



Universiteit
Leiden
The Netherlands

Left-to-right ventricular volume ratio and outcome in heart failure with preserved ejection fraction

Aimo, A.; Teis, A.; Kasa, G.; Juncà, G.; Lupón, J.; Domingo, M.; ... ; Delgado, V.

Citation

Aimo, A., Teis, A., Kasa, G., Juncà, G., Lupón, J., Domingo, M., ... Delgado, V. (2023). Left-to-right ventricular volume ratio and outcome in heart failure with preserved ejection fraction. *Journal Of Cardiovascular Medicine*, 24(8), 552-560. doi:10.2459/JCM.0000000000001500

Version: Publisher's Version

License: [Creative Commons CC BY-NC-ND 4.0 license](https://creativecommons.org/licenses/by-nc-nd/4.0/)

Downloaded from: <https://hdl.handle.net/1887/3762544>

Note: To cite this publication please use the final published version (if applicable).

Left-to-right ventricular volume ratio and outcome in heart failure with preserved ejection fraction

Alberto Aimo^{a,b}, Albert Teis^c, Gizem Kasa^c, Gladys Juncà^c, Josep Lupón^c, Mar Domingo^c, Elena Ferrer^c, Nuria Vallejo^c, Germán Cediél^c, Pau Codina^c, Jorge López-Ayerbe^c, Georgios Georgiopoulos^{a,f,g}, Nicola Martini^b, Michele Emdin^{a,b}, Antoni Bayes-Genís^{c,d,e}, Claudio Rapezzi^{f,g,h,*} and Victoria Delgado^{c,i}

Background Age-specific and gender-specific reference values for left ventricular (LV) and right ventricle volumes are available. The prognostic implications of the ratio between these volumes in heart failure and preserved ejection fraction (HFpEF) have never been evaluated.

Methods We examined all HFpEF outpatients undergoing a cardiac magnetic resonance from 2011 to 2021. The left-to-right ventricular volume ratio (LRVR) was defined as the ratio between the LV and right ventricle end-diastolic volume indexes (LVEDVi/RVEDVi).

Results Among 159 patients [median age 58 years (interquartile range 49–69), 64% men, LV ejection fraction 60% (54–70%)] the median LRVR was 1.21 (1.07–1.40). Over 3.5 years (1.5–5.0), 23 patients (15%) experienced all-cause death or heart failure hospitalization, and 22 (14%) cardiovascular death or heart failure hospitalization. The risk of all-cause death or heart failure hospitalization increased with an LRVR less than 1.0 or at least 1.4. An LRVR less than 1.0 was associated with a higher risk of all-cause death or heart failure hospitalization [hazard ratio 5.95, 95% confidence interval (CI) 1.67–21.28; $P = 0.006$] and cardiovascular death or heart failure hospitalization (hazard ratio 5.68, 95% CI 1.58–20.35; $P = 0.008$) as compared with LRVR 1.0–1.3. Furthermore, an LRVR at least 1.4 was associated with a higher risk of all-cause

death or heart failure hospitalization (hazard ratio 4.10, 95% CI 1.58–10.61; $P = 0.004$) and cardiovascular death or heart failure hospitalization (hazard ratio 3.71, 95% CI 1.41–9.79; $P = 0.008$) as compared with LRVR 1.0–1.3. These results were confirmed in patients without dilation of either ventricle.

Conclusion LRVR values less than 1.0 or at least 1.4 are associated with worse outcomes in HFpEF. LRVR may become a valuable tool for risk prediction in HFpEF.

J Cardiovasc Med 2023, 24:552–560

Keywords: cardiac magnetic resonance, heart failure, left ventricle, prognosis, ratio, right ventricle

^aScuola Superiore Sant'Anna, ^bCardiology Division, Fondazione Toscana Gabriele Monasterio, Pisa, Italy, ^cHeart Institute, Hospital University Germans Trias i Pujol, Badalona, ^dCIBERCV, Carlos III Institute of Health, Madrid, ^eDepartment of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain, ^fKing's College, London, UK, ^gCardiology Centre, University of Ferrara, Ferrara, ^hMaria Cecilia Hospital, GVM Care & Research, Cotignola (Ravenna), Italy and ⁱDepartment of Cardiology, Leiden University Medical Center, the Netherlands

Correspondence to Alberto Aimo, MD, PhD, FESC, FHFA, Scuola Superiore Sant'Anna and Fondazione Toscana Gabriele Monasterio, Piazza Martiri della Libertà 33, 56124 Pisa, Italy
Tel: +39 50 3153521; fax +39 50 3152109;
e-mail: a.aimo@santannapisa.it, aimoal@ftgm.it

Received 9 January 2023 Revised 24 April 2023
Accepted 26 April 2023

Introduction

The size and function of ventricular chambers may change over time in response to myocardial insults and the beneficial effects of therapies. Asymptomatic left ventricular (LV) dilation is a strong predictor of future heart failure (HF) development.^{1,2} In patients with HF and LV ejection fraction (LVEF) less than 50%, both LV and right ventricular end-diastolic volume indexes (LVEDVi/RVEDVi) have been associated with survival free from death or heart transplantation.³ Furthermore, in patients with heart failure with

preserved ejection fraction (HFpEF) and pulmonary hypertension, an association between RVEDVi and all-cause mortality has been described.⁴ In patients with HF, one or both ventricles may be dilated, and even when both ventricles are not dilated, there may be an imbalance between their volumes. Reference values for the left-to-right ventricular volume ratio (LRVR) in adult patients have been proposed, and are centered on the unit (0.85–1.15 in men, 0.86–1.12 in women),⁵ denoting that the volumes of the LV and right ventricle should be balanced. A comparison between LV and right ventricular size is usually performed just in specific cases with cardiac conditions where the right

* Claudio Rapezzi deceased.

ventricle is primarily affected, and most commonly to differentiate an athlete's heart from arrhythmogenic right ventricular cardiomyopathy.⁶

An echocardiographic study identified the ratio between right ventricular and LV diameters as a predictor of heart failure hospitalization in patients with HFpEF, with an added value beyond clinical and echocardiographic variables and B-type natriuretic peptide.⁷ In this study, we employed cardiovascular magnetic resonance (CMR), as the gold standard technique for volume quantification, to investigate the relationship between the left and right ventricular volumes and more clinically relevant end points (all-cause or cardiovascular mortality and HF hospitalization).

Methods

Patient population

All adult patients with no intracardiac or extracardiac shunt or congenital heart disease diagnosed with HFpEF who underwent a CMR exam at the Hospital Universitari Germans Trias i Pujol (Badalona, Spain) from 2011 to 2021 ($n = 159$) were included. HFpEF was diagnosed according to contemporary European Society of Cardiology (ESC) Guidelines.^{8–13}

Biomarkers were measured at the time of the nearest visit to the Heart Failure Unit of the same Institution. N-terminal pro-B-type natriuretic peptide (NT-proBNP) was measured with the electrochemiluminescence immunoassay (ECLIA) monoclonal assay using the Cobas e411 platform (Roche Diagnostics, Basel, Switzerland). Glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation.

Information about demographic data, comorbidities, biomarkers, and HF therapies was retrieved from electronic health records. The study complied with the law protecting personal data and the international guidelines on clinical investigations from the World Medical Association's Declaration of Helsinki. The local ethics committee approved the study (ethic code REGI-UNIC PI-18–037 and ICOR-2019–04-EB-IDI).

Cardiovascular magnetic resonance

The CMR scans were performed in a 1.5T (Achieva dStream; Philips, the Netherlands) or a 3T (Verio; Siemens Medical Imaging, Erlangen, Germany) scanner, with the patient in the supine position and a 16-element phased-array coil placed over the chest. Images were acquired during breath-holds with ECG gating. We used a segmented k-space steady-state free-precession sequence [repetition time 44.70 ms; echo time 1.26 ms; flip angle 78; matrix 272; spatial resolution $(1.3–1.5) \times (1.3–1.5) \times 8$ mm

depending on the field of view] for cine imaging in parallel short-axis (contiguous slices of 8-mm thickness, 2-mm gap, covering from base to apex) and three long-axis views of the LV. Delayed enhancement images were acquired with a segmented gradient-echo inversion-recovery sequence [repetition time (600–800) ms depending on the cardiac heart rate; echo time $3.24 \times$ ms; flip angle 25; matrix 256; spatial resolution $1.3 \times 1.3 \times 8$ mm] at matching cine-image slice locations 10–20 min after intravenous gadolinium-DTPA administration (0.15 mmol/kg; Gadovist, Bayer Schering Pharma AG, Berlin, Germany).¹⁴ We optimized the inversion time to null the normal myocardium and adjusted views per segment and trigger delay according to the patient's heart rate.

All images were reviewed and analyzed off-line with specialized postprocessing software (Intellispace Portal v8, Philips) blinded to the clinical data and outcome. LV and right ventricular endocardial borders (papillary muscles were excluded) were manually traced on all short-axis cine images at the end-diastolic and end-systolic frames to determine the LV and right ventricular end-diastolic and end-systolic volumes, respectively. LV mass was calculated by subtracting the endocardial volume from the epicardial volume at end diastole and then multiplying by the tissue density (1.05 g/ml).¹⁵ LV and RV end-diastolic volumes (LVEDV/RVEDV) were then indexed by body surface area of the patient, calculated by the DuBois and DuBois formula.¹⁶ The LRVR was defined as the ratio between LVEDVi and RVEDVi.

Late gadolinium enhancement (LGE) was codified as present or absent for each cardiac segment by a level 3 CMR expert. Moreover, pattern of LGE was described as subendocardial, mid-wall, subepicardial, or diffuse according to its location and distribution within the LV wall.^{17,18} LGE extent was codified from 0 to 17 according to the number of segments affected.

Left and right atrial volumes and ejection fraction were derived off-line from long-axis cine CMR images using QStrain (Medis, the Netherlands) by tracing the left and right end-diastolic and end-systolic atrial wall, respectively.

Follow-up

All patients were followed up regularly at the HF clinic according to their clinical needs and treated according to a unified protocol, based on contemporary ESC HF guideline recommendations.^{8–13} Follow-up visits included a minimum of one visit with a nurse every 3 months and one visit with a physician (cardiologist, internist, or family physician) every 6 months, as well as additional visits with other specialties as needed.

Study end points

The end points were the composite of all-cause death or HF hospitalization, and cardiovascular death or HF hospitalization. The definition of cardiovascular death conformed to the 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials [‘deaths that result from an (acute myocardial infarction), sudden cardiac death, death due to HF, death due to stroke, death due to CV procedures, death due to CV hemorrhage, and death due to other CV causes’].¹⁹ Fatal events were identified from the clinical records of patients with HF, hospital wards, the emergency room, general practitioners, and by contacting the patient's relatives and adjudicated by an ad hoc committee. Possible discrepancies about the main cause of death were solved through discussion. Data were verified by the databases of the Catalan and Spanish Health Systems and the Spanish National Death Registry (INDEF) by the same authors. Hospitalizations were identified from the clinic records of patients with HF, hospital wards, and the electronic Catalan history record. As an additional end point, we evaluated repeated hospitalizations. Follow-up was closed on 31 December 2021.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics (version 22, 2013) and R (<http://www.r-project.org/>, version 3.2.3, 2015). Normal distribution was assessed by plotting a histogram and running the Shapiro–Wilk test. Variables with normal distribution were presented as mean $\pm$ standard deviation, while those with nonnormal distribution were presented as median and interquartile interval. Mean differences among groups were evaluated through the unpaired Student's *t*-test, the Mann–Whitney *U* test or the one-way ANOVA test, as appropriate. Discrete variables were compared by the chi-square test with Yates correction or the Fisher exact test. The ‘one-in-ten’ rule was followed to avoid model overfitting.²⁰ Cubic spline interpolation was carried out to represent the change in risk of the combined end point according to the LRVr; five knots were considered. Cut-off values corresponding to hazard ratio = 1 were identified. Patient survival according to these cut-off values was assessed through the log-rank test (Mantel–Cox) on Kaplan–Meier curves. The crude incidence of HF hospitalizations was calculated. The incidence of HF hospitalizations was calculated through multivariable binomial negative regression analysis adjusting for age and sex. To increase the robustness of the analysis (i.e. internal validation), we performed bootstrapping with resample clusters and derived bootstrapped 95% CI for the hazard ratios of LRVr categories compared to the reference group across 1,000 replicates. *P*-values <0.05 were deemed statistically significant.

Results

Patient population

The main patient characteristics are reported in Table 1. The median age was 58 years (interquartile range 49–69), and 64% were men. Hypertrophic cardiomyopathy was the most common cause (46%). Despite elevated NT-proBNP levels [512 ng/l (138–1600)], patients were clinically stable, as indirectly confirmed by the low percentage of patients (35%) currently on loop diuretics. At CMR examination, median LVEF was 60% (54–70%), LVEDVi 73 ml/m² (65–87), RVEDVi 62 ml/m² (50–74), and LRVr 1.21 (1.07–1.40).

Left-to-right ventricular volume ratio and outcomes

Over a 3.5-year follow-up (1.5–5.0), all-cause death or first HF hospitalization occurred in 23 patients (15%) and cardiovascular death or first HF hospitalization in 22 (14%). Specifically, 11 patients died: 5 from cardiovascular causes (HF progression, *n* = 2; sudden cardiac death, *n* = 2; myocardial infarction, *n* = 1), and the other 6 from other causes (COVID-19, *n* = 2; cancer, *n* = 2; decline, *n* = 1; suicide, *n* = 1). Nineteen patients were hospitalized for HF, and nine patients were hospitalized for HF more than once (*n* = 5 with two hospitalizations, *n* = 1 with three hospitalizations, *n* = 2 with four hospitalizations, and *n* = 1 with five hospitalizations).

Spline curve analysis showed a bimodal relationship between LRVr and both outcomes, with a steep increase in risk if the ratio was less than 1.0 and at least 1.4 (Graphical Abstract, <http://links.lww.com/JCM/A536>). Clinical characteristics and HFpEF causes, NT-proBNP values, HF therapies, and most CMR findings, including the presence, extent, and location of LGE, did not differ significantly across the LRVr subgroups (<1.0, 1.0–1.3, $\geq$ 1.4; Table 1 and Supplemental Table 1, <http://links.lww.com/JCM/A537>).

In agreement with spline curve analysis, patients with either LRVr less than 1.0 or at least 1.4 experienced more events (Table 2), and had a much shorter survival free from both end points than patients with LRVr 1.0–1.3 (Fig. 1). LRVr less than 1 was associated with a higher risk of all-cause death or HF hospitalization [hazard ratio 5.95, 95% confidence interval (CI) 1.67–21.28; *P* = 0.006], and a higher risk of cardiovascular death or HF hospitalization (hazard ratio 5.68, 95% CI 1.57–20.37; *P* = 0.009). Furthermore, LRVr at least 1.4 was associated with a higher risk of all-cause death or first HF hospitalization (hazard ratio 4.10, 95% CI 1.58–10.61; *P* = 0.004) and a higher risk of cardiovascular death or first HF hospitalization (hazard ratio 3.70, 95% CI 1.40–9.77; *P* = 0.010). These findings were confirmed after bootstrapping with 1000 replicates: all-cause death or first HF hospitalization, 95% bootstrapped CI 1.25–13.50,

Table 1 Patient characteristics

	HFpEF (n=159)	LRVR <1.0 (n=18) (11%)	LRVR 1.0–1.3 (n=90) (57%)	LRVR ≥1.4 (n=51) (32%)	P
Age (years)	58 (49–69)	58 (50–72)	56 (46–69)	61 (55–69)	0.219
Male sex [n (%)]	102 (64)	13 (72)	58 (64)	31 (61)	0.682
History of CAD [n (%)]	14 (9)	2 (11)	8 (9)	4 (8)	0.914
Hypertension [n (%)]	78 (49)	7 (39)	46 (51)	25 (49)	0.639
Diabetes [n (%)]	33 (21)	4 (22)	18 (20)	11 (22)	0.963
Obesity [n (%)]	54 (34)	5 (28)	30 (33)	19 (37)	0.752
Current or former smoker [n (%)]	70 (44)	8 (44)	41 (46)	21 (41)	0.880
COPD [n (%)]	11 (7)	0 (0)	5 (6)	6 (12)	0.178
Atrial fibrillation/flutter [n (%)]	19 (12)	3 (17)	12 (13)	4 (8)	0.506
eGFR (ml/min/1.73 m ²)	84 (61–100)	72 (31–100)	86 (67–103)	79 (55–99)	0.195
NT-proBNP (ng/l)	512 (138–1600)	627 (288–1700)	401 (132–1022)	601 (92–2891)	0.061
HF duration (months)	3 (1–35)	8 (2–84)	3 (1–28)	11 (0–48)	0.294
HF causes [n (%)]					
Hypertrophic cardiomyopathy	73 (46)	8 (44)	38 (42)	27 (53)	0.118
Dilated cardiomyopathy	27 (17)	0 (0)	19 (21)	8 (16)	
Ischemic cardiomyopathy	11 (7)	0 (0)	8 (9)	3 (6)	
Valve heart disease	7 (4)	3 (17)	2 (2)	2 (4)	
Hypertensive heart disease	6 (4)	1 (6)	3 (3)	2 (4)	
Cardiac amyloidosis	7 (4)	1 (6)	5 (6)	1 (2)	
Other	28 (18)	5 (28)	15 (17)	8 (16)	
HF therapies					
ACEi/ARB/ARNI ^a [n (%)]	73 (46)	7 (39)	41 (46)	25 (49)	0.756
Beta-blocker [n (%)]	97 (61)	7 (39)	57 (63)	33 (65)	0.122
MRA [n (%)]	43 (27)	4 (22)	23 (26)	16 (31)	0.671
Loop diuretic [n (%)]	56 (35)	7 (39)	30 (33)	19 (37)	0.844
CMR					
LVEDVi (ml/m ²)	73 (65–87)	66 (62–72)	74 (64–91)	77 (69–89)	0.033
LVESVi (ml/m ²)	29 (21–38)	26 (19–32)	29 (21–40)	32 (22–39)	0.190
LVSV (ml)	84 (72–105)	73 (66–97)	89 (74–107)	83 (72–111)	0.113
LVEF (%)	60 (54–70)	60 (56–71)	61 (55–69)	57 (53–70)	0.758
LVMI (g/m ²)	74 (58–98)	68 (55–83)	73 (57–93)	93 (69–112)	<0.001
LGE presence [n (%)]	103 (65)	11 (61)	57 (63)	35 (69)	0.771
Segments with LGE (n)	2 (0–4)	1 (0–3)	1 (0–4)	4 (0–5)	0.170
LGE location [n (%)]					
Subendocardial	30 (19)	12 (24)	15 (17)	3 (17)	0.587
Mid-wall	77 (48)	27 (53)	42 (47)	8 (44)	0.725
Subendocardial	6 (4)	1 (2)	5 (6)	0 (0)	0.376
Diffuse	8 (5)	3 (6)	4 (4)	1 (6)	0.927
LAESVi (ml/m ²)	90 (67–116)	83 (61–112)	87 (66–110)	96 (73–120)	0.587
LAEF (%)	49 (38–57)	50 (40–57)	48 (35–57)	49 (28–63)	0.663
RVEDVi (ml/m ²)	62 (50–74)	78 (68–98)	66 (57–79)	49 (44–57)	<0.001
RVESVi (ml/m ²)	20 (14–28)	32 (22–45)	23 (17–31)	15 (11–20)	<0.001
RVSV (ml)	75 (62–89)	90 (79–112)	80 (70–92)	62 (54–72)	<0.001
RVEF (%)	66 (61–73)	58 (54–67)	65 (59–71)	68 (64–76)	0.001
RAESVi (ml/m ²)	66 (48–87)	95 (66–130)	71 (54–93)	48 (41–66)	<0.001
RAEF (%)	44 (31–51)	41 (30–48)	44 (36–52)	34 (26–50)	0.537
LRVR	1.21 (1.07–1.40)	0.90 (0.75–0.93)	1.16 (1.08–1.25)	1.48 (1.41–1.66)	<0.001

^a Five patients with heart failure and recovered ejection fraction. ACEi/ARB/ARNI, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor neprilysin inhibitor; CAD, coronary artery disease; CMR, cardiac magnetic resonance; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LAEF, left atrial ejection fraction; LAESVi, left atrial end-systolic volume index; LGE, late gadolinium enhancement; LRVR, left-to-right ventricular volume ratio; LV, left ventricle; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index; LVMI, left ventricular mass index; LVSV, left ventricular stroke volume; MRA, mineralocorticoid receptor antagonist; RAEF, right atrial ejection fraction; RAESVi, right atrial end-systolic volume index; RV, right ventricle; RVEDVi, right ventricular end-diastolic volume index; RVESVi, right ventricular end-systolic volume index; RVSV, right ventricular stroke volume.

$P=0.02$ for LRVR <1, and 95% bootstrapped CI 3.05–11.60, P less than 0.001 for LRVR at least 1.4; cardiovascular death or first HF hospitalization, 95% bootstrapped CI 1.03–13.32, $P=0.043$ for LRVR less than 1, and 95% bootstrapped CI 2.18–14.94, P less than 0.001 for LRVR at least 1.4.

Nine patients (6%) had more than one HF hospitalization. The crude incidence of HF hospitalizations was much higher in patients with LRVR less than 1.0 (16.7 per 100 patient-years) or at least 1.4 (10.3 per 100 patient-years) than in those with LRVR 1–1.3 (1.9 per 100 patient-years).

years; both $P<0.001$). LRVR less than 1.0 was associated with a much higher risk of HF hospitalizations than patients with LRVR 1.0–1.3 after adjusting for age and gender [incidence rate ratio (IRR) 9.74, 95% CI 4.66–20.37], and LRVR at least 1.4 with a higher risk than patients with LRVR 1.0–1.3 (IRR 7.00, 95% CI 2.20–22.33) (Fig. 2).

Subgroup analysis: patients with no dilation of either ventricle

Twenty-eight patients (18%) had a dilated LV, and 12 (8%) a dilated RV, according to LVEDVi or RVEDVi

Table 2 Patient outcomes

	HFpEF (n = 159)	LRVR <1.0 (n = 18) (11%)	LRVR 1.0–1.3 (n = 90) (57%)	LRVR ≥1.4 (n = 51) (32%)	P
All-cause death or HF hospitalization [n (%)]	23 (15)	4 (22)	7 (8)	12 (24)	0.023
CV death or HF hospitalization [n (%)]	22 (14)	4 (22)	7 (8)	11 (22)	0.036
FU death or HF hospitalization (years)	3.5 (1.5–5.0)	1.9 (0.8–4.3)	3.9 (2.2–5.6)	3.3 (1.5–4.6)	0.011
All-cause death [n (%)]	11 (7)	4 (22)	4 (4)	3 (6)	0.024
CV death [n (%)]	5 (3)	3 (17)	1 (1)	1 (2)	0.018
HF hospitalization [n (%)]	19 (12)	4 (22)	5 (6)	10 (20)	0.017

CV, cardiovascular; FU, follow-up; HFpEF, heart failure with preserved ejection fraction; LRVR, left-to-right ventricular volume ratio; LV, left ventricle; RV, right ventricle.

cut-offs for age and gender (Supplemental Table 2, <http://links.lww.com/JCM/A537>), leaving a total of 127 patients (80%) with no dilation of either ventricle. In this last subgroup, there was a trend toward a bimodal relationship between LRVR and outcome, with a modest increase in risk of all-cause death and first HF hospitalization and cardiovascular death or first HF hospitalization for LRVR values less than 1.1, and a steeper increase in risk of both end points for LRVR at least 1.4.

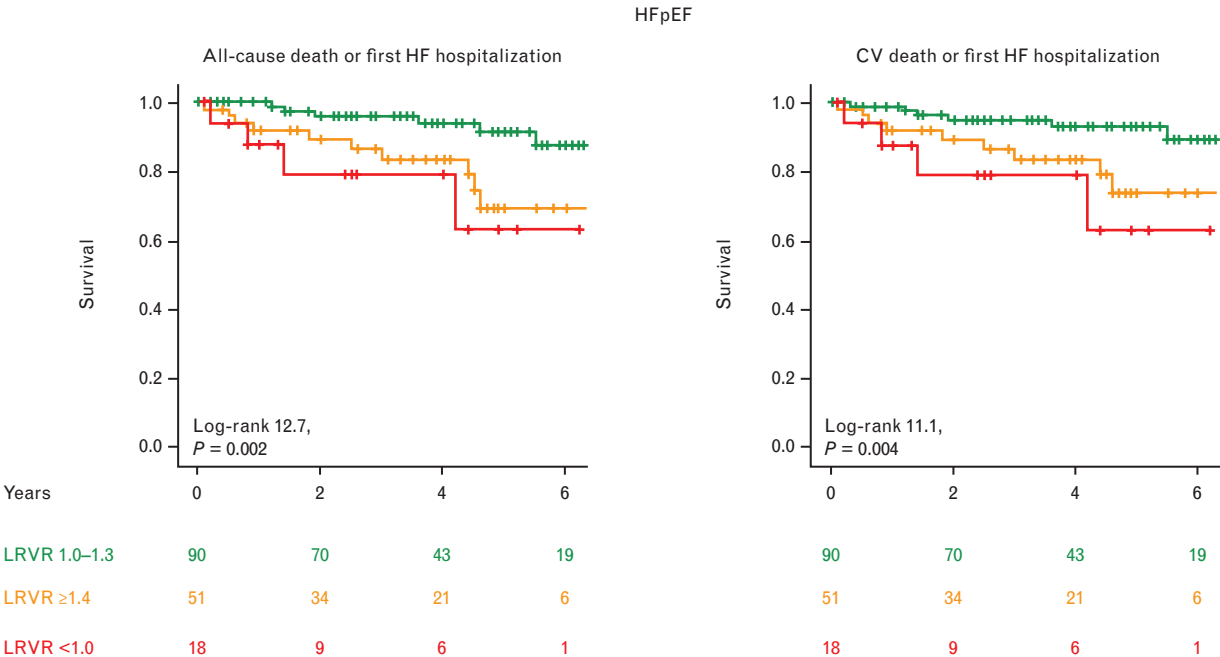
When stratifying patients according to the 1.4 cut-off, those with LRVR at least 1.4 had a shorter survival than those with LRVR less than 1.4 (Fig. 3 and Table 3). Additionally, LRVR at least 1.4 was associated with a higher risk of recurrent HF hospitalizations than patients with LRVR less than 1.4, with a crude incidence of 10.6 per 100 patient/years for LRVR at least 1.4 vs. 1.9 per

100 patient/years for LRVR <1.4 ($P < 0.001$). LRVR at least 1.4 was associated with a higher risk of heart failure hospitalizations than patients with LRVR 1.0–1.3 after adjusting for age and gender (IRR 6.77, 95% CI 1.86–24.68) (Fig. 2).

Discussion

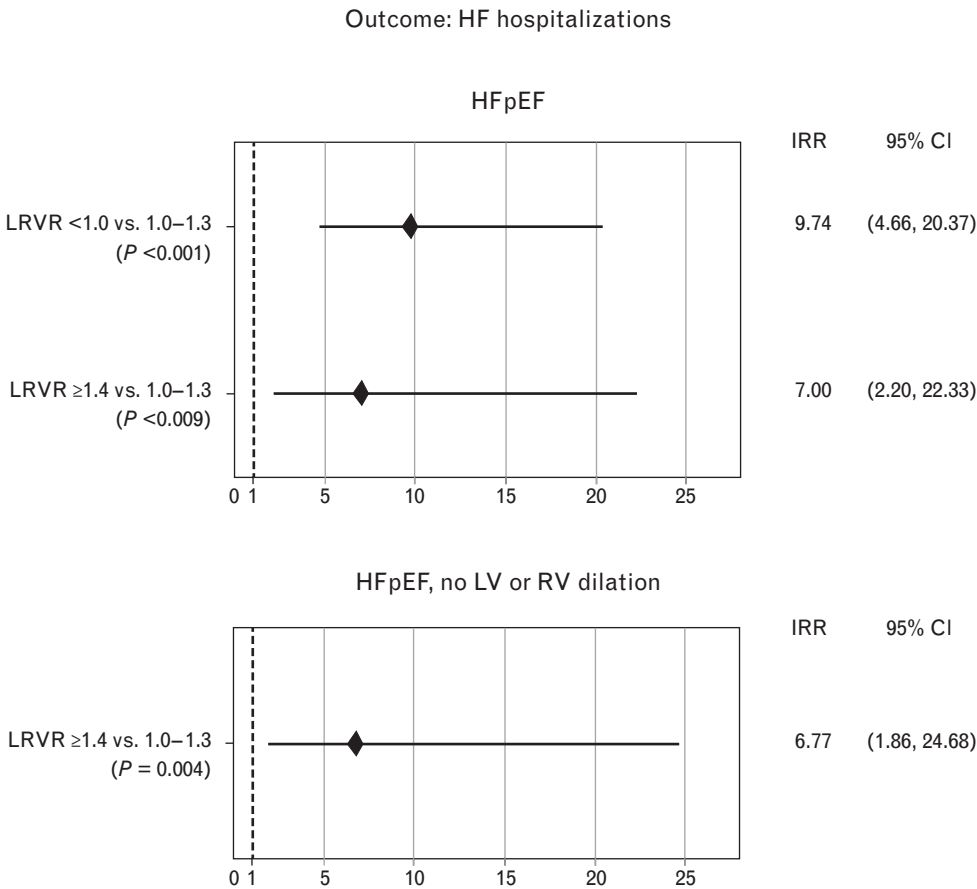
In patients with HFpEF undergoing CMR examination, the LRVR (defined as the ratio between LVEDVi and RVEDVi) displayed a bimodal relationship with the risk of all-cause death or first HF hospitalization or cardiovascular death or HF hospitalization. Low ratio values (i.e. an overt or initial RV dilation with preserved or reduced LV volume) or high values (i.e. an overt or initial LV dilation with preserved or reduced RV volume) were associated with an increased risk for the occurrence of HF hospitalizations, cardiovascular mortality and all-cause death. Three risk categories

Fig. 1



Left-to-right ventricular volume ratio and survival: Kaplan–Meier analysis. The cut-off points derived from spline curve analysis. See text for details. CV, cardiovascular; HFpEF, heart failure with preserved ejection fraction.

Fig. 2



Risk of heart failure hospitalizations according to categories of left-to-right ventricular volume ratio. Multivariable binomial negative regression analysis adjusting for age and sex. CI, confidence interval; IRR, incidence rate ratio.

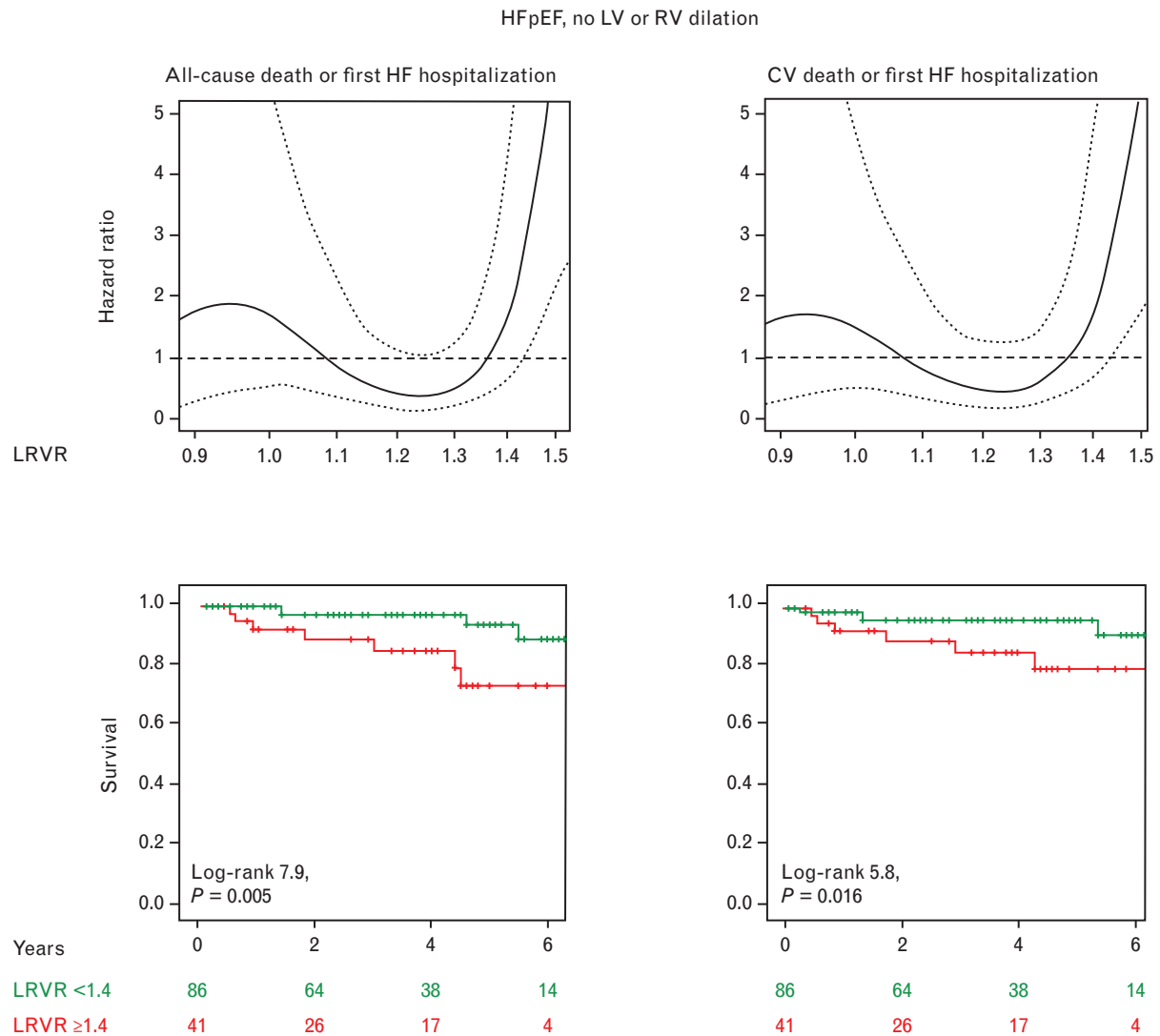
could be identified: LRVR less than 1.0, 1.0–1.3, and at least 1.4. When excluding patients with dilation of one or both ventricles, there was a trend toward a bimodal distribution of risk; the most prominent increase in risk was found with an LRVR at least 1.4.

The burden of HFpEF is increasing worldwide, and patients with HFpEF typically have a poor prognosis.^{21–23} An accurate prediction of individual patient prognosis may be important to define tailored care strategies (e.g. frequency of clinic visits, home follow-up by healthcare professionals, or prognosis-related discussions with the patient and his/her family members). Finding new tools to identify patients who have a greater risk of decompensation and death is quite important, especially as there is a lack of established prognostic models for patients with HFpEF except for a biomarker-driven prognostic model²⁴ that could not be applied to our patients because of the lack of biomarker data. Echocardiography is the cornerstone to demonstrate structural and/or functional alterations of the heart as the underlying cause for the clinical

presentation, but CMR represents the noninvasive gold standard to assess cardiac morphology, function, and tissue changes.^{2,25,26} Several CMR variables have been associated with hard clinical end points, including LV and right ventricular volumes^{3,27,28} and LGE,^{29,30} which is a surrogate of myocardial fibrosis. However, a metric as simple as the ratio between the end-diastolic volumes of the two ventricles (here introduced as LRVR) has never been investigated.

We evaluated a cohort of patients with HFpEF and a spectrum of disease causes skewed toward hypertrophic cardiomyopathy, likely reflecting the preferential referral to CMR examination of patients with known or suspected cardiomyopathy. When evaluating the ratio between LV and right ventricular volumes in this cohort, we found that patients with balanced LV and right ventricular volumes (LRVR 1.0–1.3) had a much lower risk of all-cause death and first HF hospitalization or cardiovascular death and first HF hospitalization than patients with a larger RV than LV (LRVR <1.0) or those with a much larger LV than right

Fig. 3



Left-to-right ventricular volume ratio and outcomes in patients with no ventricular dilation. Patients without dilation of either the LV or the RV ventricle were considered. Above: spline curve analysis. The cut-off points (i.e. those where the spline curve crosses the line corresponding to a hazard ratio of 1) are 1.1 and 1.4. The LRVR ratio value of 1 is highlighted. Below: Kaplan–Meier curves considering the 1.4 cut-off.

ventricle ($\text{LRVR} \geq 1.4$). We then excluded patients with dilation of one or both ventricles, to avoid the possible instance of a normalization of LRVR because of the dilation of both ventricles. The increase in risk below 1

Table 3 Left-to-right ventricular volume ratio at least 1.4 and outcome in patients without left ventricular or right ventricular dilation

	No LV or RV dilation		
	HR	95% CI	P
All-cause death or HF hospitalization [n (%)]	4.75	1.43–15.82	0.011
CV death or HF hospitalization [n (%)]	4.06	1.18–13.91	0.026

Univariate Cox regression analysis. CI, confidence interval; CV, cardiovascular; FU, follow-up; HF, heart failure; HR, hazard ratio.

was blunted when excluding patients with right ventricular and/or LV dilation, while the increase in risk for high LRVR values was confirmed, with the same 1.4 cut-off. Furthermore, the burden of HF hospitalizations was much greater in patients with extreme LRVR categories. The higher risk associated with LRVR values less than 1.0 in the whole cohort is primarily driven by patients with overt RV dilation, who have the greatest probability of having right ventricular dysfunction and pulmonary hypertension. Even when excluding these patients, spline curves show an increased risk for patients with a larger right ventricular than LV, who might be progressing toward right ventricular dilation and dysfunction. On the other extreme of the spectrum, patients whose LV is much larger than their right ventricle

also have a poor outcome. In this condition, LVEF is preserved despite enlarged LV volumes, with a likely shift to the right in the pressure–volume relationship that implies a greater workload, compensated by an increase in LV mass. According to the classical studies by Meerson, the next stage is characterized by the exhaustion of compensatory mechanisms, further LV dilation and LVEF decline.³¹ This corresponds to the progression from HFpEF to HF with mildly reduced or reduced ejection fraction, which was reported in 39% of patients in the Swedish Heart Failure Registry and associated with an increased risk of all-cause death or HF hospitalization.³² LV dysfunction leads to secondary pulmonary hypertension and over time may have detrimental effects on the right ventricle. When the right ventricle dilates, LRVV may start to decrease again, confounding the relationship between LRVV values and outcomes. Nonetheless, this is not the case for patients with HFpEF, especially when those with LV (and right ventricular) dilation are excluded. We thus propose LRVV as a simple tool for risk stratification in early-stage disease, before either ventricle is dilated.

Several limitations must be acknowledged in this hypothesis-generating study. First, the proposed prognostic marker is only applicable to HFpEF patients undergoing CMR, which is much less available than echocardiography but remains the gold standard technique for the assessment of biventricular volumes. Accurate volumetric assessment with echocardiography can be performed only with new 3D probes and dedicated postprocessing software, with the right ventricular volumes the most challenging. Unfortunately, echocardiographic 3D volumetric assessment was not available during the inclusion period of this cohort. Second, we evaluated a rather small cohort from a single center. Furthermore, the prognostic value of LRVV could be usefully investigated in HFpEF cohorts with a lower proportion of patients with cardiomyopathy. The limited number of deaths or first HF hospitalizations did not allow adjustment for potential confounders or competing risks, although survival analyses showed a clear bimodal relationship between LRVV values and outcomes. The validation obtained in the bootstrapping analysis with 1000 replications confirmed the results. The limited number of patients and events did not allow performance of further subgroup analysis that could have allowed a better understanding of the prognostic value of the LRVV ratio in specific patient subgroups, such as those without LGE, or with specific LGE patterns. Finally, we could not evaluate if LRVV values are predictive of arrhythmias because arrhythmic events were not systematically recorded. On the other hand, clinically relevant arrhythmias are quite uncommon in patients with HFpEF, and arrhythmias were not considered as stand-alone events or as part of composite end points in a

dedicated consensus report.¹⁹ Finally, we focused on the interplay between the LRVV at a single time point and clinically relevant end points, although changes in medical and device therapy could modify disease trajectories and then the prognostic value of LRVV.

Conclusion

In conclusion, an RVEDVi larger than the LVEDVi, or an LVEDVi at least 40% larger than the RVEDVi are significantly associated with worse outcomes in patients with HFpEF. LRVV may emerge as a valuable and simple tool for risk prediction in patients with HFpEF.

Conflicts of interest

There are no conflicts of interest.

References

- 1 Yeboah J, Bluemke DA, Hundley WG, Rodriguez CJ, Lima JA, Herrington DM. Left ventricular dilation and incident congestive heart failure in asymptomatic adults without cardiovascular disease: multiethnic study of atherosclerosis (MESA). *J Card Fail* 2014; **20**:905–911.
- 2 Georgiopoulos G, Aimo A, Barison A, Magkas N, Emdin M, Masci PG. Imaging predictors of incident heart failure: a systematic review and meta-analysis. *J Cardiovasc Med* 2021; **22**:378–387.
- 3 Gulati A, Ismail TF, Jabbour A, *et al.* The prevalence and prognostic significance of right ventricular systolic dysfunction in nonischemic dilated cardiomyopathy. *Circulation* 2013; **128**:1623–1633.
- 4 Garg P, Lewis RA, Johns CS, *et al.* Cardiovascular magnetic resonance predicts all-cause mortality in pulmonary hypertension associated with heart failure with preserved ejection fraction. *Int J Cardiovasc Imaging* 2021; **37**:3019–3025.
- 5 Aquaro GD, Camastra G, Monti L, *et al.*, working group ‘Applicazioni della Risonanza Magnetica’ of the Italian Society of Cardiology. Reference values of cardiac volumes, dimensions, and new functional parameters by MR: a multicenter, multivendor study. *J Magn Reson Imaging* 2017; **45**:1055–1067.
- 6 Luijckx T, Velthuis BK, Prakken NH, *et al.* Impact of revised Task Force Criteria: distinguishing the athlete’s heart from ARVC/D using cardiac magnetic resonance imaging. *Eur J Prev Cardiol* 2012; **19**:885–891.
- 7 Burke MA, Katz DH, Beussink L, *et al.* Prognostic importance of pathophysiologic markers in patients with heart failure and preserved ejection fraction. *Circ Heart Fail* 2014; **7**:288–299.
- 8 Remme WJ, Swedberg K, Task Force for the Diagnosis and Treatment of Chronic Heart Failure, European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J* 2001; **22**:1527–1560.
- 9 Swedberg K, Cleland J, Dargie H, *et al.*, Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005; **26**:1115–1140.
- 10 Dickstein K, Cohen-Solal A, Filippatos G, *et al.* ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. *Eur J Heart Fail* 2008; **10**:933–989.
- 11 McMurray JJ, Adamopoulos S, Anker SD, *et al.* ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *Eur Heart J* 2012; **33**:1787–1847.
- 12 McDonagh TA, Metra M, Adamo M, *et al.*, ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur J Heart Fail* 2022; **24**:4–131.
- 13 Ponikowski P, Voors AA, Anker SD, *et al.* 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur J Heart Fail* 2016; **18**:891–975.
- 14 Simonetti OP, Kim RJ, Fieno DS, *et al.* An improved MR imaging technique for the visualization of myocardial infarction. *Radiology* 2001; **218**:215–223.

- 15 Kramer CM, Barkhausen J, Bucciarelli-Ducci C, Flamm SD, Kim RJ, Nagel E. Standardized cardiovascular magnetic resonance imaging (CMR) protocols: 2020 update. *J cardiovasc Magn Res* 2020; **22**:17.
- 16 Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. *Nutrition* 1989; **5**: 303–311.
- 17 Mahrholdt H, Wagner A, Judd RM, Sechtem U, Kim RJ. Delayed enhancement cardiovascular magnetic resonance assessment of nonischemic cardiomyopathies. *Eur Heart J* 2005; **26**:1461–1474.
- 18 Hundley WG, Bluemke DA, Bogaert J, et al. Society for Cardiovascular Magnetic Resonance (SCMR) guidelines for reporting cardiovascular magnetic resonance examinations. *J Cardiovasc Magn Res* 2022; **24**:29.
- 19 Hicks KA, Mahaffey KW, Mehran R, et al. 2017 cardiovascular and stroke endpoint definitions for clinical trials. *Circulation* 2018; **137**:961–972.
- 20 Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. *Am J Epidemiol* 2007; **165**: 710–718.
- 21 Cimino G, Pancaldi E, Tomasoni D, Lombardi CM, Metra M, Adamo M. Updates in heart failure: sodium glucose co-transporter 2 inhibitors and beyond - major changes are coming. *J Cardiovasc Med (Hagerstown)* 2022; **23**:761–769.
- 22 Iacovoni A, Palmieri V, Abete R, et al. Right and left ventricular structures and functions in acute HFpEF: comparing the hypertensive pulmonary edema and worsening heart failure phenotypes. *J Cardiovasc Med (Hagerstown)* 2022; **23**:663–671.
- 23 Casebeer A, Horter L, Hayden J, Simmons J, Evers T. Phenotypic clustering of heart failure with preserved ejection fraction reveals different rates of hospitalization. *J Cardiovasc Med* 2021; **22**:45–52.
- 24 Pocock SJ, Ferreira JP, Packer M, et al. Biomarker-driven prognostic models in chronic heart failure with preserved ejection fraction: the EMPEROR-Preserved trial. *Eur J Heart Fail* 2022; **24**:1869–1878.
- 25 Barison A, Aimo A, Todiere G, Grigoratos C, Aquaro GD, Emdin M. Cardiovascular magnetic resonance for the diagnosis and management of heart failure with preserved ejection fraction. *Heart Fail Rev* 2022; **27**:191–205.
- 26 Bosso G, Valvano A, Guarnaccia F, et al., ALERT-HF Investigators. Adherence to guidelines in the management of patients with chronic heart failure follow-up: role of periodic echocardiographic examinations. *J Cardiovasc Med* 2020; **21**:216–222.
- 27 Hombach V, Merkle N, Torzewski J, et al. Electrocardiographic and cardiac magnetic resonance imaging parameters as predictors of a worse outcome in patients with idiopathic dilated cardiomyopathy. *Eur Heart J* 2009; **30**:2011–2018.
- 28 Xu Y, Lin J, Liang Y, et al. Prognostic value of left ventricular remodelling index in idiopathic dilated cardiomyopathy. *Eur Heart J Cardiovasc Imaging* 2021; **22**:1197–1207.
- 29 Becker MAJ, Cornel JH, van de Ven PM, et al. The prognostic value of late gadolinium-enhanced cardiac magnetic resonance imaging in nonischemic dilated cardiomyopathy: a review and meta-analysis. *JACC Cardiovasc Imaging* 2018; **11**:1274–1284.
- 30 Kanagala P, Cheng ASH, Singh A, et al. Relationship between focal and diffuse fibrosis assessed by cmr and clinical outcomes in heart failure with preserved ejection fraction. *JACC Cardiovasc Imaging* 2019; **12**:2291–2301.
- 31 Meerson FZ. Compensatory hyperfunction of the heart and cardiac insufficiency. *Circ Res* 1962; **10**:250–258.
- 32 Savarese G, Vedin O, D'Amario D, et al. Prevalence and prognostic implications of longitudinal ejection fraction change in heart failure. *JACC Heart Fail* 2019; **7**:306–317.