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RESEARCH ARTICLE

Diagnostic scores predict morbidity and mortality in patients hospitalized for heart failure with preserved ejection fraction

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Aims To investigate the prognostic value of diagnostic scores for heart failure (HF) with preserved ejection fraction (HFpEF).

Methods and results Consecutive patients with HFpEF admitted for unequivocal decompensated HF treated with intravenous loop diuretics were evaluated ($n = 443$; mean age 78 ± 12 years; 60% women). The HFA-PEFF and H_2FPEF scores were calculated for all patients with echocardiography data available within 1 year and the population was stratified according to HFA-PEFF scores 2–4 ($n = 79$), 5 ($n = 93$), or 6 ($n = 271$) and H_2FPEF score probabilities <90% ($n = 80$), 90–95% ($n = 61$), and 96–100% ($n = 293$). HF readmission rates (95% confidence intervals) increased from 28.9 (22.7–35.0) per 100 patient-years in HFA-PEFF 2–4 to 46.0 (38.5–53.5) in HFA-PEFF 5 and 45.0 (40.1–49.8) in HFA-PEFF 6. Similarly, HF readmission rates increased with increasing H_2FPEF probability: <0.90 [31.8 (25.3–38.2) per 100 patient-years], 0.90–0.95 [41.5 (32.9–50.1)], and 0.96–1.00 [45.9 (41.2–50.6]. Median survival was 65 months (36–89 months) in HFA-PEFF score 2–4, 45 months (26–59 months) in HFA-PEFF score 5, and 28 months (22–42 months) in HFA-PEFF score 6 ($P < 0.001$), while the hazard ratio (95% confidence interval) for all-cause mortality was 1.16 (1.02–1.32) per 0.10 increase in H_2FPEF probability.

Conclusions Among patients hospitalized with HFpEF, higher HFpEF probability according to diagnostic scores is associated with increased risk of subsequent HF readmissions and all-cause mortality.

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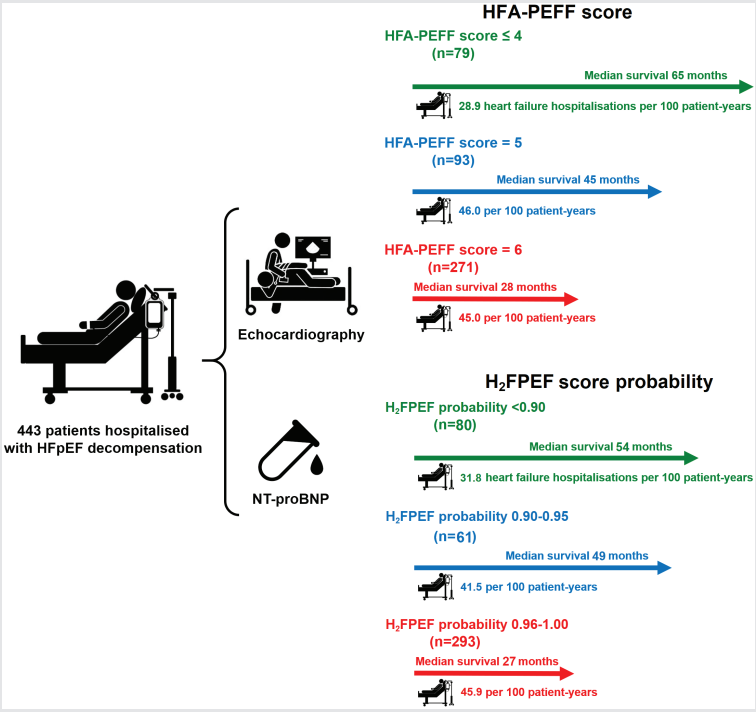
Graphical Abstract



Application of both the HFA-PEFF score (*top*) and H_2FPEF score (*bottom*) stratified by time to death or heart failure hospitalization in patients following initial hospitalization for heart failure. HFpEF, heart failure with preserved ejection fraction; NT-proBNP, N-terminal pro-hormone B-type natriuretic peptide.

Keywords Cause of death • Diastolic heart failure • Mortality • Patient readmission • Risk assessment

Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) accounts for more than half of all hospital admissions for HF decompensation.[1] As the general population grows older, with an increasing prevalence of obesity and diabetes, this problem will likely become even larger in the future. While outcomes are generally more favourable in HFpEF as compared to HF with reduced ejection fraction (HFrEF), these differences disappear among hospitalized patients, wherein 5-year mortality rates exceed 70% in both conditions.[2,3] It is important to identify patients where the risk for adverse outcomes is increased to help with clinical decision-making and guide intensity of care to improve outcomes.

In the outpatient setting, the diagnosis of HFpEF can be challenging.[4] Therefore, the H_2FPEF score has been developed and validated against invasively measured haemodynamics to predict the pre-test probability that HFpEF is present.[5] In addition, the Heart Failure Association (HFA) of the European Society of Cardiology has recently proposed a new scoring system (the HFA-PEFF diagnostic algorithm) based upon expert consensus opinion to aid in the diagnostic evaluation of HFpEF.[6] The algorithm is based upon functional (tissue Doppler e′, E/e′ ratio, tricuspid valve regurgitation velocity, and global longitudinal strain), morphological (left ventricular hypertrophy and left atrial volume), and natriuretic peptide criteria, from which a score between 0 and 6 is calculated. According to this algorithm, lower scores are deemed to exclude HFpEF, higher scores of 5–6 are taken as proof that HFpEF is present, and intermediate scores require additional evaluation using exercise testing.[6]

While both risk scores were developed to aid in the diagnostic evaluation of HFpEF, many of their input variables have previously been associated with outcomes.[7–10] This led us to hypothesize that elevations in the HFA-PEFF or H_2FPEF score could also serve to identify patients at increased risk for HF readmissions or death among patients admitted with overt congestion and volume overload, where the diagnosis was not in question. Accordingly, the present study was undertaken to assess the prognostic value of both scores in a representative population sample of contemporary patients with definite HFpEF, admitted to the hospital with decompensation.

Methods

Study design

This retrospective cohort study includes consecutive patients with HFpEF, who were hospitalized because of signs or symptoms of congestion and treated with intravenous loop diuretics. All patients were admitted to a single tertiary care facility (Mayo Clinic, Rochester, MN, USA) between January 2010 and December 2015. The HFA-PEFF and continuous H_2FPEF scores (online supplementary *Figure S1*) were calculated in all subjects with echocardiography data available within 1 year of the admission date (either before or after).[5,6] Stratification was performed according to the HFA-PEFF score (2–4, =5, or =6), while the continuous H_2FPEF score is expressed as a probability ranging from 0 to 1. HF readmissions, all-cause mortality and death causes were obtained through retrospective chart review with censoring at the moment of last patient contact or 28 August 2019, whatever came first. HF readmissions were defined as any hospital readmission during which HF was listed as a primary diagnosis. This required typical HF signs or symptoms for which intravenous diuretics were administered, or the dose of oral loop diuretics was increased. Clinical outcomes were compared according to HFA-PEFF score groups. The study complies with the Declaration of Helsinki and was approved by the Mayo Clinic institutional review board. All authors had full access to the data, take responsibility for its integrity, contributed to the writing of the manuscript, and agree to this report as written. The manuscript was drafted according to the STROBE statement for observational studies.

Study population

The initial study sample was created by using ICD codes for HF in combination with filtering according to the terms *decompensated* or *acute* within the clinical notes. Patients were included only at the time of first HF hospitalization and were required to have an echocardiography result within 1 year of admission that demonstrated a left ventricular ejection fraction ≥50%. To provide a definite cohort of HFpEF patients, only those who received intravenous loop diuretics within 24 h of admission and for a duration of ≥48 h were included. All charts were manually reviewed by a board-certified cardiologist to confirm acute HF as the primary diagnosis of admission. Patients with a prior low left ventricular ejection fraction <50%, alternate causes of HF including an acute coronary syndrome, primary valve disease, cardiomyopathy, isolated right-sided HF, high output HF, and pericardial disease, or acute HF as complication of a non-cardiac procedure were excluded.

Echocardiography measurements and calculations

Comprehensive transthoracic echocardiography examinations were performed according to contemporary guidelines and carried out by experienced sonographers, as clinically indicated according to treating physicians.[11,12] Measurements were extracted from the clinical protocols through the electronic medical record whenever available. In case of missing data, relevant images were re-analysed and re-measured offline by a single cardiologist. Relative wall thickness was calculated as twice the posterior wall thickness divided by the left ventricular end-diastolic diameter. Left ventricular mass was determined according to the Devereux formula. Right ventricular systolic pressure was measured from the tricuspid valve regurgitation continuous-wave Doppler signal and included the estimated central venous pressure based on inferior vena cava diameter and respiratory variability. Data on global longitudinal strain were not available, which was a limitation for calculation of the HFA-PEFF score.

Outcome assessment

Patient follow-up was initiated on the day of admission and censored at the last follow-up contact that the patient was confirmed to be alive, or 28 August 2019, whatever came first. Vital status was determined from the Mayo Clinic registration database (Accurint) and the Rochester Epidemiology Project death database. Mortality data were ascertained from medical records, death certificates, obituaries, and notices of death in the local newspapers. Data on all Minnesota deaths were obtained from the State of Minnesota annually. To ascertain the cause of death, autopsy reports were given the highest priority when available, over mortality causes listed in death certificates, or (when both were unavailable) a thorough screening of the last reports available in the electronic medical record. HF as a contributing cause of death required listing in the autopsy report or death certificate, or alternatively a hospitalization for which HF was listed as (one of) the primary reason(s) for admission resulting in mortality. Patients referred to hospice care with terminal diagnosis such as cancer or HF were assumed to have died from that specific cause of death unless there were subsequent records that specified alternative causes.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation if normally distributed, or otherwise as median (interquartile range, IQR). The ANOVA or Kruskal–Wallis *H* test was used for comparison among groups as indicated with the Tukey–Kramer honest significant difference test used to compare individual groups when the overall result was significant. Categorical data are expressed as percentages and compared with Pearson's χ^2 test. Incidence rates for the total number of HF readmissions per 100 patient-years of follow-up are reported with exact Poisson 95% confidence intervals (CIs). To compare between strata, incidence rate differences and their exact Poisson 95% CIs were compared with a χ^2 test. Kaplan–Meier product limit estimator was employed to construct survival curves. Median survival and 95% CI are reported, with the log-rank test used for comparison between groups. In case of any missing data to calculate the HFA-PEFF score ($n = 35/443$; 8%), a conservative estimation whereby the missing value was scored as 0 was used for the primary analysis that is reported throughout this manuscript, unless explicitly stated otherwise. Sensitivity analysis was performed according to the complete-case scenario (excluding patients with missing data) as well as worst-case scenario (with missing values imputed by their maximally possible value). A Cox-proportional hazards model was used to adjust mortality for key baseline variables including age, gender, body mass index (BMI), systolic blood pressure, diabetes, coronary artery disease, atrial fibrillation, and estimated glomerular filtration rate (eGFR) according to the Chronic Kidney Disease Epidemiology Collaboration formula.[13] Statistical significance was always set at a two-tailed probability level of <0.05. All statistics were performed using JMP 14.1.0. (SAS Institute, Cary, NC, USA).

Results

Study population

A total of 3823 patients with preserved ejection fraction (≥50%) were admitted between January 2010 and December 2015 for possible acute HF. From this group, 443 met the inclusion/exclusion criteria and represent the final study population (*Figure 1*). The average age of the population was 78 ± 12 years, with 60% women. N-terminal pro-hormone B-type natriuretic peptide (NT-proBNP) levels were available during the index admission in 413/443 cases (93%) and were elevated at 2841 ng/L (1205–5573 ng/L). The HFA-PEFF score ranged from 2 to 6, and was low (2–4) in 79, intermediate (=5) in 93, and high (=6) in 271 patients (*Figure 2A*). The median H_2FPEF probability was 0.98 (0.94–0.99) with the overall distribution of the score depicted in *Figure 2B*. The time interval between the echo measurements to calculate the HFpEF risk scores and the admission date was 1 day (1–6 days). In the large majority of cases ($n = 308$; 70%) the echo result represented the transthoracic echocardiogram performed around the time of admission.

Baseline characteristics of the study population are described in *Table 1*. Patients with a higher HFA-PEFF score were older, more frequently women, with higher systolic blood pressure, worse renal function and less frequently a history of atrial fibrillation. BMI was lowest in patients with a high score. By the nature of selection based upon the specific parameters of the HFA-PEFF score, patients with higher scores had more elevated NT-proBNP levels, more pronounced left ventricular hypertrophy, greater left atrial volume, worse diastolic function, and higher estimated cardiac filling pressures on echocardiography (*Table 1*).

Heart failure readmissions according to HFA-PEFF score groups

Over 1337 cumulative patient-years of follow-up, 230 patients (52%) had a total of 557 hospital readmissions for which HF was a primary diagnosis. The incidence rate per 100 patient-years of follow-up was 28.9 (22.7–35.0) in the low, 46.0 (38.5–53.5) in the intermediate, and 45.0 (40.1–49.8) in the high HFA-PEFF group (*Figure 3*). Differences between the low and intermediate as well as between the low and high group were statistically significant ($P < 0.001$), while the difference between the intermediate and high group was not ($P = 0.813$). The complete-case scenario yielded similar findings with incidence rates of 32.9 (23.8–42.0), 46.3 (38.7–53.9), and 45.0 (40.1–49.8) in the low, intermediate, and high HFA-PEFF group, respectively ($P = 0.037$ for the difference between low and intermediate; $P = 0.039$ for the difference between low and high; and $P = 0.773$ for the difference between intermediate and high HFA-PEFF score). The worse-case scenario also corroborated these findings with incidence rates of 29.9 (21.8–38.0), 44.7 (37.9–51.6), and 42.8 (38.3–47.3), respectively ($P = 0.011$ for the difference between low and intermediate; $P = 0.015$ for the difference between low and high; and $P = 0.635$ for the difference between intermediate and high HFA-PEFF score).

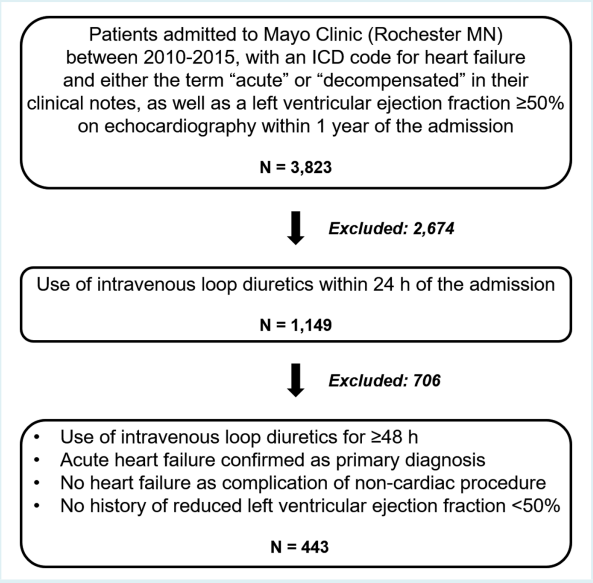


Figure 1 Study flowchart.

When patients were stratified according to H_2FPEF probability <0.90 ($n = 80$), 0.90–0.95 ($n = 61$) or 0.96–1.00 ($n = 293$) to yield comparable group sizes, corresponding incidence rates for heart failure readmissions were 31.8 (25.3–38.2), 41.5 (32.9–50.1), and 45.9 (41.2–50.6; *Figure 3*).

All-cause mortality according to heart failure with preserved ejection fraction risk scores

Over a median (IQR) of 28 months (8–59 months) follow-up, 304 patients died (69%). Median survival (95% CI) was 35 months (28–42 months) in the overall study population, 65 months (36–89 months) in the low, 45 months (26–59 months) in the intermediate, and 28 months (22–42 months) in the high HFA-PEFF group, with significant differences between groups (*Figure 4A*). The complete-case analysis ($P = 0.012$) and worst-case analysis ($P = 0.001$) were consistent. Differences in survival were most strongly driven by the morphology criteria (online supplementary *Figures S2–S4*). In a Cox-proportional hazards model adjusting for baseline characteristics, every 1 point increase in HFA-PEFF score was associated with a hazard ratio of 1.25 (95% CI 1.07–1.46) for all-cause mortality ($P = 0.004$). Subgroup analysis according to the presence of atrial fibrillation is presented in online supplementary *Figure S5*. Every 10% increase in H_2FPEF probability was associated with a hazard ratio of 1.16 (95% CI 1.02–1.32; $P = 0.014$) for all-cause mortality, after adjusting for the same baseline characteristics except for age, atrial fibrillation and BMI (to avoid collinearity as those are input variables of the H_2FPEF score). Kaplan–Meier curves for H_2FPEF probability <0.90, 0.90–0.95 vs. 0.96–1.00 are presented in *Figure 4B*.

Survival free from the combined endpoint of HF readmission or all-cause mortality was greater in patients with a low HFA-PEFF

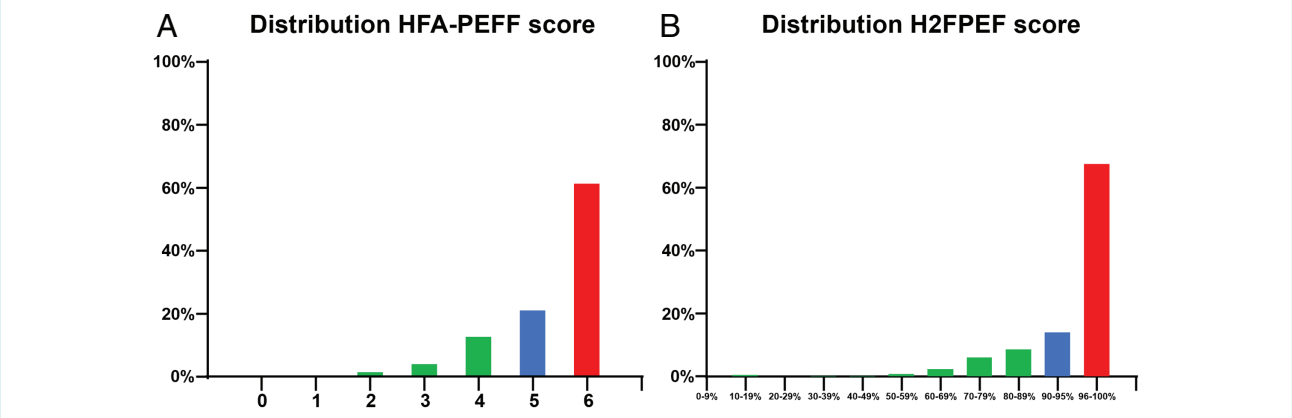


Figure 2 Distribution of the (*A*) HFA-PEFF score and (*B*) H_2FPEF probability across the study population.

score [22 months (8–49 months)] as compared to an intermediate [14 months (8–23 months)] and high score [10 months (7–12 months); $P = 0.002$; *Figure 5A*]. In a Cox-proportional hazards model adjusting for baseline characteristics, every 1 point increase in HFA-PEFF score was associated with a hazard ratio of 1.19 (95% CI 1.04–1.38) for all-cause mortality or HF readmission ($P = 0.013$). Subgroup analysis according to the presence of atrial fibrillation is presented in online supplementary *Figure S6*. Every 10% increase in H_2FPEF probability was associated with a hazard ratio of 1.17 (95% CI 1.05–1.33; $P = 0.004$) for all-cause mortality or HF readmission, after adjusting for the same baseline characteristics except for age, atrial fibrillation and BMI (to avoid collinearity as those are input variables of the H_2FPEF score). Kaplan–Meier curves for H_2FPEF probability <0.90, 0.90–0.95 vs. 0.96–1.00 are presented in *Figure 5B*.

A discrepancy analysis was performed to investigate patient characteristics of the groups with a low HFpEF score despite an early (90-day) death or HF event, as well as of the groups with a high HFpEF score despite 1-year event-free survival (online supplementary *Tables S1–S4*). In general, patients with poor outcomes despite lower scores had worse kidney function and more diastolic dysfunction on echocardiography. Patients with event-free survival despite higher scores were younger, with higher blood pressure and better kidney function.

Cause of death according to the HFA-PEFF score

Cause of death could be ascertained in 252/304 cases (83%). Data were missing in 8/43 cases (19%) in the low, 7/60 cases (12%) in the intermediate, and 37/201 (18%) cases in the high HFA-PEFF group ($P = 0.458$). A comprehensive list of all causes of death is presented in *Table 2*. The frequency of HF as a contributing cause of death was similar among HFA-PEFF strata (49% vs. 49% vs. 52% of mortality cases with increasing HFA-PEFF score, respectively; $P = 0.903$), as was the contribution of cardiovascular death (60% vs. 57% vs. 63%, respectively; $P = 0.662$). Overall, there was little difference in patterns of mortality causes among strata. The only significant difference between groups was a lower contribution of primary respiratory disease (mainly chronic obstructive pulmonary disease) to mortality in patients with a higher HFA-PEFF score (26% vs. 19% vs. 6%, respectively; $P < 0.001$).

Discussion

The current study assessed the prognostic value of the recently developed HFpEF probability scores (i.e. the H_2FPEF and HFA-PEFF scores) in a contemporary population of hospitalized patients with definite HFpEF. Although the primary reason for the development of these scores was to facilitate making a diagnosis of HFpEF, the score is based upon numerous parameters known to predict clinical outcomes.[5–10] It is important to emphasize that this study did not evaluate the diagnostic performance of either the H_2FPEF score or HFA-PEFF algorithm, because the clinical diagnosis of HFpEF was unequivocally established based upon hospitalization for decompensation.

The novel finding is that both scores can be used for prognostication in hospitalized patients with HFpEF (*Graphical Abstract*). Patients with an HFA-PEFF score ≥ 5 displayed an increased risk of HF readmissions, with 12–17 more hospitalizations due to HF per 100 patient-years compared to patients with an HFA-PEFF score < 5. Increasing HFA-PEFF score was associated with gradually increased mortality risk. Median survival time decreased from 65 months in patients with an HFA-PEFF score 2–4, over 45 months in patients with a score of 5, to only 28 months in patients with a score of 6. Morphology criteria contributed strongest to this discriminative capacity, as most patients had a maximal score on functional and biomarker criteria. Similarly, a 10% increase in H_2FPEF probability was associated with a 16% increased mortality risk and a 17% increased risk of HF readmission or death. Both risk scores performed similarly well to predict risk, despite important differences in distribution among the population studied (*Figure 3*). Cardiovascular and HF-related mortality were more common as compared to previous reports, and the proportions of HF-specific, cardiovascular, and non-cardiovascular death were not significantly different among HFA-PEFF score groups, with the

Table 1 Baseline characteristics of the study population

	HFA-PEFF 2–4 (*n* = 79)	HFA-PEFF = 5 (*n* = 93)	HFA-PEFF = 6 (*n* = 271)	*P*-value
Age (years)[†‡]	75 ± 14	75 ± 12	80 ± 12	<0.001
Men/women[‡]	54%/46%	42%/58%	36%/64%	0.012
Race				0.538
White	97.4%	98.9%	95.6%	
Black	1.3%	0	2.6%	
Other	1.3%	1.1%	1.8%	
Body mass index (kg/m^2)[*†]	35 ± 10	39 ± 12	33 ± 9	<0.001
Blood pressure (mmHg)				
Systolic[*‡]	125 ± 19	134 ± 22	134 ± 23	0.008
Diastolic	66 ± 12	66 ± 14	66 ± 15	0.924
Heart rate (bpm)	76 ± 18	70 ± 15	72 ± 16	0.081
Comorbid conditions				
Diabetes	54%	71%	61%	0.071
Coronary artery disease	47%	49	54%	0.443
Atrial fibrillation[*‡]	71%	53%	58%	0.043
Laboratory measurements				
NT-proBNP (ng/L)[‡]	861 (435–1862)	1983 (1155–4910)	3334 (1608–6525)	<0.001
Haemoglobin (g/dL)	11.7 ± 1.9	11.6 ± 2.0	11.3 ± 1.9	0.203
eGFR (mL/min/1.73 m^2)[‡]	58 ± 26	54 ± 26	49 ± 24	0.011
Blood urea nitrogen (mg/dL)	22 (16–33)	26 (18–40)	27 (19–42)	0.070
Blood urea nitrogen (mmol/L)	7.9 (5.7–11.8)	9.3 (6.4–14.3)	9.6 (6.8–15.0)	0.070
Sodium (mmol/L)	138 ± 5	139 ± 5	138 ± 5	0.768
Electrocardiogram				
Sinus rhythm	44%	58%	54%	0.182
QRS width (ms)	96 (82–116)	92 (82–110)	96 (86–118)	0.118
QRS width ≥ 120 ms	20%	16%	24%	0.228
Echocardiogram				
Ejection fraction (%)	62 ± 5	63 ± 5	62 ± 6	0.871
IVS thickness (mm)[‡]	11.1 ± 2.2	11.6 ± 1.5	12.0 ± 2.0	<0.001
PW thickness (mm)[‡]	10.6 ± 2.0	10.9 ± 1.6	11.3 ± 2.0	0.010
LVEDD (mm)	48.3 ± 5.5	49.0 ± 6.3	48.4 ± 6.3	0.676
Relative wall thickness[‡]	0.44 ± 0.08	0.46 ± 0.10	0.47 ± 0.10	0.020
LV mass index (g/m^2)[†‡]	93 ± 27	95 ± 19	110 ± 30	<0.001
LAVI (mL/m^2)[*†‡]	39 ± 13	34 ± 8	52 ± 12	<0.001
Stroke volume index (mL/m^2)[‡]	40 ± 9	44 ± 10	45 ± 12	0.017
Cardiac index (L/min/m^2)	2.92 (2.52–3.35)	2.92 (2.43–3.34)	3.00 (2.63–3.52)	0.136
E-wave velocity (m/s)[‡]	0.99 ± 0.31	1.07 ± 0.31	1.17 ± 0.39	<0.001
A-wave velocity (m/s)	0.6 (0–0.9)	0.7 (0–1.0)	0.5 (0–0.9)	0.308
E/A ratio	1.07 (0.80–1.50)	1.17 (0.80–1.45)	1.22 (0.85–1.83)	0.228
e′ medial velocity (m/s)[†‡]	0.069 ± 0.020	0.064 ± 0.019	0.058 ± 0.018	<0.001
e′ lateral velocity (m/s)[‡]	0.088 ± 0.027	0.079 ± 0.023	0.074 ± 0.025	<0.001
Averaged E/e′[†‡]	11.9 (9.3–16.0)	14.6 (11.7–17.9)	16.9 (13.0–22.9)	<0.001
TR velocity (m/s)[*†‡]	2.73 ± 0.51	2.93 ± 0.41	3.08 ± 0.47	<0.001
RVSP (mmHg)[†‡]	40 ± 15	43 ± 12	49 ± 13	<0.001
More than moderate MR	0	1.08%	2.95%	0.200
More than moderate TR[†]	7.59%	2.17%	14.39%	0.003
Medication use prior to admission				
RAS blocker[*†]	42%	61%	49%	0.032
Beta-blocker	62%	70%	73%	0.144
MRA	10%	4%	6%	0.265
Loop diuretic[†‡]	53%	56%	72%	<0.001

eGFR, estimated glomerular filtration rate according to the Chronic Kidney Disease Epidemiology Collaboration formula; IVS, interventricular septum; LAVI, left atrial volume index; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; MR, mitral valve regurgitation; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal of the pro-hormone of B-type natriuretic peptide; PW, posterior wall; RAS, renin–angiotensin system; RVSP, right ventricular systolic pressure; TR, tricuspid valve regurgitation.
[*]$P < 0.05$ for HFA-PEFF 2–4 vs. =5.
[†]$P < 0.05$ for HFA-PEFF =5 vs. =6.
[‡]$P < 0.05$ for HFA-PEFF 2–4 vs. =6.

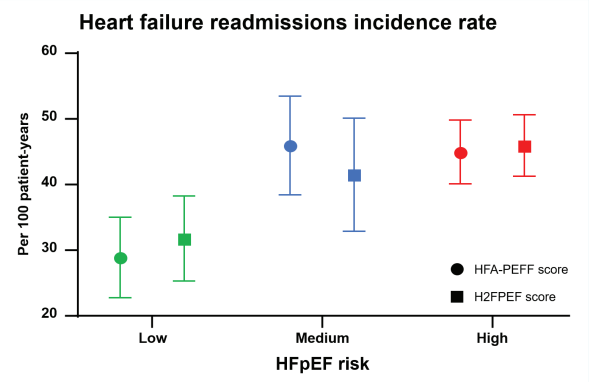


Figure 3 Incidence rates of repeated heart failure readmissions per 100 patient-years of follow-up according to the heart failure with preserved ejection fraction (HFpEF) risk calculated by the HFA-PEFF score (dots with 95% confidence intervals) and the logistic H_2FPEF score (squares with 95% confidence intervals). For the HFA-PEFF score, low risk was defined as a score 2–4, medium risk as score = 5 and high risk as a score = 6. For the H_2FPEF probability, <90% was defined as low risk, 90–95% as medium risk, and 96–100% as high risk.

exception of a lower risk of pulmonary death in the high score group. Finally, our results further reinforce the use of HFpEF probability scores to aid the diagnosis of HFpEF, as almost none of our patients with definite HFpEF had a low score using either model (*Figure 2*). Interestingly, in our population with well-established HFpEF and decompensation in whom the diagnosis was unequivocal, nearly 18% of patients had a HFA-PEFF score 2–4, which would have necessitated further testing to establish the HFpEF diagnosis when the score would have been used for diagnostic purposes.

While the H_2FPEF score was validated against invasive haemodynamics, development of the HFA-PEFF score was based on expert consensus opinion, based upon review of the literature, founded upon findings from echocardiography and natriuretic peptide levels. The present study tested a different application of both scores, as a means to stratify risk for adverse events, since the diagnosis of HFpEF itself was unambiguous due to the presence of gross volume overload requiring treatment with intravenous loop diuretics. Particular strengths of the current study are its long-term follow-up, meticulous adjudication of HFpEF hospitalization diagnosis after exclusion of alternate causes of HF, high number of clinical events, and detailed description of causes of death from an experienced cardiologist. In this way, our data complement earlier findings by Selvaraj *et al.*[14] who applied the HFA-PEFF and H_2FPEF score in patients from the Atherosclerosis Risk in Communities (ARIC) study. Similar to the findings of the current study, the authors found that both risk scores predicted HF hospitalizations and death. However, the population evaluated in the latter study was at much lower risk with 77% asymptomatic patients and only 10% with HFpEF according to their medical records. The present data importantly extend upon this earlier study in a much sicker cohort where the disease prevalence is 100%, showing that the ability of both scores to stratify risk is maintained.

The HFA-PEFF score has three components that each contribute equally to the overall score.[6] One component relies upon natriuretic peptide levels, which have been shown to be strongly related to adverse clinical outcomes in HFpEF as well as HFrEF.[8,15] The second component of the score relies on morphological criteria such as left atrial volume index and left ventricular mass. Left atrial volume index in particular has been demonstrated to be among the most powerful echocardiography predictors of future HF events and reflects the risk of atrial fibrillation, stroke, and cardiovascular mortality as well.[16–18] Finally, the third component of the HFA-PEFF score is represented by functional parameters that reflect left ventricular diastolic dysfunction and/or elevated cardiac filling pressures. One of the parameters incorporated is tricuspid valve regurgitation velocity, with high values indicating

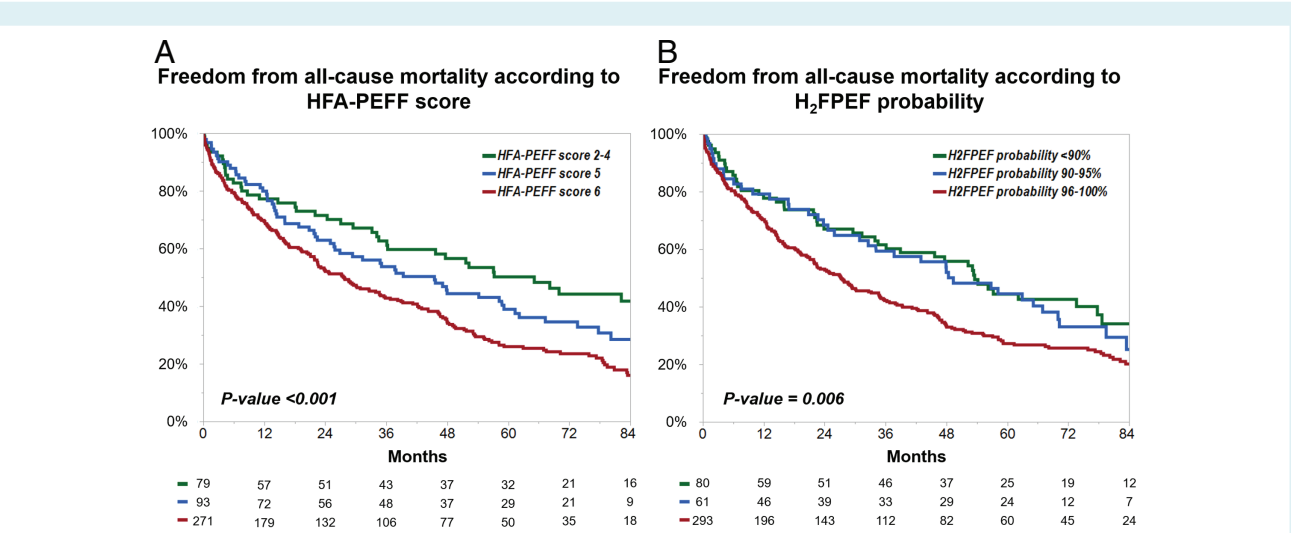


Figure 4 Freedom from all-cause mortality according to (*A*) HFA-PEFF score and (*B*) H_2FPEF probability.

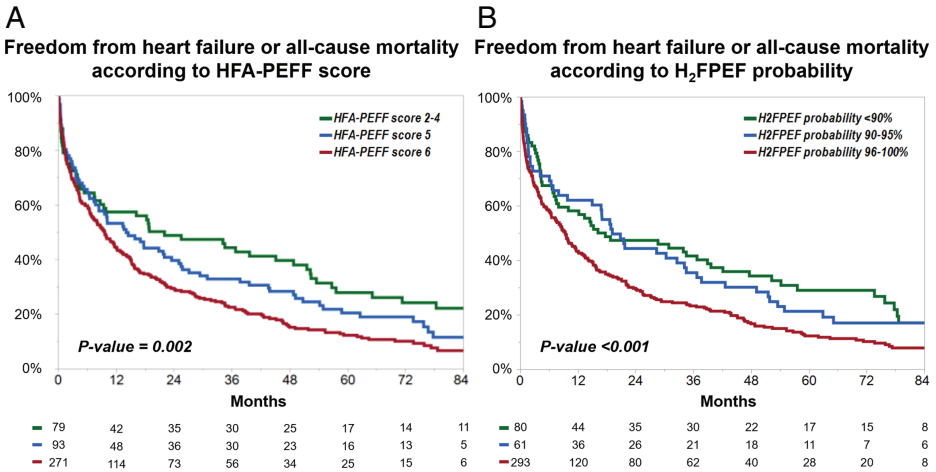


Figure 5 Freedom from heart failure readmission or all-cause mortality according to (*A*) HFA-PEFF score and (*B*) H_2FPEF probability.

Table 2 Death causes according to the HFA-PEFF score

Mortality cause	HFA-PEFF 2–4 (*n* = 35 deaths)	HFA-PEFF = 5 (*n* = 53 deaths)	HFA-PEFF = 6 (*n* = 164 deaths)
Primary cardiovascular death	18 (51.4%)	28 (52.8%)	100 (61.0%)
Heart failure*	13 (37.0%)	22 (41.4%)	75 (45.7%)
Heart failure and COPD	3 (8.6%)	2 (3.8%)	4 (2.4%)
Heart failure and pneumonia or sepsis	1 (2.9%)	2 (3.8%)	6 (3.7%)
Sudden death	3 (8.6%)	2 (3.8%)	8 (4.9%)
Myocardial infarction	0	0	4 (2.4%)
Endocarditis	0	1 (1.9%)	1 (0.6%)
Venous thromboembolism	1 (2.9%)	0	0
Pneumonia or sepsis	2 (5.7%)	3 (5.7%)	16 (9.8%)
COPD or primary respiratory failure	6 (17.1%)	8 (15.0%)	6 (3.7%)
Renal failure	1 (2.9%)	2 (3.8%)	4 (2.4%)
Cancer	2 (5.7%)	2 (3.8%)	22 (13.4%)
Ischaemic stroke	0	1 (1.9%)	6 (3.7%)
Intracranial haemorrhage	0	1 (1.9%)	1 (0.6%)
Gastrointestinal bleeding	1 (2.9%)	1 (1.9%)	1 (0.6%)
Trauma	0	0	1 (0.6%)
Multifactorial debility leading to hospice	2 (5.7%)	6 (11.3%)	9 (5.5%)

COPD, chronic obstructive pulmonary disease.
*$P < 0.05$.

pulmonary hypertension, which is strongly associated with mortality in HFpEF.[19] In this study of HFpEF patients hospitalized with gross volume overload, morphology criteria seemed to contribute most to risk stratification. Notably, NT-proBNP measurements and most echocardiography assessments were performed during a phase of acute decompensation, resulting in maximal scores for a large majority of patients. Nevertheless, combination of the individual components of the HFA-PEFF score seemed to work best in the current study as a comprehensive tool for risk stratification.

If further studies confirm the present results, the currently used HFpEF diagnostic scores could be provided to caregivers in an automated echocardiography protocol or integrated within the electronic medical record to guide discussions of prognosis in HFpEF. Using language recognition programming and artificial intelligence, it should be straightforward in the future for a given patient's HFA-PEFF score or H_2FPEF probability to be automatically calculated for both diagnostic purposes (as previously shown) and prognostication, as shown in the present study. Both scores are being increasingly reported as baseline characteristics in HFpEF studies and trials which (in analogy to natriuretic peptide levels) might be useful to enrich patient populations and stratify risk. Although immediate therapeutic limitations remain limited at present, it would still be important to identify patients at particular risk for adverse outcomes, who might need closer follow-up, further treatment optimization, or evaluation for palliative care discussions early in the course of their treatment. In addition, such

patients may be of particular interest to consider the addition of drugs that potentially decrease HF readmissions such as spironolactone, sacubitril/valsartan, or sodium–glucose co-transporter 2 inhibitors.[20–22] Alternatively, such patients may be the focus of clinical trials testing innovative treatment strategies in HFpEF.[23,24]

The rates of cardiovascular and HF-related death in the present cohort are higher than those reported in other studies of HFpEF.[25–29] This is likely related to the fact that rigorous criteria were used in the present study to support the veracity of the diagnosis of decompensated HFpEF, including early and sustained use of intravenous diuretics. This suggests that these criteria might be helpful to enrich future studies with patients with HFpEF where true decompensation is present, and to help distinguish from patients where HFpEF is merely a comorbid condition that is captured and coded in the record for billing purposes. In this regard, the careful manual adjudication of the index hospitalization, as well as subsequent hospitalizations and causes of death is a strength compared to prior studies that have relied upon ICD coding or discharge diagnoses, which may be less accurate. Notably, even in this population of severe HFpEF patients, there was a large contribution of death that could not be ascribed to HF, with a 40% contribution of non-cardiovascular to overall death, most often due to respiratory causes.

Study limitations

Complete data to calculate the HFA-PEFF score were absent in a minority of patients (8%), mainly due to the absence of NT-proBNP levels. However, extensive sensitivity analysis with a complete-case scenario as well as worst-case scenario corroborates the study findings. Global longitudinal strain data, which are a component of the functional score, were not available in this study. However, the absence of these data would not be expected to significantly influence the results, as global longitudinal strain values of <16% could result in a maximum of seven patients crossing over from the HFA-PEFF score 2–4 to the five group. Although patients were censored at the moment of their last contact within a Mayo Clinic affiliated centre, the possibility that they were readmitted for HF in between at a non-affiliated centre cannot be excluded. Therefore, incidence rates of recurrent HF readmissions should be interpreted as a conservative estimate. Finally, mortality causes were missing in 14% of cases, which was inherent to the retrospective nature of the present study design.

Conclusions

The results of this study suggest that both the HFA-PEFF and the H_2FPEF scores, which were designed to help guide diagnostic evaluation for HFpEF, are highly prognostic in patients that have been hospitalized with HFpEF. An HFA-PEFF of 6 as compared to 2–4 was associated with 16 more HF readmissions per 100 patient-years of follow-up and a greater than 3-year decrease in survival. Similarly, a 10% increase in H_2FPEF probability was associated with a 16% increased mortality risk and a 17% increased risk of HF readmission or death.

Supplementary Information

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

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