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ORIGINAL ARTICLE

Heart failure with mildly reduced ejection fraction: retrospective study of ejection fraction trajectory risk

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Abstract

Aims Heart failure with mildly reduced ejection fraction (HFmrEF) is associated with a favourable prognosis compared with heart failure (HF) with reduced ejection fraction (EF). We assessed whether left ventricular ejection fraction (LVEF) trajectory can be used to identify groups of patients with HFmrEF who have different clinical outcomes in a large retrospective study of patients with serial imaging.

Methods and results Patients with HF and ≥2 echocardiograms performed ≥6 months apart were included if the LVEF measured 40–49% on the second study. Patients were classified as HFmrEF-Increasing if LVEF had increased ≥10% (n = 450), HFmrEF-Decreasing if LVEF had decreased ≥10% (n = 512), or HFmrEF-Stable if they did not meet other criteria (n = 389). The primary outcome was all-cause mortality or cardiovascular hospitalization after the second echocardiogram. Associations with time to first event were assessed with multivariable Cox analyses adjusted for age, co-morbidities, and medications.

In total, 1351 patients with HFmrEF (median age 74, 64.2% male) were included with 28.8% exhibiting stable LVEF. During median follow-up of 15.3 months, the composite outcome occurred in 811 patients. During follow-up, patients with HFmrEF-Increasing were less likely to experience the primary outcome [adjusted hazard ratio (HR) 0.72, 95% confidence interval (CI) 0.60–0.88, $P < 0.001$] compared with HFmrEF-Stable. Patients with HFmrEF-Decreasing were more likely to experience the composite outcome in unadjusted analyses (unadjusted HR 1.19, 95% CI 1.01–1.40, P = 0.040) but not adjusted analyses (adjusted HR 1.16, 95% CI 0.98–1.37, P = 0.092). Associations with death or HF hospitalizations were similar (HFmrEF-Increasing: adjusted HR 0.72, 95% CI 0.59–0.88, P = 0.005; HFmrEF-Decreasing: adjusted HR 1.20, 95% CI 1.01–1.44, P = 0.044). Patients with HFmrEF-Decreasing had a similar risk of the composite outcome as patients with HF with reduced EF (adjusted HR 1.03, 95% CI 0.89–1.20, P = 0.670). Patients with HFmrEF-Increasing were less likely to experience the composite outcome compared with patients with HF with preserved EF (adjusted HR 0.73, 95% CI 0.62–0.87, $P < 0.001$).

Conclusions Amongst patients with HFmrEF, those exhibiting positive LVEF trajectory were less likely to experience adverse outcomes after correcting for important confounders including medical therapy. Categorizing HFmrEF patients based on LVEF trajectory provides meaningful clinical information and may assist clinicians with management decisions.

Keywords Heart failure; LVEF; Echocardiogram; Heart failure with mildly reduced ejection fraction; LVEF trajectory

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Introduction

Patients with heart failure (HF) are broadly categorized into groups according to ventricular function. As a result, patients with HF are classified as having HF with reduced left ventricular ejection fraction (LVEF) if their LVEF is <40%, HF with mildly reduced LVEF (HFmrEF) if LVEF is 40–49%, and HF with preserved LVEF if their LVEF is >50%.[1–4] While these categories are helpful in guiding physicians with respect to management and prognosis, patients frequently change categories.[5] As a result, patients can be further categorized by the trajectory of change in LVEF as having improving, stable, or

deteriorating ventricular function to provide additional risk stratification.[5]

Studies evaluating cohorts of patients with HFmrEF at a single point in time have shown favourable prognosis compared with patients with reduced LVEF and similar survival to patients with preserved LVEF.[6] However, patients with HFmrEF represent a heterogeneous group of patients, which have not been well represented in clinical trials. These patients can potentially be categorized according to LVEF trajectory as patients with stable LVEF (HFmrEF-Stable), with decreasing LVEF (HFmrEF-Decreasing), and with increasing LVEF (HFmrEF-Increasing). There have been relatively few studies of these subgroups to date. In a study that included 287 patients with HFmrEF, patients with HFmrEF-Increasing had a lower risk of death, left ventricular assist device implant, or transplant compared with patients with HF with reduced LVEF or HFmrEF without recovered LVEF.[7] In a study of 168 patients with HFmrEF, the authors identified improved unadjusted clinical outcomes for patients with HFmrEF-Increasing compared with those with HFmrEF-Decreasing.[8] However, only 16 patients were categorized as HFmrEF-Stable, and the study was too small to adjust for relevant confounders.[8]

We assessed whether LVEF trajectory can be used to identify groups of patients with HFmrEF who have different clinical outcomes in a retrospective study of patients with a clinical diagnosis of HF and at least two echocardiograms 6 or more months apart.

Methods

Patient population

We identified a cohort of all patients living in Alberta with a physician-assigned diagnosis of HF (at least one hospitalization or emergency department visit with a diagnosis of HF (ICD-10 Code I50.x)] between 1 April 2008 and 31 March 2016.[5] We included patients over age 18 who had undergone at least two echocardiograms at least 6 months apart.[5] We excluded patients who underwent cardiac transplant or left ventricular assist device implantation between the two echocardiograms. Any patients who died prior to the second echocardiogram would have been excluded, because they did not have a second echocardiogram. The second echocardiogram was used as the baseline because this allowed us to better isolate the potential associations between absolute LVEF and change in LVEF with clinical outcomes. This design allowed us to identify a cohort of patients with HFmrEF when follow-up for clinical events begins while also knowing the patients' LVEF trajectories. However, we performed a secondary analysis where associations were assessed in patients with HFmrEF classified based on the first echocardiogram. Follow-up was censored at first event, 31 March 2017, or date of known migration out of the province. To comply with Alberta's Health Information Protection Act, the data set used for this study cannot be made publicly available, but requests to access the de-identified data set from qualified researchers trained in human subject confidentiality protocols may be sent to the corresponding author (Dr Finlay A. McAlister).

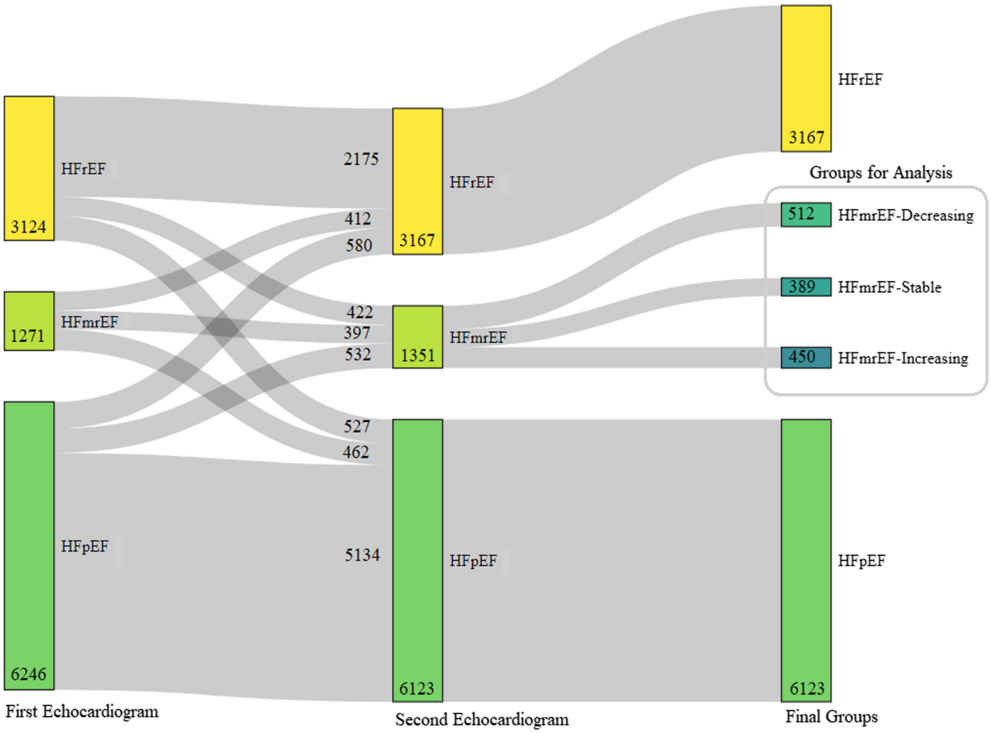
Data sources and elements

Baseline covariates were identified using Alberta healthcare administrative databases for all hospitalizations in the 12 months prior to the initial echocardiogram until the second echocardiogram anywhere in the province of Alberta, Canada. Therefore, these covariates are reflective of patient characteristics at the time of the second (index) echocardiogram. Co-morbidities were determined using standard ICD-10-CA codes and case definitions in Alberta administrative databases, which have been previously validated.[9,10] Duration of HF was determined as the time from first presentation for HF to index (second) echocardiogram. Pampalon material deprivation index, which includes six socio-economic indicators,[11] was derived from postal codes as previously validated.[12,13] Medications [angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), beta-blockers, eplerenone, hydralazine, long-acting nitrates, loop diuretics, and spironolactone] were identified using the pharmacy information network, which captures $>$90% of all prescriptions in Alberta,[14] with use defined as at least two dispensations in the time between echocardiograms (with the maximum duration of prescriptions in our region being 3 months). There were no prescriptions for angiotensin receptor neprilysin inhibitor, ivabradine, or sodium–glucose cotransporter-2 inhibitors in this cohort as they were not available in Alberta during the time frame studied. There were no missing data; however, it is possible that some medical history may be missing because we relied on ICD-10-CA codes and some medical therapies may not be captured.

Our study sample was linked to echocardiogram databases at the Mazankowski Alberta Heart Institute (Edmonton) and Libin Cardiovascular Institute (Calgary), which include a mix of outpatient and inpatient echocardiograms.[5] We only considered echocardiograms with quantification of LVEF. In patients with multiple echocardiograms, the second echocardiogram was the earliest study performed at least 6 months after the initial echocardiogram.

Patient classification is outlined in *Figure 1*. Patients were classified into one of three groups according to their second (index) echocardiogram as follows: (i) HF with reduced LVEF (LVEF $<$ 40%, n = 3167), (ii) HFmrEF (LVEF 40–49%, n = 1351), or (iii) HF with preserved LVEF (LVEF $\geq$ 50%, n = 5134). Characteristics of patients with HF with reduced

Figure 1 Patient flow diagram outlining patient classification. Patients were primarily classified by the left ventricular ejection fraction (LVEF) on the second echocardiogram into heart failure with reduced ejection fraction (HFrEF, LVEF < 40%), HF with mid-range LVEF (HFmrEF, LVEF 40–49%), and HF with preserved LVEF (HFpEF, LVEF ≥ 50%). Patients with HFmrEF were further classified based on absolute change from the first echocardiogram as HFmrEF-Increasing (if LVEF increased ≥10%), HFmrEF-Decreasing (if LVEF decreased ≥10%), and otherwise as HFmrEF-Stable.



LVEF, HFmrEF, and HF with preserved LVEF are shown in Supporting Information, *Table S1*. Patients with HFmrEF on their second echocardiogram were further classified based on the change from their first echocardiogram as (i) HFmrEF-Increasing if LVEF had an absolute increase ≥10% compared with their initial echocardiogram (n = 450), (ii) HFmrEF-Decreasing if LVEF had an absolute decrease ≥10% from their initial echocardiogram (n = 512), or (iii) HFmrEF-Stable if they do not meet either of the other criteria (n = 389). A threshold of 10% was chosen because this is greater than the physiological variability that would be expected with 2D echocardiography[15] or standard measurement errors.[16]

Clinical outcomes

The primary outcome was a composite outcome including all-cause mortality or cardiovascular hospitalization after the second echocardiogram. The secondary outcomes included a composite outcome of all-cause mortality or HF hospitalization as well as the individual components of the composite outcomes (all-cause mortality, HF hospitalization, and other cardiovascular hospitalization).

Statistical analysis

Continuous variables were summarized as mean ± standard deviation if normally distributed and otherwise as median (inter-quartile range). Categorical variables were summarized as number (proportion). Continuous variables were compared using analysis of variance as appropriate. Categorical variables were compared using χ^2 test.

We assessed associations with the primary outcome using univariable and multivariable Cox proportional hazards analysis. The multivariable model included age, sex, medical history, and all baseline medications as covariates as well as LVEF and time between echocardiograms. These variables were selected based on known clinical significance. Residuals were visually inspected to confirm there were no major violations of the proportional hazards assumption, with no violations identified. The primary analysis considered time to first event during the entire follow-up period, which started after the second (index) echocardiogram. However, a sensitivity analysis was performed to assess associations with time to first event during the first year of follow-up only. Outcomes that included death were modelled using Cox proportional hazards models, while outcomes not including death were modelled using Fine–Gray sub-distribution hazard models, with death considered to be a competing risk.

All statistical tests were two-sided with a *P*-value <0.05 considered significant, and analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC) and R Version 3.5.2 (R, Vienna, Austria). This study complies with the Declaration of Helsinki and was approved by the conjoint health research ethics board at the University of Calgary and the University of Alberta.

Results

Patient population

From the overall population, 1351 (12.7%) patients were classified as having HFmrEF on their second echocardiogram (*Figure 1*). In patients with HFmrEF, the median age was 74 (inter-quartile range 62–82) and 867 (64.2%) patients were male. Population characteristics at the time of the second echocardiogram are shown in *Table 1*. Patients with HFmrEF-Increasing were younger (median age 70) compared with patients with HFmrEF-Stable or HFmrEF-Decreasing (median for both 75, $P < 0.001$). Patients with HFmrEF-Increasing (68.7%) or HFmrEF-Stable (66.8%) were more likely to be male compared with HFmrEF-Decreasing (58.2%, $P = 0.001$). The use of ACEi or ARB, beta-blocker, digoxin, and spironolactone or eplerenone during the time between echocardiograms was all more common in patients with HFmrEF-Increasing compared with HFmrEF-Stable or HFmrEF-Decreasing (all $P < 0.001$). Characteristics of patients with HF with reduced LVEF, HFmrEF, and HF with preserved LVEF are shown in Supporting Information, *Table S1*.

Echocardiographic characteristics

Echocardiographic characteristics in patients with HFmrEF are shown in *Table 2*. Only 28.8% of patients exhibited stability on serial echocardiograms, while 33.3% of patients were classified as HFmrEF-Increasing, and 37.9% were classified as HFmrEF-Decreasing. Time between echocardiograms was shortest for patients with HFmrEF-Increasing (median 14 months) and longest for patients with HFmrEF-Decreasing (median 18 months, $P = 0.016$). On the

Table 1 Characteristics of patients with HFmrEF on their second echocardiogram

Variable value	HFmrEF-Stable (n = 389)	HFmrEF-Increasing (n = 450)	HFmrEF-Decreasing (n = 512)	*P*-value
Age, median (IQR)	75 (63, 83)	70 (59, 79)	75 (65, 83)	<0.001
Male, *n* (%)	260 (66.8%)	309 (68.7%)	298 (58.2%)	0.001
Duration of HF, median (IQR)	574 (191, 1306)	475 (227, 1026)	294 (5, 1010)	0.008
Pampalon material deprivation index quintiles, *n* (%)				
1 (highest)	76 (19.5%)	97 (21.6%)	100 (19.5%)	0.801
2	87 (22.4%)	81 (18.0%)	101 (19.7%)	
3	82 (21.1%)	89 (19.8%)	98 (19.1%)	
4	64 (16.5%)	88 (19.6%)	104 (20.3%)	
5 (lowest)	75 (19.3%)	85 (18.9%)	101 (19.7%)	
9 (missing)	5 (1.3%)	10 (2.2%)	8 (1.6%)	
Region, *n* (%)				
Metropolitan	271 (69.7%)	288 (64.0%)	371 (72.5%)	0.072
Regional	75 (19.3%)	97 (21.6%)	87 (17.0%)	
Rural	43 (11.1%)	65 (14.4%)	54 (10.5%)	
Medical history, 1 year before first echo until second echo, *n* (%)				
Atrial fibrillation	65 (16.7%)	80 (17.8%)	87 (17.0%)	0.911
Ischaemic heart disease	88 (22.6%)	109 (24.2%)	105 (20.5%)	0.382
Anaemia	14 (3.6%)	17 (3.8%)	24 (4.7%)	0.664
Cancer	13 (3.3%)	11 (2.4%)	20 (3.9%)	0.441
Chronic kidney disease	65 (16.7%)	79 (17.6%)	91 (17.8%)	0.911
COPD	35 (9.0%)	44 (9.8%)	61 (11.9%)	0.321
Dementia	1 (0.3%)	8 (1.8%)	12 (2.3%)	0.039
Depression	10 (2.6%)	17 (3.8%)	16 (3.1%)	0.608
Diabetes mellitus	45 (11.6%)	71 (15.8%)	68 (13.3%)	0.200
Hypertension	87 (22.4%)	128 (28.4%)	123 (24.0%)	0.103
Prior stroke or TIA	13 (3.3%)	13 (2.9%)	22 (4.3%)	0.483
Medications dispensed between first echo and second echo—two dispensations, *n* (%)				
ACEi or ARB	303 (77.9%)	375 (83.3%)	366 (71.5%)	<0.001
Digoxin	46 (11.8%)	71 (15.8%)	30 (5.9%)	<0.001
Beta-blockers	294 (75.6%)	397 (88.2%)	362 (70.7%)	<0.001
Loop diuretics	210 (54.0%)	241 (53.6%)	249 (48.6%)	0.187
Spironolactone or eplerenone	59 (15.2%)	156 (34.7%)	57 (11.1%)	<0.001
Hydralazine	24 (6.2%)	22 (4.9%)	23 (4.5%)	0.509
Nitrates (regularly scheduled, not prn)	103 (26.5%)	125 (27.8%)	129 (25.2%)	0.663

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; IQR, inter-quartile range; TIA, transient ischaemic attack.

Table 2 Echocardiographic characteristics of patients with HFmrEF on their second echocardiogram

Variable name	HFmrEF-Stable (n = 389)	HFmrEF-Increasing (n = 450)	HFmrEF-Decreasing (n = 512)	P-value
First echocardiogram				
LVEF, mean (SD)	45.51 (2.75)	31.10 (8.74)	55.87 (4.42)	<0.001
EDV, mean (SD)	119.08 (45.94)	155.24 (63.08)	95.39 (45.38)	<0.001
ESV, mean (SD)	62.32 (27.82)	110.34 (53.63)	41.23 (22.05)	<0.001
LVEDD, mean (SD)	5.10 (0.74)	5.49 (0.82)	4.72 (0.73)	<0.001
MR severity, *n* (%)[a]				
Trace or mild	243 (74.3%)	271 (66.7%)	347 (81.6%)	<0.001
Mild to moderate	31 (9.5%)	58 (14.3%)	30 (7.1%)	
Moderate	34 (10.4%)	44 (10.8%)	33 (7.8%)	
Moderate to severe	14 (4.3%)	21 (5.2%)	6 (1.4%)	
Severe	5 (1.5%)	12 (3.0%)	9 (2.1%)	
RVSP, mean (SD)	42.13 (13.34)	41.21 (13.44)	41.91 (13.81)	0.743
Months between studies, median (IQR)	16 (10, 28)	14 (9, 26)	18 (10, 31)	0.016
Second echocardiogram				
LVEF, mean (SD)	45.13 (1.79)	45.06 (1.93)	44.84 (1.68)	0.039
EDV, mean (SD)	112.98 (47.23)	130.13 (55.87)	104.57 (45.95)	<0.001
ESV, mean (SD)	59.75 (26.41)	68.68 (32.32)	54.67 (25.72)	<0.001
LVEDD, mean (SD)	5.09 (0.72)	5.10 (0.76)	4.85 (0.73)	<0.001
MR severity, *n* (%)[a]				
Trace or mild	236 (70.4%)	337 (82.8%)	306 (69.2%)	<0.001
Mild to moderate	43 (12.8%)	35 (8.6%)	58 (13.1%)	
Moderate	32 (9.6%)	22 (5.4%)	56 (12.7%)	
Moderate to severe	18 (5.4%)	10 (2.5%)	14 (3.2%)	
Severe	6 (1.8%)	3 (0.7%)	8 (1.8%)	
Trace	104 (31.0%)	176 (43.2%)	132 (29.9%)	
RVSP, mean (SD)	42.82 (14.52)	37.99 (13.08)	45.16 (14.96)	<0.001

EDV, end-diastolic volume; ESV, end-systolic volume; HFmrEF, heart failure with mildly reduced ejection fraction; IQR, inter-quartile range; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; RVSP, right ventricular systolic pressure estimate; SD, standard deviation.
[a]MR severity was not available for all patients, and values reflect the proportion in which data were available.

first echocardiogram, patients with HFmrEF-Increasing had the highest end-diastolic volume (155 ± 63) followed by HFmrEF-Stable (119 ± 46) and HFmrEF-Decreasing (95 ± 45). There were also significant differences in end-diastolic volume on the second echocardiogram (HFmrEF-Increasing 130 ± 56, HFmrEF-Stable 113 ± 47, and HFmrEF-Decreasing 105 ± 46, $P < 0.001$).

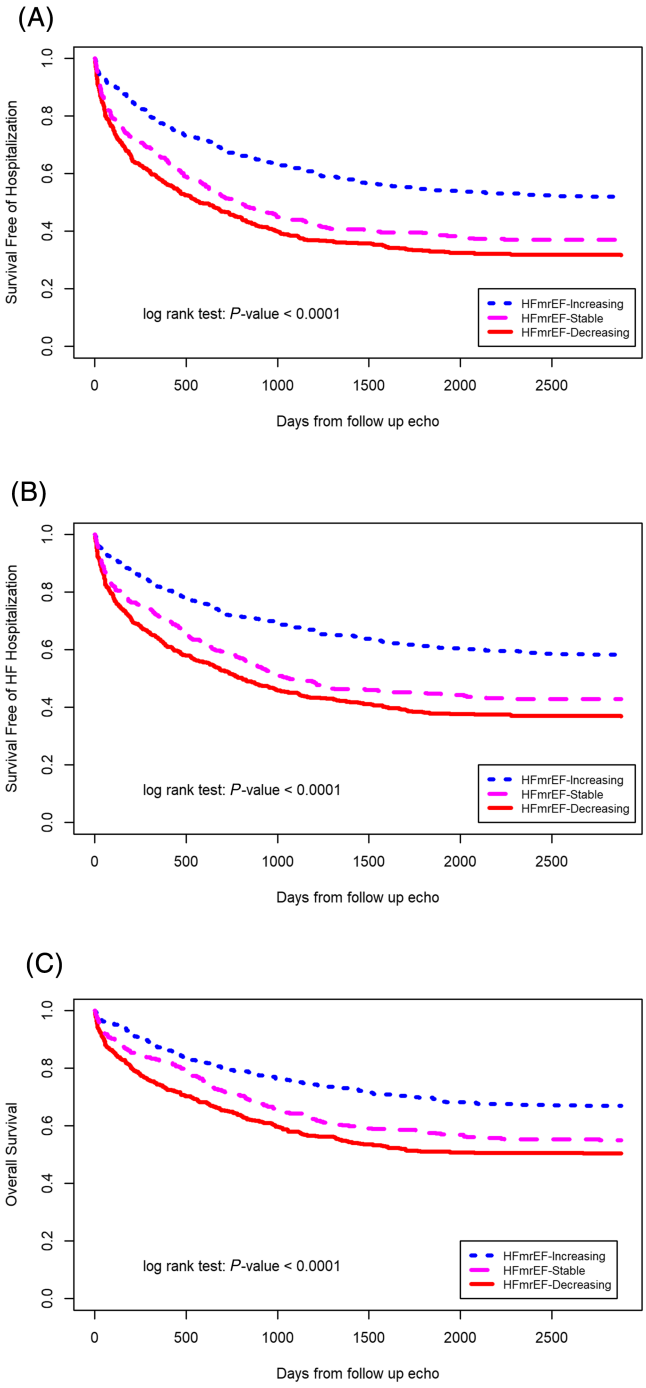
Outcomes

During a median follow-up of 15.3 months after the second echocardiogram, the composite outcome occurred in 811 patients. The first event included 302 HF hospitalizations, 185 other cardiovascular hospitalizations, and 324 deaths. Kaplan–Meier curves for survival free of the composite outcome are shown in *Figure 2A*. Patients with HFmrEF-Increasing were less likely to experience the composite outcome compared with patients with HFmrEF-Stable or HFmrEF-Decreasing (log-rank $P < 0.001$). Additionally, patients with HFmrEF-Stable were less likely to experience the composite outcome compared with patients with HFmrEF-Decreasing (log-rank $P < 0.001$). Similar results were seen for survival free of HF hospitalization (*Figure 2B*) and all-cause mortality (*Figure 2C*).

Associations with the composite outcome are shown in *Figure 3* and Supporting Information, *Table S2*. HFmrEF-Increasing was associated with a lower incidence of the composite outcome compared with patients with HFmrEF-Stable [adjusted hazard ratio (HR) 0.72, 95% confidence interval (CI) 0.60–0.88, $P < 0.001$]. Patients with HFmrEF-Decreasing were more likely to experience the composite outcome compared with HFmrEF-Stable in unadjusted analyses (unadjusted HR 1.19, 95% CI 1.01–1.40, $P = 0.040$) but not multivariable analysis (adjusted HR 1.16, 95% CI 0.98–1.37, $P = 0.092$). Older age (adjusted HR 1.30, 95% CI 1.22–1.38 per 10 years) and use of beta-blockers (adjusted HR 0.82, 95% CI 0.69–0.99) were also independently associated with the composite outcome.

Associations with the secondary outcomes are shown in Supporting Information, *Table S3*. Using the same multivariable model as the primary analysis, patients with HFmrEF-Increasing had a lower risk of death or HF hospitalization (adjusted HR 0.72, 95% CI 0.59–0.88, $P = 0.005$), and patients with HFmrEF-Decreasing had a significantly higher risk of death or HF hospitalization (adjusted HR 1.20, 95% CI 1.01–1.44, $P = 0.044$). Associations with the individual components of the composite outcome (all-cause mortality, HF hospitalizations, and other cardiovascular hospitalizations) were similar to the primary analysis.

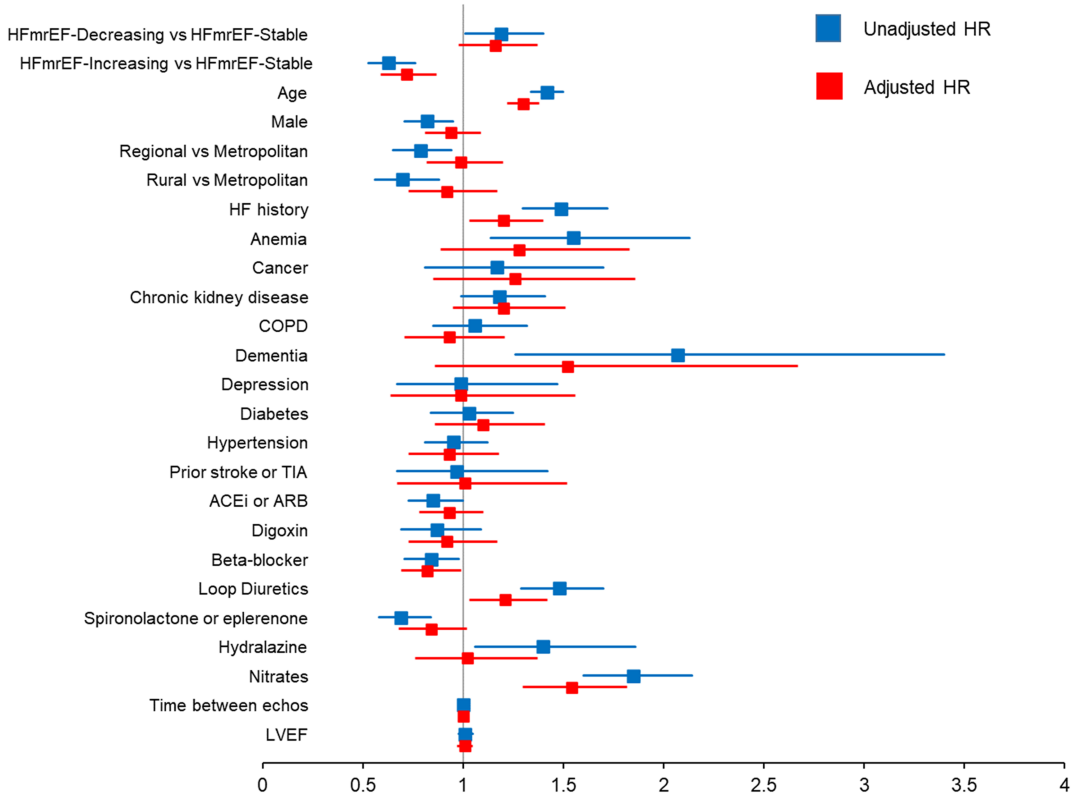
Figure 2 Kaplan–Meier curves stratified by heart failure with mildly reduced ejection fraction (HFmrEF) categories. Kaplan–Meier curves for (A) survival free of cardiovascular hospitalization, (B) survival free of heart failure (HF) hospitalization, and (C) overall survival.



Associations with outcomes during the first year of follow-up are shown in Supporting Information, *Table S4*, and were similar to results in the primary analysis. Patients with HFmrEF-Increasing continued to be at lower risk (adjusted HR 0.68, 95% CI 0.52–0.89, P = 0.005), and there was a trend towards higher risk in patients with HFmrEF-Decreasing (adjusted HR 1.21, 95% CI 0.97–1.51, P = 0.097).

Associations with the primary outcome in patients with HFmrEF on the first echocardiogram are shown in Supporting Information, *Table S5*. The multivariable model was the same as that used in the primary analysis, and time to first event

Figure 3 Unadjusted and adjusted associations with the composite outcome. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HR, hazard ratio; LVEF, left ventricular ejection fraction; TIA, transient ischaemic attack.



was calculated from the second echocardiogram. In unadjusted analyses, patients with HFmrEF on first echocardiogram with LVEF decline ≥10% (unadjusted HR 1.49, $P < 0.001$) were at increased risk, and patients with LVEF increase ≥10% were at lower risk (unadjusted HR 0.71, $P = 0.022$). In multivariable analysis, neither LVEF drop ≥10% (adjusted HR 1.14, $P = 0.419$) nor LVEF increase ≥10% (adjusted HR 0.97, $P = 0.854$) was associated with the primary outcome. However, LVEF drop ≥10% (adjusted HR 1.47, $P < 0.001$) was associated with increased risk if LVEF at index (second) echocardiogram was not included in the multivariable model.

Comparisons with heart failure with reduced and preserved ejection fraction

Kaplan–Meier curves for overall survival and survival free of the composite outcome in patients with HFmrEF as well as reduced or preserved LVEF are shown in Supporting Information, *Figures S1* and *S2*, respectively. Using the multivariable model outlined earlier, patients with HFmrEF-Decreasing had a similar risk of the composite outcome to patients with HF with reduced ejection fraction (EF) (adjusted HR 1.03, 95% CI 0.89–1.20, $P = 0.670$). Patients with HFmrEF-Stable also had similar outcomes compared with patients with HF with reduced EF (adjusted HR 0.96, 95% CI 0.82–1.13, $P = 0.624$). Conversely, patients with HFmrEF-Increasing were less likely to experience the composite outcome compared with patients with HF with preserved EF (adjusted HR 0.73, 95% CI 0.62–0.87, $P < 0.001$).

Discussion

In our study, patients frequently transitioned between HF categories based on LVEF, and we identified three distinct groups of patients with HFmrEF with different characteristics and outcomes. Patients with HFmrEF-Increasing started at lower LVEF with a more dilated LV, and patients with HFmrEF-Decreasing started with higher LVEF and less dilated LV. There were significant differences in risk of the composite outcome across these subgroups with patients classified as HFmrEF-Increasing having the best outcomes followed by HFmrEF-Stable and HFmrEF-Decreasing. Importantly, in multivariable analysis, patients with HFmrEF-Decreasing were at a similarly high risk as patients with HF with reduced LVEF,

while patients with HFmrEF-Increasing were at lower risk even compared with patients with HF with preserved LVEF. This information may help guide clinicians to pursue more aggressive monitoring and medical therapy in patients with HFmrEF-Stable and HFmrEF-Decreasing.

A significant proportion of patients (>70%) with HFmrEF on their second echocardiogram had transitioned from another LVEF category. Lupón *et al*. found that a minority of patients with HF with preserved LVEF transitioned to either HFmrEF or HF with reduced EF.[17] In our study, a larger proportion of patients transitioned from HF with preserved EF during follow-up (17.8%); however, this difference could be explained by not excluding patients with specific cardiomyopathies in our study. Our results are similar to those of Savarese *et al*., where 300 (63%) of patients with HFmrEF at follow-up had transitioned from another category.[18] However, they classified patients using absolute LVEF categories, and therefore, patients may have changed categories with minimal change in LVEF. We also identified significant differences in patient characteristics across these categories of patients with HFmrEF. We identified higher LVEDV in patients with HFmrEF-Increasing at both the first and second echocardiograms. Additionally, similar to Nadruz *et al*.,[7] we identified lower median age in patients with HFmrEF-Increasing. In our study, patients with HFmrEF-Decreasing had lower LVEDV at the first and second echocardiograms. Rastogi *et al*. did not identify differences in LV end-diastolic dimension in their smaller cohort but did identify smaller LV end-systolic dimension in patients with HFmrEF-Decreasing.[8] This information could potentially be used clinically to stratify patients classified as HFmrEF on their initial echocardiogram, particularly if there was a delay between initial clinical diagnosis of HF and echocardiogram.

In addition to distinct patient characteristics, we identified significant differences in patient outcomes across groups. We identified that patients with HFmrEF-Increasing were less likely to experience the composite outcome after adjusting for important confounding factors, with lower risk even when compared with patients with HF preserved LVEF. Similarly, Nadruz *et al*. demonstrated in a cohort of 277 patients with HFmrEF (including 170 with HFmrEF-Increasing) that patients with HFmrEF-Increasing had a lower risk of death, left ventricular assist device implant, or transplant compared with patients with HFmrEF without recovered LVEF.[7] In our study, in addition to studying a larger population allowing adjustment for relevant co-morbidities and medical therapy, we also differentiated the subgroup of patients with HFmrEF-Decreasing. These patients were more likely to experience the composite outcome in unadjusted analysis, with a trend towards worse outcomes even after adjustment in multivariable models. However, they had a significantly higher risk of experiencing the secondary outcome of death or HF hospitalization even in adjusted analyses. Previous studies have also demonstrated a similar gradation of risk, but without statistically significant increased risk in HFmrEF-Decreasing because of low sample sizes.[8,18] Importantly, in our study, we demonstrated that patients with HFmrEF-Decreasing had outcomes that were essentially identical to patients with HF with reduced LVEF in adjusted analyses. This suggests that these patients may be on transitioning towards an HF with reduced LVEF phenotype and therefore may benefit from more aggressive initiation of medical therapy. We have proposed a simple classification of patients with HFmrEF based on two points in time. However, it is important to consider that patients may continue to transition between classifications. For example, recently, it has been demonstrated that the hospitalization for HF attenuates reverse remodelling in patients with HF with recovered LVEF.[19]

Our study adds to the growing body of literature suggesting that LVEF trajectory has important clinical implications and the HFmrEF may be a transition phenotype.[20] Our group previously demonstrated that patients with HF with recovered LVEF were less likely to experience all-cause mortality, all-cause hospitalization, and all-cause emergency room visits compared with patients with persistent HF with reduced EF. Similarly, Basuray *et al*. demonstrated that patients with HF with recovered LVEF (defined as LVEF improved from <50% to >50%) were less likely to experience a composite cardiovascular compared with patients with reduced or preserved LVEF.[21] This observation was also confirmed in a Spanish cohort of 1057 patients.[22] In a longitudinal cohort of patients with HF with preserved EF, declining LVEF was associated with reduced survival.[23] One study suggested that patients demonstrate a characteristic trajectory with early LVEF recovery lasting for up to 10 years.[24] In the same study, patients who died had a lower LVEF and were more likely to have a decline in LVEF in the period preceding death compared with survivors.[24] Overall, these results suggest that considering LVEF trajectory in conjunction with absolute LVEF provides meaningful, clinically relevant, risk stratification.

Our study has a few important limitations in addition to residual confounding related to its retrospective nature. One underlying assumption of this study is that patient classification at a single point in time is clinically meaningful. However, patients clearly move between classifications over time, and similarly, we would expect patients to have different LVEF trajectory over time as well. All echocardiograms were ordered during routine care and may have been prompted by change in clinical status, which may be particularly relevant for patients with HFmrEF-Decreasing. Additionally, all patients had a clinical diagnosis of HF from a hospitalization or ED presentation, and therefore, the population may not be representative of patients with less symptomatic HF. Although we adjusted for baseline medication prescriptions, we do not have longitudinal prescription information or insight into patient adherence, which are likely important confounding factors. Additionally, we do not have information regarding use of device therapies such as cardiac

resynchronization therapy in our cohort. Patients may shift between typical categories of HF classification as a result of small differences in LVEF (e.g. LVEF increasing from 39% to 41%), which may be related to differences in technical quality or physician interpretation. Lastly, we used an absolute difference in LVEF of ≥10% based on existing literature, but smaller changes are potentially important as well.[25]

Conclusions

We identified three categories of patients with HFmrEF based on their LVEF trajectory. Patients with HFmrEF-Increasing were less likely to experience the composite outcomes, while patients with HFmrEF-Decreasing were at the highest risk. Categories based on LVEF trajectory provide meaningful clinical information and may help physicians make decisions regarding which patients to pursue more aggressive monitoring and medical therapy.

Conflict of interest

None declared.

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Supporting information

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

Table S1. Overall population characteristics.
Table S2. Associations with the composite outcome.
Table S3. Associations with the secondary outcomes.
Table S4. Association with composite outcome in the first year.
Table S5. Associations in patients classified as having heart failure mid-range ejection fraction on first echocardiogram.
Figure S1. Kaplan–Meier curves for overall survival. HFmrEF – heart failure with mildly reduced ejection fraction, HFpEF – heart failure with preserved ejection fraction, HFrEF – heart failure with reduced ejection fraction.
Figure S2. Kaplan–Meier curves for survival free of cardiovascular hospitalization. HFmrEF – Heart failure with mid-range ejection fraction, HFpEF – heart failure with preserved ejection fraction, HFrEF – heart failure with reduced ejection fraction.

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