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ORIGINAL RESEARCH

Characterizing Heart Failure Across the Spectrum of the Preserved Ejection Fraction: Does Heart Failure With Supranormal Ejection Fraction Exist? Data From the Swedish Heart Failure Registry

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BACKGROUND: Sparce data suggest higher mortality in heart failure (HF) with left ventricular ejection fraction (EF) >65% to 70%. We characterized EF distribution, characteristics, and outcomes in patients with HF and EF ≥50%.

METHODS AND RESULTS: There were 5576 patients enrolled in the Swedish HF registry between 2017 and 2021 and included in the study; 21% had EF ≥60%, 5% EF ≥65%, and 1.5% EF ≥70%. Patient characteristics independently associated with EF ≥60% were assessed by multivariable logistic regression and were identified as being a diagnosis of hypertrophic cardiomyopathy, worse New York Heart Association class, hypertension, and valvular disease, whereas use of medications and devices also recommended for HF with reduced EF, male sex, history of ischemic heart disease, peripheral artery disease, and chronic obstructive pulmonary disease were associated with an EF of 50% to 59%. Outcomes (all-cause, cardiovascular, and noncardiovascular death; all-cause and HF hospitalizations) were assessed by univariable and multivariable Cox regressions with EF modeled as a spline. The risk of all-cause and noncardiovascular mortality and first all-cause hospitalization was higher with EF values >55% in crude but not adjusted analyses.

CONCLUSIONS: Among patients with HF with preserved EF, 21% had EF ≥60%. A higher EF was characterized by more severe symptoms, hypertrophic cardiomyopathy, hypertension, female sex, and valvular disease. Crude higher but not adjusted risk of all-cause and noncardiovascular mortality and of all-cause hospitalization was observed with EF values >55%, suggesting that prognostically impactful conditions were more prevalent in the upper bound of the EF spectrum.

Key Words: heart failure ■ heart failure with preserved ejection fraction ■ heart failure with supranormal ejection fraction ■ registry ■ SwedeHF

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Left ventricular (LV) ejection fraction (EF) is the most used parameter to quantify LV systolic function for diagnostic and prognostic purposes, and is commonly used for treatment selection and as inclusion criterion in clinical studies in heart failure (HF).[1] The current paradigm considers an inverse relationship between EF and risk of cardiovascular outcomes up to an EF of 40% to 45%.[2,3] However, recent studies have suggested a U-shaped relationship between EF and risk of death,[4,5] leading to the hypothesis of the

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CLINICAL PERSPECTIVE

What Is New?

- In heart failure with preserved ejection fraction, a higher ejection fraction was associated with hypertrophic cardiomyopathy, hypertension, and valvular disease, and was more likely in women and in more symptomatic patients.
- After adjustments, a higher ejection fraction was not linked with worse prognosis.

What Are the Clinical Implications?

- When a high ejection fraction is observed during an echocardiographic exam, clinicians should consider underlying conditions such as cardiomyopathies or valvular disease.

Nonstandard Abbreviations and Acronyms

HCM	hypertrophic cardiomyopathy
SwedeHF	Swedish Heart Failure registry

existence of a further phenotype in the upper range of the EF spectrum (ie, HF with supranormal EF).

The evidence that sacubitril/valsartan may reduce mortality/morbidity only in patients with EF below ~60% and the potential attenuation of empagliflozin effect with an EF ≥65% might corroborate the existence of the HF with supranormal EF phenotype.[6,7] The latter finding, however, was not confirmed with dapagliflozin in the DELIVER trial (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure).[8] Additionally, some previous analyses of HF populations failed to demonstrate a U-shaped relationship between EF and risk of death and hospitalization.[9,10]

Previous studies on supranormal EF have been heterogenous in terms of cutoffs for supernormality (EF 65%–70%), of enrolled populations (mixed,[5] critically ill,[11] acute HF,[9,12] chronic HF,[10] patients under investigation for coronary artery disease,[13–15] healthy individuals[16]), and had either small sample size or low data granularity. Most of them poorly controlled for confounding, and there was limited availability of data on cardiomyopathies characterized by an EF ≥60% (eg, cardiac amyloidosis, hypertrophic cardiomyopathy [HCM]).[4,11,16]

Therefore, in an HF population with EF ≥50% from a large and well-characterized nationwide registry, we aimed to investigate the EF distribution and the patient characteristics and outcomes associated with increasing EF.

METHODS

Data Sources

The ongoing SwedeHF (Swedish Heart Failure) registry collects data on both out- and inpatients, mostly from specialized care in Sweden.[17] A clinical diagnosis of HF is the only inclusion criterion, which has been defined after April 2017 as an *International Statistical Classification of Diseases, Tenth Revision* (*ICD-10*) code I50.0, I50.1, I50.9, I42.0, I42.6, I42.7, I25.5, I11.0, I13.0, or I13.2. About 80 baseline variables were collected (ie, demographics, organizational and clinical characteristics, comorbidities, and treatments). Since 2017, EF can be registered not only as a categorical variable (ie, <30%, 30%–39%, 40%–49%, ≥50), but also as a continuous measurement. The coverage of the registry was 32% for prevalent HF, and >90% of the Swedish hospitals enrolled patients in 2021.[17,18]

For the current analysis, SwedeHF was linked through the unique personal identification number, which all residents in Sweden have, with (1) the Cause of Death Register providing date and cause of death, (2) the National Patient Register providing data on cause-specific hospitalizations as outcomes and additional comorbidities, and (3) Statistics Sweden for socioeconomical data. The index date was defined as either the day of the outpatient visit or of hospital discharge linked with the registration in SwedeHF. Patients who died during the index hospitalization were excluded.

The study, including the linkage across different registries, was approved by the Swedish Ethical Review Authority. Individual consent was not required, but patients were informed of entry into SwedeHF and able to opt out.

Study Population

Patients enrolled in SwedeHF between January 1, 2017 and December 31, 2021 were considered (due to the availability of EF as a continuous measurement from 2017). Patients with an EF ≥50% were included. If the same patient had multiple registrations in SwedeHF, the first one was selected to allow for longer follow-up. Patients with EF >80% were excluded, because they were considered potential outliers (n=4). A flowchart presenting patient selection is shown in Figure S1.

Statistical Analysis

The data that support the findings of this study are available from the corresponding author, provided that data sharing is permitted by European Union General Data Protection Regulation regulations and appropriate ethics committees.

Patient characteristics for the EF groups (EF 50%–59% and EF ≥60%) were compared using the *t* test or

Wilcoxon rank sum test for continuous variables, depending on their distribution, and the χ^2 test for categorical variables.

Patient characteristics independently associated with an EF ≥60% were evaluated through multivariable logistic regression, with EF ≥60% (versus EF 50%–59%) as the dependent variable and selected patient characteristics (marked with the superscript * in the Table) as covariates. Results were reported as odds ratio (OR) with 95% CI.

Two sensitivity analyses were performed: (1) categorizing EF as ≥65% versus <65%, and (2) excluding patients with amyloidosis and HCM, because they could be considered as separate entities mimicking HF.

We separately analyzed the following outcomes: all-cause, cardiovascular, and noncardiovascular mortality, time to first HF hospitalization, and all-cause hospitalization. The associations between continuous EF values and outcomes were assessed by Cox proportional hazards models (unadjusted and adjusted for all the variables marked with the superscript * in the Table) with EF modeled with a restricted cubic spline with 3 knots placed according to the percentiles. The assumptions of the Cox models (the proportional hazard assumption and the presence of influential outliers) were checked visually. For the variable hospitalized at enrolment, there was signal for nonproportional hazard, and this variable was therefore stratified for in the models instead of included as a covariate.

Associations between EF and outcomes were also assessed with EF categorized as 50% to 54% (as reference), 55% to 59%, 60% to 64%, ≥65%, and the results were reported as event rate and hazard ratio (HR) with 95% CI. Censoring was performed at death, if itself not the outcome, or emigration from Sweden on December 31, 2021. Missing data for the variables included in the multivariable models were handled by multiple imputations (10 imputed data sets, 10 iterations, R package: mice). A list with variable source and definition is included in Table S1. All analyses were performed using the statistical software R version 4.1.1.

RESULTS

Baseline Characteristics

Of 5576 patients with heart failure with preserved ejection fraction (HFpEF) included in the analyses (median age 76 years [68–82]; 45% women), 1180 (21%) had an EF ≥60%, 299 (5%) had an EF ≥65%, and 86 (1.5%) had an EF ≥70 (Figure 1).

Baseline Characteristics

Baseline characteristics are presented in Table 1. Compared with patients with EF 50% to 59%, patients with EF ≥60% were older, women, had lower income, higher New York Heart Association class, more likely had a diagnosis of hypertension, valvular disease, and HCM. They were less likely to have a diagnosis of ischemic heart disease and peripheral artery disease, and to be treated with β-blockers, renin-angiotensin system inhibitors/angiotensin renin-neprilysin inhibitors, mineralocorticoid receptor antagonists, anticoagulants, and HF devices (implantable cardioverter-defibrillator or cardiac resynchronization therapy). They were more commonly scheduled for follow-up in specialty care and hospitalized at enrolment, whereas they were less likely to be referred to a HF nurse-led unit.

Independent Associations Between Patient Characteristics and EF

Independent associations between patient characteristics and EF ≥60% are shown in Figure 2. A diagnosis of HCM, a scheduled follow-up in specialty care, higher New York Heart Association class, hypertension, and valvular disease were all independently associated with an EF ≥60%. Conversely, having an HF device, a follow-up in an HF nurse-led unit, male sex, treatment with β-blockers, anticoagulants, renin-angiotensin system inhibitors/angiotensin renin-neprilysin inhibitors, a history of peripheral artery disease, ischemic heart disease, and higher heart rate were associated with EF 50% to 59%. The sensitivity analysis considering an EF ≥65% as the cutoff and the one excluding patients with HCM and amyloidosis showed overall consistent results, although statistical significance was often not achieved due to the more limited sample size (Figures S2 and S3).

Outcome Analysis

During a median follow-up time of 25 months (interquartile range, 12–38 months), a total of 1218 (22%) patients died, and of these, 588 (48%) of cardiovascular causes, and 985 (18%) were hospitalized for HF.

The unadjusted spline analysis showed an increasing risk of all-cause and noncardiovascular mortality and of all-cause hospitalization up to EF ~55%, but no association between EF and the remaining outcomes. After adjustments, there were no differences in risk of any of the outcomes assessed across the EF spectrum (Figure 3). Modeling EF as a categorical variable in 4 strata led to consistent results (Table S2; patient characteristics of the population according to the EF strata reported in Table S3).

The outcome analysis excluding patients with HCM and amyloidosis yielded consistent findings (Figure S4 and Table S4).

DISCUSSION

We investigated EF distribution, heterogeneity in patient characteristics, and prognosis across the EF

Table 1. Baseline Characteristics

Characteristic	EF 50%–59%	EF ≥60%		
n=5576	4396 (79%)	1180 (21%)	*P* value	Missing
Sociodemographics				
Sex, men*	2513 (57%)	564 (48%)	<0.001	0.00%
Age, y	76 [68–82]	77 [69–83]	0.046	0.00%
≥75 y*	2445 (56%)	692 (59%)	0.068	0.00%
Education*			0.881	1.2%
Compulsory school	1474 (34%)	405 (35%)		
Secondary school	1865 (43%)	494 (42%)		
University	1002 (23%)	267 (23%)		
Income ≥ medium for index y*	2246 (51%)	546 (46%)	0.004	0.1%
With children*	3734 (85%)	1013 (86%)	0.465	0.00%
Organization				
Hospitalized*	571 (13%)	208 (18%)	<0.001	0.00%
Follow-up in HF unit*	3082 (76%)	754 (70%)	<0.001	7.5%
Follow-up in specialty care*	2569 (61%)	783 (70%)	<0.001	4.4%
Clinical and laboratory variables				
NYHA III–IV*	1046 (31%)	313 (39%)	<0.001	26.1%
BMI ≥30 kg/m^2*	1038 (34%)	293 (35%)	0.554	30.9%
MAP, mm Hg	93±12	93±13	0.76	4.3%
MAP ≥90 mm Hg*	2321 (56%)	636 (57%)	0.616	5.9%
HR, bpm	70 [61–80]	70 [60–80]	0.760	4.3%
HR ≥70 bpm*	1900 (47%)	506 (46%)	0.826	7.4%
eGFR class*			0.084	6.3%
30–59 mL/min per 1.73m^2	2514 (61%)	639 (58%)		
≥60 mL/min per 1.73m^2	1434 (35%)	404 (37%)		
<30 mL/min per 1.73 m^2	175 (4%)	60 (5%)		
NT-proBNP, pg/L	1250 [476–2550]	1353 [520–2850]	0.092	21.8%
NT-proBNP ≥ median*	1692 (49%)	489 (52%)	0.104	21.8%
Comorbidities				
Diabetes*	1191 (27%)	329 (28%)	0.615	0.00%
Hypertension*	3327 (76%)	946 (80%)	0.001	0.00%
IHD*	1787 (41%)	439 (37%)	0.035	0.00%
PAD*	402 (9%)	85 (7%)	0.041	0.00%
Stroke/TIA*	658 (15%)	185 (16%)	0.576	0.00%
AF*	2794 (64%)	740 (63%)	0.616	0.00%
Valvular disease*	1214 (28%)	379 (32%)	0.003	0.00%
Cancer*	625 (14%)	164 (14%)	0.816	0.00%
COPD*	593 (13%)	147 (12%)	0.379	0.00%
Musculoskeletal disease*	1550 (35%)	445 (38%)	0.127	0.00%
Amyloidosis*	480 (11%)	153 (13%)	0.055	0.00%
Aortic stenosis	361 (8%)	137 (12%)	<0.001	0.00%
HCM*	22 (1%)	41 (3%)	<0.001	0.00%
Hemochromatosis	13 (0%)	0 (0%)	0.126	0.00%
Anemia*	1290 (34%)	352 (35%)	0.722	14.2%
Smoking*	229 (8%)	48 (7%)	0.294	33.9%
Treatments				
β-Blockers*	3793 (86%)	955 (81%)	<0.001	0.1%

(*Continued*)

Table 1. Continued

Characteristic	EF 50%–59%	EF ≥60%		
n=5576	4396 (79%)	1180 (21%)	*P* value	Missing
RASi/ARNi*	3451 (79%)	827 (70%)	<0.001	0.3%
MRA*	1780 (41%)	409 (35%)	<0.001	0.2%
Diuretics*	3100 (71%)	841 (71%)	0.599	0.2%
Nitrates*	381 (9%)	103 (9%)	0.996	0.2%
Antiplatelets*	955 (22%)	275 (23%)	0.265	0.2%
Anticoagulants*	2637 (60%)	656 (56%)	0.008	0.1%
Statins*	2112 (48%)	538 (46%)	0.144	0.2%
Digoxin*	413 (9%)	117 (10%)	0.614	0.1%
CRT/ICD*	261 (6%)	37 (3%)	<0.001	0.3%

Data are presented as absolute (relative) frequency, mean±SD, and median [interquartile range], and were compared by χ^2 test, *t* test, and Wilcoxon rank sum test, respectively. AF indicates atrial fibrillation; ARNi, angiotensin receptor-neprilysin inhibitor; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; EF, ejection fraction; eGFR, estimated glomerular filtration rate (calculated by Chronic Kidney Disease Epidemiology Collaboration formula); HCM, hypertrophic cardiomyopathy; HF, heart failure; HR, heart rate; ICD, implantable cardioverter-defibrillator; IHD, ischemic heart disease; MAP, mean arterial pressure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association functional class; PAD, peripheral artery disease; RASi, renin-angiotensin system inhibitor; and TIA, transient ischemic attack.

*Labeled variables were included in the multiple imputation, in the multivariable logistic regression, and in the adjusted Cox proportional hazards models.

spectrum within the HFpEF subtype (EF ≥50%) in a well-characterized national registry cohort. We observed that (1) ~20% had an EF ≥60% and ~5% had an EF ≥65%; (2) the patients with a higher EF, regardless of the adopted cutoff, were more likely women, with worse functional class, HCM, hypertension, and valvular disease; (3) crude, but not adjusted risk of all-cause and noncardiovascular mortality and of all-cause hospitalization was higher, with EF values ≥55%.

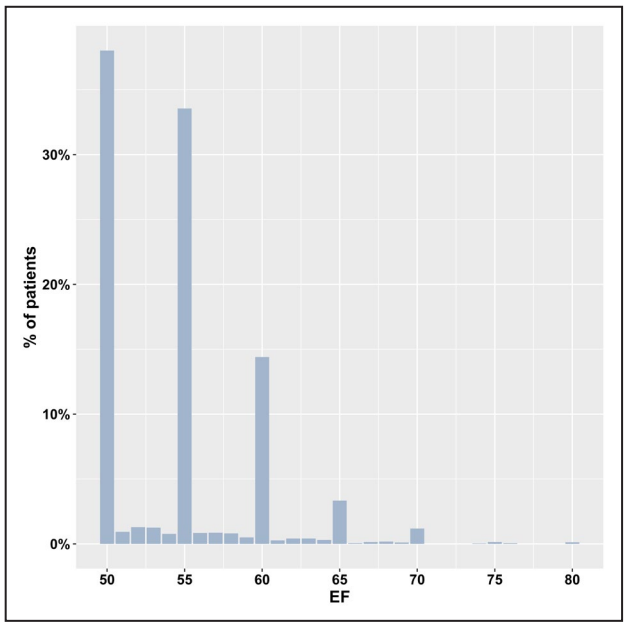

Figure 1. Distribution of EF.
EF indicates ejection fraction.

EF Distribution

In our HF cohort, the proportion of patients with EF ≥60%, ≥65%, and ≥70% was 21%, 5.4%, and 1.5%, respectively. These estimates are lower than in a previous analysis of the RELAX-AHF-2 (RELAXin in Acute Heart Failure-2) study enrolling patients with acute HF, where the group with EF ≥65% accounted for almost 10% of the population with EF ≥50%.[12] Even higher proportions have been previously reported. In an individual patient level meta-analysis of 6 HF trials, an EF ≥60% was observed in 42% of patients with an EF >50%.[10] In a Japanese study enrolling hospitalized patients with HF with EF ≥50%, as many as 37% had EF ≥65%.[9] The higher prevalence of a higher EF in trials versus our registry analysis might be due to specific trial selection criteria and enriching strategies, but underreporting in the SwedeHF of patients with cardiomyopathies and/or higher EF is another potential explanation. Consistently, it has been previously observed that an EF of ≥70% or a high genetic risk score for EF ≥70% was associated with a decreased probability of diagnosing HF together with higher mortality.[19] The heterogeneity among the provided estimates highlights that further epidemiological studies are needed to better define the prevalence of HF across the EF spectrum.

Patient Profiles Associated With Higher EF

Patients with EF ≥60% were more likely women, which is in line with previous research showing that women have higher EF than men, and that EF increases more in women versus men with aging, with a significant drop in LV end-diastolic volume.[20] Patients with EF

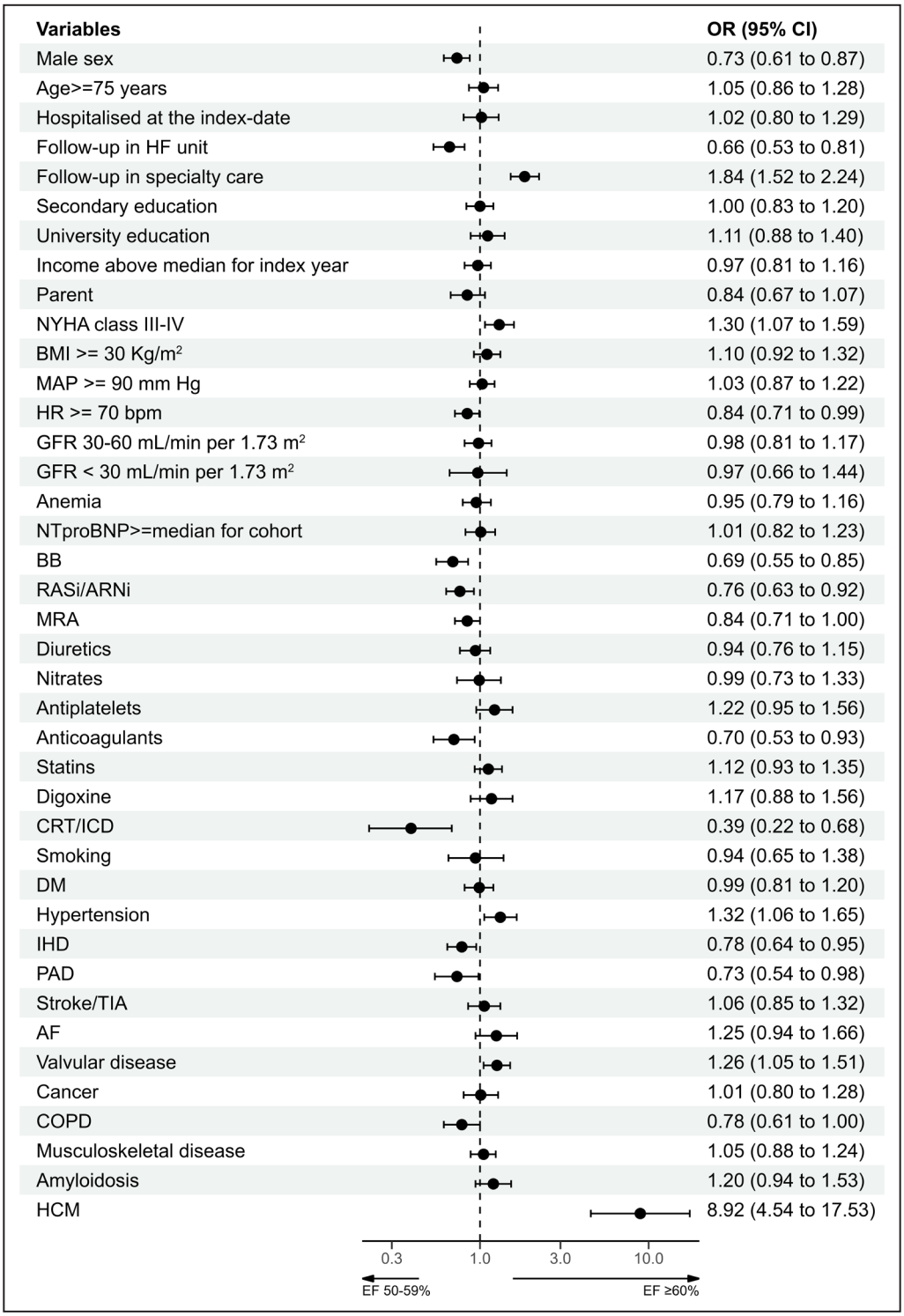

Figure 2. Patient characteristics independently associated with an EF ≥60% versus EF 50% to 59%.

AF indicates atrial fibrillation; ARNi, angiotensin receptor-neprilysin inhibitor; BB, β-blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; DM, diabetes mellitus; EF, ejection fraction; GFR, glomerular filtration rate (calculated by Chronic Kidney Disease Epidemiology Collaboration formula); HCM, hypertrophic cardiomyopathy; HF, heart failure; HR, heart rate; ICD, implantable cardioverter-defibrillator; IHD, ischemic heart disease; MAP, mean arterial pressure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association functional class; OR, odds ratio; PAD, peripheral artery disease; RASi, renin-angiotensin system inhibitor; and TIA, transient ischemic attack.

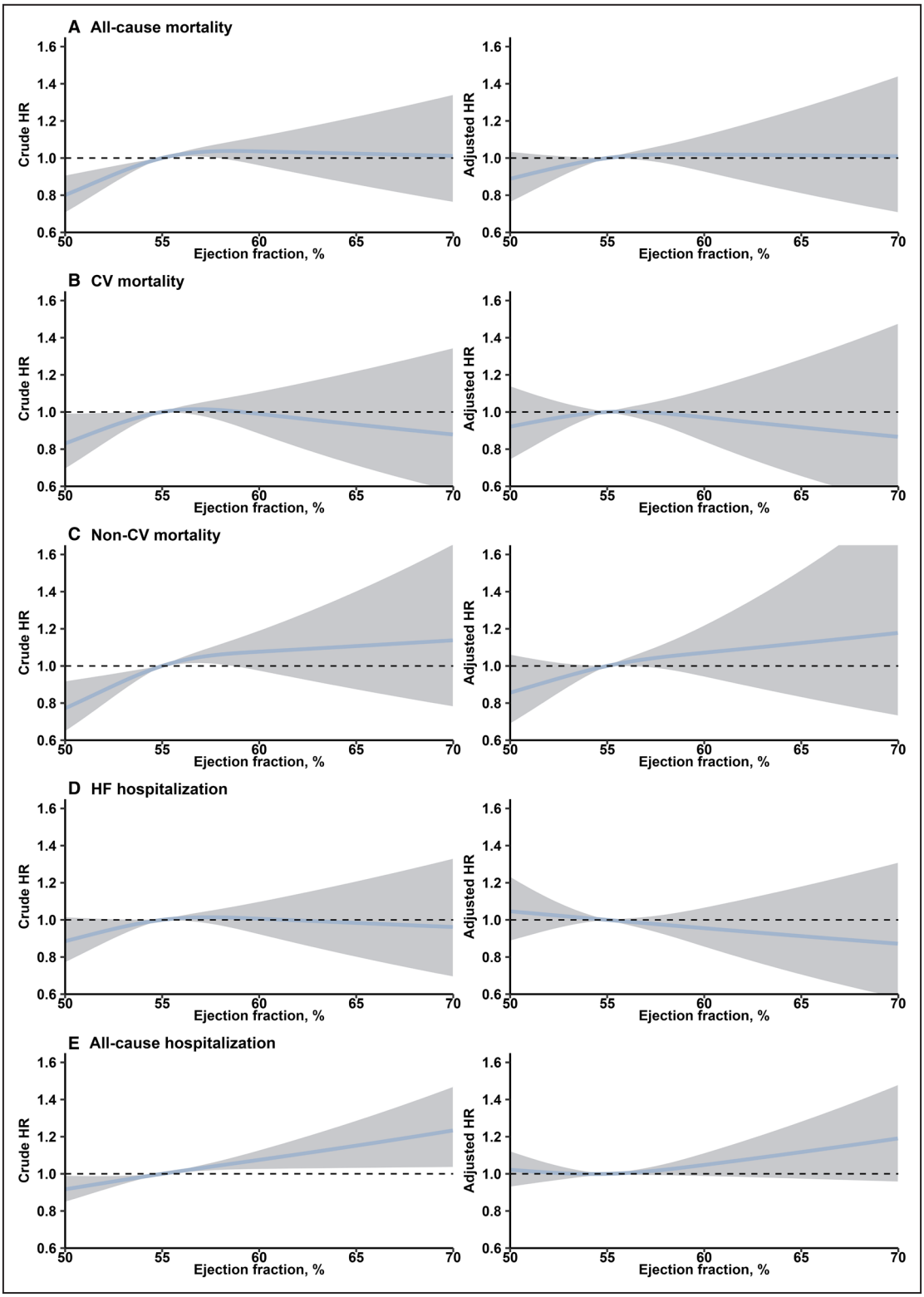

Figure 3. Association between EF and outcomes.
EF 55% is set as the reference; the unadjusted HR model is on the left and the adjusted model is on the right. **A**, All-cause mortality. **B**, CV mortality. **C**, Non-CV mortality. **D**, HF-related hospitalization. **E**, All-cause hospitalization. CV indicates cardiovascular; EF, ejection fraction; HF, heart failure; and HR, hazard ratio.

≥60% had more severe symptoms as shown by the higher New York Heart Association class and the fact that they were more often planned for a follow-up in specialty care, as well as a specific comorbid profile characterized by HCM, hypertension, and valvular disease. All of these conditions may explain the higher EF, because they lead to concentric LV hypertrophy, decreased LV end-diastolic volume, and as a result higher EF. The presence of amyloidosis showed a trend toward a statistically significant association with an EF ≥60% (OR, 1.20 [95% CI, 0.94–1.53]), which may still be relevant considering the underdiagnosis of amyloidosis. The prevalence of amyloidosis in our study group was 11% in patients with an EF of 50% to 60% and 13% for those with an EF ≥60%. Our estimates are high, which might also reflect the inclusion of both transthyretin and light chain amyloidosis, with the first having a prevalence of 5.0 per 100 000 inhabitants and the latter 9.0 per 1 million inhabitants (with 70% to 80% of these cases involving cardiac amyloidosis).[21–23]

Treatment with β-blockers and renin-angiotensin system inhibitors/angiotensin renin-neprilysin inhibitors was associated with lower EF. This might seem counterintuitive, because β-blockers and renin-angiotensin system inhibitors are also used as antihypertensive agents, and the prevalence of hypertension increased with higher EF. However, a proportion of patients with EF 50% to 59% might have received these treatments due to a prior indication for HF with reduced or mildly reduced EF, because this group was also more frequently equipped with implantable cardioverter-defibrillator/cardiac resynchronization therapy devices. This is consistent with findings from the TRED-HF study (Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy) results, showing that patients with HF and improved EF discontinuing HF with reduced EF treatment are at higher risk of relapse.[24] Interestingly, the prevalence of atrial fibrillation was similar in the 2 EF groups; nevertheless, the group with EF ≥60% was less likely to be treated with anticoagulants, which might be considered as a proxy for frailty. Our results on patient profiles characterized by higher EF are overall consistent with previous analyses.[7,9,10,12] Also, our findings support the importance of adopting a more phenotype-based approach to the diagnosis and treatment of patients with HFpEF, by highlighting that different HFpEF profiles, as well as HFpEF mimickers (eg, cardiomyopathies and valvular heart disease), coexist in the higher EF range, and are in need of a proper diagnosis for a tailored treatment.[25]

Outcome

We found a higher crude risk of all-cause and noncardiovascular mortality and all-cause hospitalization with increasing EF, reaching a plateau at an EF of ~55%, which could be explained by (1) a more pronounced prognostic role for noncardiovascular conditions in the upper bound of the EF spectrum and (2) the lower risk of mortality in the subgroup of patients with HF and improved EF which we likely identified as having an EF of 50% to 60%.[26]

In a US study analyzing 400 000 echocardiograms, routinely measured EF had a U-shaped relationship with the risk of death, with the nadir being at EF 60% to 65% both before and after adjustments. Interestingly, when the analysis was restricted to the HF outpatient subgroup, the nadir was lower (ie, 55% to 60%), and after including NT-proBNP (N-terminal pro-B-type natriuretic peptide) in the multivariable analysis, the strength of the association was blunted.[4] The partial discrepancy when comparing these with our results could be explained by the more extensive adjustment in our analysis (including cardiomyopathies).

As in our study, an individual patient meta-analysis of 6 randomized HF trials showed that the adjusted risk of all-cause mortality was flat when EF was >50%.[10] The higher risk of noncardiovascular mortality with increasing EF shown in our analysis was consistent with what was observed in the RELAX-AHF-2 study; however, the association remained statistically significant even after adjustments.[12] Assessing the risk of noncardiovascular events might be challenging in analyses of trials, because randomized controlled trials are designed to minimize competing risk rising from noncardiovascular conditions. In a Japanese registry cohort that enrolled patients hospitalized for HF, those with EF ≥65% had similar crude and adjusted risk of all-cause, cardiovascular, and noncardiovascular mortality as compared with those with EF 50% to 64%, but lower risk of HF hospitalization even after adjustments.[9] The same result in terms of HF hospitalization were observed in the individual patient level meta-analysis of 6 HF trials at an EF >70%, and in the placebo arm of the pooled analysis assessing the effect of empagliflozin across the EF spectrum at EF >65%.[7,10] Similar trends for lower risk of HF hospitalization with higher EF were also observed in our analyses, but the smaller sample size might have prevented statistical significance.

Few studies aimed to explain the pathophysiology behind a potential higher risk of mortality/morbidity in patients with an EF above normal. Smaller end-systolic and end-diastolic volumes and higher diastolic stiffness have been observed in patients with HF with EF >60% as compared with EF 50% to 60%,[27] which suggests that higher EF might merely be a surrogate marker of low stroke volume. Consistently among healthy individuals with EF above the normal range (≥57%) undergoing cardiac magnetic resonance, those with an EF in the highest quartile (EF ~80%) had a significantly higher risk of major adverse cardiac events compared with the lowest quartile, but only when the stroke volume was low.[16]

Limitations and Strengths

We analyzed a large population from a registry with high quality and data granularity. There was complete coverage for outcomes and almost no loss to follow-up. However, although SwedeHF is a large national registry, it might not be fully representative of the general HF population due to the limited coverage.[28] We could only include patients enrolled after 2017 when EF started to be registered as a continuous variable, which limited the sample size and the observation period. We retrieved information on the diagnosis of cardiomyopathies (included amyloidosis) through linkage with the national patient registry containing *ICD-10* codes, and therefore there is a chance of misdiagnosis. Although EF is commonly used to phenotype patients with HF, it is a biomarker with inherent difficulties. There is a degree of inter- and intraindividual variability in its measurement, which can lead to misclassification. Different imaging modalities may yield different EF measurements for the same patient.[29,30] Additionally, factors such as atrial fibrillation, dehydration, anemia, and hypoxia can also impact EF measurement, further complicating its reliability.

CONCLUSIONS

In a nationwide population with HFpEF, ~20% patients had an EF ≥60%, which was linked with more severe symptoms, HCM, hypertension, and valvular disease. The crude, but not adjusted, risk of all-cause and noncardiovascular mortality and all-cause hospitalization increased with increasing EF until reaching a plateau at an EF of ~55%. These findings might indicate that the higher crude risk associated with higher EF may be driven by prognostically relevant conditions more frequently retrieved in the upper bound of the EF spectrum, and highlights the potential challenges rising from competing risk when enrolling patients with higher EF in randomized controlled trials.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S4
Figures S1–S4

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