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RESEARCH ARTICLE

Value of the HFA-PEFF and H_2FPEF scores in patients with heart failure and preserved ejection fraction caused by cardiac amyloidosis

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Aims The HFA-PEFF and H_2FPEF scores have been developed to diagnose heart failure with preserved ejection fraction (HFpEF), and hold prognostic value. Their value in patients with HFpEF caused by cardiac amyloidosis (CA) has never been investigated.

Methods and results We evaluated the diagnostic and prognostic value of the HFA-PEFF and H_2FPEF scores in 304 patients from three cohorts with HFpEF caused by transthyretin CA ($n = 160$, 53%) or immunoglobulin light-chain CA ($n = 144$, 47%). A diagnosis of HFpEF was more likely using the HFA-PEFF score with 2 (1%), 71 (23%), and 231 (76%) patients ranked as having a low (0–1), intermediate (2–4), or high (5, 6) probability of HFpEF, respectively. Conversely, 36 (12%), 179 (59%) and 89 (29%) of patients ranked as having a low (0–1), intermediate (2–5), or high (6–9) probability of HFpEF using the H_2FPEF score. During a median follow-up of 19 months (interquartile range 8–40), 132 (43%) patients died. The HFA-PEFF score, but not the H_2FPEF score, predicted a high risk of all-cause death which remained significant after adjustment for age, AL-CA diagnosis, high-sensitivity troponin T, N-terminal pro-B-type natriuretic peptide, and echocardiographic parameters, including left ventricular global longitudinal strain, left ventricular diastolic function and right ventricular function (hazard ratio 1.51, 95% confidence interval 1.16–1.95, $p = 0.002$ for every 1-point increase in HFA-PEFF).

Conclusions The HFA-PEFF score has a higher diagnostic utility in HFpEF caused by CA and holds independent prognostic value for all-cause mortality, while the H_2FPEF score does not.

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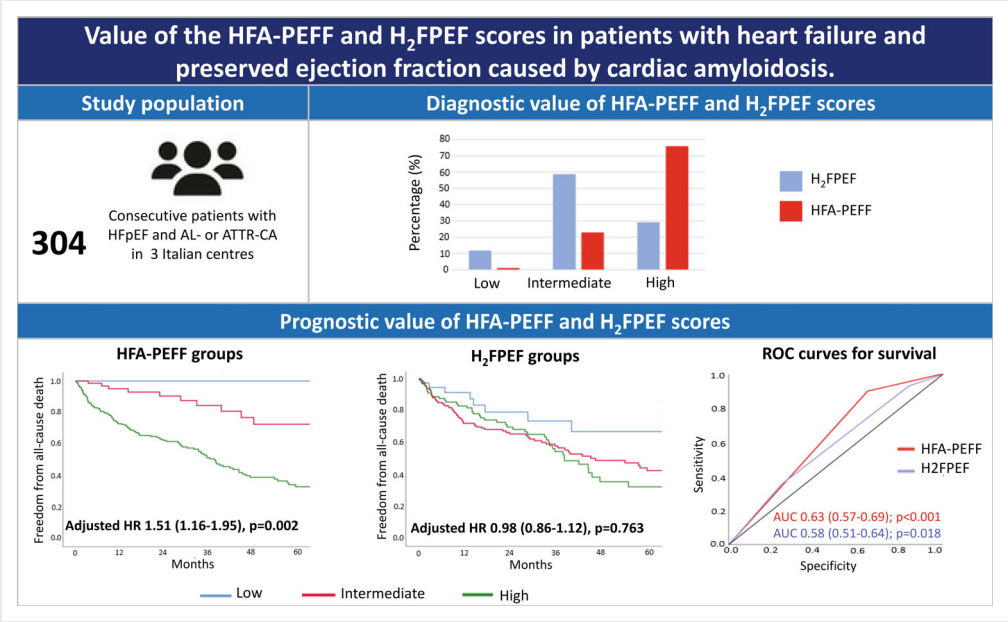
Graphical Abstract



The HFA-PEFF score outperforms the H_2FPEF score as a diagnostic tool in patients with heart failure with preserved ejection fraction (HFpEF) caused by cardiac amyloidosis and holds independent prognostic value for all-cause mortality, while the H_2FPEF score does not. AL, immunoglobulin light-chain; ATTR, transthyretin; AUC, area under the curve; CA, cardiac amyloidosis; HR, hazard ratio; ROC, receiver-operating characteristic.

Keywords Cardiac amyloidosis • Heart failure with preserved ejection fraction • HFA-PEFF score • H_2FPEF score • Diagnosis • Prognosis

Introduction

More than half of patients with heart failure (HF) have preserved ejection fraction (HFpEF), and this proportion is expected to increase over time.[1,2] The diagnosis of HFpEF remains challenging.[3] To facilitate the identification of patients with HFpEF, two scores have been proposed.[4,5] The H_2FPEF score includes six demographic, clinical and echocardiographic variables: obesity, atrial fibrillation, age >60 years, treatment with two or more antihypertensive drugs, E/e′ ratio >9, and pulmonary artery systolic pressure (PASP) >35 mmHg. The H_2FPEF score ranges from 0 to 9, may rule out HFpEF among patients with low scores (0–1), and allows to diagnose HFpEF with reasonable accuracy when high (6–9), while patients with intermediate scores need additional testing (2–5).[4] The HFA-PEFF algorithm has been developed by the Heart Failure Association (HFA) of the European Society of Cardiology (ESC), and requires a multistep approach. First, HFpEF is suspected based on signs and symptoms of HF. The second step requires calculation of the HFA-PEFF score, based on echocardiographic and laboratory findings. The HFA-PEFF score ranges from 0 to 6; a total score ≤1 denotes a very low probability of HFpEF, while a score ≥5 allows to diagnose HFpEF. The intermediate values need further investigation with stress echocardiography or invasive haemodynamics (third step). In the fourth step, HFpEF aetiology is investigated.[5] When applied to different cohorts, the H_2FPEF and HFA-PEFF scores showed a variable diagnostic performance.[6–10] In many studies these two scores were also predictive of outcome.[11–16]

Cardiac amyloidosis (CA) is characterized by extracellular deposition of misfolded proteins, most commonly transthyretin (ATTR-CA) or immunoglobulin light-chains (AL-CA), leading to increased biventricular wall thickness and increased myocardial stiffness, typically with preserved left ventricular (LV) systolic function.[17,18] The incidence of novel CA is increasing due to population ageing, the introduction of non-invasive diagnostic tools and greater disease awareness. However, it remains often overlooked in everyday clinical practice.[17]

Cardiac amyloidosis often presents as HFpEF, and screening studies have demonstrated that around 10% of men with HFpEF have ATTR-CA.[5,19] However, the diagnostic utility and the assessment of prognostic value of the H_2FPEF and HFA-PEFF scores to this condition have never been investigated. We performed for the first time this analysis on a large multicentre cohort of patients with CA.

Methods

Study population and data collection

We retrospectively evaluated 304 patients diagnosed with AL- or ATTR-CA from 2011 to 2021 at three Italian centres: Cardiology, ASST Spedali Civili and University of Brescia, Brescia (n = 142, 47%); Cardiology Department, Fondazione Toscana Gabriele Monasterio, Pisa (n = 133, 44%); Cardiovascular Department, Azienda Sanitaria Universitaria Integrata, Trieste (n = 29, 9%). These patients had a LV ejection fraction (LVEF) ≥50% and met the diagnostic criteria for HFpEF according to current ESC guidelines,[3] and had available data to calculate the HFA-PEFF and H_2FPEF scores. The flowchart of patient selection is reported in online supplementary *Figure S1*. CA was diagnosed when AL or ATTR amyloid was demonstrated on tissue specimens from endomyocardial biopsy, or when there was imaging evidence of cardiac involvement plus tissue amyloid in a peripheral tissue biopsy (as suggested by current recommendations).[18,20] After 2016, ATTR-CA was diagnosed non-invasively in cases with an intense myocardial uptake of bone tracers (Perugini scores 2–3) and no monoclonal protein.[21] Online supplementary *Figure S2* shows how the diagnosis was confirmed in the whole population. Patient data including demographics, medical history, physical examination, laboratory and echocardiographic findings, treatment and outcomes were extracted from electronic health records. Different stages of the disease were reported using universally accepted staging systems, namely Gillmore and Mayo stages for ATTR-CA and AL-CA patients, respectively.[18,22] Echocardiographic measurements were performed in agreement with the American Society of Echocardiography guidelines.[23,24] This study complied with the Declaration of Helsinki and was approved by the ethics committee of each centre. Patients did not give informed consent, since it was not possible nor deemed necessary in this retrospective electronic health record review.

H_2FPEF and HFA-PEFF score calculation and subgroups

The H_2FPEF score is calculated as follows: presence of atrial fibrillation, 3 points; obesity, defined as body mass index (BMI) >30 kg/m^2, 2 points; all other criteria (age >60 years, treatment with ≥2 antihypertensive drugs, E/e′ ratio >9 and PASP >35 mmHg), 1 point each (online supplementary *Table S1*).

The HFA-PEFF score is calculated as the sum of functional, morphological, and laboratory domains. Within each domain, a major criterion scores 2 points and a minor criterion 1 point. Each domain can contribute to up to 2 points, if any major criterion from this domain is positive, or 1 point if no major but any minor criterion is positive. Major and minor criteria for each domain are reported in online supplementary *Table S2*.

Patients were divided according to the criteria used in the original score studies into subgroups at low (<10%), intermediate and high (>90%) probability of HFpEF.[4,5] Thus, according to the H_2FPEF score, patients were ranked as having a low, intermediate and high probability of HFpEF when their score was 0–1, 2–5 and >5, respectively.[4] According to HFA-PEFF score values, patients were ranked as having a low, intermediate and high probability of HFpEF when their score was 0–1, 2–4 and 5–6, respectively.[5]

NT-proBNP and high-sensitivity troponin T assays

N-terminal pro-B-type natriuretic peptide (NT-proBNP) was measured through the electrochemiluminescence (ECLIA) monoclonal method (Roche Diagnostics), and troponin T (TnT) through a high sensitivity (hs) assay (Roche Diagnostics). The analytical characteristics of these assays are presented in dedicated papers.[25,26]

Follow-up

Data regarding death, cardiovascular death and cardiovascular events were collected during follow-up using electronic health records, chart review and patient reporting or phone calls to patients or relatives. Follow-up was performed twice a year and some patients were lost during follow-up. Among cardiovascular events, we assessed hospitalization due to decompensated HF, major arrhythmias (defined as any arrhythmias requiring medical intervention such as hospitalization or device implantation), and thromboembolic events, as previously defined.[27]

Statistical analysis

Normal distribution of continuous variables was explored through the Shapiro–Wilk tests. Continuous variables are presented as mean ± standard deviation when normally distributed, and as median and interquartile range (IQR) when non-normally distributed. Categorical variables are presented as counts and percentages. To compare groups, unpaired Student's t-test, ANOVA test, Mann–Whitney U test, or Kruskal–Wallis test for continuous variables and the Chi-square or Fisher exact tests for categorical variables were used, as appropriate. A p-value <0.05 was considered statistically significant. Survival curves were obtained using the Kaplan–Meier method and compared using the log-rank test. Patients lost to follow-up were censored. Cox regression analysis was performed to identify the variables independently associated with an increased risk of death. Variables already considered into the scores were not included into the Cox model (except for age). The other variables entered into the model were strong univariate predictors of death (all $p < 0.001$): age, AL-CA vs. ATTR-CA, systolic blood pressure, previous HF hospitalization, estimated glomerular filtration rate, hs-TnT, and furosemide therapy (online supplementary *Table S3*). The analysis was repeated in the AL-CA and ATTR-CA subgroups. Additional exploratory analyses were performed for other variables potentially related with death or CA severity. Each of these variables was entered into the previous model and the analysis repeated. Additional variables included clinical (sex, New York Heart Association [NYHA] class and other concomitant medications), laboratory (NT-proBNP, haemoglobin, international normalized ratio [INR]) and echocardiographic findings (LVEF, LV global longitudinal strain [GLS], E/A ratio, E-wave deceleration time, E/e′ ratio, left atrial volume index, tricuspid annular plane systolic excursion, PASP, inferior vena cava, pericardial effusion). Missing data were discarded. Multicollinearity was excluded by calculating the variance inflation factor. Receiver operating characteristic (ROC) analysis was used to compare the prognostic utility of HFpEF scores with the gold standard for prognostic evaluation, namely Gillmore and Mayo stages in ATTR-CA and AL-CA patients, respectively.[28] Statistical analyses were performed using the SPSS software, version 21 (SPSS Inc., Chicago, IL, USA).

Table 1 Clinical characteristics, laboratory and echocardiographic findings, treatment and outcome of the study population stratified by the H_2FPEF groups (low vs. intermediate vs. high)

Variable	All (n = 304)	Low H_2FPEF score (n = 36)	Intermediate H_2FPEF score (n = 179)	High H_2FPEF score (n = 89)	p-value
Clinical characteristics					
Age at inclusion (years)	77 (69–82)	60 (53–72)	76 (69–81)	82 (76–85)	**<0.001**
Male sex, *n* (%)	197 (65)	21 (58)	110 (62)	66 (74)	0.084
Weight (kg)	73 (62–82)	69 (57–72)	71 (61–81)	77 (66–83)	**0.021**
BMI (kg/m^2)	25 (23–29)	24 (23–26)	25 (23–28)	26 (24–29)	**0.015**
SBP (mmHg)	120 (110–140)	120 (106–135)	120 (109–135)	120 (110–140)	0.445
DBP (mmHg)	70 (60–80)	65 (60–80)	70 (60–80)	70 (65–80)	**0.043**
HR (bpm)	70 (62–80)	72 (65–85)	70 (63–82)	70 (59–79)	0.120
Type of amyloidosis, *n* (%)					
ATTR	160 (53)	10 (28)	80 (45)	70 (79)	**<0.001**
AL	144 (47)	26 (72)	99 (55)	19 (21)	**<0.001**
Hypertension, *n* (%)	186 (61)	15 (43)	105 (59)	66 (74)	**0.003**
Dyslipidaemia, *n* (%)	112 (37)	13 (37)	63 (35)	36 (40)	0.722
Diabetes, *n* (%)	54 (18)	4 (11)	26 (15)	24 (27)	**0.023**
CAD, *n* (%)	47 (15)	2 (6)	27 (15)	18 (20)	0.118
COPD, *n* (%)	24 (8)	2 (6)	15 (8)	7 (8)	0.863
History of atrial fibrillation, *n* (%)	131 (43)	0 (0)	45 (25)	86 (97)	**<0.001**
Previous HF hospitalization, *n* (%)	140 (46)	6 (17)	73 (41)	56 (63)	**<0.001**
NYHA class, *n* (%)					
I–II	198 (65)	27 (75)	118 (66)	45 (51)	**<0.001**
III–IV	106 (35)	5 (14)	57 (32)	44 (49)	**<0.001**
Angina, *n* (%)	45 (15)	4 (11)	24 (14)	17 (19)	0.396
Fatigue, *n* (%)	69 (23)	3 (9)	38 (21)	28 (32)	**0.016**
Syncope, *n* (%)	36 (12)	5 (14)	18 (10)	13 (15)	0.509
Laboratory findings					
Haemoglobin (g/dl)	12.5 ± 1.7	12.6 ± 1.7	12.4 ± 1.7	12.7 ± 1.6	0.355
White blood cell count (per µl)	3998 ± 4020	5477 ± 3642	4270 ± 4039	3086 ± 3934	**0.018**
Platelet count (×10∧3/µl)	222 ± 95	254 ± 120	223 ± 91	212 ± 93	0.171
Creatinine (mg/dl)	1.1 (0.9–1.5)	0.9 (0.8–1.5)	1.2 (0.9–1.5)	1.2 (0.9–1.6)	0.289
eGFR (ml/min)	55 (39–76)	67 (39–88)	55 (39–75)	53 (38–72)	0.195
Serum sodium (mEq/L)	140 (137–142)	140 (137–142)	140 (137–142)	139 (137–141)	0.118
Serum potassium (mEq/L)	4.1 ± 0.5	4 ± 0.6	4.1 ± 0.5	4.1 ± 0.6	0.858
Serum chloride (mmol/L)	103 ± 5	104 ± 5	103 ± 5	102 ± 5	0.097
BUN (mg/dl)	56 (44–77)	47 (27–80)	56 (45–77)	58 (46–78)	0.236
Glucose (mg/dl)	98 (85–112)	93 (88–105)	98 (84–98)	99 (88–114)	0.365
Aspartate transaminase (µ/L)	23 (18–32)	27 (19–37)	23 (19–32)	23 (18–32)	0.322
Alanine aminotransferase (µ/L)	20 (15–30)	21 (18–36)	20 (15–30)	21 (15–28)	0.311
Gamma-glutamyl transpeptidase (µ/L)	44 (20–90)	48 (19–223)	35 (18–78)	57 (26–103)	0.060
INR	1.1 (1.0–1.3)	1 (0.9–1.1)	1.1 (1.0–1.2)	1.3 (1.1–1.7)	**<0.001**
Lactate dehydrogenase (µ/L)	327 ± 172	300 ± 19	304 ± 131	376 ± 236	**0.021**
Uric acid (mg/dl)	6.7 ± 2.1	6.4 ± 2.2	6.6 ± 1.8	6.9 ± 2.4	0.479
Total cholesterol (mg/dl)	157 (130–90)	223 (171–287)	161 (132–195)	148 (124–174)	**<0.001**
NT-proBNP (ng/L)	3052 (1020–7808)	532 (133–469)	2395 (830–7484)	4633 (2794–9311)	**<0.001**
hs-TnT (ng/L)	40 (25–72)	22 (15–35)	37 (23–69)	59 (36–82)	**<0.001**
Echocardiographic findings					
LVEF (%)	57 (53–62)	62 (56.5–66)	58 (54–62)	55 (52–60)	**<0.001**
IVS (mm)	15 (13–18)	14 (12–16)	15 (13–17)	17 (14–20)	**<0.001**
LVPW (mm)	14 (12–15)	12 (10–14)	14 (11–15)	15 (13–16)	**<0.001**
LVEDD (mm)	45 (40–49)	43 (38–50)	44 (40–48)	45 (41–49)	0.461

Table 1 (Continued)

Variable	All (n = 304)	Low H_2FPEF score (n = 36)	Intermediate H_2FPEF score (n = 179)	High H_2FPEF score (n = 89)	p-value
LVESD (mm)	30 (26–33)	27 (23–33)	30 (26–33)	32 (28–34)	**0.005**
LV GLS (%)	−13.6 ± −4.7	−15.1 ± −5.4	−13.9 ± −4.5	−12.2 ± −4.6	**0.002**
Medial S′ (cm/s)	6 (5–7)	8 (6–9)	6 (5–7)	4 (3–6)	**<0.001**
Lateral S′ (cm/s)	5 (7–8)	8 (7–11)	7 (5–8)	5 (4–6)	**<0.001**
E/A	1.2 (0.8–2.0)	0.8 (0.7–1.2)	1.1 (0.8–1.9)	2.0 (1.6–2.7)	**<0.001**
EDT (ms)	190 (155–225)	207 (181–228)	194 (157–229)	171 (140–205)	**0.003**
E/e′	15 (11–18)	9 (9–12)	15 (11–18)	17 (14–22)	**<0.001**
LA diameter (mm)	44 (40–48)	40 (35–45)	43 (39–46)	47 (44–51)	**<0.001**
LA area (cm^2)	28 ± 16	19.6 ± 5.1	25.3 ± 9.1	33.8 ± 23.3	**<0.001**
LAVI (ml/m^2)	42 (32–50)	30 (26–35)	40 (32–48)	50 (42–61)	**<0.001**
RA volume (ml)	53 ± 27	40 ± 16	51 ± 27	75 ± 27	**0.044**
RV wall thickness (mm)	7.7 ± 2.1	7.6 ± 2.1	7.6 ± 1.8	8.4 ± 2.9	0.475
TAPSE (mm)	19 ± 5	21 ± 5	19 ± 5	17 ± 4	**<0.001**
s′ TDI (cm/s)	12 ± 3	14 ± 3	12 ± 3	10 ± 2	**<0.001**
FAC (%)	39 (34–45)	43 (25–48)	41 (36.8–45)	36 (33–42)	**0.038**
PASP (mmHg)	36 (30–45)	30 (25–33)	35 (30–42)	45 (40–51)	**<0.001**
IVC diameter during expiration (mm)	19 (16–24)	15 (11–20)	18 (15–23)	22 (18–25)	**<0.001**
Pericardial effusion, n (%)	107 (35)	7 (19)	70 (39)	30 (34)	0.074
Treatment					
ASA, n (%)	91 (31)	10 (42)	65 (38)	16 (19)	**0.008**
ACEi/ARBs, n (%)	134 (44)	4 (11)	77 (43)	53 (60)	**<0.001**
Beta-blockers, n (%)	155 (53)	9 (26)	91 (53)	55 (62)	**0.001**
MRAs, n (%)	113 (39)	14 (41)	51 (30)	48 (56)	**<0.001**
Direct oral anticoagulants, n (%)	72 (25)	0 (0)	27 (16)	45 (53)	**<0.001**
VKA, n (%)	48 (16)	0 (0)	20 (12)	28 (33)	**<0.001**
Furosemide, n (%)	202 (69)	15 (42)	114 (64)	73 (82)	**<0.001**
Furosemide dosage (mg)	50 (12.5–75)	12.5 (0–50)	31.25 (12.5–75)	50 (25–118.8)	**<0.001**
Specific therapy[a]	81 (27)	14 (39)	50 (28)	17 (19)	0.064
Outcomes, n (%)					
HF hospitalizations	121 (44)	7 (21)	64 (40)	50 (64)	**<0.001**
Thromboembolic events	15 (6)	0 (0)	12 (8)	3 (4)	0.162
Arrhythmia	64 (25)	2 (6)	36 (24)	26 (35)	**0.006**
Death	132 (43)	9 (25)	77 (43)	46 (52)	**0.024**
CV death	66 (64)	1 (17)	38 (64)	27 (71)	**0.036**

Values are reported as mean ± standard deviation, or median (interquartile range), unless otherwise indicated.
ACEi, angiotensin-converting enzyme inhibitor; AL, immunoglobulin light chain; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; ATTR, transthyretin; BMI, body mass index; BUN, blood urea nitrogen; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; DBP, diastolic blood pressure; EDT, E-wave deceleration time; eGFR, estimated glomerular filtration rate; FAC, fractional area change; HF, heart failure; HR, heart rate; hs-TnT, high-sensitivity troponin T; INR, international normalized ratio; IVC, inferior vena cava; IVS, interventricular septum; LA, left atrial; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LV GLS, left ventricular global longitudinal strain; LVESD, left ventricular end-systolic diameter; LVPW, left ventricular posterior wall; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; MRA, mineralocorticoid receptor antagonist; PASP, pulmonary artery systolic pressure; RA, right atrial; RV, right ventricular; SBP, systolic blood pressure; TAPSE, tricuspid annular plane systolic excursion; TDI, tissue Doppler imaging; VKA, vitamin K antagonist.
[a]Specific therapy refers to tafamidis or patisiran in the case of ATTR-CA whereas it refers to chemotherapy in patients with AL-CA.

Results

Clinical baseline characteristics

The study population included 304 patients, with a median age of 77 years (IQR 69–82), and 197 males (65%). ATTR-CA was diagnosed in 160 (53%) patients and AL-CA in 144 (47%). Baseline characteristics are summarized in *Table 1*.

Distribution of score values

Figure 1 shows the distribution of the two scores across the study population. A minority of patients displayed extreme H_2FPEF score values, while the majority were quite equally distributed across the central values (*Figure 1A*). Conversely, the proportion of patients with different HFA-PEFF scores increased in parallel with score values, with only one patient (0.3%)

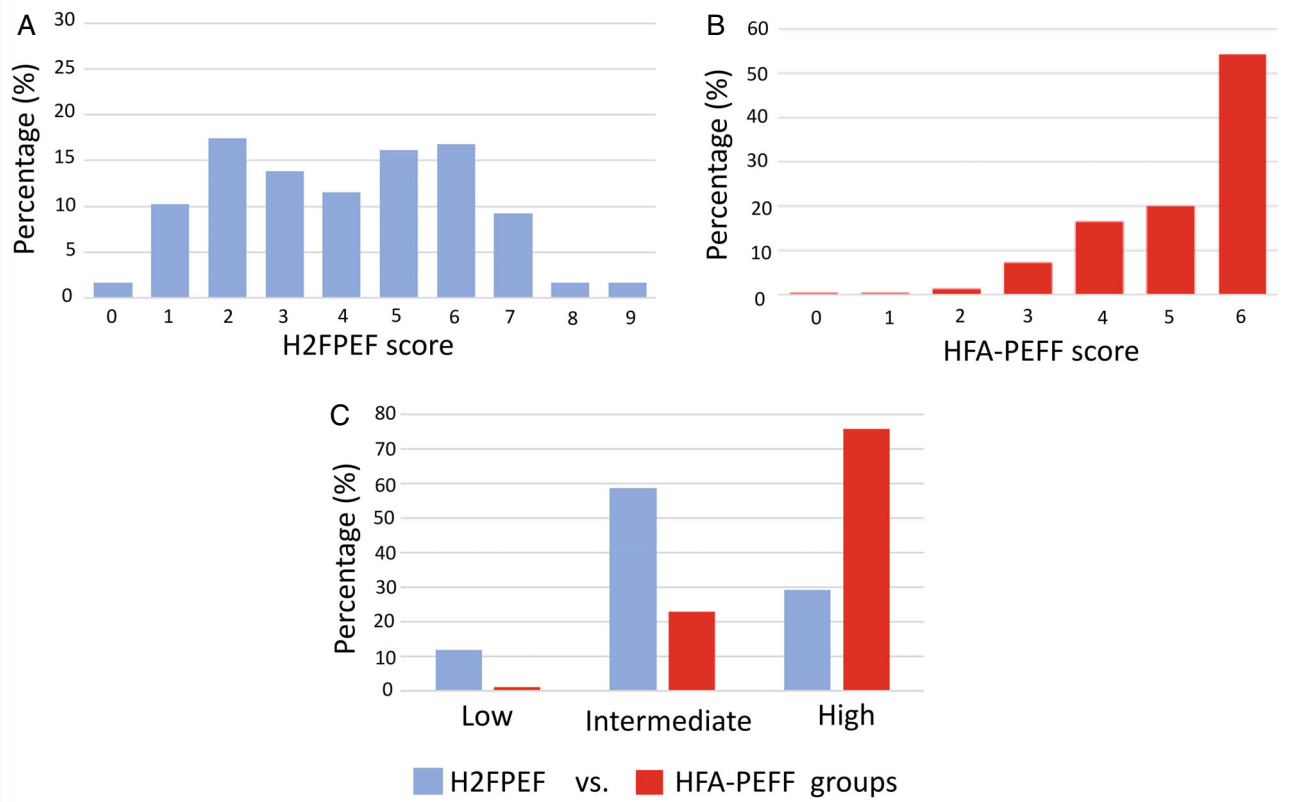


Figure 1 Distribution of the (*A*) H_2FPEF and (*B*) HFA-PEFF scores across the study population. (*C*) Distribution of the low, intermediate and high H_2FPEF and HFA-PEFF groups across the study population.

presenting with a score = 0 and 165 (54%) patients scoring 6 (*Figure 1B*).

When considering subgroups according to standardized cut-offs, <1% of patients were ranked as having a low probability of HFpEF using the HFA-PEFF score, while 71 (23%), and the majority (76%) were ranked as having an intermediate and high probability of HFpEF, respectively. The likelihood of HFpEF, applying the H_2FPEF score, was low in 36 (12%), intermediate in 179 (59%) and high in 89 patients (29%) (*Figure 1C*).

Correlates of H_2FPEF and HFA-PEFF score levels

Baseline characteristics of the study population stratified by H_2FPEF and HFA-PEFF groups are summarized in *Tables 1* and *2*. Due to the limited number of cases, the two patients with a low HFA-PEFF score (1%) were excluded from this analysis, and patients with a high HFA-PEFF score were compared to those with an intermediate score. Patients with a high H_2FPEF score were older, had a higher BMI and more often a history of hypertension, diabetes, atrial fibrillation and previous HF hospitalizations than those with low and intermediate scores. The prevalence of ATTR-CA was higher in patients with a high H_2FEPF score, while the majority of patients with a low H_2FPEF score were diagnosed with AL-CA. Furthermore, patients with a high H_2FPEF score had higher hs-TnT and NT-proBNP, greater LV thickness, worse LV systolic and diastolic function, larger left and right atria, higher PASP and worse right ventricular (RV) systolic function (*Table 1*).

Conversely, there were no significant differences in age, comorbidities and subtype of amyloidosis between the two HFA-PEFF groups. Patients with a high HFA-PEFF score had lower systolic blood pressure, were more symptomatic for dyspnoea, had a worse renal function and higher levels of hs-TnT and NT-proBNP. Moreover, they displayed worse systolic longitudinal function, more pronounced LV hypertrophy, greater left atrial enlargement, higher RV wall thickness, worse RV systolic function, and more frequently presented pericardial effusion. Patients with a high HFA-PEFF score were more likely to receive furosemide and higher diuretic doses (*Table 2*).

Finally, patients with more advanced stages, defined as Gillmore and Mayo stages in ATTR-CA and AL-CA, respectively, had higher HFpEF scores (online supplementary *Tables S4–S7*).

Outcome

Over a median follow-up of 19 (8–40) months, 132 patients died (43%), with 66 deaths out of 103 with available data (64%) due

Table 2 Clinical characteristics, laboratory and echocardiographic findings, treatment and outcome of the study population stratified by the HFA-PEFF groups (intermediate vs. high)

Variable	Intermediate HFA-PEFF score (2–4) (*n* = 71)	High HFA-PEFF score (5, 6) (*n* = 231)	*p*-value
Clinical characteristics			
Age at inclusion (years)	77 (69–82)	77 (69–82)	0.989
Male sex, *n* (%)	50 (70)	147 (64)	0.294
Weight (kg)	79 (60–83)	74 (62–82)	0.581
BMI (kg/m^2)	25 (23–28)	25 (23–28)	0.470
SBP (mmHg)	130 (120–140)	120 (105–135)	**0.001**
DBP (mmHg)	70 (60–80)	70 (60–80)	0.679
HR (bpm)	70 (61–80)	70 (62–81)	0.842
Type of amyloidosis, *n* (%)			0.143
ATTR	43 (61)	117 (51)	
AL	28 (39)	114 (49)	
Hypertension, *n* (%)	44 (62)	142 (61)	0.940
Dyslipidaemia, *n* (%)	27 (38)	85 (37)	0.851
Diabetes, *n* (%)	12 (17)	42 (18)	0.805
CAD, *n* (%)	14 (20)	33 (14)	0.269
COPD, *n* (%)	8 (11)	16 (7)	0.237
History of atrial fibrillation, *n* (%)	23 (32)	108 (47)	**0.033**
Previous HF hospitalization, *n* (%)	25 (35)	115 (50)	**0.042**
NYHA class, *n* (%)			**0.003**
I–II	58 (82)	138 (60)	
III–IV	13 (18)	93 (40)	
Angina, *n* (%)	13 (18)	32 (14)	0.356
Asthenia, *n* (%)	14 (20)	55 (24)	0.507
Syncope	7 (10)	29 (13)	0.540
H_2FPEF group, *n* (%)			**<0.001**
Low (0–1)	18 (25)	16 (7)	
Intermediate (2–5)	44 (62)	135 (58)	
High (6–9)	9 (13)	80 (35)	
Laboratory findings			
Haemoglobin (g/dl)	12.5 ± 1.5	12.5 ± 1.7	0.785
White blood cell count (per μl)	6180 ± 3191	3556 ± 4033	**<0.001**
Platelet count (×10∧3/μl)	227 ± 98	221 ± 95	0.743
Lactate dehydrogenase (μ/L)	271 ± 86	338 ± 184	**0.036**
Creatinine (mg/dl)	1.0 (0.8–1.4)	1.1 (0.9–1.6)	**0.012**
eGFR (ml/min)	61 (45–80)	53 (38–73)	**0.043**
Serum sodium (mEq/L)	140 (138–142)	139 (137–142)	0.388
Serum potassium (mEq/L)	4.1 ± 0.6	4.1 ± 0.5	0.449
Serum clhoride (mmol/L)	104 ± 4	102 ± 5	0.108
BUN (mg/dl)	45 (30–57)	58 (46–78)	**0.009**
Glucose (mg/dl)	100 (90–114)	97 (85–112)	0.359
Aspartate transaminase (μ/L)	28 (20–33)	22 (18–32)	0.057
Alanine aminotransferase (μ/L)	19 (15–28)	20 (15–31)	0.978
Gamma-glutamyl transpeptidase (μ/L)	34 (17–69)	46 (21–98)	0.161
INR	1.1 (1.0–1.3)	1.1 (1.0–1.3)	0.321
Uric acid (mg/dl)	5.9 ± 1.7	6.8 ± 2.1	**0.022**
Total cholesterol (mmol/L)	165 (129–193)	156 (130–186)	0.874
NT-proBNP (ng/L)	555 (167–2149)	3473 (1702–8382)	**<0.001**
hs-TnT (ng/L)	20 (16–33)	46 (29–77)	**<0.001**
Echocardiographic findings			
LVEF (%)	58 (55–65)	57 (53–62)	0.137
IVS (mm)	14 (12–17)	16 (14–18)	**0.002**
LVPW (mm)	12 (10–14)	14 (12–16)	**<0.001**

Table 2 (Continued)

Variable	Intermediate HFA-PEFF score (2–4) (n = 71)	High HFA-PEFF score (5, 6) (n = 231)	p-value
LVEDD (mm)	47 (43–51)	44 (40–48)	**0.010**
LVESD (mm)	31 (28–34)	30 (26–33)	0.232
LV GLS (%)	−14.6 ± 3.9	−13.2 ± 4.9	**0.036**
Medial S′ (cm/s)	7 (6–8)	6 (4–7)	**0.007**
Lateral S′ (cm/s)	8 (5–9)	6 (5–8)	0.077
E/A	0.9 (0.7–1.3)	1.3 (0.9–2.2)	**0.003**
EDT (ms)	200 (178–230)	182 (150–222)	**0.027**
E/e′	11 (9–14)	16 (12–20)	**<0.001**
LA diameter (mm)	42 (36–47)	45 (40–48)	0.059
LA area (cm^2)	23 ± 5	29 ± 17	**0.038**
LAVI (ml/m^2)	32 (26–42)	43 (36–51)	**<0.001**
RA volume (ml)	39 ± 19	58 ± 27	**0.011**
RV wall thickness (mm)	6.4 ± 2.7	8.1 ± 1.7	**0.004**
TAPSE (mm)	20 ± 4	18 ± 5	**0.003**
s′ TDI (cm/s)	13 ± 2	12 ± 3	**0.013**
FAC (%)	44 (39–47)	39 (33–44)	**0.049**
PASP (mmHg)	30 (28–35)	39 (32–47)	**<0.001**
IVC diameter during expiration (mm)	17 (14–20)	20 (16–24)	**0.004**
Pericardial effusion, n (%)	15 (21)	92 (40)	**0.009**
Treatment			
ASA, n (%)	24 (35)	67 (30)	0.053
ACEi/ARBs, n (%)	26 (37)	108 (47)	0.271
Beta-blockers, n (%)	30 (44)	125 (56)	0.840
MRAs, n (%)	16 (24)	97 (44)	**0.041**
Direct oral anticoagulants, n (%)	11 (16)	61 (27)	0.181
VKA, n (%)	9 (13)	39 (18)	0.701
Furosemide, n (%)	35 (49)	167 (72)	**<0.001**
Furosemide dosage (mg)	25 (0–50)	50 (25–100)	**<0.001**
Specific therapy,[a] n (%)	18 (25)	62 (27)	0.732
Outcomes, n (%)			
HF hospitalizations	16 (24)	104 (51)	**<0.001**
Thromboembolic events	1 (1)	14 (7)	0.212
Arrhythmia	8 (12)	56 (29)	**0.005**
Death	12 (17)	120 (52)	**<0.001**
CV death	3 (23)	63 (70)	**0.001**

Values are reported as mean ± standard deviation, or median (interquartile range), unless otherwise indicated.
ACEi, angiotensin-converting enzyme-inhibitor; AL, immunoglobulin light chain; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; ATTR, transthyretin; BMI, body mass index; BUN, blood urea nitrogen; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; DBP, diastolic blood pressure; EDT, E-wave deceleration time; eGFR, estimated glomerular filtration rate; FAC, fractional area change; HF, heart failure; HR, heart rate; hs-TnT, high-sensitivity troponin T; INR, international normalized ratio; IVC, inferior vena cava; IVS, interventricular septum; LA, left atrial; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LV GLS, left ventricular global longitudinal strain; LVESD, left ventricular end-systolic diameter; LVPW, left ventricular posterior wall; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; MRA, mineralocorticoid receptor antagonist; PASP, pulmonary artery systolic pressure; RA, right atrial; RV, right ventricular; SBP, systolic blood pressure; TAPSE, tricuspid annular plane systolic excursion; TDI, tissue Doppler imaging; VKA, vitamin K antagonist.
[a]Specific therapy refers to tafamidis or patisiran in the case of ATTR-CA while it refers to chemotherapy in patients with AL-CA.

to cardiovascular causes. Mortality rates were higher in patients with higher H_2FPEF score (low score, 25%; intermediate score, 43%, high score, 52%; p = 0.024) (*Table 1*) and in patients with a high HFA-PEFF score, compared to those with an intermediate score (17% vs. 52%, $p < 0.001$) (*Table 2*). The risk of other cardiovascular events, namely HF hospitalizations and arrhythmias requiring intervention, was higher in patients with high HFA-PEFF or H_2FPEF scores. There was no difference in thromboembolic events (*Tables 1* and *2*). Of note, no patients underwent left atrial appendage closure.

Survival at 5 years was significantly different across HFA-PEFF (log-rank $p < 0.001$) (*Figure 2*), but not H_2FPEF categories (log-rank p = 0.078) (*Figure 3*). Excluding patients with a score of 0–2 due to the limited number of cases, survival was significantly different

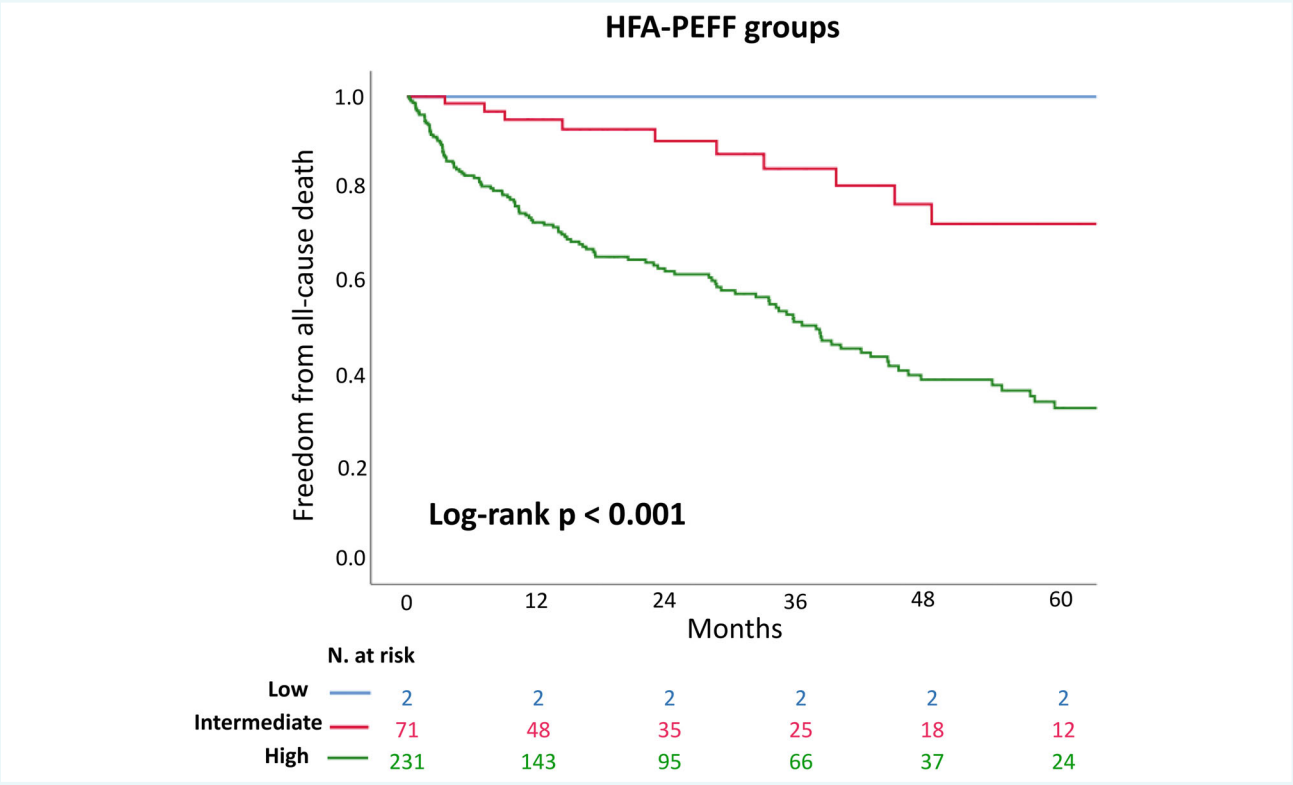


Figure 2 Freedom from all-cause mortality according to the HFA-PEFF groups (low vs. intermediate vs. high).

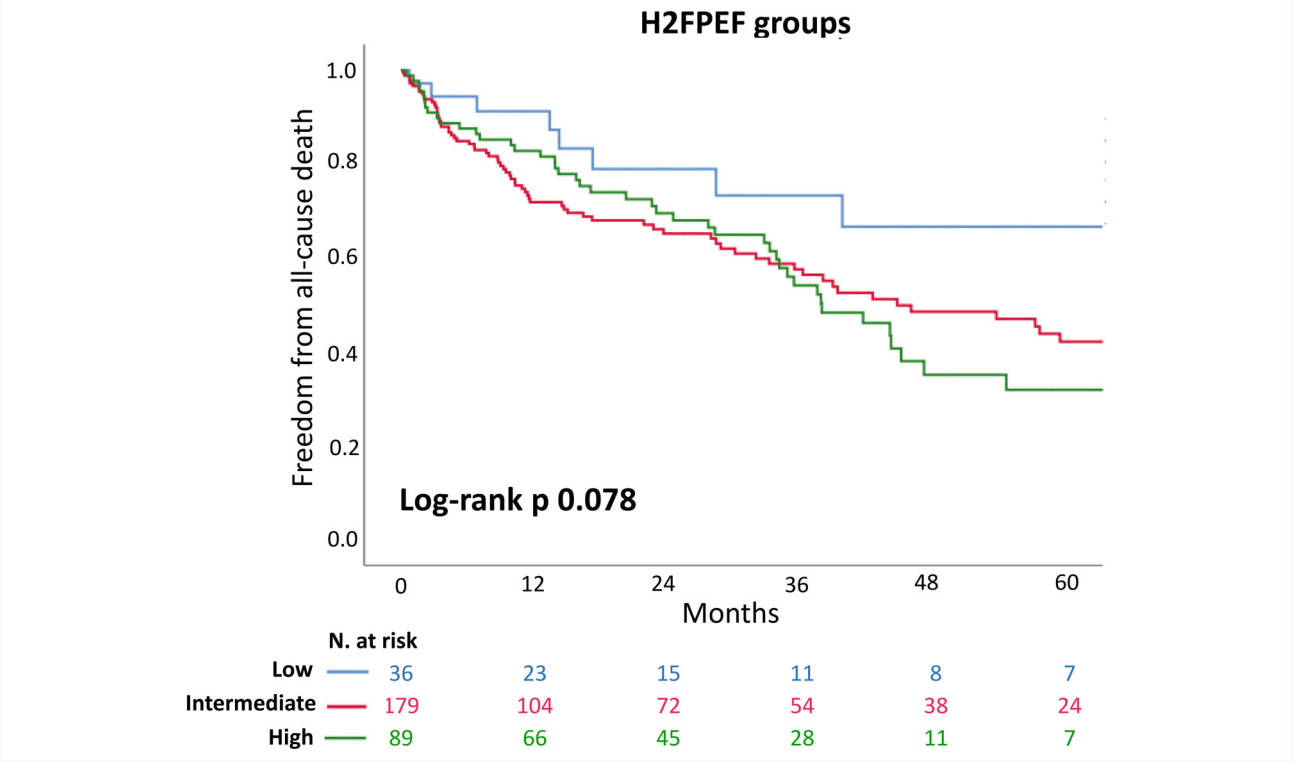


Figure 3 Freedom from all-cause mortality according to the H_2FPEF groups (low vs. intermediate vs. high).

Table 3 Univariable and multivariable Cox regression model for all-cause death

	Univariable		Multivariable	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Clinical characteristics				
Age at inclusion (years)	1.01 (0.99–1.03)	0.263	1.04 (1.01–1.08)	**0.006**
Type of amyloidosis (AL vs. ATTR)	2.11 (1.48–3.00)	**<0.001**	3.63 (2.14–6.16)	**<0.001**
SBP	0.98 (0.97–0.99)	**<0.001**	0.988 (0.978–0.998)	**0.025**
Previous HF hospitalization	1.91 (1.35–2.70)	**<0.001**	1.87 (1.18–2.95)	**0.008**
Laboratory findings				
eGFR	0.98 (0.97–0.99)	**<0.001**	0.99 (0.98–1.00)	0.061
hs-TnT	1.01 (1.01–1.01)	**<0.001**	1.006 (1.004–1.009)	**<0.001**
Therapy				
Furosemide	2.65 (1.68–4.18)	**<0.001**	1.25 (0.71–2.20)	0.439
HFpEF scores				
HFA-PEFF score	1.57 (1.29–1.93)	**<0.001**	1.51 (1.16–1.95)	**0.002**
H_2FPEF score	1.10 (1.02–1.20)	**0.017**	0.98 (0.86–1.12)	0.763

AL, immunoglobulin light chain; ATTR, transthyretin; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; hs-TnT, high-sensitivity troponin T; SBP, systolic blood pressure.

also among the single HFA-PEFF sum scores ($p < 0.001$) (online supplementary *Figure S3*).

The HFA-PEFF score values were associated with the risk for all-cause death at both univariate (hazard ratio [HR] 1.57; 95% confidence interval [CI] 1.29–1.93; $p < 0.001$) and multivariate analysis (adjusted HR 1.51, 95% CI 1.16–1.95, $p = 0.002$ for every 1-point increase in the HFA-PEFF score). The H_2FPEF score was associated with an increased risk for death at univariate (HR 1.10; 95% CI 1.02–1.20, $p = 0.017$), but not at multivariate analysis (HR 0.98; 95% CI 0.86–1.12; $p = 0.763$) (*Table 3*). Similar results were observed when the analyses were performed in the subgroups of patients with ATTR-CA and AL-CA (online supplementary *Table S8* and *Figure S4*). The association between the HFA-PEFF score and all-cause mortality was not modified even when forcing other relevant laboratory, clinical and echocardiographic variables into the model (*Table 4*). The area under the curve (AUC) for the prediction of adverse outcomes was 0.63 (95% CI 0.57–0.69; $p < 0.001$) and 0.58 (95% CI 0.51–0.64; $p = 0.018$) for the HFA-PEFF and H_2FPEF score, respectively (*Figure 4A*). *Figure 4B* and *4C* shows the AUC for the prediction of adverse outcomes for HFpEF scores, Mayo staging system in AL-CA patients and Gillmore staging system in ATTR-CA patients. HFA-PEFF and H_2FPEF scores did not add prognostic utility compared to the gold standard for prognostic evaluation.

Discussion

This is the first study to assess the diagnostic and prognostic utility of two diagnostic scores for HFpEF in the specific setting of HFpEF related to CA. Our main findings are the following: (i) the HFA-PEFF score outperformed the H_2FPEF score as a diagnostic tool in patients with CA; (ii) higher HFpEF score values were associated with an increased risk of mortality and cardiovascular events; and (iii) HFA-PEFF, but not H_2FPEF, score values were independent predictors of mortality (*Graphical Abstract*).

The H_2FPEF and HFA-PEFF scores were developed as diagnostic tools for HFpEF, particularly in the outpatient setting. However, HFpEF is a heterogeneous condition and the diagnostic performance of these two scores differs across different populations.[9,29,30] In the current study, the majority of patients with CA (76%) would have been diagnosed with HFpEF using the HFA-PEFF score. On the contrary, H_2FPEF classified more than a half of patients into the intermediate likelihood category, requiring further investigations (i.e. diastolic stress test). Furthermore, using a 'rule-out' approach (i.e. excluding HFpEF in patients with a low score), the HFA-PEFF score presented a high sensitivity (99%), whereas the H_2FPEF score had a lower sensitivity (88%), potentially missing the diagnosis in 12% of patients. Importantly, the majority of patients with a low H_2FPEF score had AL-CA, with a consequent possible delay in diagnosis and treatment in this high-risk population. Notably, we evaluated the sensitivity of the two scores in a population with an established diagnosis of CA, although it would be better to test the performance of a score from populations with a different disease prevalence.

Heart failure with preserved ejection fraction is a clinical syndrome with multiple aetiologies, phenotypes and clinical expressions.[5] The suboptimal performance of the H_2FPEF score in this setting may be explained by the inclusion of variables that mostly depict the classical phenotype of HFpEF (an elderly, obese, hypertensive patient with a history of atrial fibrillation).[31] Conversely, patients with CA may be hypotensive (or normotensive if previous hypertensive), and only some criteria may correctly identify CA patients (elderly age in ATTR-CA but not AL-CA patients, atrial fibrillation, E/e′ ratio >9, and PASP >35 mmHg). On the other hand, the HFA-PEFF score relies on echocardiographic parameters that are frequently altered in CA (increased LV wall thickness and mass, atrial enlargement, elevated filling pressure and reduced GLS).[32–34]

Table 4 Hazard ratio for HFA-PEFF and H_2FPEF scores for all-cause death with the inclusion of additional potentially relevant variables in multivariable Cox regression analysis

	HR for additional variable				HR for HFA-PEFF		HR for H_2FPEF	
	Univariable		Multivariable		Multivariable		Multivariable	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Main model[a]								
+ Sex	0.82 (0.58–1.17)	0.269	1.12 (0.70–1.78)	0.630	1.51 (1.16–1.95)	**0.002**	0.98 (0.86–1.12)	0.800
+ NYHA class	1.40 (1.12–1.75)	0.003	0.91 (0.67–1.24)	0.561	1.53 (1.17–1.99)	**0.002**	0.98 (0.86–1.16)	0.770
+ NT-proBNP (log)	3.11 (2.17–4.44)	<0.001	1.79 (1.08–2.94)	**0.023**	1.39 (1.03–1.87)	**0.029**	0.95 (0.83–1.08)	0.438
+ Haemoglobin	0.83 (0.75–0.92)	0.001	1.08 (0.94–1.24)	0.261	1.50 (1.14–1.98)	**0.004**	0.98 (0.86–1.12)	0.796
+ INR	1.52 (1.18–1.97)	0.001	1.21 (0.85–1.74)	0.291	1.67 (1.22–2.29)	**0.002**	0.96 (0.83–1.11)	0.547
+ Cholesterol	0.99 (0.99–0.998)	0.002	0.997 (0.991–1.002)	0.216	1.70 (1.24–2.35)	**0.001**	0.92 (0.80–1.07)	0.284
+ LVEF	0.99 (0.96–1.02)	0.349	1.01 (0.97–1.04)	0.744	1.51 (1.16–1.96)	**0.002**	0.99 (0.86–1.12)	0.819
+ LV GLS	1.10 (1.06–1.15)	<0.001	1.07 (1.01–1.13)	**0.022**	1.52 (1.16–2.00)	**0.003**	0.98 (0.86–1.12)	0.800
+ E/A	1.26 (1.06–1.49)	0.010	1.06 (0.83–1.34)	0.642	1.33 (1.004–1.78)	**0.047**	1.08 (0.90–1.30)	0.387
+ EDT	0.99 (0.99–0.997)	0.001	0.99 (0.99–1.002)	0.269	1.50 (1.15–1.96)	**0.003**	0.98 0.85–1.12)	0.765
+ E/e′	1.07 (1.05–1.01)	<0.001	1.04 (1.01–1.08)	**0.021**	1.39 (1.07–1.81)	**0.013**	0.95 (0.83–1.09)	0.951
+ LAVI	1.02 (1.01–1.03)	0.003	1.01 (0.90–1.02)	0.580	1.50 (1.13–1.98)	**0.004**	0.98 (0.86–1.12)	0.779
+ TAPSE	0.91 (0.88–0.95)	<0.001	0.95 (0.90–0.99)	**0.026**	1.38 (1.04–1.83)	**0.024**	0.96 (0.83–1.10)	0.531
+ PASP	1.02 (1.01–1.04)	0.004	0.99 (0.97–1.02)	0.574	1.59 (1.19–2.11)	**0.002**	0.99 (0.86–1.14)	0.899
+ IVC	1.07 (1.03–1.10)	<0.001	1.05 (1.00–1.10)	**0.048**	1.62 (1.17–2-25)	**0.004**	0.93 (0.80–1.08)	0.337
+ Pericardial effusion	1.91 (1.35–2.71)	<0.001	1.24 (0.78–1.97)	0.367	1.46 (1.16–1.91)	**0.006**	0.98 (0.86–1.12)	0.752
+ MRA	1.58 (1.10–2.25)	0.011	1.19 (0.76–1.85)	0.444	1.51 (1.16–1.96)	**0.002**	0.98 (0.86–1.11)	0.975
+ VKA	1.65 (1.09–2.51)	0.019	1.00 (0.57–1.77)	0.988	1.50 (1.16–1.94)	**0.002**	0.98 (0.86–1.12)	0.742
+ Specific therapy[b]	1.26 (0.86–1.86)	0.237	0.55 (0.31–0.98)	**0.042**	1.56 (1.20–2.03)	**0.001**	0.94 (0.82–1.08)	0.386

CI, confidence interval; EDT, E-wave deceleration time; HR, hazard ratio; INR, international normalized ratio; IVC, inferior vena cava; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LV GLS, left ventricular global longitudinal strain; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PASP, pulmonary artery systolic pressure; TAPSE, tricuspid annular plane systolic excursion; VKA, vitamin K antagonist.

[a]The main model was developed with the inclusion of age, type of amyloidosis (immunoglobulin light chain vs. transthyretin), systolic blood pressure, previous heart failure hospitalization, estimated glomerular filtration rate, high-sensitivity troponin T, furosemide and heart failure with preserved ejection fraction scores.

[b]Specific therapy refers to tafamidis or patisiran in the case of transthyretin cardiac amyloidosis whereas it refers to chemotherapy in patients with immunoglobulin light chain cardiac amyloidosis.

Similarly, natriuretic peptides are disproportionally elevated to the degree of HF in CA.[18] Thus, the HFA-PEFF score may be more effective in identifying patients with HFpEF and CA, including the challenging scenario of AL-CA.

It must be acknowledged that the diagnosis of HFpEF is challenging and the broad clinical applicability of these score-based algorithms remains limited. The most recently published ESC guidelines for the management of HF highlight the variability of their diagnostic performance. Furthermore, the access to all the specialized tests recommended by the two algorithms may be limited in several centres, namely in those patients resulting at intermediate probability of HFpEF and requiring heart catheterization (at rest or during exercise) or non-invasive diastolic stress test.[3]

Several retrospective studies showed that HFpEF scores were associated with outcomes in HFpEF[11] as well as in the general population with cardiovascular risk factors.[12,13,15,16] In our cohort, HFA-PEFF score values, but not H_2FPEF, independently predicted mortality in patients with CA. Importantly, the HFA-PEFF score showed an independent prognostic value, over each single variable included in the score and beyond other traditional predictors of mortality in CA. Our finding that the H_2FPEF score was not independently associated with outcome differs from previous studies, which were nonetheless conducted in different HFpEF phenotypes. In addition, the higher proportion of patients with AL-CA in the low H_2FPEF group may have affected the results. AL-CA is a strong predictor of poorer outcome with a 3.6-fold increased risk of mortality, in agreement with previous findings.[35–37] About one fifth of patients with AL-CA had a low H_2FPEF score. Thus, the HFA-PEFF score may provide a greater advantage in this high-risk population, with an early diagnosis that possibly allows a timely targeted treatment with a consequent improvement in prognosis.

As for other predictors of outcome, LVEF did not predict survival in our cohort with LVEF ≥50%, whereas reduction in systolic longitudinal function, which presents early in the disease process, was confirmed as a predictor of all-cause death, in line with previous reports (HR for GLS 1.07; 95% CI 1.01–1.13; $p = 0.022$).[38] LVEF is typically preserved in the early stages of the disease, and then deteriorates with disease progression, identifying patients at higher risk.[39] A somehow unexpected finding of our study is that estimated glomerular filtration rate (eGFR) did not reach statistical significance as an independent predictor of mortality ($p = 0.061$), in contrast with the literature.[28,40] Particularly, the Gillmore staging system, the gold standard for prognostic evaluation in patients with ATTR-CA, considers NT-proBNP and eGFR for prognostic stratification. Compared to previous studies, we considered eGFR as a continuous, and not as a dichotomous, variable. In addition, the results are likely influenced by the exclusion of patients with a more advanced disease stage (those with LVEF <50% and, thus, with a more evident cardio-renal syndrome). Furthermore, when applied to our population, the Gillmore and Mayo staging systems were confirmed as predictors of outcome with a higher accuracy than HFpEF scores, confirming the primary role of HFpEF scores as diagnostic tools.

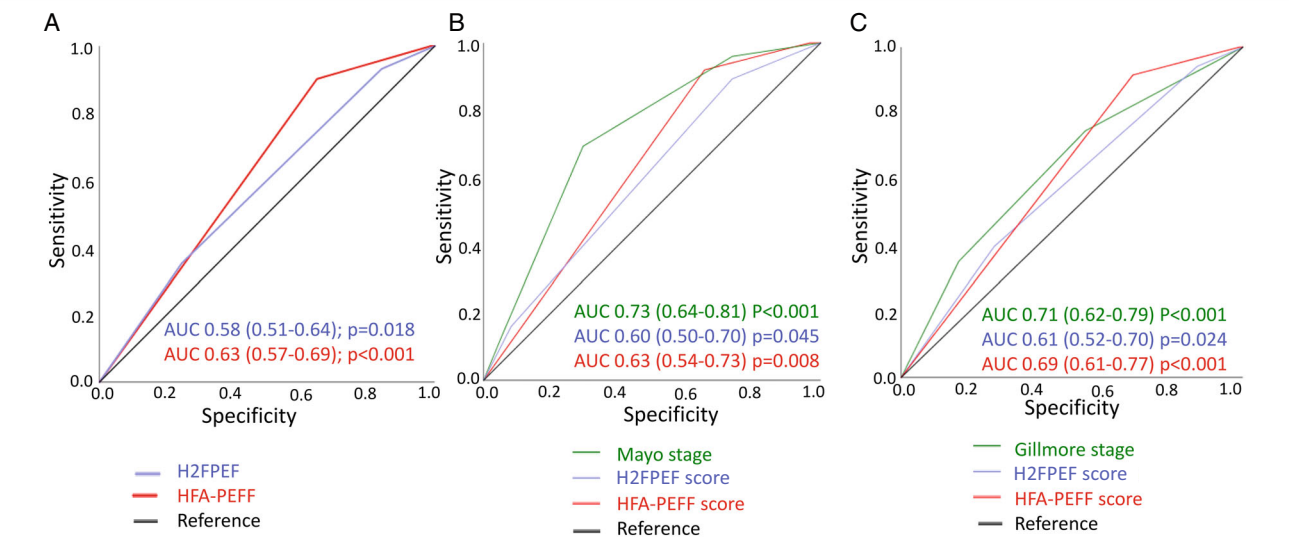


Figure 4 (*A*) Receiver operating characteristic curves for HFA-PEFF and H_2FPEF scores to predict all-cause mortality in the whole population. (*B*) Receiver operating characteristic curves for survival in immunoglobulin light-chain cardiac amyloidosis patients (Mayo staging system vs. H_2FPEF score vs. HFA-PEFF score). (*C*) Receiver operating characteristic curves for survival in transthyretin cardiac amyloidosis patients (Gillmore staging system vs. H_2FPEF score vs. HFA-PEFF score). AUC, area under the curve.

Cardiac biomarkers (i.e. hs-TnT and NT-proBNP) were independent predictors of mortality. Several studies have described the prognostic role of troponin and NT-proBNP in CA and, more recently, their integration in a multi-parametric prognostic score with other clinical and imaging variables has been proposed.[41–43]

Limitations

Several limitations should be acknowledged. First, we evaluated the diagnostic utility of the HFA-PEFF and H_2FPEF scores in a population with an established diagnosis of CA, although this did not allow to test its diagnostic accuracy as normal subjects or subjects without CA or HFpEF were not included. This was a retrospective study assessing a highly specific setting, namely only patients with HFpEF and CA. Second, some data were missing; namely, some echocardiographic parameters (i.e. RV volumes and RV fractional area change) were not routinely performed in the three centres and were only available in a small number of patients. Thus, these variables could not be explored as potential prognostic factors. Third, we evaluated a cohort of patients with both ATTR-CA and AL-CA, which are characterized by a different natural history. However, we have adjusted for the AL-CA diagnosis in the Cox model and separately evaluated the two scores in the two subpopulations without significant differences.

Conclusions

In patients with HFpEF caused by CA, the HFA-PEFF score has a higher diagnostic and prognostic utility, compared to the H_2FPEF score. On the whole, a low HFA-PEFF score successfully rules out CA, while the majority of patients with CA show a high HFA-PEFF score, confirming HFpEF diagnosis. On the other hand, some CA patients present a low H_2FPEF score, potentially misleading the diagnosis, and the majority had an intermediate H_2FPEF score, requiring further investigations. HFA-PEFF, but not H_2FPEF score values independently predicted mortality.

Supplementary Information

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

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Conflict of interest: none declared.

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