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RESEARCH ARTICLE

Predictors and outcomes of heart failure with mid-range ejection fraction

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Aims While heart failure with preserved (HFpEF) and reduced ejection fraction (HFrEF) are well described, determinants and outcomes of heart failure with mid-range ejection fraction (HFmrEF) remain unclear. We sought to examine clinical and biochemical predictors of incident HFmrEF in the community.

Methods and results We pooled data from four community-based longitudinal cohorts, with ascertainment of new heart failure (HF) classified into HFmrEF [ejection fraction (EF) 41–49%], HFpEF (EF ≥50%), and HFrEF (EF ≤40%). Predictors of incident HF subtypes were assessed using multivariable Cox models. Among 28 820 participants free of HF followed for a median of 12 years, there were 200 new HFmrEF cases, compared with 811 HFpEF and 1048 HFrEF. Clinical predictors of HFmrEF included age, male sex, systolic blood pressure, diabetes mellitus, and prior myocardial infarction (multivariable adjusted $P \leq 0.003$ for all). Biomarkers that predicted HFmrEF included natriuretic peptides,

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cystatin-C, and high-sensitivity troponin ($P \leq 0.0004$ for all). Natriuretic peptides were stronger predictors of HFrEF [hazard ratio (HR) 2.00 per 1 standard deviation increase, 95% confidence interval (CI) 1.81–2.20] than of HFmrEF (HR 1.51, 95% CI 1.20–1.90, $P = 0.01$ for difference), and did not differ in their association with incident HFmrEF and HFpEF (HR 1.56, 95% CI 1.41–1.73, $P = 0.68$ for difference). All-cause mortality following the onset of HFmrEF was worse than that of HFpEF (50 vs. 39 events per 1000 person-years, $P = 0.02$), but comparable to that of HFrEF (46 events per 1000 person-years, $P = 0.78$).

Conclusions We found overlap in predictors of incident HFmrEF with other HF subtypes. In contrast, mortality risk after HFmrEF was worse than HFpEF, and similar to HFrEF.

Keywords Heart failure • Risk factor • Ejection fraction

Introduction

The recognition of distinct heart failure (HF) subtypes is important, not only because this classification broadly frames differences in underlying pathophysiology, but also because HF subtypes delineate differential therapeutic approaches.[1,2] In general, HF subtypes are classified based on left ventricular ejection fraction (LVEF), with an LVEF of ≥50% defining HF with preserved ejection fraction (HFpEF), and LVEF of ≤40% defining HF with reduced ejection fraction (HFrEF).[1,2] Previous comparisons of HFpEF and HFrEF have often dichotomized the LVEF cut-point, and some have omitted a mid-range. These approaches raise the question of whether individuals with HF and an LVEF 41–49%, referred to as mid-range ejection fraction (HFmrEF),[3] might be a distinct phenotype.

The majority of previous studies focused on HFmrEF have studied samples with existing HF and described cross-sectional associations with clinical characteristics, and described it as an intermediate phenotype with some features more akin to HFpEF and others to HFrEF.[4–7] Potential clinical and biochemical features that precede the development of HFmrEF, however, have not been fully characterized in an inception cohort. Further, few studies have examined outcomes after HFmrEF with mixed results, describing similar outcomes to HFpEF vs. HFrEF.[7–9]

We have previously described differences in clinical predictors for incident HFpEF vs. HFrEF among four large community-based samples, however participants with HFmrEF were not examined in this previous study.[10] Therefore, in order to better characterize the HFmrEF phenotype, we sought to focus specifically on HFmrEF for this present analysis, and to conduct a comprehensive evaluation not only of risk factors and cardiovascular biomarkers, but also of prognosis after HFmrEF onset. To do so, we leveraged an international collaboration of four large community-based cohorts with prospective ascertainment of over 2500 incident HF events, which were classified into three HF subtypes.[10]

Methods

Study sample

We included participant-level data from four prospective, observational community-based cohorts with prospectively adjudicated HF outcomes.[10] For the present investigation, participants attending the following baseline examinations were included: Framingham Heart Study (FHS) original cohort exam 16 (1979–1982) or 24 (1995–1998), FHS offspring cohort exam 2 (1979–1983) or 6 (1995–1998), Cardiovascular Health Study (CHS) exam 1 (1989–1990; 1992–1993 for supplemental African-American cohort), Prevention of Renal and Vascular Endstage Disease (PREVEND) exam 1 (1997–1998), and Multi-Ethnic Study of Atherosclerosis (MESA) exam 1 (2000–2002). From this sample, we excluded participants with prevalent HF ($n = 472$), age < 30 years at baseline examination due to extremely low likelihood of developing HF ($n = 379$), and those with missing covariates ($n = 2177$), leaving 28 820 individuals available for the primary analysis.

Clinical assessment

Participants underwent a detailed medical history, physical examination, fasting blood draw with subsequent laboratory assessment, and electrocardiography. Variables were harmonized across cohorts whenever possible.[10] Blood pressure was taken as the average of two seated measurements. Body mass index (BMI) was calculated as weight divided by height^2 and expressed as kg/m^2. Diabetes mellitus was defined as a fasting glucose ≥126 mg/dL, random glucose ≥200 mg/dL, or the use of hypoglycaemic medications. Electrocardiographic left ventricular hypertrophy was defined based on accepted voltage and ST-segment criteria, as described previously.[10] Prior history of coronary heart disease was ascertained systematically in each parent cohort using a combination of self-report, electrocardiogram, review of all available prior medical records, and physician contact.[10] Estimated glomerular filtration rate (eGFR) was calculated using baseline creatinine concentrations.[11]

Laboratory assessment

Biomarkers were assessed within each cohort, with details summarized in the supplementary material online, *Table S1*. The following biomarkers were available in at least two cohorts and were included in this analysis: natriuretic peptides, high-sensitivity troponin, C-reactive protein, urinary albumin to creatinine ratio, D-dimer, fibrinogen, soluble ST2, cystatin-C, galectin-3, and interleukin-6, with the range in coefficients of variation between 2.3% and 12.2%. B-type natriuretic peptide (BNP) was measured in FHS, and its amino terminal cleavage equivalent (NT-proBNP) in the other cohorts. Similarly, high-sensitivity troponin I was measured in FHS, and high-sensitivity troponin T in the remaining cohorts.

Definition of incident heart failure subtypes

Incident HF was prospectively ascertained and adjudicated using established protocols by study investigators within each cohort after review of all available outpatient and hospital records. We reviewed imaging reports at or near the HF onset date to abstract LVEF (92% within 30 days of HF onset), with the majority of LVEF assessments ascertained via echocardiography (>88% of cases). HF was defined using a combination of signs, symptoms, and/or treatment, as described.[5] Each first incident HF event was categorized as HFpEF (LVEF ≥50%), HFmrEF (40% < LVEF <50%), HFrEF (LVEF ≤40%), or unclassified (no left ventricular function assessment available).

Statistical analysis

Individual-level data were harmonized and pooled for all four cohorts—FHS, PREVEND, CHS, and MESA. Baseline clinical characteristics were summarized by incident HF subtype (HFpEF, HFmrEF, HFrEF), unclassified HF, and no HF. A one-way analysis of variance (ANOVA) was calculated for each baseline characteristic to detect differences amongst HFpEF, HFmrEF, and HFrEF.

We calculated directly standardized incidence rates (sex- and age-standardized with 10-year age strata) of HFpEF, HFmrEF, and HFrEF. Cumulative incidence rates of the three HF subtypes were estimated using a Kaplan–Meier-like method accounting for competing risks of death, other HF subtypes, and unclassified HF. We also examined age- and sex-standardized incidence rates of all-cause mortality after HF onset. A Kaplan–Meier curve was generated for survival after onset of HF and group log-rank and pairwise *P*-values were estimated. To examine the association of clinical predictors with HF subtype, cause-specific Cox models were fitted separately for HFpEF, HFmrEF, and HFrEF. We accounted for multiple competing risks as above. Covariates known to be associated with HF were entered in the multivariable model,[10] including age, sex, race, systolic blood pressure, hypertension treatment, BMI, diabetes mellitus, smoking status, and previous myocardial infarction. In secondary analysis, previous myocardial infarction was replaced with previous coronary heart disease. A strata statement was included to specify study cohorts within the pooled analysis.

Cause-specific Cox models were then fitted for each biomarker in each HF subtype separately, after adjusting for the previously mentioned clinical covariates. Cause-specific hazard ratios (HRs) were calculated per 1 standard deviation increase in each natural log-transformed biomarker. In secondary analyses, we examined whether clinical covariates and biomarkers were associated differentially with risk of HFpEF vs. HFmrEF and HFrEF vs. HFmrEF. We took all covariate and biomarker models, and compared subtype-specific coefficients using the Lunn–McNeil method.[12] All statistical analyses were conducted with SAS version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

A total of 28 820 participants (mean age of 60 ± 14 years, 54% women) from four community-based longitudinal cohorts were included in this sample. Over a mean follow-up of 12 ± 4 years, a total of 2749 participants developed incident HF with an average of 11 ± 4 years to HF. A total of 2059 (75%) had left ventricular function assessment at or around the time of HF, permitting subtype classification. Among participants with classified new-onset HF, 811 (39%) had HFpEF, 200 (10%) had HFmrEF, and 1048 (51%) had HFrEF.

Baseline clinical characteristics preceding incident HF are presented by HF subtype in *Table 1*. Of participants who developed HF, more women were classified as HFpEF vs. HFrEF (59% vs. 36%), and the proportion of women among participants developing HFmrEF was intermediate (48%). With respect to clinical risk factors, participants with future HFmrEF shared some baseline similarities with the HFrEF group, including lower BMI than HFpEF (27.8 kg/m^2 in HFmrEF, 27.9 kg/m^2 in HFrEF vs. 28.6 kg/m^2 in HFpEF), with lower prevalence of obesity (26% in HFmrEF, 29% in HFrEF, 33% in HFpEF), higher prevalence of coronary heart disease than HFpEF (24% in HFmrEF, 25% in HFrEF, 16% in HFpEF) and lower high-density lipoprotein cholesterol (*Table 1*). Other clinical characteristics of participants with future HFmrEF were intermediate between those with future HFpEF and HFrEF.

Incidence rates of new-onset heart failure by subtype

Age- and sex-standardized incidence rates by HF subtype are summarized in *Figure 1* and in the supplementary material online, *Table S1*, and demonstrate an incidence rate of 6.7 cases per 10 000 person-years for HFmrEF. Corresponding rates for HFpEF and HFrEF were 26.9 and 34.9 cases per 10 000 person-years. Cumulative incidence plots by HF subtype are shown in *Figure 2*.

Clinical predictors of incident heart failure with mid-range ejection fraction

In multivariable adjusted analyses, older age, male sex, higher systolic blood pressure, hypertension treatment, diabetes mellitus, and prior myocardial infarction predicted incident HFmrEF ($P < 0.05$ for all, *Table 2*). The effect of clinical predictors on risk of future HFpEF, HFmrEF, and HFrEF is depicted in *Figure 3*. In secondary analyses, we examined prevalent coronary heart disease in place of previous myocardial infarction, and found an independent association with HFpEF [HR 1.45, 95% confidence interval (CI) 1.19–1.77], HFmrEF (HR 2.04, 95% CI 1.39–3.02), and HFrEF (HR 2.42, 95% CI 2.04–2.87). When added to the multivariable model, interim myocardial infarction had a nearly three-fold increased hazard for HFrEF, over two-fold increased hazard of HFmrEF, and 34% increased hazard of HFpEF (HR 2.91, 95% CI 2.37–3.57 for HFrEF; HR 2.23, 95% CI 1.36–3.65 for HFmrEF; and HR 1.34, 95% CI 1.02–1.77 for HFpEF). The median time between interim myocardial infarction and HF onset was 0.7 years (25th percentile 0.02 years, 75th percentile 3.4 years).

We tested whether a given clinical predictor had differential effects on risk of HFmrEF, HFpEF, and HFrEF using the Lunn–McNeil method (*Table 2*).[12] The impact of male sex on risk of HFmrEF (HR 1.63, 95% CI 1.18–2.24) was significantly different compared both with HFpEF (HR 1.03, 95% CI 0.89–1.20) and HFrEF (HR 2.25, 95% CI 1.95–2.59, $P = 0.005$ for HFmrEF vs. HFpEF and $P = 0.046$ for HFmrEF vs. HFrEF comparisons). We also observed a stronger association of BMI with HFpEF than HFmrEF

Table 1 Baseline characteristics preceding incident clinical outcomes by heart failure subtype

	Incident HF					
	HFpEF ($n = 811$)	HFmrEF ($n = 200$)	HFrEF ($n = 1048$)	*P* ANOVA	No HF ($n = 26\,071$)	Unclassified HF ($n = 690$)
Demographics						
Age, years	71 (9)	72 (8)†	70 (10)	0.0003	58 (14)	75 (7)
Women, *n* (%)	477 (59)	95 (48)*†	379 (36)	<0.0001	14151 (54)	366 (53)
Race, *n* (%)				0.15		
White	692 (85)	175 (88)	917 (88)		21160 (81)	584 (85)
Black	84 (10)	21 (11)	92 (9)		2394 (9)	90 (13)
Other	34 (4)	4 (2)	37 (4)		2465 (9)	16 (2)
Clinical covariates						
Systolic blood pressure, mmHg	142 (22)	142 (22)	142 (22)	0.99	129 (20)	142 (22)
Diastolic blood pressure, mmHg	73 (11)	72 (11)†	75 (12)	0.0001	74 (10)	71 (12)
Hypertension treatment, *n* (%)	435 (54)	106 (53)	550 (52)	0.88	6846 (26)	412 (60)
Heart rate, b.p.m.	68 (11)	68 (11)	68 (12)	0.87	67 (11)	69 (12)
Body mass index, kg/m^2	28.6 (5.5)	27.8 (4.6)*	27.9 (4.7)	0.002	26.8 (4.8)	27.4 (5.2)
Diabetes mellitus, *n* (%)	156 (19)	39 (20)	232 (22)	0.30	1980 (8)	158 (23)
Diabetes medications, *n* (%)	97 (12)	29 (15)	123 (12)	0.54	1149 (4)	93 (14)
Current smoker, *n* (%)	108 (13)	27 (14)	206 (20)	0.0007	5800 (22)	91 (13)
Modest alcohol use, *n* (%)	130 (16)	45 (23)	215 (21)	0.03	6009 (23)	98 (14)
Myocardial infarction, *n* (%)	66 (8)	22 (11)	184 (18)	<0.0001	779 (3)	87 (13)
Coronary heart disease, *n* (%)	131 (16)	47 (24)*	260 (25)	<0.0001	1341 (5)	190 (28)
Cerebrovascular disease, *n* (%)	32 (4)	10 (5)	71 (7)	0.03	370 (1)	33 (5)
Hyperlipidaemia treatment, *n* (%)	76 (9)	16 (8)	100 (10)	0.90	1897 (7)	53 (8)
Laboratory covariates, *n* (%)						
Total cholesterol	211 (40)	209 (38)	209 (45)	0.63	209 (41)	209 (39)
HDL cholesterol	50 (15)	47 (14)*	47 (14)	<0.0001	52 (16)	51 (16)
eGFR, mL/min/1.73 m^2	67 (19)	63 (19)*	66 (20)	0.048	76 (18)	63 (18)
ECG covariates, *n* (%)						
Atrial fibrillation	43 (5)	19 (10)	61 (6)	0.07	274 (1)	45 (7)
Left ventricular hypertrophy	46 (6)	13 (7)	99 (9)	0.006	642 (2)	56 (8)
Left bundle branch block	16 (2)	5 (3)	59 (6)	0.0002	156 (0.6)	15 (2)

eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.
P for ANOVA denotes testing for between-group differences among incident HF subtypes (HFpEF, HFmrEF, HFpEF).
*$P < 0.05$ for HFmrEF vs. HFpEF.
†$P < 0.05$ for HFmrEF vs. HFrEF.

(HR 1.30, 95% CI 1.23–1.38 for HFpEF, and HR 1.12, 95% CI 0.99–1.28 for HFmrEF, $P = 0.03$ for comparison). In contrast, the association of BMI with HFmrEF was similar to that with HFrEF ($P = 0.86$ for comparison).

Biomarker predictors of incident heart failure with mid-range ejection fraction

The associations of individual biomarker analyses (adjusting for clinical variables) with incident HFpEF, HFmrEF, and HFrEF are summarized in *Table 2* and *Figure 4*. Biomarker predictors of HFmrEF included natriuretic peptides, with each 1 standard deviation increase in log-transformed natriuretic peptide associated with a 1.5-fold increased hazard of HFmrEF (HR 1.51, 95% CI 1.20–1.90). Similarly, higher cystatin-C and high-sensitivity troponin were associated with higher risk of HFmrEF (HR 1.49, 95% CI 1.30–1.70, and HR 1.41, 95% CI 1.17–1.70, respectively). In analyses adjusting for both clinical variables and natriuretic peptides, high-sensitivity troponin and cystatin-C remained significant predictors of HFmrEF (HR 1.34, 95% CI 1.02–1.56, and HR 1.36, 95% CI 1.15–1.60, respectively).

We directly compared the effect of a single biomarker on HFmrEF, HFpEF, and HFrEF to examine whether differential effects exist (*Table 2*). We found that natriuretic peptides had similar effects on risk of HFmrEF and HFpEF, whereas the risk of HFrEF associated with a 1 standard deviation change in biomarker was greater than for HFmrEF (HR 2.00, 95% CI 1.81–2.20 vs. HR 1.51, 95% CI 1.20–1.90, $P = 0.01$ for comparison).

All-cause mortality rates after heart failure onset

After the onset of HF, there were 63 deaths among 200 participants with HFmrEF, 231 deaths among 811 with HFpEF, and 312 deaths

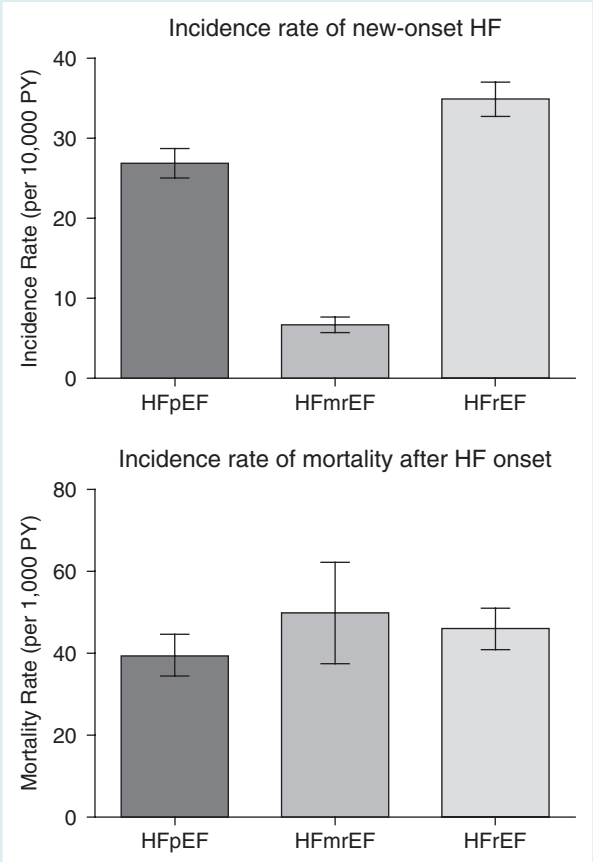

Figure 1 Incidence rates of new-onset heart failure (HF) and mortality after HF onset for HF subtypes. HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; PY, person-years.

among 1048 with HFrEF. The all-cause mortality rate was 497 events per 10 000 person-years among participants with HFmrEF, 394 per 10 000 person-years in those with HFpEF, and 459 per 10 000 person-years in those with HFrEF. As shown in the survival curves in *Figure 5*, survival was lower among participants with HFmrEF than in those with HFpEF (log-rank $P = 0.02$) and similar to those with HFrEF (log-rank $P = 0.78$).

Discussion

We examined clinical and biochemical predictors of new-onset HFmrEF, and outcomes after diagnosis of HFmrEF within the context of a unique international collaboration of four large community-based cohorts. Our principal findings were as follows: (i) clinical predictors are shared among HF subtypes, with a few notable differences; (ii) biochemical predictors of HFmrEF include natriuretic peptides, cystatin-C, and high-sensitivity troponin; and (iii) all-cause mortality after new-onset HF is similar among those classified as HFmrEF and HFrEF, but worse than in those classified as HFpEF.

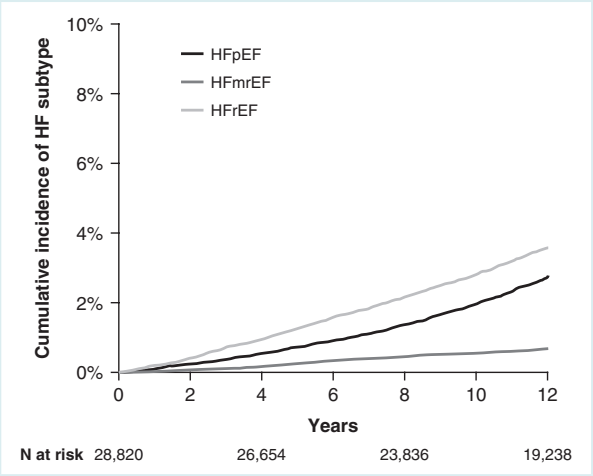

Figure 2 Cumulative incidence of heart failure (HF) subtype. Incident HF outcomes are denoted by colors, with black representing HF with preserved ejection fraction (HFpEF), medium gray representing HF with mid-range ejection fraction (HFmrEF), and light gray representing HF with reduced ejection fraction (HFrEF).

Previous studies have noted similarities among clinical profiles of patients with HFmrEF and HFpEF, including older age, and higher prevalences of hypertension, atrial fibrillation, and diabetes mellitus.[4,7,13,14] The consistent exception is a higher frequency of coronary artery disease among those with HFmrEF compared with HFpEF.[4,6,7,14] We now extend previous observations to examine predictors of new-onset HF. Our findings demonstrate that age, sex, blood pressure, diabetes mellitus, and previous myocardial infarction all predict incident HFmrEF. When comparing the effect of a given clinical covariate on the risk of HFmrEF vs. other HF subtypes, we note that men had a risk of HFmrEF which was lower than the risk of HFrEF, but more pronounced than the risk of future HFpEF. Further, BMI was more strongly related to HFpEF than HFmrEF or HFrEF.

Biochemical profiles of patients with HFmrEF have demonstrated natriuretic peptide concentrations that are largely intermediate between those with HFrEF, who have the highest neurohormonal activation, and the group with HFpEF with lowest natriuretic peptide levels.[13,14] Our study demonstrates that natriuretic peptide concentrations among generally healthy adults help predict future risk of HFmrEF. Interestingly, the magnitude of the risk estimate for natriuretic peptides was similar for HFmrEF and HFpEF, and greatest for HFrEF. In contrast, we find that cystatin-C and high-sensitivity troponin predict HFmrEF with similar effect sizes as HFpEF and HFrEF. We find that eGFR is not associated with future HFpEF or HFmrEF, with a borderline association for HFrEF. The difference between cystatin-C and creatinine-based eGFR is consistent with prior studies demonstrating greater sensitivity of cystatin-C as a marker for future risk of adverse outcomes.[15]

Among patients with existing HF enrolled in cross-sectional registries or clinical trials, the prevalence of HFmrEF has ranged

Table 2 Multivariable adjusted clinical predictors of incident heart failure with mid-range ejection fraction and other heart failure subtypes

	HFpEF ($n = 811$)		HFmrEF ($n = 200$)		HFrEF ($n = 1048$)		*P* for equality		
	HR	95% CI	HR	95% CI	HR	95% CI	All groups	HFmrEF vs. HFpEF	HFmrEF vs. HFrEF
Clinical covariates									
Age (per 10 years)	2.65	2.42–2.89	2.29	1.91–2.76	2.28	2.09–2.47	0.03	0.12	0.93
Male sex	1.03	0.89–1.20	1.63	1.18–2.24	2.25	1.95–2.59	<0.0001	0.005	0.046
Race	0.78	0.60–1.00	1.14	0.69–1.89	0.93	0.73–1.19	0.81		
Systolic BP (per 20 mmHg)	1.20	1.12–1.28	1.25	1.07–1.45	1.25	1.17–1.33	0.66		
Hypertension treatment	1.49	1.24–1.79	1.41	1.02–1.95	1.49	1.29–1.72	0.91		
Body mass index (per 4 kg/m^2)	1.30	1.23–1.38	1.12	0.99–1.28	1.14	1.07–1.21	0.003	0.03	0.86
Diabetes mellitus	1.75	1.46–2.11	1.81	1.22–2.68	2.10	1.77–2.50	0.31		
Smoking status	1.31	1.07–1.62	1.33	0.85–2.09	1.68	1.41–1.99	0.16		
Previous myocardial infarction	1.74	1.34–2.26	2.20	1.31–3.71	3.36	2.78–4.05	0.0001	0.39	0.10
eGFR (per 30 mL/min/1.73 m^2)	1.02	0.85–1.21	0.71	0.48–1.04	0.84	0.71–0.99	0.11		
Biomarkers									
Natriuretic peptide	1.56	1.41–1.73	1.51	1.20–1.90	2.00	1.81–2.20	0.0003	0.68	0.01
Cystatin-C	1.23	1.12–1.35	1.49	1.30–1.70	1.33	1.24–1.43	0.10		
High-sensitivity troponin	1.26	1.16–1.37	1.41	1.17–1.70	1.52	1.43–1.63	0.003	0.24	0.40
D-dimer	1.18	1.05–1.34	1.21	0.91–1.62	1.34	1.21–1.48	0.30		
Interleukin-6	1.24	1.12–1.38	1.19	1.00–1.42	1.25	1.13–1.38	0.92		
Galectin-3	1.10	1.01–1.21	1.18	0.93–1.48	1.14	1.05–1.24	0.82		
Soluble ST2	1.13	1.01–1.26	1.18	0.90–1.53	1.05	0.93–1.19	0.58		
C-reactive protein	1.12	1.02–1.23	1.12	0.93–1.35	1.31	1.21–1.42	0.02	0.95	0.10
Fibrinogen	1.18	1.08–1.30	1.11	0.91–1.34	1.17	1.07–1.28	0.83		
UACR	1.42	1.28–1.58	1.00	0.74–1.35	1.32	1.21–1.48	0.06	0.03	0.06

BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; UACR, urinary albumin to creatinine ratio.
HR represent HRs of HF subtype associated with the presence vs. absence of a dichotomous variable, or per increment in continuous variable as denoted in the table. HR for race is comparison of black vs. white race. Multivariable adjusted models include age, sex, race, systolic BP, hypertension treatment, body mass index, diabetes mellitus, smoking status, previous myocardial infarction. Biomarker models include all clinical covariates plus individual biomarkers.
P for difference between HFmrEF vs. HFpEF and HFmrEF vs. HFrEF listed if $P < 0.10$ for equality between all groups.

between 13–24%.[4,6–8,13] We now estimate incidence rates in an inception cohort, which suggest that the incidence rate of HFmrEF is about a tenth of total HF. Data on outcomes for patients with HFmrEF have been discrepant, with some studies showing a clear association of lower LVEF with worse outcomes, including a recent analysis of the TOPCAT trial demonstrating lower survival among those with LVEF 44–50% than those with LVEF >50%.[9,14,16,17] Other studies have shown no significant differences in mortality among HF subtypes parsed by LVEF.[7,8,13,18] Certainly, among population-based cohorts in the *absence* of HF, an asymptomatically reduced LVEF in the same mid-range of 40–50% bears a worse prognosis than normal LVEF,[19,20] which appears to extend even into the 50–55% LVEF range.[21] One important note is that, unlike our study, no prior studies were inception cohorts, which may have contributed to mixed results. Among participants with new-onset HF in the community, we found that those with incident HFmrEF have similarly poor survival to those with incident HFrEF, and slightly worse survival than those with incident HFpEF.

Our study had a number of limitations. While our findings show that HFmrEF shares antecedent clinical and biomarker predictors with HFpEF (BMI and natriuretic peptides), as well as HFrEF (coronary artery disease), and a clinical course similar to HFrEF, we were not able to ascertain whether HFmrEF is a phenotype in transition,[22] given the lack of serial LVEF data after HF onset. A previous study in patients with HFmrEF undergoing exercise testing shows a favourable prognosis among those with previously low LVEF.[5] This highlights the importance of understanding LVEF longitudinally among patients with HF, as LVEF is known to be dynamic over time, with longitudinal increases in LVEF among those with HFrEF, and decreases in LVEF among those with HFpEF.[23] HF subtypes were classified based on left ventricular function assessment performed as part of clinical care at the time of HF presentation, thus echocardiographic imaging was not standardized, and the narrow range of LVEF defining HFmrEF may have resulted in misclassification. This also left 27% of cases as unclassified, which may have led to differential bias. Participants under age 30 and those with missing key covariates were excluded, resulting in potential bias. Clinical information after HF onset was limited, including the use of HF-specific therapies and devices potentially influencing mortality analyses after HF onset. Lastly, we were not able to determine the exact pathogenesis of HF.

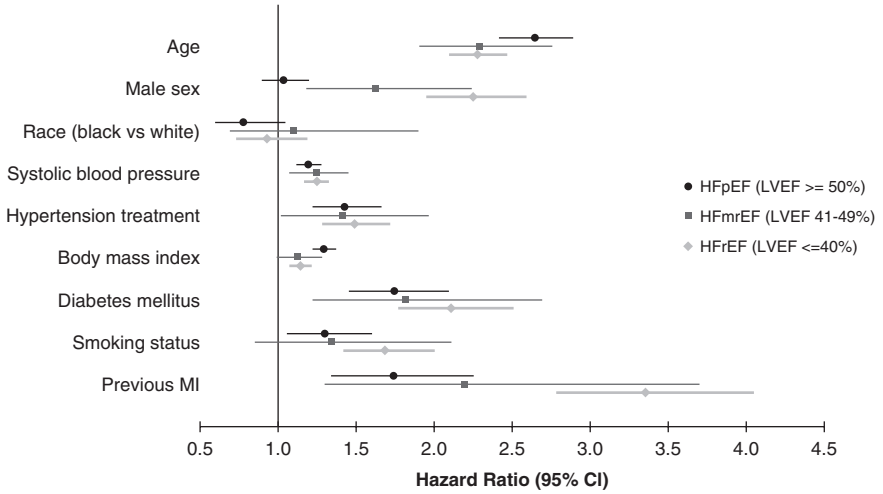

Figure 3 Clinical predictors of heart failure (HF) subtype. Incident HF outcomes are denoted by colors, with black representing HF with preserved ejection fraction (HFpEF), medium gray representing HF with mid-range ejection fraction (HFmrEF), and light gray representing HF with reduced ejection fraction (HFrEF). Point estimate represents multivariable adjusted hazard ratio (for the presence vs. absence of dichotomous traits, and per 10-year increase in age, and per 4 kg/m^2 increase in body mass index), and whiskers denote 95% confidence intervals (CI). MI, myocardial infarction.

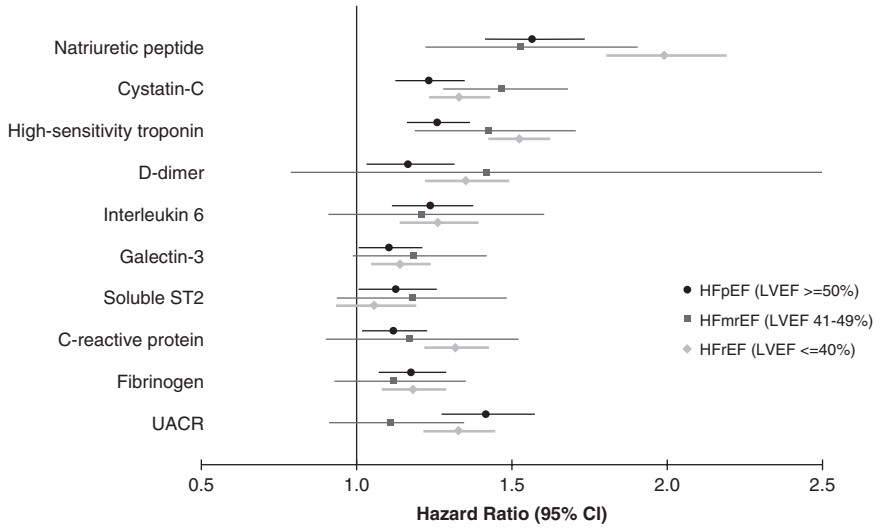

Figure 4 Biomarker predictors of heart failure (HF) subtype. Incident HF outcomes are denoted by colors, with black representing HF with preserved ejection fraction (HFpEF), medium gray representing HF with mid-range ejection fraction (HFmrEF), and light gray representing HF with reduced ejection fraction (HFrEF). Point estimate represents multivariable adjusted hazard ratio (per 1 standard deviation increase in log-transformed biomarker), and whiskers denote 95% confidence intervals (CI). UACR, urinary albumin to creatinine ratio.

In summary, we found overlap in clinical and biochemical predictors of incident HFmrEF with other HF subtypes. Age, male sex, blood pressure, diabetes mellitus, and previous myocardial infarction predicted HFmrEF, as did natriuretic peptides, cystatin-C, and high-sensitivity troponin. Despite shared features, we found a few notable differences—higher BMI was a predictor of HFpEF but not HFmrEF, and natriuretic peptides were stronger predictors of HFrEF than of HFmrEF. While predictors of HFmrEF had some shared features with HFpEF vs. HFrEF, all-cause mortality after new-onset HF was worse for HFmrEF than HFpEF, but similar to HFrEF. The fact that outcomes after HFmrEF mirror those after HFrEF suggests that HFmrEF may be more akin to HFrEF with respect to clinical course. This raises the question of whether potential therapies thus far reserved for patients with HFrEF may be of benefit in those with intermediate LVEF.

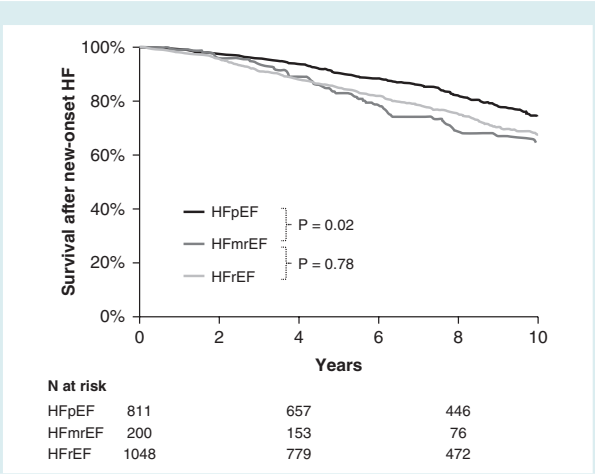

Figure 5 Survival after new-onset heart failure (HF) by HF subtype. Incident HF outcomes are denoted by colors, with black representing HF with preserved ejection fraction (HFpEF), medium gray representing HF with mid-range ejection fraction (HFmrEF), and light gray representing HF with reduced ejection fraction (HFrEF). *P*-value is pairwise log-rank test as indicated.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Incidence rates for new-onset heart failure (HF) and mortality after HF onset by HF subtypes.

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Conflict of interests: J.R.K. reports stock ownership from Gilead Sciences, Inc., Pfizer, Inc. and Amgen. M.N. reports grants from NHLBI. C.R.dF. reports grants and personal fees from Roche Diagnostics; personal fees from Radiometer, Alere, Siemens, Ortho Diagnostics, Metanomics, Quintiles, UpToDate, Medscape, and grants from Abbott Diagnostics. M.J.B. reports grants and personal fees from FDA and Amgen/Amgen Foundation; grants from NIH/NHLBI, AHA and Aetna Foundation; personal fees from ACC, Novartis, MedImmune, Sanofi/Regeneron, and Akcea. C.S.F. is currently an employee of Merck. H.K.G. reports grants and personal fees from Roche Diagnostics; grants from Portola; personal fees from Amgen, Ortho clinical; clinical endpoint committee for EchoSense and Radiometer. T.M.B. reports grants from NIH. E.J.B. reports grants from NIH/NHLBI, Assoc. Editor for AHA/NIH and CARDIA OSMB from NIH/NCBI. J.L.J. reports grants and personal fees from Roche, Siemens; grants from Prevencio and Singulex; personal fees from Abbott, Philips and Ortho Clinical. A.G.B. reports grants from NIH/NHLBI. R.A.dB. reports grants from AstraZeneca, Bristol Meyers Squibb, Trevena, Roche, and Novartis. J.E.H. reports grants from National Institutes of Health and Massachusetts General Hospital. The other authors have no conflicts to disclose.

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