Does etiology matter only in HFmrEF? Data from the HEart failuRe ObsErvational Study (HEROES)

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Abstract

Introduction: Heart failure (HF) with mildly reduced ejection fraction (HFmrEF) is a heterogeneous phenotype, and whether the prognostic weight of ischemic versus non-ischemic etiology differs across left ventricular ejection fraction (LVEF) categories remains uncertain. We examined whether the association between etiology and long-term all-cause mortality is modified by HF phenotype.

Material and methods: Within the prospective multicenter HEROES registry, 1,410 patients with HF were classified as having ischemic or non-ischemic etiology and categorized by LVEF. All-cause mortality was obtained through national administrative linkage with complete follow-up. Entropy balancing (13 covariates) and weighted Cox models were applied within each phenotype, with formal testing for etiology-by-phenotype interaction. Robustness was evaluated using restricted mean survival time (RMST), the E-value, and sensitivity analyses.

Results: Over a median follow-up of 14.8 months, 219 (15.5%) deaths occurred. Crude mortality was identical between etiologies (15.5% vs. 15.5%; $p = 0.93$). After balancing, no difference was observed in HFrEF (adjusted hazard ratio [aHR] 1.03, 95% CI: 0.68–1.58) or HFpEF (aHR = 0.84, 95% CI: 0.37–1.90), whereas non-ischemic etiology was associated with higher mortality in HFmrEF (aHR = 3.99, 95% CI: 1.51–10.51; $p = 0.005$). The etiology-by-phenotype interaction was significant ($p = 0.032$). In HFmrEF, the RMST difference at 23 months was -2.38 months (95% CI: –3.69 to –1.00), with an E-value of 4.55 (lower confidence limit 1.99); findings were consistent across sensitivity analyses.

Conclusions: The prognostic impact of HF etiology appears phenotype-dependent, concentrated within HFmrEF, where non-ischemic etiology substantially worse survival. Given the limited number of events, this phenotype-specific signal is hypothesis-generating and warrants confirmation.

Key words: prognosis, heart failure, all-cause mortality, heart failure with mildly reduced ejection fraction, mildly reduced ejection fraction, ischemic etiology, entropy balancing, restricted mean survival time.

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Introduction

Heart failure (HF) is a complex clinical syndrome and a major public health challenge, affecting approximately 1–3% of the adult population in developed countries, with prevalence increasing markedly with age [1]. Owing to demographic aging, the growing burden of cardiovascular risk factors, and improved survival following acute cardiovascular events, the number of individuals living with HF continues to rise worldwide [2]. Consequently, HF is associated with substantial morbidity, mortality, healthcare utilization, and economic burden. Beyond its high prevalence, HF represents a highly heterogeneous syndrome encompassing diverse clinical presentations, comorbidity profiles, pathophysiological mechanisms, and underlying etiologies [3–6]. Contemporary guidelines classify HF into three major phenotypes according to left ventricular ejection fraction (LVEF): heart failure with reduced ejection fraction (HFrEF), mildly reduced ejection fraction (HFmrEF), and preserved ejection fraction (HFpEF) [7, 8].

Patient outcomes in HF are influenced by multiple factors, among which disease etiology represents a key determinant. Ischemic heart disease remains the leading cause of death globally and constitutes one of the most important contributors to disability and premature mortality [9]. As the predominant cause of myocardial injury and adverse ventricular remodeling, ischemic heart disease plays a central role in the development and progression of HF [10].

In addition, ischemic etiology has been associated with a poor prognosis in HF patients in some studies [11], but not in other [12]. The second factor affecting prognosis is HF subtype according to the LVEF. As known, HFmrEF represents a clinically significant yet heterogeneous phenotype within the HF spectrum [13]. What is more, HF etiologies seem to differ across the LVEF spectrum, with ischemic etiology being more prevalent in HFrEF and HFmrEF, whereas hypertension and metabolic factors are more frequently observed among patients with HFpEF [14, 15]. HFmrEF is increasingly recognized as a heterogeneous phenotype that may encompass distinct clinical trajectories, including patients with previously preserved or reduced ejection fraction and those with improvement or deterioration of left ventricular systolic function [16]. Some studies showed that ischemic etiology was a marker of poor prognosis in patients with HFrEF [17, 18].

High-quality, phenotype-specific clinical evidence for HFmrEF remains scarce, largely due to inconsistent definitions, variability in LVEF thresholds, and under-representation in major randomized controlled trials. Therefore, in a contemporary and nationwide HF registry, we aimed to (i) assess clinical characteristics of patients with ischemic etiology of HF according to the subtypes, and (ii) associations between ischemic etiologies across HF subtypes, and all-cause mortality during follow-up.

Material and methods

Study design and setting

HEROES (the HEart failurE ObsErvational Study) is a prospective, multicenter registry of observational data organized by the Polish Cardiac Society across 41 cardiology centers nationwide. The registry enrolled adults with any HF type admitted to hospital or seen in outpatient clinics who provided informed consent from April 2022 to January 2024. Its primary purpose was to describe the real-world characteristics of Polish HF patients without interfering with routine care. The detailed rationale and design have been published [19]. Reporting follows the STROBE recommendations for cohort studies and the RECORD extension for studies using routinely collected health data.

Participants and study population

The sole exclusion criterion was the absence of consent. Of 1,422 enrolled participants, 12 who died during the index hospitalization were excluded, yielding an analytic cohort of 1,410. According to the current classification, patients with LVEF below 40% were categorized as HFrEF, 40–49% as HFmrEF, and at least 50% as HFpEF; LVEF-based classification was available for 1,210 (85.8%) patients.

Exposure and etiological classification

Two etiological groups were defined: ischemic and non-ischemic. Etiological classification was performed at enrolment by the physician responsible for the patient's clinical assessment at the participating center, based on the patient's medical history, available clinical documentation, and previously established cardiovascular diagnoses. Ischemic etiology was defined by a documented history of prior myocardial infarction and/or coronary revascularization, including percutaneous coronary intervention or coronary artery bypass grafting. Patients who did not meet these criteria were classified as having non-ischemic HF. When multiple potential etiological factors coexisted, the predominant underlying cause was assigned by the responsible physician based on clinical judgment and the available clinical documentation. The classification was established before outcome ascertainment and statistical analysis

and was therefore not based on subsequent clinical outcomes or survival.

Variables and data sources

Baseline demographics, medical history, comorbidities, diagnostic results, and pharmacotherapy were recorded. Kidney function was expressed as the estimated glomerular filtration rate using the Cockcroft-Gault equation. Thirteen confounders, specified by the analyst before analysis, informed the balancing model: age, sex, body mass index, heart rate, systolic and diastolic blood pressure, HF duration, care setting (inpatient vs outpatient), New York Heart Association class (I–II vs. III–IV), diabetes mellitus, chronic kidney disease, atrial fibrillation, and arterial hypertension. Treatment and device variables were treated as descriptive rather than as confounders, given their position downstream of etiology. Natriuretic peptide concentration was likewise excluded from the primary confounder set, both because it lies partly on the disease-severity pathway and because it was incompletely recorded; its potential confounding role was examined in a dedicated sensitivity analysis.

Outcome ascertainment and follow-up

The single endpoint was all-cause mortality. Vital status was obtained by linkage with the Polish Ministry of Digital Affairs under the General Data Protection Regulation; the linked dataset contained only the date of death. Linkage proceeded. Through a validated registry key, and complete survival data were available for all participants, with no loss to follow-up. No protocol-mandated follow-up visits were scheduled.

Statistical analysis

Continuous variables are summarized as median (first to third quartile) and categorical variables as counts (percentages). Across ischemic subtypes, omnibus comparisons used the Kruskal-Wallis test for continuous variables and the Pearson χ^2 or Fisher exact test for categorical variables; pairwise comparisons are reported as unadjusted, exploratory analyses.

The target estimand was the average treatment effect of non-ischemic versus ischemic etiology (reference) on all-cause mortality within each LVEF phenotype, under conditional exchangeability, positivity, and consistency. Entropy balancing was applied independently within each phenotype using the 13-covariate specification (HF classification, constant within strata, was excluded); because it equalizes covariate means exactly, standardized mean differences after weighting are zero by construction, and a 0.10 threshold served as the adequacy criterion for the stabilized-weighting sensitivity analysis. Weighted Cox proportional-hazards models containing etiology as the sole term were then fitted, with robust (sandwich) standard errors; covariate adjustment was thus achieved through the weights rather than through the outcome model. To formally test whether the etiology effect differed across phenotypes, a weighted Cox model incorporating an etiology-by-phenotype interaction was fitted and the interaction assessed by a Wald test. The proportional-hazards assumption was examined using scaled Schoenfeld residuals.

Two complementary robustness analyses were specified before analysis. As a proportional-hazards-free, clinically interpretable measure, the weighted difference in restricted mean survival time (RMST) was estimated at 12 and 23 months, with 95% confidence intervals obtained by bootstrap resampling (1,000 replications, with re-estimation of balancing weights in each replicate). To quantify the potential influence of unmeasured confounding, an E-value was computed for the HFmrEF estimate and its confidence limit.

The primary analysis used complete cases with documented LVEF, which defines the analytic strata (assumed missing at random given the covariates); multiple imputation of phenotype (20 imputations, Rubin's rules) served as a sensitivity analysis. The full sensitivity battery comprised: an unadjusted (crude) model; a doubly robust model combining weighting with covariate adjustment; stabilized inverse probability of treatment weighting derived from a logistic propensity model and trimmed at the 99th percentile; the multiple imputation analysis; additional balancing on $\log_{10}$(NT-proBNP) in the subset with available values; and a leave-one-out influence analysis in the HFmrEF stratum. Because three phenotype strata were examined, the interaction test served as the principled primary inference, and subgroup and pairwise comparisons are regarded as exploratory and hypothesis-generating. All tests were two-sided at $\alpha = 0.05$.

Analyses were performed in R 4.3.3. The registry was not powered a priori for this analysis; a retrospective assessment indicated approximately 98% power to detect the observed HFmrEF hazard ratio and 80% power for hazard ratios of at least 2.63 (Supplementary Table SV).

Results

Cohort and baseline characteristics

A total of 1,422 patients providing informed consent were enrolled; after excluding 12 who died in hospital, the analytic cohort comprised 1,410 patients (median age: 69.3 years, interquartile range: 60.3–76.2; 400 women [28.4%] and

1,010 men [71.6%]). Most were enrolled during an inpatient admission (1,131; 80.2%) rather than in outpatient settings (279; 19.8%). LVEF-based phenotyping, available in 1,210 (85.8%) patients, identified 627 with HFrEF (51.8%), 262 with HFmrEF (21.7%), and 321 with HFpEF (26.5%); the 200 (14.2%) patients without LVEF classification were retained in the cohort and addressed in the sensitivity program. Ischemic etiology was assigned to 579 (41.1%) patients and non-ischemic etiology to 831 (58.9%), the latter comprising dilated cardiomyopathy (191; 13.5%), hypertensive HF (170; 12.1%), valvular HF (151; 10.7%), and other etiologies (319; 22.6%). Thus, the non-ischemic category represented a heterogeneous group rather than a single disease entity, comprising several distinct underlying myocardial and cardiovascular conditions. Over a median follow-up of 14.8 months (interquartile range: 11.5–18.4), 219 (15.5%) deaths occurred. Mortality was higher among patients without documented LVEF than among those with it (36/200 [18.0%] vs. 183/1,210 [15.1%]); these patients also had longer HF duration, so missing LVEF was not independent of outcome (Supplementary Table SIV).

Distribution of phenotypes across etiologies

The distribution of LVEF phenotypes differed markedly by etiology (Table I; $p < 0.001$). Among patients with ischemic etiology, HFrEF was the predominant phenotype (61.2%) and HFpEF comparatively infrequent (15.1%), whereas the non-ischemic group showed a more even distribution with substantially greater representation of HFpEF (34.6%).

Clinical characteristics of ischemic subtypes

Within the ischemic stratum, the three phenotypes diverged across multiple domains (Table II; Supplementary Figures S1 and S2). A graded relationship with declining ejection fraction was evident for natriuretic peptide concentration and other continuous characteristics (median NT-proBNP 722, 1,624 and 3,284 pg/ml in HFpEF, HFmrEF

Table I. Distribution of heart failure subtypes across etiological groups

HF subtype	Ischemic (n = 498)	Non-ischemic (n = 712)	*P*-value
HFrEF	305 (61.2)	322 (45.2)	< 0.001
HFmrEF	118 (23.7)	144 (20.2)	
HFpEF	75 (15.1)	246 (34.6)	

Restricted to the 1,210 patients with documented LVEF. Values are n (column %). HFmrEF – heart failure with mildly reduced ejection fraction, HFpEF – preserved ejection fraction, HFrEF – reduced ejection fraction.

Table II. Clinical characteristics of patients with ischemic heart failure stratified by ejection-fraction phenotype

Characteristic	All ischemic (n = 498)	HFpEF (n = 75)	HFmrEF (n = 118)	HFrEF (n = 305)	*P*-value overall	*P*-value pEF vs. mrEF	*P*-value pEF vs. rEF	*P*-value mrEF vs. rEF
Demographics								
Age [years]	69.8 (64.0–76.2)	72.8 (66.0–80.6)	70.5 (64.9–75.9)	69.2 (62.8–75.8)	0.016	0.102	0.006	0.179
Sex								
Female	98 (19.7)	25 (33.3)	27 (22.9)	46 (15.1)	0.001	0.153	< 0.001	0.078
Male	400 (80.3)	50 (66.7)	91 (77.1)	259 (84.9)				
Comorbidities								
Arterial hypertension	363 (72.9)	60 (80.0)	88 (74.6)	215 (70.5)	0.226	0.488	0.132	0.474
Atrial fibrillation	226 (45.4)	32 (42.7)	42 (35.6)	152 (49.8)	0.027	0.405	0.325	0.011
Diabetes mellitus	241 (48.4)	35 (46.7)	51 (43.2)	155 (50.8)	0.355	0.748	0.606	0.196
Stroke or transient ischemic attack	41 (8.2)	9 (12.0)	11 (9.3)	21 (6.9)	0.312	0.724	0.218	0.519
Chronic kidney disease	162 (32.5)	26 (34.7)	30 (25.4)	106 (34.8)	0.169	0.224	1.000	0.084

Table II. Cont.

Characteristic	All ischemic (*n* = 498)	HFpEF (*n* = 75)	HFmrEF (*n* = 118)	HFrEF (*n* = 305)	*P*-value overall	*P*-value pEF vs. mrEF	*P*-value pEF vs. rEF	*P*-value mrEF vs. rEF
Criteria of ischemic etiology								
Myocardial infarction	372 (74.7)	46 (61.3)	79 (66.9)	247 (81.0)	< 0.001	0.521	< 0.001	0.003
PCI	305 (61.2)	40 (53.3)	66 (55.9)	199 (65.2)	0.066	0.837	0.075	0.096
CABG	99 (19.9)	13 (17.3)	30 (25.4)	56 (18.4)	0.220	0.255	0.968	0.138
Anthropometric and vital signs								
Body mass index [kg/m^2]	27.5 (24.9–31.2)	28.7 (25.9–32.4)	27.2 (24.8–32.0)	27.4 (24.7–30.8)	0.109	0.220	0.031	0.561
Heart rate [beats/min]	75.0 (65.0–85.0)	72.0 (63.0–80.0)	72.5 (63.2–81.8)	76.0 (67.0–89.0)	0.007	0.452	0.006	0.030
Systolic blood pressure [mm Hg]	127 (114–140)	130 (120–147)	130.0 (116.2–144.0)	122.0 (110.0–136.0)	< 0.001	0.713	< 0.001	< 0.001
Diastolic blood pressure [mm Hg]	77.0 (70.0–83.8)	80.0 (73.5–85.0)	78.0 (70.0–84.5)	75.0 (68.0–82.0)	0.018	0.263	0.008	0.110
Lab tests								
NT-proBNP [pg/ml]	2368 (863–6544)	722 (307–2567)	1624 (548–4110)	3284 (1162–7661)	< 0.001	0.098	< 0.001	0.001
Heart failure details								
Heart failure duration [years]	4.1 (1.1–11.3)	2.3 (0.9–7.3)	2.9 (1.0–8.9)	5.1 (1.5–12.5)	0.002	0.598	0.004	0.008
NYHA class								
I/II	271 (54.4)	49 (65.3)	75 (63.6)	147 (48.2)	0.002	0.923	0.011	0.006
III/IV	227 (45.6)	26 (34.7)	43 (36.4)	158 (51.8)				
Treatment								
ACE inhibitor or ARB	328 (66.4)	68 (91.9)	98 (83.8)	162 (53.5)	< 0.001	0.161	< 0.001	< 0.001
B-blocker	458 (92.7)	65 (87.8)	103 (88.0)	290 (95.7)	0.005	1.000	0.022	0.008
SGLT2 inhibitor	356 (72.1)	26 (35.1)	65 (55.6)	265 (87.5)	< 0.001	0.009	< 0.001	< 0.001
MRA	355 (71.9)	25 (33.8)	71 (60.7)	259 (85.5)	< 0.001	< 0.001	< 0.001	< 0.001
ARNI	128 (25.7)	1 (1.3)	11 (9.3)	116 (38.0)	< 0.001	0.031	< 0.001	< 0.001
Oral anticoagulant (DOAC + VKA)	240 (48.6)	32 (43.2)	44 (37.6)	164 (54.1)	0.006	0.533	0.121	0.003
Statins	450 (91.1)	68 (91.9)	102 (87.2)	280 (92.4)	0.233	0.437	1.000	0.137
ICD	129 (26.0)	4 (5.3)	10 (8.5)	115 (37.8)	< 0.001	0.592	< 0.001	< 0.001
CRT	49 (9.9)	1 (1.3)	5 (4.2)	43 (14.1)	< 0.001	0.408	0.004	0.007
Clinical outcomes								
Deaths	74 (14.9)	9 (12.0)	7 (5.9)	58 (19.0)	0.002	0.222	0.208	0.001
Follow-up [months]	14.9 (11.9–18.4)	14.4 (12.2–18.0)	15.7 (13.2–18.9)	14.8 (11.3–18.2)	0.078	0.122	0.650	0.029

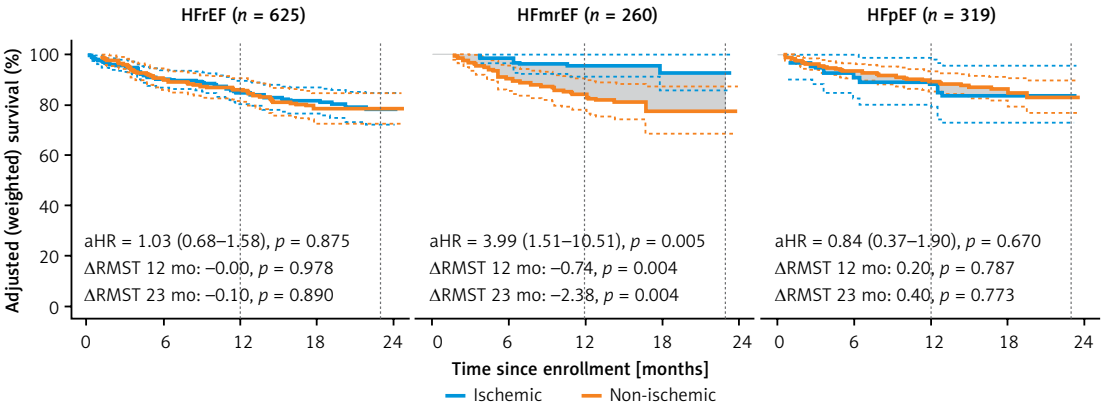
Restricted to ischemic patients with documented LVEF (n = 498); 81 ischemic patients without LVEF were not included. Continuous variables are median (Q1–Q3); categorical variables n (%). Overall p from the Kruskal–Wallis or χ^2/Fisher test; pairwise p-values are unadjusted and exploratory. CABG – coronary artery bypass grafting, PCI – percutaneous coronary intervention, other abbreviations as in Table I.

and HFrEF, respectively; $p < 0.001$; Supplementary Figure S1), as well as for disease-modifying therapy and device use, with mineralocorticoid receptor antagonists, sodium–glucose cotransporter-2 inhibitors, angiotensin receptor–neprilysin inhibitors, implantable cardioverter-defibrillators and cardiac resynchronization therapy all increasing as ejection fraction fell (Supplementary Figure S2). Notably, crude mortality among the ischemic patients was lowest in HFmrEF (5.9%), intermediate in HFpEF (12.0%) and highest in HFrEF (19.0%).

Etiology, phenotype and all-cause mortality

In the overall cohort, crude mortality was identical between etiological groups (ischemic 90/579 [15.5%] vs. non-ischemic 129/831 [15.5%]; log-rank $p = 0.93$), indicating no association between etiology and mortality when phenotype was ignored. A different picture emerged on phenotype-stratified, entropy-balanced analysis, in which, as expected under entropy balancing, first-moment balance was exact by construction (all standardized mean differences = 0.00). Deaths by etiology within each phenotype were 58/305 vs. 48/322 in HFrEF, 7/118 (5.9%) vs, 28/144 (19.4%) in HFmrEF, and 9/75 vs. 33/246 in HFpEF (ischemic versus non-ischemic). In HFrEF the weighted survival curves were essentially superimposable (aHR = 1.03, 95% CI: 0.68–1.58; $p = 0.875$), and in HFpEF no difference was detected (aHR = 0.84, 95% CI: 0.37–1.90; $p = 0.670$), although the wide interval, reflecting only 75 ischemic patients, does not exclude a clinically relevant effect. In HFmrEF, by contrast, non-ischemic etiology was associated with a nearly fourfold higher mortality hazard (aHR = 3.99, 95% CI: 1.51–10.51; $p = 0.005$) – the only statistically significant stratum-specific association (Figure 1). The formal etiology-by-phenotype interaction confirmed that the effect of etiology was not uniform across phenotypes (Wald $\chi^2 = 6.89$; $p = 0.032$). The proportional-hazards assumption was satisfied in all strata (Schoenfeld global $p > 0.05$). The weighted analyses are fitted on the analytic sample with complete follow-up and balancing covariates (HFrEF 625, HFmrEF 260, HFpEF 319; 105, 34 and 42 events, respectively); the 6 patients excluded from the full phenotype counts in Table I lacked complete follow-up or covariates, one of them (in HFmrEF) having died, which reconciles the 35 phenotype deaths with the 34 events in the fitted model. Figure 1 show the analytic sample entering the weighted models (HFrEF $n = 625$, HFmrEF $n = 260$, HFpEF $n = 319$); Table I reports the full phenotype distribution (627, 262 and 321).

The HFmrEF association proved both clinically substantial and statistically robust. On the absolute scale, non-ischemic etiology was associated with a loss of –2.38 months of survival over 23 months (95% CI: –3.69 to –1.00; $p = 0.004$) and –0.74 months over 12 months (95% CI: –1.25 to –0.24; $p = 0.004$), whereas the RMST difference was negligible in HFrEF and HFpEF. The E-value for the HFmrEF estimate was 4.55 (lower confidence limit 1.99), indicating that an unmeasured confounder would need to be associated with both etiology and mortality by a risk ratio of at least 1.99 to render the lower confidence bound compatible with the null.



Dashed: 95% confidence limits. Shaded: between curve area to τ = 23 mo (ΔRMST). Dotted verticals: 12 and 23 mo.

Number at risk															
Ischemic	304	268	212	81	3	117	114	95	37	0	75	70	60	19	0
Non-ischemic	321	291	236	97	4	143	126	101	31	0	344	226	171	60	0

Figure 1. Adjusted (weighted) survival by heart failure etiology (ischemic vs. non-ischemic) within LVEF phenotypes. Curves are entropy-balanced Kaplan–Meier estimates; dashed lines denote 95% pointwise confidence limits; the shaded area represents the between-curve difference up to τ = 23 months (the restricted mean survival time difference), with dotted verticals at 12 and 23 months. Adjusted hazard ratios and ΔRMST values are annotated within each panel

Sensitivity analyses

The HFmrEF finding was stable across the entire sensitivity battery (Supplementary Table SI): the adjusted hazard ratio was 4.25 (crude), 3.99 (entropy balancing, primary), 4.09 (doubly robust), 4.05 (stabilized inverse-probability weighting), and 3.60 (multiple imputation). Additionally balancing on $\log_{10}$(NT-proBNP) in the subset with available values (n = 157, 24 events) yielded aHR 4.98 (95% CI: 1.25–19.76), within this available case subsample, which differed from the remainder of the stratum (Supplementary Table SVII), the estimate remained consistent with the primary result. Effective sample sizes and maximum weights for all three strata are reported in Supplementary Table SII; in HFmrEF the effective sample sizes were 91 (ischemic) and 125 (non-ischemic) with a maximum weight of 6.95, consistent with adequate overlap, whereas the larger maximum weight in HFpEF (19.32) reflects more limited overlap and the corresponding imprecision of that estimate. In leave-one-out analysis, the adjusted hazard ratio ranged from 3.71 to 5.84 across all 260 re-estimations, never approaching unity, confirming that the association was not driven by individual observations (Supplementary Figure S3). The null associations in HFrEF and HFpEF were likewise consistent across methods. Firth's penalized likelihood regression, which corrects the small-sample bias of the Wald approach, confirmed the HFmrEF association (crude aHR = 3.42, 95% CI: 1.61–8.25; adjusted 2.94, 95% CI: 1.36–7.18), and the profile-likelihood interval for the weighted estimate (1.51–10.51) coincided with the Wald interval, indicating no Hauck-Donner effect (Supplementary Table SV). Additionally balancing on continuous renal function, hemoglobin and left-ventricular end-diastolic diameter left the estimate unchanged to slightly stronger (Supplementary Table SVI).

Discussion

In this large, prospective, multicenter registry with complete mortality ascertainment, we observed that the prognostic relevance of HF etiology was not uniform across LVEF-defined phenotypes. Three principal findings emerged. First, HFmrEF represented approximately one-fifth of the overall HF population, confirming its substantial contribution to the contemporary burden of HF. Second, within the ischemic stratum, patients with HFmrEF displayed clinical characteristics intermediate between those observed in HFpEF and HFrEF, supporting the concept that HFmrEF occupies a distinct position within the HF spectrum. Third, and most importantly, the association between HF etiology and mortality during follow-up was confined to the HFmrEF phenotype. While outcomes were comparable between ischemic and non-ischemic patients in HFrEF and HFpEF, non-ischemic etiology was associated with a nearly fourfold higher adjusted mortality risk among patients with HFmrEF.

The prevalence of HFmrEF in the present cohort (21.7%) is consistent with contemporary registry data indicating that HFmrEF accounts for approximately 15–25% of the overall HF population [20, 21]. In the Swedish Heart Failure Registry, HFmrEF represented approximately 24% of patients, while analyses from the ESC Heart Failure Long-Term Registry and other multinational cohorts reported proportions ranging between 17% and 24% [21–26].

The similarity between the HEROES registry and these contemporary real-world datasets supports the external validity of our findings and confirms that HFmrEF constitutes a substantial proportion of patients encountered in routine clinical practice. Since its formal recognition as a separate phenotype in contemporary HF guidelines, HFmrEF has progressively evolved from being viewed as a simple intermediate category toward a clinically relevant subgroup with distinctive epidemiological, biological, and therapeutic characteristics [7, 14, 15]. Nevertheless, uncertainty persists regarding its pathophysiological identity. Increasing evidence suggests that HFmrEF comprises several distinct trajectories, including patients with recovered LVEF, patients transitioning from HFpEF toward HFrEF, and individuals presenting de novo within the mildly reduced EF range [15, 16]. Such heterogeneity likely contributes to the variability in outcomes reported across studies and complicates efforts to define a uniform prognostic profile for this phenotype [22, 24].

Within the HFmrEF subgroup, ischemic etiology was identified in 45.0% of patients, whereas 55.0% were classified as having non-ischemic HF. This distribution is remarkably similar to observations from large contemporary registries and reviews, including the Swedish Heart Failure Registry, in which ischemic heart disease accounted for approximately 40–55% of HFmrEF cases [26]. The relatively high prevalence of ischemic etiology in our cohort may be explained by the predominantly hospital-based recruitment strategy and the high burden of established cardiovascular disease characteristic of contemporary HF populations. Patients with ischemic HFmrEF demonstrated clinical features that were intermediate between HFpEF and HFrEF, particularly with respect to natriuretic peptide concentrations, disease duration, and implementation of guideline-directed therapies [15, 16]. These observations support the concept that HFmrEF occupies a transitional yet clinically meaningful position within the HF spectrum. At the same time, the non-ischemic HFm-

rEF population remained highly heterogeneous, encompassing dilated, hypertensive, valvular, and other myocardial disorders. Such heterogeneity may partly explain the substantial variability in prognosis observed among HFmrEF cohorts and suggests that etiology may represent an important source of biological heterogeneity within this phenotype [22, 24]. Mortality, the within-phenotype ischemic/non-ischemic distribution, and HF duration for all six phenotype-by-etiology subgroups, including the non-ischemic stratum, are reported in Supplementary Table SIII.

The most important finding of the present analysis relates to the phenotype-specific prognostic significance of HF etiology. Notably, the overall comparison between ischemic and non-ischemic HF revealed no difference in mortality. However, stratification according to LVEF uncovered substantial heterogeneity that would have remained obscured in a pooled analysis. This observation illustrates the limitations of treating HF as a homogeneous syndrome and highlights the importance of phenotype-specific investigation.

In patients with HFrEF, etiology did not independently influence survival during follow-up after adjustment for baseline characteristics [12, 17, 18]. This finding is consistent with previous studies suggesting that in advanced systolic dysfunction, prognosis is predominantly determined by the severity of ventricular impairment, neurohormonal activation, and response to guideline-directed medical therapy rather than by the initial etiological insult. Similarly, no significant association between etiology and mortality was observed in HFpEF. However, interpretation of the HFpEF results requires caution because of the relatively small number of ischemic patients and limited statistical power [23].

In contrast, HFmrEF emerged as the only phenotype in which etiology carried substantial prognostic information. This finding contrasts with observations from predominantly HFrEF populations, where ischemic etiology is often associated with worse outcomes [11, 17, 18]. One possible explanation is the marked heterogeneity of HFmrEF. Patients with ischemic HFmrEF frequently have established coronary disease and access to effective secondary prevention and revascularization strategies [23, 24], whereas non-ischemic HFmrEF encompasses diverse myocardial disorders, including cardiomyopathic, inflammatory, valvular, and hypertensive forms of heart disease [9, 10]. Consequently, non-ischemic HFmrEF may identify a subgroup with ongoing myocardial remodeling and disease progression that is not fully reflected by LVEF alone. This interpretation is consistent with emerging evidence indicating substantial biological heterogeneity within the HFmrEF population. The prognostic impact of etiology in HFmrEF remains insufficiently studied [24]. While previous reports, largely based on HFrEF populations, have often associated ischemic etiology with worse outcomes, we observed the opposite pattern within the HFmrEF subgroup, with higher mortality among patients with non-ischemic HF. One possible explanation is the marked heterogeneity of non-ischemic HFmrEF, which may include patients with progressive myocardial disease and less clearly defined therapeutic targets [22, 25]. In contrast, patients with ischemic HFmrEF may benefit from established secondary prevention strategies and coronary revascularization, potentially contributing to their more favorable prognosis. Interestingly, the observed effect was driven by significantly worse outcomes among patients with non-ischemic HFmrEF. This finding challenges the traditional expectation that ischemic heart disease invariably confers the greatest risk across the HF spectrum. Several explanations may account for this observation. Patients classified as having ischemic HFmrEF often have a clearly identifiable disease substrate, established secondary prevention pathways, and opportunities for coronary revascularization and intensive risk-factor modification [24]. In contrast, the non-ischemic HFmrEF population represents a heterogeneous group encompassing dilated, hypertensive, valvular, and other forms of myocardial disease. Such heterogeneity may include patients with advanced myocardial remodeling, progressive cardiomyopathy, or unrecognized pathological processes that are less amenable to targeted intervention. Because the HFmrEF estimate rests on only seven deaths in the ischemic arm (5.9%, lower than ischemic HFpEF at 12.0% despite higher natriuretic peptide), the data are equally compatible with an unexpectedly favorable prognosis in ischemic HFmrEF as with a worse prognosis in the non-ischemic arm; with so few events, chance may contribute materially to the estimate.

The present findings therefore support the growing concept that HFmrEF should not be regarded solely as a transitional phenotype but rather as a clinically meaningful subgroup requiring dedicated investigation and individualized risk stratification [16]. The significant interaction between etiology and HF phenotype suggests that the biological mechanisms driving disease progression may differ substantially across the LVEF spectrum [15, 22, 25]. Consequently, prognostic markers identified in HFrEF or HFpEF cannot necessarily be extrapolated to HFmrEF [22, 25].

From a clinical perspective, our observations suggest that careful etiological characterization may be particularly important in patients with HFmrEF. Whereas ischemic and non-ischemic eti-

ologies appeared to have limited prognostic implications in HFrEF and HFpEF, respectively, etiology provided meaningful risk stratification within the HFmrEF population. These findings raise the possibility that non-ischemic HFmrEF may represent a subgroup requiring closer surveillance and potentially more individualized management strategies. Whether more intensive diagnostic evaluation or phenotype-specific therapeutic approaches can improve outcomes in this population remains uncertain and warrants further investigation.

Taken together, our findings provide further evidence that HFmrEF occupies a unique position within the HF continuum. The observation that the prognostic impact of etiology was confined to HFmrEF, despite the absence of any overall association between etiology and mortality, underscores the importance of considering phenotype-specific mechanisms in contemporary HF research. Given the relatively limited number of events within the HFmrEF subgroup, these findings should be regarded as hypothesis-generating and require confirmation in larger cohorts. Nevertheless, they support the growing recognition of HFmrEF as a distinct and clinically relevant phenotype deserving dedicated investigation in future studies.

Strengths include the prospective multicenter design, classification of etiology at enrolment rather than at analysis, complete mortality ascertainment through national linkage with no loss to follow-up, and a rigorous causal-inference framework combining entropy balancing, a formal interaction test, a proportional-hazards-free RMST analysis, an E-value, and a comprehensive sensitivity battery.

Several limitations temper interpretation. First, as an observational study, residual and unmeasured confounding cannot be excluded, although the E-value indicates moderate robustness. In addition, NT-proBNP, an established marker of HF severity and prognosis, was incompletely recorded and was therefore not included in the primary confounder set. Although additional entropy balancing on $\log_{10}$(NT-proBNP) in the subset with available measurements yielded results consistent with the primary analysis, this available-case approach does not fully account for missing NT-proBNP data and cannot exclude residual confounding related to natriuretic peptide concentration. Second, the HFmrEF stratum contained few events (34), so the confidence interval is wide and the doubly robust model – which adds covariates to an event-sparse outcome model – is susceptible to overfitting and is therefore regarded as supportive rather than definitive; the concordant stabilized-weighting, multiple-imputation and Firth's penalized-likelihood results mitigate but do not remove this concern, and no analytic method adds information beyond the available events. Third, LVEF-based classification was missing in 14.2% of patients; the primary analysis used complete cases, with multiple imputation as a sensitivity analysis. Fourth, only all-cause mortality was available, without adjudication of cause-specific or cardiovascular death. Fifth, because three phenotype strata were examined, the stratum-specific and pairwise comparisons are exploratory; the interaction test provides the principled inference. Finally, this is a single-country registry, which may limit the generalizability of our findings. The binary ischemic/non-ischemic classification was based on documented prior myocardial infarction and/or coronary revascularization and therefore does not exclude clinically relevant coronary artery disease in patients without these events. The non-ischemic category should consequently not be interpreted as equivalent to the absence of coronary artery disease and necessarily simplifies a continuum of myocardial pathology. The 12 patients who died during the index hospitalization were excluded by design; this removes the earliest and highest-risk events and may attenuate absolute mortality and between-group differences. Because individual phenotype and covariate data for these patients were not part of the analytic dataset, a bounding sensitivity analysis was performed (Supplementary Table SVIII): under proportional allocation the HFmrEF association was essentially unchanged (risk ratio 2.98, $p = 0.002$) and retained its direction even in the implausible worst-case scenario in which all 12 deaths were assigned to the ischemic HFmrEF subgroup, with at least six of the twelve required in that subgroup (which comprises only ~8% of the cohort) to abolish crude significance. Importantly, LVEF phenotype is measured at enrolment, downstream of the etiological exposure; stratifying on this post-exposure variable conditions on a potential collider, and the sensitivity, RMST and E-value analyses, which all condition on the same stratification, cannot exclude that part of the HFmrEF association is design-induced [27, 28]. Myocardial fibrosis and systematic chamber-geometry imaging were not collected; where surrogate data existed (renal function, hemoglobin, ventricular diameter), additional balancing did not materially alter the HFmrEF estimate (Supplementary Table SVI).

In conclusion, in a nationwide prospective HF registry, the prognostic impact of ischemic versus non-ischemic etiology was phenotype-dependent and concentrated within HFmrEF, where non-ischemic etiology was associated with higher all-cause mortality during follow-up despite an entirely neutral overall comparison. The etiology-by-phenotype interaction, the consistent RMST and sensitivity findings, and the robustness to un-

measured confounding are consistent with a phenotype-specific association, although, because they all condition on the same post-exposure stratification, they cannot by themselves establish that the association is not partly design-induced [28–30]. Given the limited number of events, these results are hypothesis-generating and call for confirmation in larger, adequately powered cohorts.

Data availability

Data are held by the HEROES registry and may be available from the corresponding author on reasonable request, subject to governance and data protection constraints. The analysis was implemented as a numbered, reproducible R pipeline; analysis code is available from the authors on request.

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Ethical approval

The Bioethics Committee of the Medical University of Lodz approved the HEROES study (No. RNN/316/20/KE, with update KE/762/23). Informed consent was obtained from all participants.

Conflict of interest

The authors declare no conflict of interest.

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