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RESEARCH ARTICLE

Heart failure risk assessment in patients with hypertrophic cardiomyopathy based on the H_2FPEF score

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Aims The aim of this study was to investigate whether the H_2FPEF score, which was developed to improve the diagnosis of heart failure (HF) with preserved ejection fraction, is associated with HF outcomes in patients with hypertrophic cardiomyopathy (HCM).

Methods and results Patients with HCM and preserved left ventricular ejection fraction (LVEF ≥50%) were included from a multicentre registry and the H_2FPEF score was calculated. Patients were divided into three groups: low (0–1), intermediate (2–5) and high (6–9) H_2FPEF score. The primary combined endpoint was a composite of all-cause death and HF admissions, while the secondary endpoints were all-cause death and HF admissions separately. A total of 955 patients were included (age 51 ± 17 years, 310 [32.5%] female). Patients with a high H_2FPEF score ($n = 105$) were more often female, and presented with more symptoms and comorbidities. On echocardiography, patients with a high H_2FPEF score had lower LVEF, more impaired diastolic function and more frequently left ventricular outflow tract obstruction. During follow-up (median 90 months [interquartile range 49–176]), 103 (11%) patients died and 57 (6%) patients had a first HF hospitalization. Event-free survival rate for the primary combined and secondary endpoints was lower for patients with an intermediate and high H_2FPEF score. On multivariate Cox regression analysis, female sex (hazard ratio [HR] 1.670, 95% confidence interval [CI] 1.157–2.410; $p = 0.006$), Asian ethnicity (HR 6.711, 95% CI 4.076–11.048; $p < 0.001$), ischaemic heart disease (HR 1.732, 95% CI 1.133–2.650; $p = 0.011$), left atrial diameter (HR 1.028, 95% CI 1.005–1.051; $p = 0.016$) and intermediate (HR 2.757, 95% CI 1.612–4.713; $p < 0.001$) or high H_2FPEF score (HR 3.689, 95% CI 1.908–7.134; $p < 0.001$) were independently associated with the primary combined endpoint.

Conclusion The H_2FPEF score is independently associated with HF outcome in patients with HCM and may be considered for risk stratification.

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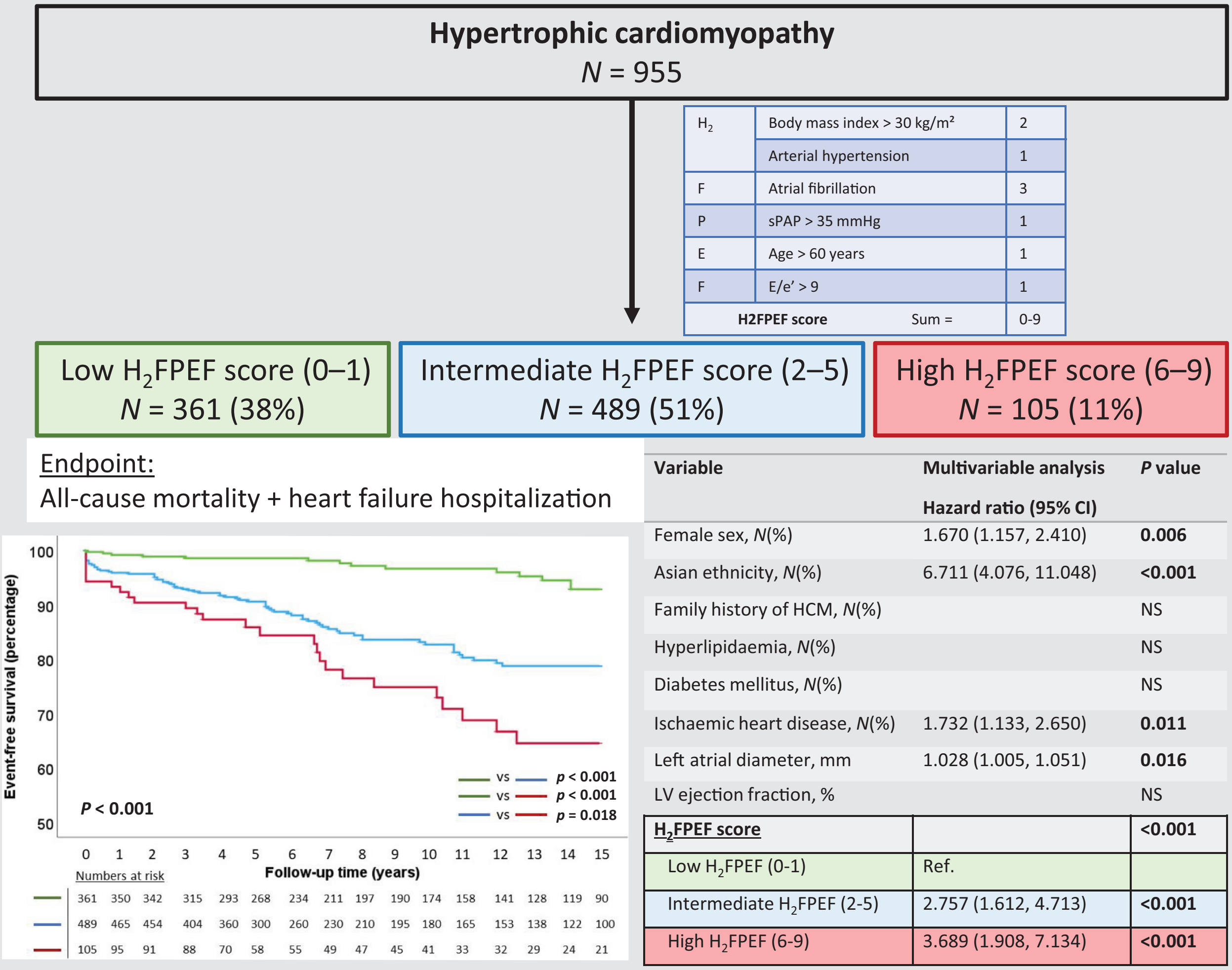
Graphical Abstract



The H_2FPEF score in hypertrophic cardiomyopathy. CI, confidence interval; HCM, hypertrophic cardiomyopathy; LV, left ventricular; sPAP, systolic pulmonary artery pressure.

Keywords Heart failure with preserved ejection fraction • Hypertrophic cardiomyopathy • Risk stratification

Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) is a disease with heterogeneous phenotypes, but generally defined by the presence of exertional dyspnoea, signs of congestion and left ventricular (LV) diastolic dysfunction with LV ejection fraction (LVEF) ≥50%.[1] Diagnosis of HFpEF may be challenging, particularly when multiple comorbidities are present, and the pathophysiology remains poorly understood. The H_2FPEF score has recently been developed by Reddy *et al.*[2] to assist in the diagnosis of HFpEF among patients with exertional dyspnoea. The score includes simple demographic, clinical and echocardiographic parameters and has been validated with invasive measurements.[2] The use of simple parameters makes the score easily applicable for everyday clinical practice, and has also demonstrated prognostic value in patients with HF[3–8] and unexplained dyspnoea.[9] Although patients with significant valvular heart disease and cardiomyopathies were excluded from the initial study which derived and validated the H_2FPEF score,[2] recent studies have shown an association of the H_2FPEF score with prognosis in patients with severe aortic stenosis who underwent transcatheter aortic valve replacement[10,11] and in patients with cardiac amyloidosis.[12]

Hypertrophic cardiomyopathy (HCM) is a primary cardiomyopathy, defined as the presence of LV hypertrophy in the absence of abnormal loading conditions. LV diastolic dysfunction is often present in HCM, due to myocardial hypertrophy, microvascular disease and the presence of LV fibrosis. Consequently, patients with HCM are at increased risk for HF, particularly HFpEF. However, risk stratification in patients with HCM has been primarily focused on predicting sudden cardiac death,[13,14] and only few studies have proposed specific parameters that might help identifying HF development in these patients. Therefore, the aim of the present study was to assess the prognostic value of the H_2FPEF score in patients with HCM and preserved LVEF.

Methods

Study population

From an ongoing HCM multicentre registry (Leiden University Medical Center, Leiden, The Netherlands; AHEPA University Hospital, Thessaloniki, Greece; National University Heart Centre, Singapore, Singapore), patients >18 years old were included in the current study. HCM was defined according to current guidelines[13–15]: a maximal LV wall thickness ≥15 mm in the absence of another cardiac, systemic or metabolic condition possibly causing the LV hypertrophy. A lower cutoff (≥13 mm) was considered sufficient for the diagnosis of HCM in patients with a positive family history of HCM or positive genetic test result. Patients with reduced LVEF (<50%) or missing values to calculate the H_2FPEF score were excluded from the current analysis. Demographic and clinical data were collected from the departmental electronic patient information system. The study complies with the Declaration of Helsinki. The local ethics committee waived the need for written informed consent because this is a retrospective analysis of clinically acquired data.

H_2FPEF score calculation

The H_2FPEF score was calculated for all patients as proposed by Reddy *et al.*[2] and based on six weighted variables: obesity (defined as body mass index >30 kg/m^2), history of atrial fibrillation, age >60 years, arterial hypertension, E/e' ratio >9, and systolic pulmonary artery pressure at echocardiography >35 mmHg. All variables were weighted equally (1 point) with the exception of obesity (2 points) and history of atrial fibrillation (3 points). According to Reddy *et al.*,[2] the probability of the diagnosis of HFpEF is >90% if a patient reaches a score ≥6 points. Accordingly, the population was divided into three groups: (1) patients with a low H_2FPEF score (defined as a score of 0–1), (2) patients with an intermediate H_2FPEF score (defined as a score of 2–5), and (3) patients with a high H_2FPEF score (defined as a score of 6–9).

Transthoracic echocardiography

Standard two-dimensional transthoracic echocardiography for the diagnosis of HCM was performed with commercially available ultrasound systems and images were digitally stored and offline analysed using proprietary software (EchoPAC 202; GE Vingmed Ultrasound, Horten, Norway). Two-dimensional, colour, spectral continuous- and pulsed-wave Doppler images were obtained from the parasternal, apical and subcostal views. From the parasternal long-axis view, LV end-diastolic diameter and left atrial diameter were measured, as recommended.[16] From the parasternal short-axis view, the maximal LV end-diastolic wall thickness was assessed at basal, mid, and apical levels. Next, from the apical four- and two-chamber views, LVEF was calculated using the Simpson's biplane method.[16] Continuous-wave Doppler was used to quantify the LV outflow tract peak gradient at rest or at provocation by Valsalva manoeuvre. LV diastolic function was assessed by pulsed-wave Doppler recordings of the transmitral flow at the tips of the mitral leaflets to obtain peak early (E) and late (A) diastolic velocities.[17] Tissue Doppler imaging at the level of the medial and lateral mitral valve annulus was used to measure e', which was averaged to calculate E/e'.[17] Systolic pulmonary artery pressure was calculated from the peak velocity of the tricuspid regurgitant jet using the Bernoulli equation, adding the right atrial pressure determined by the inspiratory collapse and diameter of the inferior vena cava.[16] Mitral regurgitation was assessed using a multiparametric approach.[18,19]

Clinical outcomes

The primary combined endpoint was defined as a composite of all-cause mortality and first HF hospitalization. The secondary endpoints were all-cause mortality and first HF hospitalization separately. The occurrence of events during follow-up was obtained from review of medical charts linked to the governmental death registry database and liaison with general practitioners.

Statistical analysis

Continuous data with normal distribution are presented as mean ± standard deviation and continuous data without normal distribution as median with interquartile range (IQR). Categorical data are shown as frequencies with percentages. Differences in clinical and echocardiographic characteristics between the patient groups were compared using the ANOVA test or the Kruskal–Wallis test, as appropriate. Post-hoc analysis was performed using the Bonferroni correction. Univariable ordinal regression analysis was performed to evaluate the factors associated with the H_2FPEF score. Variables with a p-value < 0.05 in univariable regression analysis were inserted in the multivariable ordinal regression model. Cumulative event-free survival analysis was performed using the Kaplan–Meier method for the primary combined and secondary endpoints and compared between groups using the log-rank test. Univariable proportional hazard Cox regression analysis was performed to investigate the association of variables with the primary combined endpoint. Variables with a significant association in univariable Cox regression analysis (p < 0.05) were included in the multivariable Cox regression model. The three groups with low, intermediate and high H_2FPEF score were included in the multivariable model, the variables used to calculate the score were not entered to avoid collinearity. Finally, two sensitivity analysis were performed, excluding patients with LV outflow tract obstruction and ischaemic heart disease, respectively. Two-sided p-values < 0.05 were considered statistically significant. Statistical analysis was performed using SPSS version 25.0 (IBM Corporation, Armonk, NY, USA).

Results

Patient population

A total of 955 patients from this multicentre HCM registry were included after applying the inclusion and exclusion criteria (online supplementary *Figure Appendix S1*). Baseline characteristics are presented in *Table 1*: mean age was 51 (± 17.3) years and 310

Table 1 Clinical and echocardiographic characteristics of the study population

Variable	Overall ($n = 955$)	H_2FPEF 0–1 ($n = 361$)	H_2FPEF 2–5 ($n = 489$)	H_2FPEF 6–9 ($n = 105$)	*p*-value
Clinical characteristics					
Age, years	50.9 ± 17.3	40.9 ± 15.3[b,c]	55.9 ± 15.5[a,c]	61.9 ± 15.0[a,b]	**<0.001**
Female sex, *n* (%)	310 (32.5)	83 (23.0)[b,c]	171 (35.0)[a,c]	56 (53.3)[a,b]	**<0.001**
BMI, kg/m^2	26.9 ± 4.3	25.2 ± 3.0[b,c]	27.5 ± 4.4[a,c]	29.8 ± 5.1[a,b]	**<0.001**
Family history of HCM, *n* (%)	290 (30.4)	135 (37.4)[b,c]	136 (27.8)[a,c]	19 (18.1)[a,b]	**<0.001**
Family history of SCD, *n* (%)	178 (18.6)	72 (19.9)	90 (18.4)	16 (15.2)	0.542
Ethnicity, *n* (%)					0.058
European	692 (72.5)	273 (75.6)	338 (69.1)	81 (77.1)	
Asian	263 (27.5)	88 (24.4)	151 (30.9)	24 (22.9)	
Hyperlipidaemia, *n* (%)	234 (24.5)	41 (11.4)[b,c]	154 (31.5)[a]	39 (37.1)[a]	**<0.001**
Diabetes mellitus, *n* (%)	96 (10.1)	7 (1.9)[b,c]	65 (13.3)[a,c]	24 (22.9)[a,b]	**<0.001**
Ischaemic heart disease, *n* (%)	122 (12.8)	20 (5.5)[b,c]	81 (16.6)[a]	21 (20.0)[a]	**<0.001**
NYHA class, *n* (%)					**<0.001**
I	598 (62.9)	260 (72.4)[b,c]	291 (59.9)[a,c]	47 (44.8)[a,b]	
II	289 (30.4)	89 (24.8)	158 (32.5)	42 (40.0)	
III–IV	63 (6.6)	10 (2.8)	37 (7.6)	16 (15.2)	
Septal interventions during FU, *n* (%)	57 (6.0)	10 (2.8)[b,c]	39 (8.0)[a]	8 (7.6)[a]	**0.005**
ICD implantation during FU, *n* (%)	133 (13.9)	51 (14.1)	65 (13.3)	17 (16.2)	0.732
Echocardiographic characteristics					
Maximal wall thickness, mm	19.2 ± 5.9	19.3 ± 6.0	19.2 ± 5.8	19.0 ± 5.7	0.892
LV end-diastolic diameter, mm	44.5 ± 6.6	44.0 ± 6.0[c]	44.5 ± 6.7	46.1 ± 7.4[a]	**0.015**
Left atrial diameter, mm	42.8 ± 7.6	40.0 ± 6.0[b,c]	44.0 ± 8.0[a,c]	47.0 ± 7.6[a,b]	**<0.001**
LV ejection fraction, %	69.4 ± 8.8	70.1 ± 8.8 [c]	69.2 ± 8.9	67.6 ± 8.7[a]	**0.028**
Peak LVOT gradient >30 mmHg, *n* (%)	242 (25.6)	61 (16.9)[b,c]	140 (29.1)[a,c]	41 (39.4)[a,b]	**<0.001**
Moderate to severe MR, *n* (%)	90 (9.5)	21 (5.8)[b]	57 (11.7)[c]	12 (11.4)	**0.012**
H_2FPEF score variables, *n* (%)					
H_2 BMI >30 kg/m^2	178 (16.6)	0 (0.0)[b,c]	122 (24.9)[a,c]	56 (53.3)[a,b]	**<0.001**
Arterial hypertension	359 (37.6)	27 (7.5)[b,c]	249 (50.9)[a,c]	83 (79.0)[a,b]	**<0.001**
F Atrial fibrillation	219 (22.9)	0 (0.0)[b,c]	118 (24.1)[a,c]	101 (46.1)[a,b]	**<0.001**
P sPAP >35 mmHg	110 (11.5)	6 (1.7)[b,c]	67 (13.7)[a,c]	37 (35.2)[a,b]	**<0.001**
E Age >60 years	300 (31.4)	23 (5.4)[b,c]	211 (43.1)[a,c]	66 (62.9)[a,b]	**<0.001**
F E/e' >9	709 (74.2)	183 (50.7)[b,c]	428 (87.5)[a]	98 (93.3)[a,b]	**<0.001**

BMI, body mass index; FU, follow-up; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; LV, left ventricular; LVOT, left ventricular outflow tract; MR, mitral regurgitation; NYHA, New York Heart Association; SCD, sudden cardiac death; sPAP, systolic pulmonary artery pressure.
Bonferroni correction: [a]$p < 0.05$ versus H_2FPEF score 0–1; [b]$p < 0.05$ versus H_2FPEF score 2–5; and [c]$p < 0.05$ versus H_2FPEF 6–9.

(32.5%) patients were female. *Figure 1* shows the distribution of the H_2FPEF score in the study population: 361 (38%) patients had a low H_2FPEF score (0–1), 489 (51%) patients had an intermediate H_2FPEF score (2–5) and 105 (11%) patients had a high H_2FPEF score (6–9). Patients with a high H_2FPEF score (6–9) were more frequently female and had more comorbidities including hyperlipidaemia, diabetes mellitus and ischaemic heart disease (apart from atrial fibrillation and arterial hypertension), which are known risk factors for development of HFpEF.[20] Patients with a high H_2FPEF score were more symptomatic (according to New York Heart Association class) and less frequently had a family history of HCM. By echocardiography, patients with a high H_2FPEF score had larger LV end-diastolic diameters and left atrial diameters, while LVEF was lower in patients with a high H_2FPEF score as compared to patients with a low H_2FPEF score. Inherent to the calculation of the H_2FPEF score, diastolic function parameters (E/e' and systolic pulmonary artery pressure) were more impaired in patients with a high H_2FPEF score. Interestingly, patients with a high H_2FPEF score more often had an obstructive phenotype of HCM as compared to patients with a low and intermediate H_2FPEF score, and consequently more often underwent septal interventions.

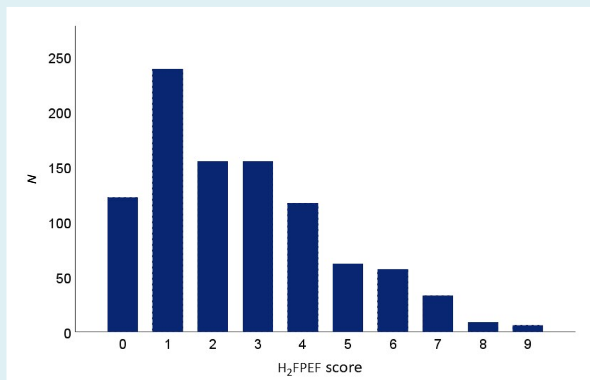


Figure 1 The H_2FPEF score among the study population.

Determinants of the H_2FPEF score in hypertrophic cardiomyopathy patients

Ordinal regression analysis was performed to evaluate the association between different clinical and echocardiographic variables with the H_2FPEF score, besides the variables included in the score. The results are presented in *Table 2*. Univariable analysis showed an association of female sex, cardiovascular risk factors (hyperlipidaemia, diabetes mellitus), ischaemic heart disease, family history of HCM, New York Heart Association class, LV end-diastolic diameter, left atrial diameter, the presence of moderate to severe mitral regurgitation and the presence of peak LV outflow tract gradient >30 mmHg with the H_2FPEF score. On multivariable analysis, female sex (odds ratio [OR] 2.851, 95% confidence interval [CI] 2.083–3.901; $p < 0.001$), hyperlipidaemia (OR 1.822, 95% CI 1.254–2.647; $p = 0.002$), diabetes mellitus (OR 3.137, 95% CI 1.854–5.308; $p < 0.001$), family history of HCM (OR 0.588, 95% CI 0.440–0.786; $p < 0.001$), New York Heart Association class II (OR 1.835, 95% CI 1.350–2.494; $p < 0.001$), New York Heart Association class III–IV (OR 2.047, 95% CI 1.200–3.493; $p = 0.009$), left atrial diameter (OR 1.098, 95% CI 1.073–1.123; $p < 0.001$) and peak LV outflow tract gradient >30 mmHg (OR 1.574, 95% CI 1.128–2.198; $p = 0.008$) remained independently associated with the H_2FPEF score.

Patient long-term outcomes

During a median follow-up of 90 months (IQR 49–176), the primary endpoint occurred in 136 (14%) patients. In total, 103 (11%) patients died and 57 (6%) patients had a first HF hospitalization. Cumulative event-free survival analyses for the primary combined and secondary endpoints are presented in *Figures 2* and *3*. Patients with a high H_2FPEF score had significantly worse event-free survival as compared to patients with a low or intermediate H_2FPEF score for the primary combined endpoint (log-rank χ^2 46.528, $p < 0.001$) and first HF hospitalization (log-rank χ^2 26.424, $p < 0.001$). Patients with an intermediate and high H_2FPEF score had significantly worse outcome as compared to patients with a low H_2FPEF score for all-cause mortality (log-rank χ^2 26.007, $p < 0.001$). Sensitivity analysis excluding patients with LV outflow tract obstruction ($n = 242$) confirmed that patients with an intermediate and high H_2FPEF score had significantly worse outcome as compared to patients with a low H_2FPEF score for the primary combined endpoint (*Figure 4A*) and the secondary endpoints (online supplementary *Figure S2A,B*). Sensitivity analysis excluding patients with ischaemic heart disease ($n = 122$) showed that patients with a high H_2FPEF score had significantly worse outcome compared to patients with a low and intermediate H_2FPEF score for the primary combined endpoint (*Figure 4B*) and first HF hospitalization (online supplementary *Figure S2D*) while patients with an intermediate and high H_2FPEF score had worse outcome as compared to patients with a low H_2FPEF score for all-cause mortality (online supplementary *Figure S2C*).

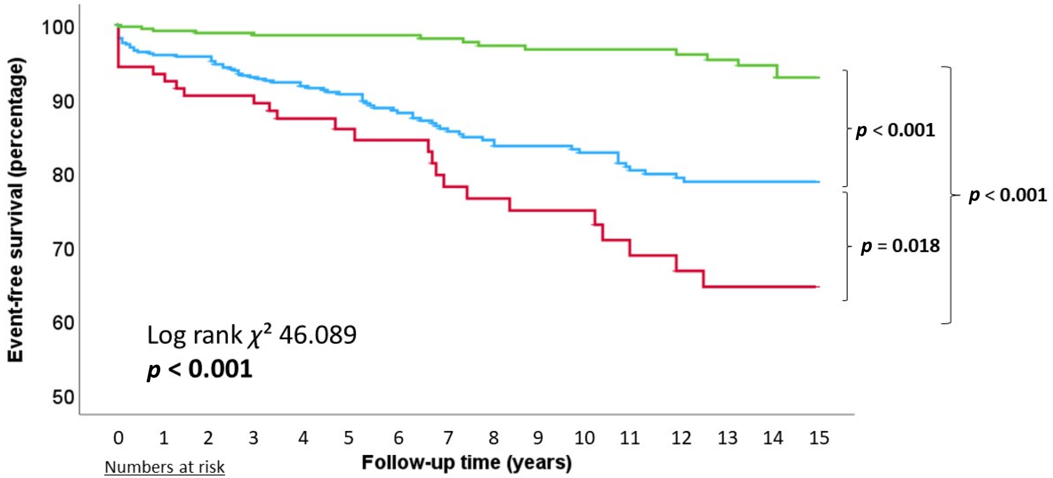
Association of the H_2FPEF score with outcome in hypertrophic cardiomyopathy patients

Univariable and multivariable Cox regression analyses for the primary combined endpoint are presented in *Table 3*. In univariable Cox regression analysis, female sex, Asian ethnicity, family history of HCM, hyperlipidaemia, diabetes mellitus, ischaemic heart disease, left atrial diameter, LVEF, all variables included in the H_2FPEF score (except for body mass index) and having an intermediate or high H_2FPEF score were associated with the primary combined endpoint of all-cause mortality and first HF hospitalization. On multivariable Cox regression analysis, female sex (hazard ratio [HR] 1.670, 95% CI 1.157–2.410, $p = 0.006$), Asian ethnicity

Table 2 Ordinal regression analysis to evaluate the association of variables with the H_2FPEF score

Variable	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Female sex	2.104 (1.653–2.679)	**<0.001**	2.851 (2.083–3.901)	**<0.001**
Asian ethnicity	0.969 (0.755–1.244)	0.807		
Family history of HCM	0.696 (0.546–0.888)	**0.004**	0.588 (0.440–0.786)	**<0.001**
Hyperlipidaemia	2.491 (1.194–3.243)	**<0.001**	1.822 (1.254–2.647)	**0.002**
Diabetes mellitus	3.292 (2.261–4.792)	**<0.001**	3.137 (1.854–5.308)	**<0.001**
NYHA class				
I	Ref.			
II	1.955 (1.523–2.509)	**<0.001**	1.835 (1.350–2.494)	**<0.001**
III–IV	3.926 (2.476–6.225)	**<0.001**	2.047 (1.200–3.493)	**0.009**
Ischaemic heart disease	2.277 (1.627–3.186)	**<0.001**	1.427 (0.831–2.448)	0.185
Maximal wall thickness	1.016 (0.997–1.036)	0.094		
LV end-diastolic diameter	1.022 (1.004–1.039)	**0.015**	1.015 (0.993–1.038)	0.174
Left atrial diameter	1.091 (1.074–1.108)	**<0.001**	1.098 (1.073–1.123)	**<0.001**
LV ejection fraction	0.985 (0.972–0.997)	**0.018**	0.983 (0.968–0.999)	0.039
Peak LVOT gradient >30 mmHg	2.070 (1.548–2.767)	**<0.001**	1.574 (1.128–2.198)	**0.008**
Moderate to severe MR	1.602 (1.094–2.346)	**0.015**	0.827 (0.515–1.329)	0.433

CI, confidence interval; HCM, hypertrophic cardiomyopathy; LV, left ventricular; LVOT, left ventricular outflow tract; MR, mitral regurgitation; NYHA, New York Heart Association.



Numbers at risk

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Low H_2FPEF	361	350	342	315	293	268	234	211	197	190	174	158	141	128	119	90
Intermediate H_2FPEF	489	465	454	404	360	300	260	230	210	195	180	165	153	138	122	100
High H_2FPEF	105	95	91	88	70	58	55	49	47	45	41	33	32	29	24	21

Bold p values indicate significant p values (<0.05).

Figure 2 Kaplan–Meier survival curve analysis for the primary combined endpoint of all-cause mortality and heart failure hospitalization.

(HR 6.711, 95% CI 4.076–11.048; $p < 0.001$), ischaemic heart disease (HR 1.732, 95% CI 1.133–2.650; $p = 0.011$), left atrial diameter (HR 1.028, 95% CI 1.005–1.051; $p = 0.016$) and an intermediate H_2FPEF score (HR 2.757, 95% CI 1.612–4.713; $p < 0.001$) or high H_2FPEF score (HR 3.689, 95% CI 1.908–7.134; $p < 0.001$) remained independently associated with the primary combined endpoint. Sensitivity analysis in patients without LV outflow tract obstruction confirmed the independent association of an intermediate (HR 2.758, 95% CI 1.514–5.021; $p < 0.001$) and high H_2FPEF score (HR 2.413, 95% CI 1.047–5.563; $p = 0.039$) as compared to a low H_2FPEF score with the primary combined outcomes (online supplementary *Table Appendix S1*). Furthermore, sensitivity analysis excluding patients with ischaemic heart disease also confirmed the independent association of an intermediate (HR 2.493, 95% CI 1.407–4.418; $p = 0.002$) and high H_2FPEF score (HR 3.376, 95% CI 1.624–7.019; $p = 0.001$) with increased risk of the primary combined endpoint (online supplementary *Table S2*).

Discussion

The current study evaluated the use of the H_2FPEF score in a large, multicentre patient cohort diagnosed with HCM. The main findings can be summarized as follows: (i) in HCM patients, higher H_2FPEF score was associated with female sex, comorbidities (diabetes mellitus and hyperlipidaemia), family history of HCM, HF symptoms, left atrial size and LV outflow tract obstruction; (ii) incidence rates of all-cause mortality and HF hospitalization were significantly higher in patients with high H_2FPEF score, which was also independently associated with the combined outcome (*Graphical Abstract*).

Assessment of heart failure in hypertrophic cardiomyopathy patients

Approximately 50% of patients with HCM experience exertional dyspnoea,[21] although typically do not display clinical signs of congestion. The cause underlying the dyspnoea in these patients is not fully understood, is often multifactorial and consequently the diagnosis of HF is not straightforward. In most of these patients, LV hypertrophy is accompanied by myocardial stiffness and fibrosis, and therefore LV diastolic dysfunction, while LVEF is frequently preserved and declines only with advanced HF. Exertional dyspnoea is therefore frequently related to increased LV end-diastolic filling pressures, similar to HFpEF,[22] but an accurate assessment of the severity of LV diastolic dysfunction in HCM can be challenging, since the majority of standard echocardiographic parameters do not perform as robust as in other settings. Another important cause of HF symptoms in these patients is the presence of LV outflow tract obstruction, which leads to elevation of LV end-systolic pressure and is often associated with mitral regurgitation. While LV outflow tract obstruction may be present at rest,[23,24] in 30% of the patients it can only be identified through provocation manoeuvres[25,26], which should be systematically performed.

The H_2FPEF score was developed as a diagnostic tool in patients experiencing exertional dyspnoea and has facilitated the diagnosis of patients with HFpEF.[2,27] The score includes simple demographic, clinical and echocardiographic parameters that are easily applicable in the outpatient setting and the score is routinely applied in dyspnoea clinics.[28] Although never applied in HCM patients, this score could be helpful in their clinical assessment.

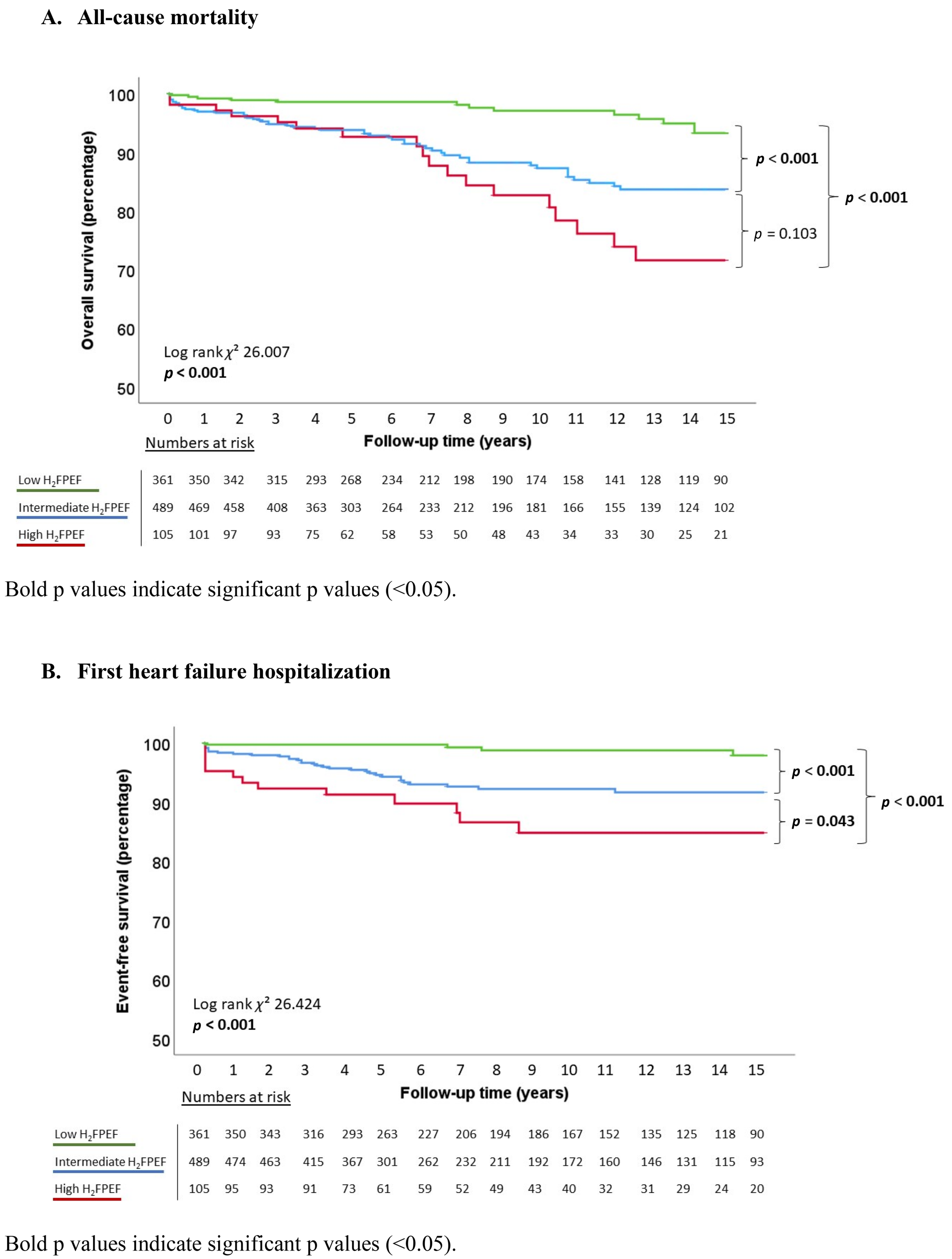


Figure 3 Kaplan–Meier survival curve analysis for the secondary endpoints. (*A*) All-cause mortality. (*B*) First heart failure hospitalization.

In the current study, the H_2FPEF score showed a wide range of values in HCM patients, but with more than 60% of patients having an intermediate or high score. Furthermore, the score was independently associated not only with HF symptoms but also with several characteristics that suggest predisposition to diastolic dysfunction and increased LV filling pressures, such as female sex, comorbidities (diabetes mellitus and hyperlipidaemia), LV outflow tract obstruction and left atrial remodelling.

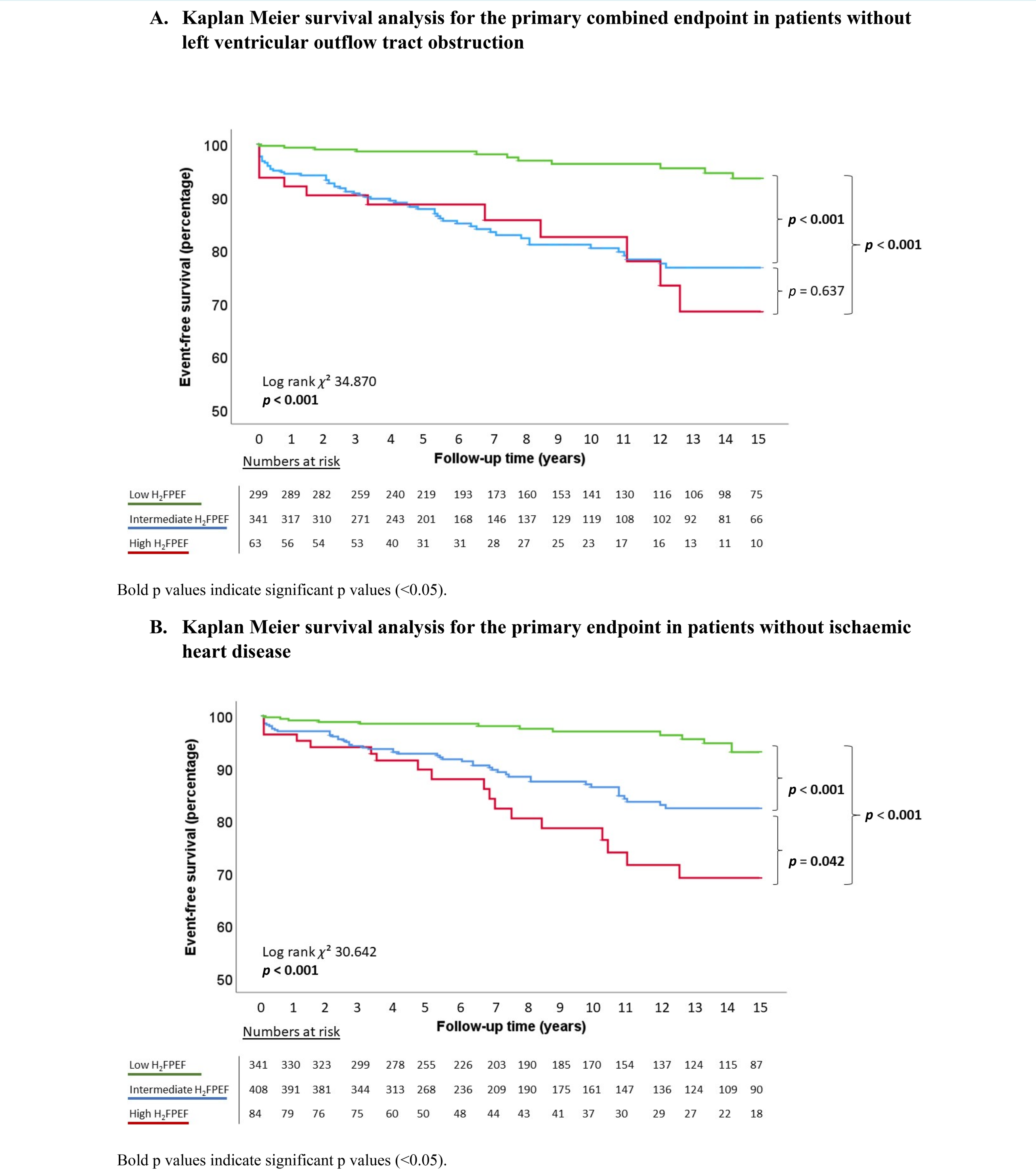


Figure 4 Sensitivity analysis excluding patients with left ventricular outflow tract obstruction (*A*) and excluding patients with ischaemic heart disease (*B*). (*A*) Kaplan–Meier survival analysis for the primary combined endpoint in patients without left ventricular outflow tract obstruction. (*B*) Kaplan–Meier survival analysis for the primary combined endpoint in patients without ischaemic heart disease.

Table 3 Univariable and multivariable Cox regression for the association of variables with the primary combined endpoint

Variable		Univariable analysis		Multivariable analysis	
		Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Female sex		1.598 (1.134–2.251)	**0.007**	1.670 (1.157–2.410)	**0.006**
Asian ethnicity		8.320 (5.265–13.149)	**<0.001**	6.711 (4.076–11.048)	**<0.001**
Family history of HCM		0.459 (0.305–0.692)	**<0.001**		NS
Hyperlipidaemia		2.231 (1.547–3.217)	**<0.001**		NS
Diabetes mellitus		2.746 (1.773–4.253)	**<0.001**		NS
NYHA class			0.361		
I		Ref.			
II		0.762 (0.518–1.120)	0.166		
III–IV		1.010 (0.560–1.819)	0.975		
Ischaemic heart disease		3.125 (2.093–4.666)	**<0.001**	1.732 (1.133–2.650)	**0.011**
Maximal wall thickness		0.980 (0.951–1.010)	0.181		
LV end-diastolic diameter		1.006 (0.980–1.031)	0.666		
Left atrial diameter		1.052 (1.031–1.074)	**<0.001**	1.028 (1.005–1.051)	**0.016**
LV ejection fraction		0.974 (0.955–0.992)	**0.005**		NS
Peak LVOT gradient >30 mmHg		0.940 (0.632–1.398)	0.760		
Moderate to severe MR		1.297 (0.769–2.188)	0.329		
H_2FPEF score variables					
H_2	BMI >30 kg/m^2	1.237 (0.815–1.887)	0.318		
	Arterial hypertension	1.855 (1.316–2.614)	**<0.001**		
F	Atrial fibrillation	1.748 (1.229–2.486)	**0.002**		
P	sPAP >35 mmHg	2.340 (1.558–3.514)	**<0.001**		
E	Age >60 years	4.809 (3.346–6.913)	**<0.001**		
F	E/e' >9	4.060 (2.062–7.997)	**<0.001**		
H_2FPEF score			**<0.001**		**<0.001**
Low (0–1)		Ref.		Ref.	
Intermediate (2–5)		3.786 (2.301–6.227)	**<0.001**	2.757 (1.612–4.713)	**<0.001**
High (6–9)		6.049 (3.390–10.792)	**<0.001**	3.689 (1.908–7.134)	**<0.001**

BMI, body mass index; CI, confidence interval; HCM, hypertrophic cardiomyopathy; LV, left ventricular; LVOT, left ventricular outflow tract; MR, mitral regurgitation; sPAP, systolic pulmonary artery pressure.

Risk of heart failure in hypertrophic cardiomyopathy patients

In addition to its diagnostic value, the H_2FPEF score holds prognostic value in patients with HFpEF[8] or unexplained dyspnoea.[9] While originally developed for the evaluation of patients with HFpEF, the H_2FPEF score has also shown to be associated with outcomes in patients with severe aortic stenosis who undergo transcatheter interventions[10,11] and in patients with amyloid cardiomyopathy,[12] two conditions that share similarities with HFpEF.

With this perspective, the H_2FPEF score could be a promising tool for risk prediction in patients with HCM. Since the risk prediction in patients with HCM has been primarily focused on the prediction of sudden cardiac death, the use of implantable cardioverter-defibrillators has resulted in fewer sudden deaths, while HF has become an increasing problem. The H_2FPEF score could enable clinicians to identify the patients at risk who warrant a closer follow-up for the development of HF. Since the H_2FPEF score includes only two echocardiographic parameters that can easily be measured, the score can even be calculated in settings where advanced echocardiography is not available.

The present study evaluated the H_2FPEF score in a large multicentre patient cohort diagnosed with HCM. The patients with a high H_2FPEF score had significantly worse event-free survival for the combined endpoint of all-cause mortality and HF hospitalization. Additionally, the H_2FPEF score was independently associated with worse outcome. These findings were confirmed after excluding patients without LVOT obstruction and even after excluding patients with ischaemic heart disease. The results of this study suggest a potential value of the H_2FPEF score in improving risk stratification for HF in HCM patients.

Study limitations

This study has a retrospective design and should be interpreted within this context. The results were not validated in an external validation cohort; further prospective studies are warranted to confirm these findings. Nevertheless, the study included a large, multinational and multiethnic patient population. In addition, invasive ventricular and pulmonary pressure measurements were not routinely performed. Therefore, it was not possible to evaluate the diagnostic properties of the H_2FPEF score regarding the presence of elevated filling pressures in these patients. Furthermore, the HFA-PEFF score was not tested in the study population due to the lack of systematic measurement of natriuretic peptides.[29]

Conclusion

The H_2FPEF score can easily be applied in patients with HCM, using simple demographic, clinical and echocardiographic parameters. A high H_2FPEF score was independently associated with worse HF outcomes and therefore holds promise as a tool for specific HF risk stratification in these patients.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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References

1. Redfield MM, Borlaug BA. Heart failure with preserved ejection fraction: A review. *JAMA* 2023;**329**:827–838. https://doi.org/10.1001/jama.2023.2020
2. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation* 2018;**138**:861–870. https://doi.org/10.1161/CIRCULATIONAHA.118.034646
3. Segar MW, Patel KV, Berry JD, Grodin JL, Pandey A. Generalizability and implications of the H_2FPEF score in a cohort of patients with heart failure with preserved ejection fraction. *Circulation* 2019;**139**:1851–1853. https://doi.org/10.1161/CIRCULATIONAHA.118.039051
4. Tao Y, Wang W, Zhu J, You T, Li Y, Zhou X. H_2FPEF score predicts 1-year rehospitalisation of patients with heart failure with preserved ejection fraction. *Postgrad Med J* 2021;**97**:164–167. https://doi.org/10.1136/postgradmedj-2019-137434
5. Suzuki S, Kaikita K, Yamamoto E, Sueta D, Yamamoto M, Ishii M, *et al.* H_2FPEF score for predicting future heart failure in stable outpatients with cardiovascular risk factors. *ESC Heart Fail* 2020;**7**:65–74. https://doi.org/10.1002/ehf2.12570
6. Sueta D, Yamamoto E, Nishihara T, Tokitsu T, Fujisue K, Oike F, *et al.* H_2FPEF score as a prognostic value in HFpEF patients. *Am J Hypertens* 2019;**32**:1082–1090. https://doi.org/10.1093/ajh/hpz108
7. Sun Y, Wang N, Li X, Zhang Y, Yang J, Tse G, *et al.* Predictive value of H_2FPEF score in patients with heart failure with preserved ejection fraction. *ESC Heart Fail* 2021;**8**:1244–1252. https://doi.org/10.1002/ehf2.13187
8. Verbrugge FH, Reddy YNV, Sorimachi H, Omote K, Carter RE, Borlaug BA. Diagnostic scores predict morbidity and mortality in patients hospitalized for heart failure with preserved ejection fraction. *Eur J Heart Fail* 2021;**23**:954–963. https://doi.org/10.1002/ejhf.2142
9. Selvaraj S, Myhre PL, Vaduganathan M, Claggett BL, Matsushita K, Kitzman DW, *et al.* Application of diagnostic algorithms for heart failure with preserved ejection fraction to the community. *JACC Heart Fail* 2020;**8**:640–653. https://doi.org/10.1016/j.jchf.2020.03.013
10. Ludwig S, Pellegrini C, Gossling A, Rheude T, Voigtländer L, Bhadra OD, *et al.* Prognostic value of the H_2FPEF score in patients undergoing transcatheter aortic valve implantation. *ESC Heart Fail* 2021;**8**:461–470. https://doi.org/10.1002/ehf2.13096
11. Akao K, Imamura T, Tanaka S, Onoda H, Ushijima R, Sobajima M, *et al.* Prognostic impact of modified H_2FPEF score in patients receiving trans-catheter aortic valve replacement. *J Clin Med* 2023;**12**:5396. https://doi.org/10.3390/jcm12165396
12. Tomasoni D, Aimo A, Merlo M, Nardi M, Adamo M, Bellicini MG, *et al.* Value of the HFA-PEFF and H_2FPEF scores in patients with heart failure and preserved ejection fraction caused by cardiac amyloidosis. *Eur J Heart Fail* 2022;**24**:2374–2386. https://doi.org/10.1002/ejhf.2616
13. Ommen SR, Mital S, Burke MA, Day SM, Deswal A, Elliott P, *et al.* 2020 AHA/ACC Guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2020;**76**:e159–e240. https://doi.org/10.1016/j.jacc.2020.08.045
14. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, *et al.* 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: The Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J* 2014;**35**:2733–2779. https://doi.org/10.1093/eurheartj/ehu284
15. Arbelo E, Protonotarios A, Gimeno JR, Arbustini E, Barriales-Villa R, Basso C, *et al.* 2023 ESC Guidelines for the management of cardiomyopathies. *Eur Heart J* 2023;**44**:3503–3626. https://doi.org/10.1093/eurheartj/ehad194
16. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, *et al.* Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;**28**:1–39.e14. https://doi.org/10.1016/j.echo.2014.10.003
17. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, *et al.* Recommendations for the evaluation of left ventricular diastolic function by echocardiography: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016;**29**:277–314. https://doi.org/10.1016/j.echo.2016.01.011
18. Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, *et al.*; Scientific Document Committee of the European Association of Cardiovascular Imaging. Recommendations for the echocardiographic assessment of native valvular regurgitation: An executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2013;**14**:611–644. https://doi.org/10.1093/ehjci/jet105
19. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, *et al.* 2020 ACC/AHA Guideline for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2021;**143**:e72–e227. https://doi.org/10.1161/CIR.0000000000000923
20. Ho JE, Enserro D, Brouwers FP, Kizer JR, Shah SJ, Psaty BM, *et al.* Predicting heart failure with preserved and reduced ejection fraction: The international collaboration on heart failure subtypes. *Circ Heart Fail* 2016;**9**:e003116. https://doi.org/10.1161/CIRCHEARTFAILURE.115.003116
21. Rowin EJ, Maron MS, Chan RH, Hausvater A, Wang W, Rastegar H, *et al.* Interaction of adverse disease related pathways in hypertrophic cardiomyopathy. *Am J Cardiol* 2017;**120**:2256–2264. https://doi.org/10.1016/j.amjcard.2017.08.048
22. Maron BJ, Rowin EJ, Udelson JE, Maron MS. Clinical spectrum and management of heart failure in hypertrophic cardiomyopathy. *JACC Heart Fail* 2018;**6**:353–363. https://doi.org/10.1016/j.jchf.2017.09.011
23. Maron MS, Olivotto I, Betocchi S, Casey SA, Lesser JR, Losi MA, *et al.* Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. *N Engl J Med* 2003;**348**:295–303. https://doi.org/10.1056/NEJMoa021332
24. Elliott PM, Gimeno JR, Tomé MT, Shah J, Ward D, Thaman R, *et al.* Left ventricular outflow tract obstruction and sudden death risk in patients with hypertrophic cardiomyopathy. *Eur Heart J* 2006;**27**:1933–1941. https://doi.org/10.1093/eurheartj/ehl041
25. Maron MS, Olivotto I, Zenovich AG, Link MS, Pandian NG, Kuvin JT, *et al.* Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. *Circulation* 2006;**114**:2232–2239. https://doi.org/10.1161/CIRCULATIONAHA.106.644682
26. Shah JS, Esteban MT, Thaman R, Sharma R, Mist B, Pantazis A, *et al.* Prevalence of exercise-induced left ventricular outflow tract obstruction in symptomatic patients with non-obstructive hypertrophic cardiomyopathy. *Heart* 2008;**94**:1288–1294. https://doi.org/10.1136/hrt.2007.126003
27. Reddy YNV, Kaye DM, Handoko ML, van de Bovenkamp AA, Tedford RJ, Keck C, *et al.* Diagnosis of heart failure with preserved ejection fraction among patients with unexplained dyspnea. *JAMA Cardiol* 2022;**7**:891–899. https://doi.org/10.1001/jamacardio.2022.1916
28. Verwerft J, Soens L, Wynants J, Meysman M, Jogani S, Plein D, *et al.* Heart failure with preserved ejection fraction: Relevance of a dedicated dyspnoea clinic. *Eur Heart J* 2023;**44**:1544–1556. https://doi.org/10.1093/eurheartj/ehad141
29. Pieske B, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, *et al.* How to diagnose heart failure with preserved ejection fraction: The HFA-PEFF diagnostic algorithm: A consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur J Heart Fail* 2020;**22**:391–412. https://doi.org/10.1002/ejhf.1741