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Validation of the MEDIA echo score for the prognosis of heart failure with preserved ejection fraction

Short title: MEDIA echo score in HFpEF

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Abstract (word count 250)

Background: There is currently no widely used prognostic score in heart failure with preserved ejection fraction (HFpEF). The MEDIA echo score, including four variables [pulmonary arterial systolic pressure >40 mmHg, inferior vena cava collapsibility index $<50\%$, average E/e' >9 , and lateral mitral annular s' <7 cm/s] has been proposed as a useful risk stratification tool. This study aimed at further validating the MEDIA echo score in both hospitalised and ambulatory HFpEF patients.

Methods: the MEDIA echo score ranges from 0 to 4 (each criterion score 1 point). The associations between MEDIA echo score and cardiovascular outcomes were assessed in two independent HFpEF cohorts, namely patients hospitalised for worsening HFpEF (N=242, mean age 78 ± 11) and stable ambulatory HFpEF patients (N=72, mean age 65 ± 8).

Results: Using multivariable Cox models, in the worsening HFpEF cohort, patients with a MEDIA echo score 3-4 displayed a significant increased risk of death (HR 2.10, 95%CI 1.02–4.33, $P=0.043$, score 0-1 as reference). In the ambulatory HFpEF cohort, patients with a MEDIA echo score ≥ 2 had a significantly higher risk of death or HF hospitalisation (HR 3.44, 95%CI 1.27–9.30, $P=0.015$, score 0 as reference), driven by HF hospitalisation; in that cohort, adding the MEDIA echo score to the clinical model significantly improved reclassification for the combined endpoint (integrated discrimination improvement 6.2%, $P=0.006$).

Conclusions: The MEDIA echo score significantly predicted the outcome of HFpEF patients in both hospital and ambulatory settings; its use may help refine routine risk-stratification on top of well-established prognosticators in stable HFpEF patients.

Keywords Heart failure with preserved ejection fraction; MEDIA echo score; prognosis; acute setting, outpatient setting

Abbreviations

HF, heart failure

HFpEF, heart failure with preserved ejection fraction

LV, left ventricular

LVEF, left ventricular ejection fraction

HFrEF, Heart failure with reduced ejection fraction

PASP, pulmonary arterial systolic pressure

IVC, inferior vena cava

SV, stroke volume

LAVi, left atrial volume index

DT, deceleration time

TDI, tissue Doppler imaging

TAPSE, Tricuspid annular peak systolic excursion

TRV, tricuspid regurgitation velocity

eGFR, estimated glomerular filtration rate

ANOVA, analysis of variance test

BMI, body mass index

NRI, net reclassification improvement

IDI, integrated discriminative improvement

Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) accounts for approximately half of HF burden in both outpatient and inpatient settings^{1, 2}, and is increasingly recognised as a leading cause of morbidity and mortality³⁻⁵. Currently, European HF Guidelines define HFpEF according to the contemporary presence of: i) HF signs/symptoms, ii) preserved (i.e. $\geq 50\%$) left ventricular (LV) ejection fraction (LVEF), along with, iii) structural heart disease and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/increased LV filling pressures, including elevated natriuretic peptides⁶. Prognosis of HFpEF patients is generally perceived as better than that observed in HF with reduced ejection fraction (HFrEF)⁶; however, observational studies showed that their survival rates are almost superimposable^{5, 7}.

Currently, there is no widely used prognostic score in HFpEF. Several scores have been proposed in the last few years in both acute and chronic settings⁸⁻¹³, based on clinical, echocardiographic and bio-humoral variables.

We have recently developed a simple echocardiographic score (the MEDIA echo score), including four variables [pulmonary arterial systolic pressure (PASP) > 40 mmHg, inferior vena cava (IVC) collapsibility index $< 50\%$, average E/e' > 9 , and lateral mitral annular s' < 7 cm/s]. This score independently predicted clinical outcome (death or cardiovascular hospitalisation) and improved risk stratification in addition to clinical variables (including NT-proBNP) in a cohort of 515 HFpEF patients regardless of the clinical setting (chronic or at discharge for acute HF)¹⁴.

This study aimed to further validate the MEDIA echo score in two independent external cohorts of HFpEF patients (i.e. hospitalised for worsening HF and stable ambulatory patients).

Methods

Participants

In the cohort of hospitalised patients, 242 consecutive patients admitted in Nancy University Hospital for worsening HFpEF between November 2015 and May 2019 were identified using an integrated clinical and research database by the specific coding based on the International Classification of Disease (ICD-9) codes related to HF (I11.0; I50.0; I50.1; I50.9)¹⁵. Clinical data for all patients were extracted from the electronic medical record. The study was approved by the Commission nationale de l'informatique et des libertés (CNIL).

In the stable ambulatory HFpEF cohort, 76 consecutive outpatients referred to the Cardiology Clinic of the Niska Banja Institut were prospectively enrolled between June 2016 and February 2018. Participants were diagnosed according to 2016 European HF guidelines¹⁶; further details have been published elsewhere^{17, 18}. Patients were enrolled in an outpatient setting in order to assess the diagnostic and prognostic value of lung ultrasound coupled with submaximal exercise echocardiography in HFpEF^{18, 19}; baseline data were used for this analysis.

Two-dimensional-tissue Doppler echocardiography and lung ultrasonography

In the hospitalised worsening HFpEF cohort, echocardiography examinations were performed using a standard echocardiography machine (Vivid 9, E95; GE Vingmed Ultrasound AS, Horten, Norway) and reviewed using dedicated software (EchoPACS PC version 110.1.0, GE Healthcare). All echocardiographic data were acquired as part of usual clinical management within 3 days of patient admission.

In the stable HFpEF cohort, all patients underwent detailed baseline echocardiographic examination (Esaote-MyLab Alpha eHD Crystalline series 7400). Echocardiographic images, acquired using a 1–4 MHz phased-array probe, were recorded and analysed off-line. All exams were performed by a single operator (D.S.), blinded to the patients' data and who did not take part in their clinical management.

LV structure and function were evaluated from standard apical four-chamber, two-chamber, and parasternal long- and short-axis views. LV dimensions, wall thicknesses, mass and geometry were determined from two-dimensional parasternal short- and long-axis views. LV volumes, stroke volume (SV) and LVEF were calculated using the biplane method of disks (modified Simpson's rule)²⁰. All cardiac chamber volumes and mass measures were indexed to body surface area²⁰. Left atrial volume was assessed by the biplane area-length method from apical 2- and 4-chamber views at end-systole and was indexed to body surface area (LA volume index, LAVi).

Peak velocities of early (E) and late (A) waves of transmitral flow and the E-wave deceleration time (DT), were measured from the pulsed-wave Doppler obtained between the tips of the mitral leaflets. Septal and lateral mitral annular velocities (for measurement of e' and s') were obtained by pulsed tissue Doppler imaging (TDI). Average E/e' ratio was calculated using the peak E-wave velocity and the average of septal and lateral e'²¹.

Right ventricular function was estimated by measuring tricuspid annular plane peak systolic excursion (TAPSE, in mm) while PASP was estimated by adding the trans-tricuspid valve gradient [by using the Bernoulli formula according to tricuspid regurgitation velocity (TRV)] to estimated right atrial pressures (according to the maximum diameter of the IVC and IVC collapsibility index)²¹. The IVC collapsibility index was calculated as follows: (maximum diameter on expiration – minimum diameter on inspiration)/maximum diameter on expiration x100²².

Laboratory examinations

In both cohorts, peripheral venous baseline blood samples were obtained to determine blood count, sodium, potassium, creatinine [and estimated glomerular filtration rate (eGFR) by modification of diet in renal disease], and BNP. BNP concentrations were assessed by ALERETM Triage® BNP MeterPro Assay (Alere San Diego Inc., San Diego, California).

Statistical methods

The MEDIA echo score is the key variable and was calculated by taking into account the following four variables: i) PASP) > 40 mmHg, ii) IVC collapsibility index <50%, iii) average E/e' > 9, and iv) lateral mitral annular s' < 7 cm/s. Each criterion scores 1 point, resulting in a score ranging from 0 to 4.

Continuous variables are expressed as mean \pm standard deviation, and categorical variables as number and percentage. Missing data were not taken into account for the calculation of the percentages. The characteristics of the study population were described and compared according to the MEDIA echo score categories, ranging from 0 to 4 in the acute HFpEF cohort, and from 0 to 2 in the stable cohort. Differences in baseline characteristics were assessed by analysis of variance (ANOVA) or Kruskal-Wallis test for continuous variables, and by chi-square test or Fisher's exact test for categorical variables, as appropriate. Event rates by MEDIA echo score levels were analysed using the Kaplan-Meier method and survival curves were compared using the log-rank test.

The two co-primary endpoints for this analysis were i) all-cause death and ii) its composite with hospitalisation for HF during follow-up. Secondary endpoint was HF hospitalisation.

Univariable and multivariable Cox proportional hazard models were performed to assess the association between MEDIA echo score and the two co-primary endpoints. Two types of Cox models were constructed: univariable and multivariable (adjusted for age and eGFR). A score equal to 0 or 1 was taken as reference in the acute HFpEF cohort, and a score equal to 0 was taken as reference in the ambulatory cohort.

The hazard ratios are reported with their 95% confidence interval. In addition, integrated discrimination improvement (IDI) and continuous net reclassification improvement (cNRI) were performed to assess the additive prognostic value of the MEDIA echo score on top of the aforementioned clinical models.

With respect to the key variable, data were complete in the stable HFpEF cohort. In the acute HFpEF cohort, 55/242 (22.7%) patients had 1 missing criterion (N=6 for PASP > 40 mmHg, N=24 for IVC collapsibility index <50%, N=1 for average E/e' > 9, N=24 for lateral mitral annular s' < 7). Secondary analyses were performed in the subgroup with complete data (N=187). All statistical analyses were performed using SAS software and R version 3.6.1 (the R foundation for Statistical Computing). The two-sided significance level was set at p <0.05.

Results

Patient characteristics

The main clinical and echocardiographic characteristics of patients hospitalised for worsening HFpEF (N=242) and patients with stable ambulatory HFpEF (N=76) according to MEDIA echo score are provided in Tables 1 and 2. Distributions of MEDIA echo score in the cohorts are shown in *Figure S1*.

Hospitalised worsening HFpEF patients were 78±11 years old and had elevated values of both BNP (871.8±873.4 pg/ml) and average E/e' ratio (14.8±5.8) (*Tables 1 and 2*). Patients with a higher MEDIA score were older, had worse eGFR, and had higher BNP concentrations (all P-values <0.03, *Table 1*). They also had higher E/e' ratios (lateral, medial, and average) as well as higher indices of estimated pulmonary pressure (TR velocity and gradient, PASP) and IVC diameter (all P-values <0.05, *Table 2*).

Stable ambulatory HFpEF patients were 65±8 years old, and had a mean BNP value of 47.6±41.1 pg/ml while average E/e' ratio was 7.8±2.3 (*Tables 1 and 2*). There were no significant differences with respect to clinical and demographic characteristics according to MEDIA score, except a borderline significance for diabetes (*Table 1*). Patients with a higher MEDIA score had higher values of LV end-diastolic volume, A-wave velocity, lateral E/e' ratio, LAVi and SV (all P-values <0.02, *Table 2*). Since the above variables are part of the MEDIA echo score, these patients

were also more likely to have a PASP >40 mmHg, an IVC collapsibility index <50%, and an average $E/e' >9$ (all P-values <0.02, *Table 2*).

Prognostic value of the MEDIA echo score in patients hospitalised for worsening HFpEF

In the cohort of patients hospitalised for worsening HFpEF (mean follow-up 15.8 ± 10.4 months), 115 (47.7%) experienced a combined event (61 HF hospitalisations and 75 deaths). The 2-year risk of death was higher in patients with MEDIA echo scores of 3-4 (45.5%) and 2 (30.7%) compared with the MEDIA echo score 0-1 subgroup (20.5%), with significant differences across groups (log rank P-value=0.008; Panel A, Figure). Differences were not significant when considering the combined outcome (log rank P value=0.51; Panel A, Figure).

In survival models, the subgroup with a MEDIA echo score 3-4 (HR 2.45, 95% CI 1.20–5.00, P=0.014) displayed significant associations with the risk of death when taking the subgroup with score 0-1 as reference (*Table 3*), with significant associations persisting after model-adjustment (HR 2.10, 95% CI 1.02–4.33, P=0.043) (*Table 3*). No significant associations were observed for the combined endpoint (*Table 3*).

Prognostic value of the MEDIA echo score in patients with stable ambulatory HFpEF

In the stable ambulatory HFpEF cohort (mean follow-up 22.5 ± 3.9 months), 33 (43.4%) had a combined event (32 HF hospitalisations and 11 deaths). Overall, there were no significant differences across MEDIA echo score subgroups with regard to death (log rank P-value=0.63; Panel B, Figure). Patients with a MEDIA echo score 2 (20.0%) had a marginally higher event-rate when compared with those with MEDIA echo scores 0 (17.8%) and 1 (10.5%). Greater marked differences were observed when considering the combined endpoint: patients with a MEDIA score 2 displayed a higher 2-year risk of death or HF hospitalisation (70.0%) when compared with patients with score 1

(42.1%) or 0 (35.7%), with a trend toward statistical significance for overall comparison (log rank P-value=0.09; Panel B, Figure).

In survival models, no significant associations between MEDIA echo score and death were observed (Table 3). In contrast, patients with a MEDIA echo score 2 were significantly at a higher risk of combined endpoint (HR 2.72, 95% CI 1.03–7.18, P=0.043) when taking the subgroup with score 0 as reference (Table 3). Significant associations were also observed after model-adjustment (HR 3.44, 95% CI 1.27–9.30, P=0.015) (Table 3). This association was mainly driven by a higher risk of HF hospitalisation (HR 3.39, 95% CI 1.25–9.17, P=0.016) (Table S1)

Improvement in reclassification associated with MEDIA echo score

In the cohort of patients hospitalised for worsening HFpEF, addition of the MEDIA echo score to clinical model 1 (including age, estimated glomerular filtration rate) was not associated with a significant improvement in reclassification (IDI P-values for both endpoints >0.25, NRI P-values for both endpoints >0.2).

In contrast, in the stable ambulatory HFpEF cohort, addition of the MEDIA echo score to clinical model 1 was associated with a significant improvement in reclassification for the combined endpoint (IDI 6.2%, P=0.006; continuous NRI 14.2%, P =0.068). Associations were overall not significant for death (IDI 1.7%, P=0.28; continuous NRI 28.3%, P=0.24).

Discussion

The present study showed that the MEDIA echo score significantly predicted adverse outcome in HFpEF patients in different settings (hospitalised for worsening HF or ambulatory patients). More specifically, the MEDIA echo score was significantly associated with death but not with the risk of HF re-hospitalisation in patients with HFpEF, as assessed during the early phase of an HF hospitalisation (within 3 days after admission). On the other hand, the echo score was associated

with the combined endpoint (death or HF hospitalisation) in the ambulatory HFpEF cohort, an effect driven by HF hospitalisation, with no significant association with mortality.

This apparently diverging prognostic ability of the MEDIA echo score, consisting of an integrated echocardiographic score including parameters of elevated LV filling pressures, systemic venous congestion and LV dysfunction, is not surprising. In our cohort of hospitalised patients, the echocardiographic assessment was performed during the early stages of hospital admission, which more likely reflects HFpEF disease severity and its associated mortality risk. Additionally, in an acute setting, the risk of HF re-hospitalisation is probably more related to residual congestion at discharge than to congestive status upon admission. In our ambulatory HFpEF cohort, we did not find a significant association between MEDIA echo score and risk of death; however this finding is likely related to the relatively low mortality rate (~ 15%) observed at long-term in our cohort of stable HFpEF patients, also when compared with the event-rate of the hospitalised HFpEF cohort (~ 31%). Additionally, in the stable HFpEF cohort, the MEDIA echo score provided additive prognostic information (as assessed with IDI) on top of other established prognosticators with respect to the combined endpoint of death or HF hospitalisation. These findings suggest that the MEDIA echo score could be useful in stratifying the risk of HFpEF patients.

Comparison with other prognostic scores in heart failure with preserved ejection fraction

Nowadays, no echocardiographic prognostic score has had some application in HFpEF, as opposed to HFrEF, for which both echo score and prognostic models have been proposed^{23, 24}.

During the last two decades, several scores have been proposed, mostly relying on clinical or bio-humoral variables^{8-10, 12, 13}. Older age, eGFR, natriuretic peptides, atrial fibrillation, history of diabetes or chronic obstructive pulmonary disease and BMI were among the strongest independent prognosticators proposed in these scores. This is not surprising as these comorbidities (mainly non-cardiac, with high prevalence in HFpEF) are of prognostic importance in this elderly population⁷.

Transthoracic echocardiography is “recommended as the key investigation for the assessment of cardiac function” according to latest European HF Guidelines⁶. This technique is easily performed at bedside, and data are routinely acquired and available for analysis.

The HFA-PEFF score, which has been proposed in the 2019 European Recommendations on HFpEF diagnosis as part of the main diagnostic algorithm, includes functional (septal $e' < 7$ cm/s or lateral $e' < 10$ cm/s, average $E/e' \geq 15$, PASP > 35 mmHg) and morphological (increased LAVi or increased LV mass index and relative wall thickness > 0.42) echocardiographic data²⁵. The prognostic value of discharge HFA-PEFF score, which integrates a set of echocardiographic variables together with natriuretic peptides, was recently shown to be significantly associated with death or HF hospitalisation in a cohort of acutely decompensated HFpEF patients (N=804)¹¹. However, the discriminative performance of the score in this setting was low (C statistics=0.58). Taking into account that the HFA-PEFF score includes NT-proBNP cut-offs which are taken as reference in non-acute settings, this score needs to be further validated in a stable setting. In our previous seminal study¹⁴, the predictive accuracy of the MEDIA echo score (C-index= 0.703) was significantly higher than that of the HFA-PEFF score [C-index 0.611, delta C-index 0.092, P=0.03].

The H2FPEF score proposed for the diagnosis of HFpEF in 2018 include echocardiographic variables (pulmonary arterial systolic pressure, $E/e' > 9$)²⁶, and showed prognostic value in acute settings¹². We previously showed that the predictive accuracy of the MEDIA echo score was superior when compared with the H2FPEF score (delta C-index 0.120, P < 0.001) in the MEDIA cohort (N=515, approx. 90% with stable HFpEF)¹⁴.

Prognostic value of indices of systolic dysfunction in heart failure with preserved ejection fraction

Lateral mitral annular $s' < 7$ cm/s is one of the 4 variables of the MEDIA echo score. In patients with HFpEF, the value of impaired longitudinal systolic function methods has been demonstrated²⁷. A large meta-analysis by Morris et al.²⁸ including 2284 patients with HFpEF and

2302 controls showed that LV systolic function as assessed by longitudinal strain was altered in approximately two-thirds of patients with HFpEF, in a significantly different proportion than asymptomatic patients with cardiovascular risk factor; additionally, systolic impairment was found associated with a higher risk of cardiovascular mortality and HF hospitalisation²⁸. LVEF, on the other hand, is a relatively poor marker of systolic function since not sufficiently sensitive to capture subtle and early systolic dysfunction in HFpEF²⁹. Impaired systolic function as assessed by longitudinal strain may contribute to the pathophysiology of HFpEF syndrome; indeed, the former has been associated with biomarkers of increased wall stress (NT-proBNP) and increased fibrosis-collagen synthesis (i.e. circulating PIIINP) in a cohort of 187 patients from the RELAX trial³⁰. In a sub-study of the TOPCAT trial (N=447), impaired longitudinal strain significantly predicted the primary composite endpoint (HF hospitalisation, aborted sudden death, or cardiovascular death) after extensive model-adjustment (adjusted HR 2.14, 95% CI 1.26–3.66; p=0.005), and was also the strongest echocardiographic predictor of adverse outcome³¹.

Prognostic value of echocardiographic estimates of elevated central venous pressure and left ventricular filling pressure

The MEDIA echo score consists of four echocardiographic variables, three of which are mostly associated with elevated LV filling pressures (E/e' , PASP), and systemic venous congestion (IVC diameter and collapsibility)^{20, 21}.

Measurement of the IVC and its collapsibility is a simple technique that can also be easily performed at bedside with a hand-held device³²; a resulting IVC larger than 21 mm and/or that collapses <50% suggests elevated right atrial pressures²⁰. This echocardiographic technique, representing a sensitive tool in detecting systemic venous congestion in HF outpatients³³ and monitoring decongestion in acute HF³⁴, has shown its prognostic role in both acute³⁵ and outpatient settings^{36, 37}, regardless of the degree of systolic dysfunction.

Current recommendations on diagnosis of HFpEF^{6, 25} or diastolic function²¹ are based on E/e' ratio. In particular, recent European HF Guidelines proposed a resting average E/e' ratio >9 as an objective criterion of LV diastolic dysfunction/elevated LV filling pressures⁶. However, the usefulness of E/e' to predict elevated LV filling pressures still remains a matter of scientific discussion³⁸.

In addition to E/e', PASP is included in the MEDIA echo score, which can be considered as an indirect marker of filling pressure. In the present study whereby, in the stable ambulatory HFpEF cohort (76 NYHA I-II patients, mean BNP concentration 47.6 pg/ml), only 2.6% of patients exhibited a PASP >40 mmHg. Taking into account that scores ranged from 0 to 2 in this cohort, the impact of PASP in determining prognosis in this setting appears to be limited. In a sense, these two echocardiographic markers appear to complement one another in different settings, PASP being probably more relevant in acute setting and E/e' being probably more relevant in chronic settings.

Limitations

This is a two-centre cohort study with limited sample size which may limit the generalisability of these results. There may be unknown or unmeasured confounding variables which were not adjusted for, and which could have affected some or all of the observed relationships. We acknowledge that further larger studies are warranted to confirm the associations observed in our study. Patients with atrial fibrillation were excluded in the stable HFpEF cohort because of well-known limitations in the assessment of Doppler diastolic function²¹; however, given the non-negligible prevalence of atrial fibrillation among HFpEF patients⁶, this might partially limit the generalisability of our results. Finally, the lack of significant association between MEDIA echo score and death in the stable HFpEF may have been influenced by an inadequate power, occurring as the result of the relatively small sample size.

Conclusions

In this analysis, we confirm that the MEDIA echo score has prognostic value in two very different settings, namely hospitalised and stable HFpEF. Along with the seminal publication of the MEDIA echo score, the present findings provide strong support for the pleiotropic prognostic value of this tool in patients with HFpEF.

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Disclosure:

Pr Girerd. reports personal fees from AstraZeneca, Bayer, Boehringer, Lilly, Novartis, and Vifor, outside the submitted work. Pr Rossignol reports (outside this manuscript) consulting for Bayer, CinCor, G3P, Idorsia, and KBP; honoraria from Ablative Solutions, AstraZeneca, Bayer, Boehringer-Ingelheim, Corvidia, CVRx, Fresenius, Grunenthal, Novartis, Novo Nordisk, Roche, Relypsa Inc., a Vifor Pharma Group Company, Sanofi, Sequana Medical, Servier, Stealth Peptides, and Vifor Fresenius Medical Care Renal Pharma; Cofounder: CardioRenal. All of the other authors have nothing to declare.

Ethical standards:

Under french law, the analysis of mono-center hospital data do not require written informed consent or ethical committee approval. The study on the ambulatory HFpEF cohort of the Cardiology Clinic of the Niska Banja was approved by the local ethics committee and managed in accordance with Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent.

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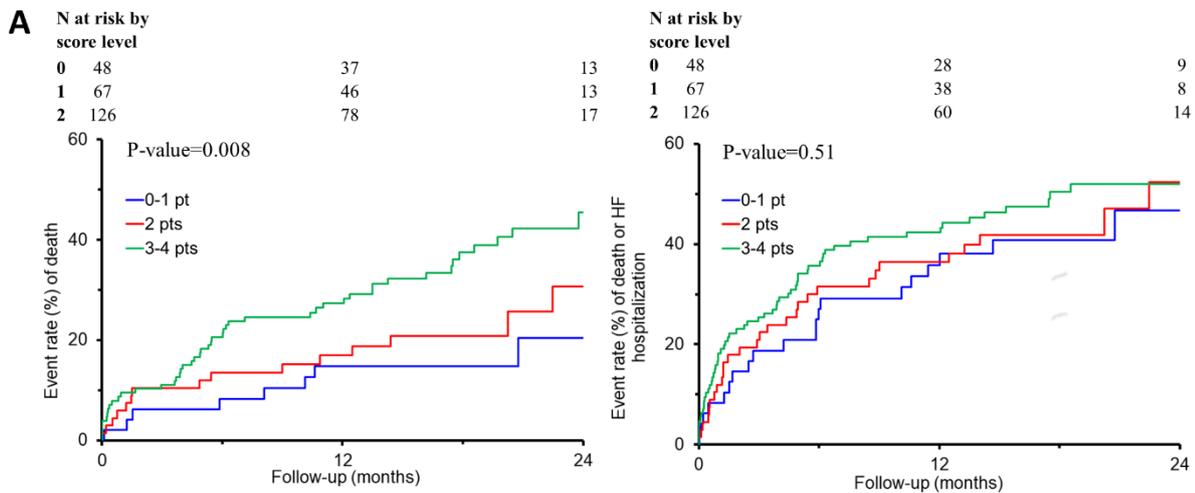
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Figure legends

Hospitalized worsening HFpEF



Stable ambulatory HFpEF

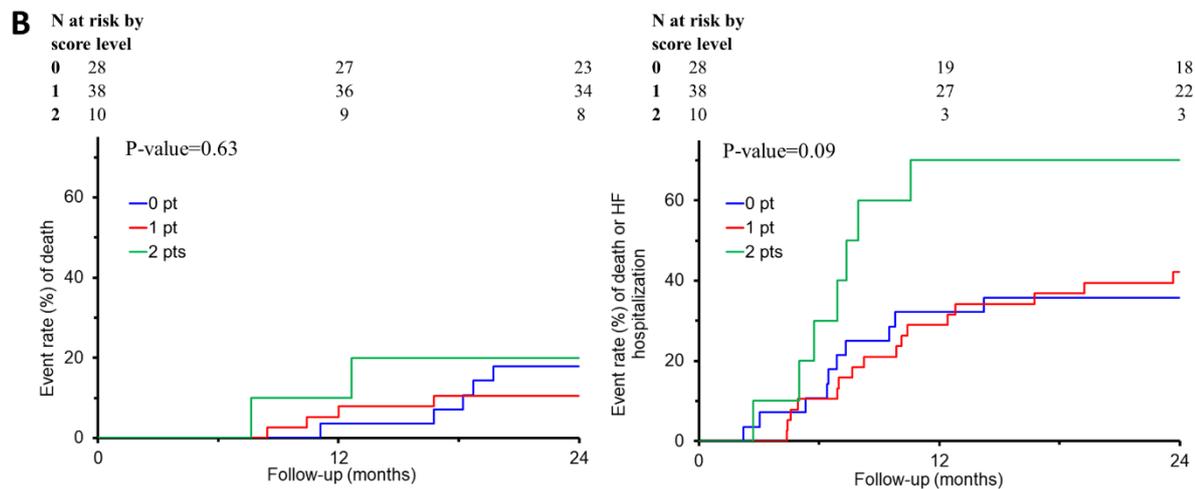


Figure: Kaplan Meier curves for death and for the combined endpoint in the hospitalised for worsening HFpEF (panel A) and stable ambulatory HFpEF (panel B) subgroups according to the MEDIA echo score.

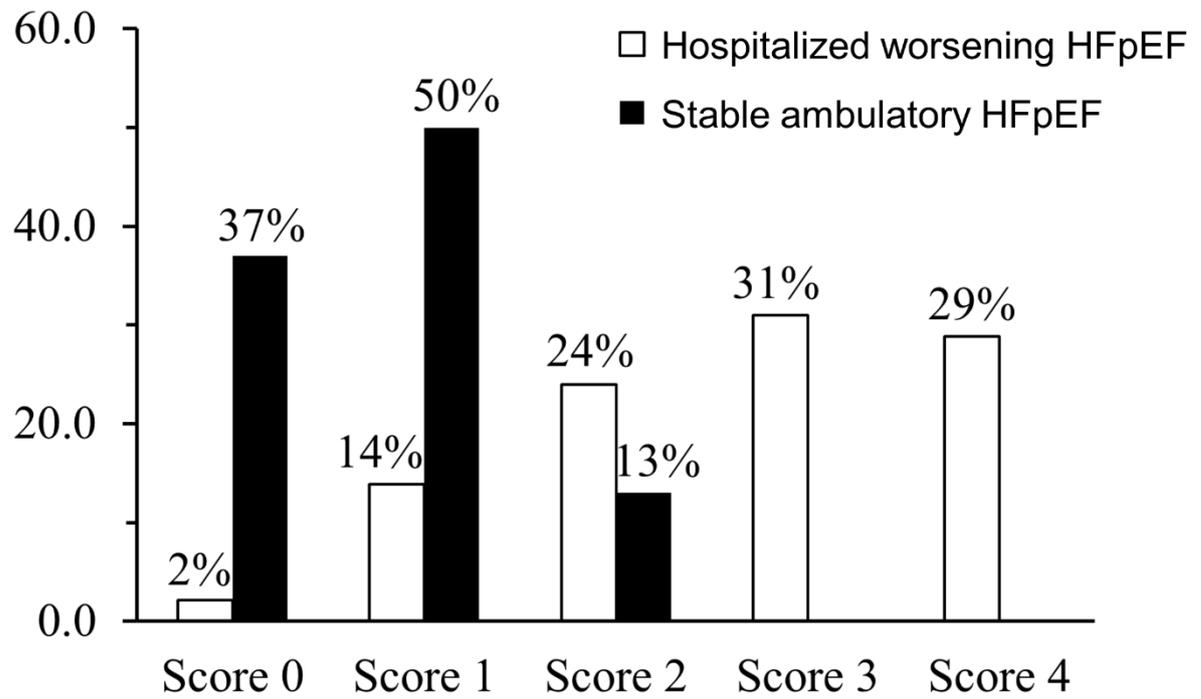


Figure S1: distributions of MEDIA echo score in the two cohorts (hospitalised for worsening HFpEF and stable ambulatory HFpEF).

Table 1. Clinical and demographic characteristics of the total hospitalised worsening and stable ambulatory HFpEF cohorts and according to MEDIA echo score

Variables	Hospitalised HFpEF (n=242)	Score=0/1 (n=48)	Score (67)	=2 Score=3 (n=73)	Score=4 (n=54)	P-value	Stable HFpEF (n=76)	Score 0 (n=28)	Score 1 (n=38)	Score 2 (n=10)	P-value
Age (years)	78 ± 11	76 ± 10	77 ± 12	77 ± 10	81 ± 11	0.018	65 ± 8	64 ± 7	66 ± 8	64 ± 12	0.76
Male sex	114 (47.1 %)	27 (56.3 %)	27 (40.3 %)	34 (46.6 %)	26 (48.1 %)	0.41	34 (44.7%)	11 (39.3 %)	18 (47.4 %)	5 (50.0 %)	
Body mass index (kg/m ²)	27.9 ± 6.5	29.3 ± 8.2	28.2 ± 6.1	28.2 ± 6.0	26.9 ± 5.8	0.53	29.4 ± 3.6	28.9 ± 3.2	30.0 ± 4.0	28.5 ± 2.9	0.37
Heart rate (bpm)	84.3 ± 23.9	87.9 ± 27.6	80.3 ± 18.3	81.9 ± 23.1	82.5 ± 24.8	0.71	65.6 ± 7.3	66.4 ± 6.4	66.0 ± 7.8	61.9 ± 7.7	0.34
Systolic BP (mmHg)	151.1 ± 34.2	153.2 ± 33.7	152.1 ± 35.1	148.5 ± 33.4	149.6 ± 35.6	0.64	124.9 ± 8.4	124.4 ± 8.8	125.8 ± 8.0	122.7 ± 9.4	0.47
Diastolic BP (mmHg)	77.1 ± 17.6	76.1 ± 15.7	77.0 ± 17.4	76.0 ± 16.8	76.1 ± 19.9	0.93	75.0 ± 7.1	74.8 ± 6.9	75.4 ± 7.6	73.7 ± 6.2	0.68
Creatinine (µmol/L)	128.0 ± 87.0	125.0 ± 80.8	115.3 ± 86.9	133.6 ± 82.6	142.7 ± 97.5	0.025	90.02 ± 21.40	88.02 ± 16.72	94.21 ± 24.48	79.72 ± 17.57	0.21
eGFR MDRD	53.0 ± 24.1	57.0 ± 25.8	58.1 ± 25.4	50.4 ± 22.7	46.2 ± 22.5	0.023	79.5 ± 20.7	79.6 ± 18.6	78.7 ± 23.2	82.1 ± 17.0	0.82
Haemoglobin (g/dL)	12.0 ± 2.1	12.4 ± 2.1	12.0 ± 1.9	11.5 ± 2.3	11.9 ± 1.9	0.12	13.4 ± 1.4	13.4 ± 1.4	13.4 ± 1.5	13.1 ± 9.4	0.65
Sodium (mmol/L)	138.8 ± 4.7	138.1 ± 4.1	138.7 ± 5.6	138.6 ± 4.3	140.4 ± 3.8	0.014	143.72 ± 3.27	143.71 ± 2.80	143.87 ± 3.40	143.16 ± 4.18	0.81
Potassium (mmol/L)	4.2 ± 0.6	4.3 ± 0.6	4.2 ± 0.6	4.2 ± 0.7	4.2 ± 0.7	0.94	4.57 ± 0.39	4.53 ± 0.46	4.59 ± 0.33	4.64 ± 0.45	0.79
BNP (pg/mL)	577.5 (351.0 - 1006.0)	353.0 (190.0 - 661.0)	537.0 (289.0 - 810.0)	640.0 (474.0 - 981.0)	671.0 (423.0 - 1418.0)	0.0001	31 (20-57)	29 (19-41)	42 (23-75)	26 (12 - 62)	0.18
ACE-inhibitors	111 (46.3 %)	18 (37.5 %)	36 (53.7 %)	31 (42.5 %)	26 (50.0 %)	0.3	61 (80.3 %)	22 (78.6 %)	31 (81.6 %)	8 (80.0 %)	0.92
ARBs	72 (30.0 %)	15 (31.3 %)	16 (23.9 %)	27 (37.0 %)	14 (26.9 %)	0.37	11 (14.5 %)	6 (21.4 %)	3 (7.9 %)	2 (20.0 %)	0.2
Sacubitril/valsartan	2 (0.8 %)	0 (0.0 %)	1 (1.5 %)	0 (0.0 %)	1 (1.9 %)	0.7	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	NA
Beta-blockers	194 (80.2 %)	32 (66.7 %)	56 (83.6 %)	60 (82.2 %)	46 (85.2 %)	0.092	76 (100 %)	28 (100 %)	38 (100 %)	10 (100 %)	NA
MRA	56 (23.1 %)	10 (20.8 %)	12 (17.9 %)	20 (27.4 %)	14 (25.9 %)	0.54	11 (14.5 %)	3 (10.7 %)	8 (21.1 %)	0 (0.0 %)	0.22
Loop diuretics	207 (85.5 %)	39 (81.3 %)	55 (82.1 %)	64 (87.7 %)	49 (90.7 %)	0.42	65 (85.5 %)	24 (85.7 %)	32 (84.2 %)	9 (90.0 %)	1.00
Medical history/physical examination											
CAD	91 (37.6 %)	16 (33.3 %)	21 (31.3 %)	30 (41.1 %)	24 (44.5 %)	0.63	24 (31.6 %)	8 (28.6 %)	13 (34.2 %)	3 (30.0 %)	0.94
Hypertension	221 (91.3 %)	44 (91.7 %)	61 (91.0 %)	67 (91.8 %)	49 (90.7 %)	1.00	76 (100%)	28 (100 %)	38 (100 %)	10 (100 %)	NA
Dyslipidemia	127 (52.5 %)	24 (50.0 %)	37 (55.2 %)	40 (54.8 %)	26 (48.1 %)	0.84	74 (97.4 %)	28 (100 %)	36 (94.7 %)	10 (100 %)	0.63
Diabetes	105 (43.4 %)	15 (31.3 %)	32 (47.8 %)	42 (57.5 %)	16 (29.6 %)	0.004	28 (36.8 %)	7 (25.0 %)	14 (36.8 %)	7 (70.0 %)	0.045
Atrial fibrillation	73 (30.2 %)	11 (22.9 %)	16 (23.9 %)	23 (31.5 %)	23 (42.6 %)	0.098	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NA
Active smoker	80 (33.1 %)	18 (37.5 %)	22 (32.8 %)	26 (35.6 %)	14 (25.9 %)	0.6	20 (26.3 %)	7 (25.0 %)	11 (28.9 %)	2 (20.0 %)	0.88
Family history of CAD	16 (6.7 %)	2 (4.2 %)	4 (6.0 %)	4 (5.6 %)	6 (11.3 %)	0.54	55 (72.4 %)	20 (71.4 %)	28 (73.7 %)	7 (70.0 %)	1.00
Class I	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)		57 (75.0 %)	22 (78.6 %)	27 (71.1 %)	8 (80.0 %)	
Class II	3 (1.2 %)	2 (4.2 %)	1 (1.5 %)	0 (0.0 %)	0 (0.0 %)		19 (25.0 %)	6 (21.4 %)	11 (28.9 %)	2 (20.0 %)	0.76
Class III	99 (40.9 %)	19 (39.6 %)	25 (37.3 %)	32 (43.8 %)	23 (42.6 %)	0.48	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NA
Class IV	140 (57.9 %)	27 (56.3 %)	41 (61.2 %)	41 (56.2 %)	31 (57.4 %)		0 (0%)	0 (0%)	0 (0%)	0 (0%)	NA
Ankle oedema	169 (69.8 %)	29 (60.4 %)	43 (64.2 %)	53 (72.6 %)	44 (81.5 %)	0.075	27 (35.5 %)	7 (25.0 %)	17 (44.7 %)	3 (30.0 %)	0.28
Jugular vein distension	84 (34.7 %)	14 (29.2 %)	19 (28.4 %)	25 (34.2 %)	26 (48.1 %)	0.11	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	NA
ECG: atrial fibrillation	86 (35.5 %)	14 (29.2 %)	22 (32.8 %)	27 (37.0 %)	23 (42.6 %)	0.52	/	/	/	/	/
ECG: LBBB	17 (7.0 %)	3 (6.3 %)	5 (7.5 %)	5 (6.8 %)	4 (7.4 %)	1.00	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	NA
Outcomes											
Hospital stay (days)	11.1 ± 10.3	10.1 ± 7.1	9.3 ± 10.5	11.2 ± 8.4	12.1 ± 12.0	0.068	/	/	/	/	/
Death	75 (31.1 %)	9 (18.8 %)	17 (25.4 %)	30 (41.1 %)	19 (35.8 %)	0.038	11 (14.5 %)	5 (17.9 %)	4 (10.5 %)	2 (20.0 %)	0.59
HF hospitalisation	61 (25.3 %)	14 (29.2 %)	18 (26.9 %)	14 (19.2 %)	15 (28.3 %)	0.52	32 (42.1 %)	10 (35.7 %)	15 (39.5 %)	7 (70.0 %)	0.17
Death or HF hospitalisation	115 (47.7 %)	22 (45.8 %)	30 (44.8 %)	37 (50.7 %)	26 (49.1 %)	0.9	33 (43.4 %)	10 (35.7 %)	16 (42.1 %)	7 (70.0 %)	0.17

BP, blood pressure; bpm, beats per minutes; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; BNP, B-type natriuretic peptide; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers; MRA, mineralcorticoid receptor antagonist; CAD, coronary artery disease; LBBB, left bundle branch block; HF, heart failure; /, not assessed; NA, not applicable

Table 2. Echocardiographic characteristics of the total hospitalised worsening and stable ambulatory HFpEF cohorts and according to MEDIA echo score

Echocardiographic parameters	Hospitalised HFpEF (n=242)	Score=0/1 (n=48)	Score =2 (67)	Score=3 (n=73)	Score=4 (n=54)	P-value	Stable HFpEF (n=76)	Score 0 (n=28)	Score 1 (n=38)	Score 2 (n=10)	P-value
Septal wall thickness (mm)	12.0 ± 2.4	11.8 ± 2.1	12.0 ± 2.5	12.2 ± 2.1	11.6 ± 2.8	0.45	13.6 ± 1.4	13.5 ± 1.5	13.6 ± 1.4	13.8 ± 1.4	0.84
Posterior wall thickness (mm)	10.8 ± 2.6	10.4 ± 2.2	10.9 ± 2.5	11.1 ± 2.6	10.5 ± 3.1	0.25	11.4 ± 1.2	11.3 ± 1.2	11.4 ± 1.2	11.8 ± 1.0	0.55
LV end-diastolic diameter (mm)	46.0 ± 8.7	45.7 ± 8.8	45.1 ± 9.2	47.1 ± 8.3	47.8 ± 8.3	0.55	50.8 ± 3.7	49.5 ± 3.6	51.8 ± 3.6	50.3 ± 3.6	0.039
LV end-systolic diameter (mm)	32.9 ± 8.2	32.2 ± 7.6	33.1 ± 7.6	34.1 ± 8.0	34.1 ± 8.8	0.8	32.7 ± 3.5	31.8 ± 3.6	33.1 ± 3.5	33.5 ± 2.7	0.22
LV mass index (g/m ²)	107.2 ± 36.4	100.6 ± 38.6	103.5 ± 34.4	113.8 ± 34.7	109.7 ± 41.8	0.14	129.5 ± 25.6	125.1 ± 23.5	129.9 ± 26.9	140.0 ± 25.1	0.27
LVEF (%)	61.9 ± 6.9	63.0 ± 7.4	60.5 ± 6.6	62.3 ± 7.0	61.5 ± 5.9	0.2	57.8 ± 6.5	56.7 ± 6.5	58.2 ± 6.5	59.8 ± 6.4	0.25
Mitral lateral TDI s' (cm/sec)	6.8 ± 1.9	8.2 ± 1.2	6.8 ± 1.6	6.9 ± 2.3	5.5 ± 1.0	< 0.0001	9.7 ± 1.4	9.7 ± 1.3	9.8 ± 1.5	9.4 ± 1.6	0.81
Mitral lateral TDI s' <7 cm/sec	122 (56.0 %)	2 (4.9 %)	32 (54.2 %)	34 (53.1 %)	54 (100 %)	< 0.0001	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	NA
LVEDVi (mL/m ²)	45.1 ± 19.5	45.4 ± 17.2	46.1 ± 23.0	45.7 ± 16.5	45.6 ± 19.0	0.87	44.2 ± 9.1	39.5 ± 8.2	45.9 ± 8.0	51.1 ± 9.7	0.0005
LVESVi (mL/m ²)	17.5 ± 9.7	17.0 ± 8.7	18.8 ± 11.8	17.6 ± 8.1	17.1 ± 7.8	0.93	18.7 ± 4.5	17.4 ± 4.6	19.3 ± 4.5	20.3 ± 3.8	0.11
E-wave (m/s)	100.5 ± 30.4	81.2 ± 22.6	98.8 ± 32.1	108.6 ± 22.8	109.1 ± 29.0	< 0.0001	56.3 ± 14.0	54.4 ± 13.6	56.3 ± 13.4	61.4 ± 17.5	0.55
A-wave (m/s)	80.2 ± 31.6	85.4 ± 28.8	78.2 ± 33.8	77.9 ± 32.3	72.2 ± 25.9	0.3	86.5 ± 19.1	78.8 ± 17.1	88.1 ± 18.3	102.1 ± 17.5	0.001
E/A ratio	1.41 ± 0.74	1.03 ± 0.55	1.41 ± 0.62	1.68 ± 0.86	1.63 ± 0.74	< 0.0001	0.7 ± 0.4	0.7 ± 0.2	0.7 ± 0.5	0.6 ± 0.2	0.17
DT (ms)	195.5 ± 75.8	200.1 ± 74.8	217.0 ± 86.4	187.3 ± 72.5	178.1 ± 71.5	0.018	245.5 ± 73.3	238.8 ± 67.0	243.1 ± 72.0	273.3 ± 94.6	0.64
Lateral e' (cm/s)	8.2 ± 2.6	9.7 ± 2.5	8.1 ± 3.4	7.8 ± 2.1	7.7 ± 2.0	0.0002	8.8 ± 2.5	9.0 ± 2.4	8.6 ± 2.0	8.5 ± 4.3	0.31
Medial e' (cm/s)	6.1 ± 1.9	7.0 ± 1.7	6.5 ± 2.5	5.5 ± 1.6	5.8 ± 1.5	0.014	6.8 ± 2.1	7.3 ± 2.3	6.2 ± 1.6	7.4 ± 2.9	0.11
Average e'	7.2 ± 2.2	8.6 ± 1.9	7.5 ± 3.0	6.5 ± 1.7	6.9 ± 1.5	0.002	7.8 ± 2.1	8.2 ± 2.2	7.4 ± 1.7	8.0 ± 3.4	0.39
Lateral E/e' ratio	13.3 ± 5.8	8.8 ± 3.1	13.9 ± 6.7	14.8 ± 5.0	15.0 ± 5.5	< 0.0001	6.8 ± 2.0	6.2 ± 1.4	6.8 ± 1.9	8.3 ± 2.9	0.013
Medial E/e' ratio	17.7 ± 7.2	12.3 ± 4.5	16.2 ± 7.1	21.7 ± 7.4	19.2 ± 6.3	< 0.0001	8.9 ± 2.9	8.0 ± 2.4	9.4 ± 2.9	9.3 ± 3.8	0.34
Average E/e' ratio	14.8 ± 5.8	9.9 ± 3.2	14.1 ± 6.3	18.0 ± 5.5	15.8 ± 4.4	< 0.0001	7.8 ± 2.3	7.1 ± 1.8	8.1 ± 2.3	8.8 ± 3.1	0.079
Average E/e' >9	115 (85.8 %)	13 (59.1 %)	31 (79.5 %)	38 (100 %)	33 (94.3 %)	< 0.0001	19 (25.0 %)	2 (7.1 %)	13 (34.2 %)	4 (40.0 %)	0.013
Mitral regurgitation grade ≥ 2	86 (36.0 %)	9 (19.1 %)	23 (35.4 %)	28 (38.4 %)	26 (48.1 %)	0.021	/	/	/	/	/
Left atrial area (cm ²)	25.4 ± 9.9	22.5 ± 7.1	25.5 ± 9.0	25.0 ± 7.8	28.5 ± 13.1	0.016	/	/	/	/	/
LAVi (mL/m ²)	52.8 ± 35.2	41.7 ± 17.7	52.9 ± 34.4	52.1 ± 23.4	59.1 ± 50.0	0.048	28.5 ± 7.5	25.1 ± 7.4	30.5 ± 7.1	30.4 ± 6.3	0.01
SV index (mL/m ²)	42.3 ± 16.3	43.5 ± 15.8	41.8 ± 13.9	44.0 ± 16.9	42.6 ± 18.6	0.78	49.4 ± 14.5	42.2 ± 10.8	53.0 ± 14.7	56.0 ± 15.7	0.0007
TAPSE (mm)	19.3 ± 5.0	20.9 ± 4.3	20.3 ± 4.6	18.5 ± 5.3	18.0 ± 5.2	0.002	22.0 ± 2.6	21.8 ± 3.0	22.1 ± 2.5	21.8 ± 1.8	0.88
Tricuspid TDI s' (cm/s)	11.0 ± 2.9	12.2 ± 2.8	11.8 ± 3.0	10.1 ± 2.6	10.2 ± 2.8	< 0.0001	14.1 ± 2.6	14.1 ± 2.9	14.3 ± 2.6	13.5 ± 1.4	0.67
TR velocity (m/s)	3.0 ± 0.6	2.6 ± 0.4	2.8 ± 0.5	3.3 ± 0.5	3.4 ± 0.5	< 0.0001	1.7 ± 0.5	1.7 ± 0.5	1.7 ± 0.5	1.8 ± 0.5	0.97
TR gradient (mmHg)	38.4 ± 14.2	27.4 ± 8.4	31.9 ± 11.5	44.3 ± 13.6	47.0 ± 11.7	< 0.0001	15.3 ± 6.3	13.2 ± 6.2	16.0 ± 5.3	17.1 ± 7.7	0.30
PASP (mmHg)	46.2 ± 17.2	31.2 ± 9.2	37.8 ± 13.8	53.6 ± 15.0	57.9 ± 13.0	< 0.0001	20.7 ± 8.3	18.2 ± 7.2	21.9 ± 8.3	23.0 ± 9.7	0.23
PASP >40 mmHg	75 (31.1 %)	9 (18.8 %)	17 (25.4 %)	30 (41.1 %)	19 (35.8 %)	0.038	2 (2.6 %)	0 (0.0 %)	0 (0.0 %)	2 (20.0 %)	0.016
IVC maximum diameter (mm)	19.8 ± 6.1	15.2 ± 4.7	18.0 ± 6.0	21.7 ± 5.5	22.8 ± 5.5	< 0.0001	19.5 ± 1.4	19.3 ± 1.3	19.6 ± 1.4	19.7 ± 1.4	0.54
IVC collapsibility index <50%	167 (65.6 %)	18 (25.0 %)	38 (47.3 %)	57 (76.8 %)	54 (100.0 %)	< 0.0001	40 (52.6 %)	1 (3.6 %)	29 (76.3 %)	10 (100.0 %)	< 0.0001

LV, left ventricular; LVEF, left ventricular ejection fraction; RWT, relative wall thickness; EDV, end-diastolic volume; ESV, end-systolic volume; DT, deceleration time; LAVi, left atrial volume index; SV, stroke volume; TAPSE, tricuspid annulus plane systolic excursion; TDI, tissue Doppler imaging; TR, tricuspid regurgitation; PASP, pulmonary artery systolic pressure; IVC, inferior vena cava; /, not assessed; NA, not applicable

Table 3. Cox proportional hazards models (univariable and multivariable) for death and for the combined endpoint in the hospitalised worsening and stable ambulatory HFpEF cohorts

Outcome	Parameter	Univariable		Multivariable		
		HR (95% CI)	P-value	Parameter	HR (95% CI)	P-value
Hospitalised worsening HFpEF						
Death	Reference Score=0/1	Ref		Reference Score=0/1	Ref	1.00
	Score 2	1.50 (0.67 - 3.37)	0.32	Score 2	1.58 (0.70 - 3.56)	0.27
	Score 3/4	2.45 (1.20 - 5.00)	0.014	Score 3/4	2.10 (1.02 - 4.33)	0.043
Death or HF hospitalisation	Reference Score=0/1	Ref		Reference Score=0/1	Ref	
	Score 2	1.02 (0.59 - 1.77)	0.94	Score 2	1.10 (0.63 - 1.91)	0.74
	Score 3/4	1.21 (0.75 - 1.97)	0.44	Score 3/4	1.12 (0.69 - 1.83)	0.65
Stable ambulatory HFpEF						
Death	Reference Score=0	Ref		Reference Score=0	Ref	
	Score 1	0.60 (0.16 - 2.24)	0.45	Score 1	0.35 (0.09 - 1.41)	0.14
	Score 2	1.24 (0.24 - 6.41)	0.79	Score 2	0.60 (0.10 - 3.57)	0.58
Death or HF hospitalisation	Reference Score=0			Reference Score=0	Reference Score=0	
	Score 1	1.12 (0.51 - 2.47)	0.77	Score 1	0.98 (0.44 - 2.19)	0.96
	Score 2	2.72 (1.03 - 7.18)	0.043	Score 2	3.44 (1.27 - 9.30)	0.015

HFpEF, heart failure with preserved ejection fraction; HF, heart failure.

Multivariable: model-adjustment for age and estimated glomerular filtration rate