kg/m^2)	23.98±2.91	24.86±4.13	0.006
Hypertension (%)	76.3	89.3	0.034
Antihypertensive drugs (n)	1.51±0.74	1.97±0.82	0.355
Diabetes mellitus (%)	17.1	40.0	0.002
Hyperlipaemia (%)	34.2	21.3	0.077
Atrial fibrillation (%)	61.8	74.7	0.091
Haemoglobin (g/L)	132.51±16.30	125.20±21.50	0.015
Diuretic (%)	51.3	85.3	< 0.0001
Spirolactone (%)	23.7	45.3	0.005
NT-proBNP (pg/mL)	2695.41±2664.53	3676.73±4161.38	0.037
Creatinine (μmol/L)	82.54±27.16	92.61±31.13	0.316
Glomerular filtration rate, (mL min^{-1}×1.73 m^{-2})	79.17±23.55	68.77±25.25	0.562
Uric acid (μmol/L)	380.09±98.92	410.47±111.3	0.388
C reactive protein (mg/L)	14.95±26.73	13.64±24.26	0.565
Thyroid function (%)	19.7	34.7	0.039
Pacemaker (%)	9.2	12	0.578
Tumour (%)	1.3	9.3	0.028
LVEF (%)	63.86±7.73	61.85±7.37	0.341
Echocardiography E/e' ratio	9.28±4.72	10.47±3.68	0.285
Pulmonary artery pressure (mm Hg)	35.36±12.58	43.21±15.55	0.027

Values are presented as mean±SD.
E/e', ratio of early diastolic mitral inflow velocity to septal mitral annulus tissue relaxation velocity; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

and treatment with ≥2 antihypertensive drugs, age >70 years, elevated filling pressures (E/e'>9) and pulmonary artery systolic pressure >35 mm Hg each contribute one point to the score.[5]

Clinical treatment

Clinical treatment was tailored to each patient's symptoms, signs, aetiologies and comorbidities. Following individualised assessment of each patient, diuretics, beta receptor blockers, ACE inhibitors, angiotensin II receptor antagonists, and aldosterone receptor antagonists were prescribed as appropriate.

End points

The primary end points were readmission for HF and all-cause mortality within 1 year. Readmission for HF was defined as the need for treatment with intravenous diuretics, inotropes and vasodilators in a hospital setting. End points were determined by contacting the patients or their families by telephone.

Statistical analysis

All statistical analyses were carried out using SPSS 22.0 (IBM, USA). Continuous variables are reported as mean±SD. Categorical variables are expressed as proportions and were compared using the χ^2 test. Multivariate Cox regression analysis was conducted to assess risk factors for 1-year readmission. Using the H_2FPEF score on a continuous scale, the predictive value was then evaluated using the area under the receiver-operating characteristic curve (AUC). Three completely agnostic models (support-vector machine, decision tree in R and Cox regression analysis) were generated, and the AUCs were compared. P<0.05 was considered to be statistically significant in this study.

Table 2 Cox regression analysis for 1-year readmission

Characteristics	HR	95% CI	P value
Body mass index >30 kg/m^2	3.440	1.873 to 6.320	0.000
Female	0.951	0.604 to 1.497	0.828
Atrial fibrillation	1.168	0.885 to 1.540	0.272
Age >70 years	3.292	1.201 to 9.021	0.021
Treatment with ≥2 antihypertensives	1.735	1.047 to 2.874	0.032
Pulmonary artery pressure >35 mm Hg	2.163	1.228 to 3.812	0.008
Echocardiography E/e' ratio >9	1.815	1.132 to 2.909	0.013
Diuretic	3.594	1.893 to 6.826	0.000
Spirolactone	1.889	1.198 to 2.978	0.006
Hypertension	1.935	0.929 to 4.029	0.078
Diabetes mellitus	2.437	1.531 to 3.879	0.000
Hyperlipaemia	0.621	0.357 to 1.079	0.091
Uric acid >420 μmol/L	1.341	0.845 to 2.129	0.213
Anaemia	1.986	1.260 to 3.130	0.003
Thyroid dysfunction	1.689	1.049 to 2.720	0.031
Pacemaker	1.253	0.624 to 2.515	0.527
Tumour	2.605	1.189 to 5.707	0.017

E/e', ratio of early diastolic mitral inflow velocity to septal mitral annulus tissue relaxation velocity.

RESULTS

Patient characteristics

The baseline characteristics of the study participants are shown in table 1. A total of 151 patients were enrolled in the study. During the 1-year follow-up period, 75 patients were readmitted with HF, and none were lost to follow-up. Patients who were readmitted within 1 year were older, had higher BMI and pulmonary artery systolic pressure and were more likely to have hypertension, diabetes mellitus and anaemia. One-year readmission tended to be positively associated with the use of diuretics and spironolactones.

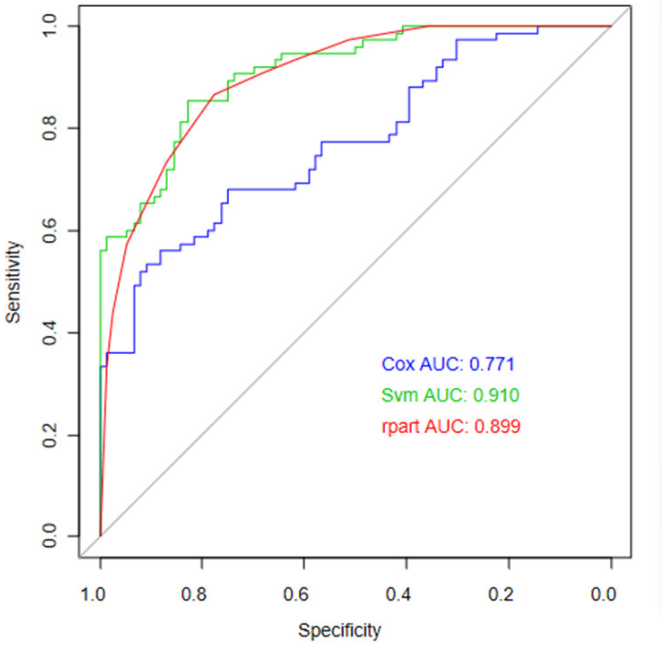

Figure 1 Receiver operating characteristic curve analysis of three models. AUC, area under the curve; rpart, decision tree in R; Svm, support vector machine.

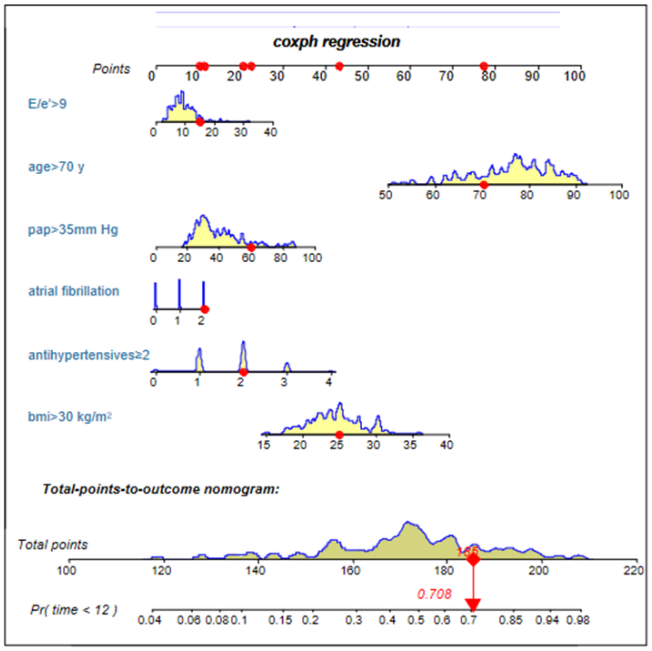

Figure 2 A specific set of data were assumed to predict 1-year readmission. BMI, body mass index; E/e', ratio of early diastolic mitral inflow velocity to septal mitral annulus tissue relaxation velocity; PAP, pulmonary artery pressure.

Multivariate COX regression analysis

As shown in table 2, obesity, age >70 years, treatment with ≥2 antihypertensives, echocardiographic E/e' ratio >9, pulmonary artery systolic pressure >35 mm Hg, use of diuretics and spironolactones, diabetes mellitus, anaemia, thyroid dysfunction and tumours were independent predictors of 1-year readmission ($p<0.05$).

Receiver operating characteristic curve analysis

As shown in figure 1, three models (support-vector machine, decision tree in R and Cox regression analysis) were established to predict 1-year readmission of patients with HFpEF. The AUCs of the three models (0.910, 0.899 and 0.771, respectively; $p<0.001$) showed that the support-vector machine had the best prognostic ability.

Individual data for a 70-year-old patient with HFpEF were used to predict 1-year readmission (figure 2). The patient suffered from AF, had a BMI of 25 kg/m^2, took two antihypertensive drugs every day, had an echocardiography E/e' ratio of 15 and pulmonary artery systolic pressure of 60 mm Hg. According to the Cox regression, the probability of the patient being hospitalised within 1 year was 70.8%.

DISCUSSION

HFpEF, which has similar morbidity and mortality to HFrEF, represents a major health burden to patients, with a significant number being readmitted to hospital after discharge because of dyspnoea.[7] There is growing recognition of the importance of HFpEF, which is both common and increasing in prevalence over time.[8] However, there is no significant improvement of survival rate due to lack of timely diagnosis and effective medication for the patients with HFpEF.[9] Compared with HFrEF, HFpEF has been shown to be associated with older age, female sex, hypertension, AF and a lower incidence of coronary artery disease.[10] Our study also supports these associations.

Sueta *et al* found that patients with HFpEF with higher H_2FPEF scores had higher probability of adverse cardiovascular events and this score could predict cardiovascular and HF-related events effectively in patients with HFpEF.[11] For patients with HFpEF, the relationship between BMI and mortality is U-shaped. This means that mortality increases significantly if the BMI lies above or below a specific range.[12] HFpEF and AF share epidemiology, pathophysiology, pathogenesis and risk factors.[13] It has been shown that both the prevalence and incidence of AF are associated with increased mortality in HFpEF.[14] Unfortunately, in our study, AF was not positively correlated with 1-year readmission of patients with HFpEF. This may be due to insufficient sample size and short follow-up time, and we cannot rule out a correlation between AF and 1-year readmission.

With the adoption of bedside ultrasound, echocardiography is now widely used as a simple and reliable technique for the diagnosis, treatment and prognosis of HFpEF. Diastolic dysfunction is common in HFpEF and can effectively predict adverse outcomes. Echocardiographic data recommended by ASE/EACVI GUIDELINES add incremental prognostic information in patients with HFpEF. They include LV hypertrophy, left atrial volumes, E/e' ratio, peak velocity of tricuspid regurgitation (TR) jet and RV function. We also know that TR jet is closely related to pulmonary pressure and RV function. Pulmonary artery systolic pressure is calculated from TR pressure and right atrial pressure. Our study included the E/e' ratio and pulmonary artery systolic pressure, and both were found to be independent predictors of readmission for HF.

HFpEF is believed to be a systemic disorder, driven in large part by comorbidities.[2] We found that the presence of diabetes mellitus, hypertension, anaemia and thyroid dysfunction all significantly increased readmission rates. We also observed that the use of diuretics and spironolactones independently increased the probability that patients with HFpEF would be rehospitalised. Pitt *et al*, on the other hand, found a significantly lower incidence of hospitalisation for HF in patients with HFpEF taking spironolactones compared with those taking placebo.[15] The difference between the two studies may be because the

Main messages

- Obesity, age >70 years, treatment with ≥2 antihypertensives, E/e' ratio >9 and pulmonary artery pressure >35 mm Hg are predictors of 1-year readmission.
- The H_2FPEF score has predictive value for 1-year rehospitalisation of heart failure patients with preserved ejection fraction.

Current research questions

- What predictors can be used to assess the prognosis of heart failure with preserved ejection fraction (HFpEF)?
- Why the H_2FPEF score is a valuable prognostic indicator in patients with HFpEF?

What is already known on the subject

- The H2FPEF score is mainly used for the diagnosis of heart failure with preserved ejection fraction.

patients in our study who took diuretics and spironolactones were more seriously ill.

Analysis of receiver operating characteristic (ROC) and AUCs in the three models showed that the H_2FPEF score provides an accurate assessment of risk of readmission for HF within 1 year. This means that the H_2FPEF score is highly valuable in both clinical practice and theoretical research. On the other hand, since the support-vector machine shows the best prognostic ability, we believe that the use of machine learning algorithms to establish a predictive model of HF survival, and to evaluate the prognosis of patients with HF, would be extremely valuable.

Our study has several limitations. First, this was a single-centre observational study, with a relatively small sample size. Second, the follow-up time was not long enough and the results need to be confirmed. Third, this new scoring system needs to be further improved in future clinical practice.

In summary, the H_2FPEF score, which can be easily and accurately calculated, has excellent predictive value for 1-year readmission of patients with HFpEF. There are, however, many factors that affect the prognosis of patients with HFpEF and multicentre large sample studies are needed to confirm the prognostic value of H_2FPEF score for patients with HFpEF.

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Contributors YT, WW and JZ performed the study and wrote the manuscript. TY and YL carried out the statistical analysis. XZ designed the study and revised the manuscript.

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