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ORIGINAL RESEARCH

Sex-Related Differences in Mortality Following Admission for Acute Heart Failure Across the Left Ventricular Ejection Fraction Spectrum

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BACKGROUND: Following a heart failure (HF)-decompensation, there is scarce data about sex-related prognostic differences across left ventricular ejection fraction (LVEF) status. We sought to evaluate sex-related differences in 6-month mortality risk across LVEF following admission for acute HF.

METHODS AND RESULTS: We retrospectively evaluated 4812 patients consecutively admitted for acute HF in a multicenter registry from 3 hospitals. Study end points were all-cause, cardiovascular, and HF-related mortality at 6-month follow-up. Multivariable Cox regression models were fitted to investigate sex-related differences across LVEF. A total of 2243 (46.6%) patients were women, 2569 (53.4%) were men, and 2608 (54.2%) showed LVEF≥50%. At 6-month follow-up, 645 patients died (13.4%), being 544 (11.3%) and 416 (8.6%) cardiovascular and HF-related deaths, respectively. LVEF was not independently associated with mortality (HR, 1.02; 95% CI 0.99–1.05; P=0.135). After multivariable adjustment, we found no sex-related differences in all-cause mortality (P value for interaction=0.168). However, a significant interaction between sex and cardiovascular and HF mortality risks was found across LVEF (P value for interaction=0.030 and 0.007, respectively). Compared with men, women had a significantly lower risk of cardiovascular and HF-mortality at LVEF<25% and <43%, respectively. On the contrary, women showed a higher risk of HF-mortality at the upper extreme of LVEF (>80%).

CONCLUSIONS: Following an admission for acute HF, no sex-related differences were found in all-cause mortality risk. However, when compared with men, women showed a lower risk of cardiovascular and HF-mortality at the lower extreme of LVEF. On the contrary, they showed a higher risk of HF death at the upper extreme.

Key Words: heart failure ■ sex ■ mortality ■ left ventricular ejection fraction

There are notable sex-related differences involving different aspects of heart failure (HF), such as epidemiology, clinical presentation, pathophysiology, response to treatments, and prognosis.[1] Different studies have consistently shown that men are predisposed to HF with reduced ejection fraction (HFrEF), whereas women are more affected by HF with preserved ejection fraction (HFpEF).[2–4] Women are more symptomatic and display poorer quality of life than men in both conditions.[1,5–8] In contrast, different studies have reported a better prognosis for women with HF.[9–11] This has been consistently shown for HFrEF,[1,5,6] but has also been reported for HFpEF.[1,8,9,11] However, most prior studies have focused on stable HF patients, and

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CLINICAL PERSPECTIVE

What Is New?

- Following an admission for acute heart failure, sex was not a determinant of 6-month all-cause mortality risk.
- Women had a lower risk of cardiovascular and heart failure-related mortality when left ventricular ejection fraction was severely or mildly reduced, respectively. On the contrary, in patients with supranormal left ventricular ejection fraction, heart failure mortality risk was higher in women versus men.

What Are the Clinical Implications?

- There are notable sex-related differences in cardiovascular and heart failure-related mortality across left ventricular ejection fraction status in heart failure patients.
- Future studies should evaluate the negative prognostic implications of a supranormal left ventricular ejection fraction in women with heart failure.

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Nonstandard Abbreviations and Acronyms

AHF	acute heart failure
ARIC	atherosclerosis risk in communities
ESC	Europen Society of Cardiology
HFmrEF	heart failure with mildly reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
GREAT	Global Research on Acute Conditions Team
LVEF	left ventricular ejection fraction
MAGGIC	Meta-Analysis Global Group in Chronic Heart Failure

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little is known about the sex-related prognostic differences following hospitalization for decompensated HF.

In HFpEF, women account for over half of the patients.[1] Women are more symptomatic, exhibit worse diastolic dysfunction, more congestion, poorer peripheral oxygen kinetics, or lower arterial compliance than men.[8,12–15] In contrast, women seem to have better survival than men, mainly in data derived from clinical trials, as it has been shown in a pooled-analysis from the I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction), TOPCAT (Treatment of Preserved

Cardiac Function Heart Failure with an Aldosterone Antagonist), and CHARM-Preserved (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) trials,[8,16] or in the recent PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure with Preserved Ejection Fraction) trial,[14] a finding that is incompletely understood. In contrast, data regarding sex-related differences in mortality risk from observational studies are more conflicting, and female sex may be related to comparable or even worse outcomes in HFpEF.[17]

This study aimed to evaluate sex-related differences in mortality across the left ventricular ejection fraction (LVEF) spectrum in a large cohort of patients from daily clinical practice following admission for acute HF (AHF).

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Group and Protocol

This is a retrospective analysis from a multicentre prospective registry of 4821 consecutive patients admitted from January 2008 to October 2019 for AHF in 3 hospitals in Comunidad Valenciana (Spain), a region of up to 5 million inhabitants, mostly of Caucasian ethnicity. Two of them (Hospital Clínico Universitario de Valencia and Hospital General Universitario de Castellón) are tertiary centers with 582 and 574 beds, respectively, while Hospital de Manises is a 325-bed community hospital. A comprehensive dataset of demographics, medical history, standard laboratory, echocardiographic parameters, and treatments at discharge were routinely recorded using pre-established registry questionnaires during the index hospitalization. Either patients with new-onset or worsening HF were enrolled in the registry. HF was defined according to the European Society of Cardiology (ESC) Clinical Practice Guidelines.[18] Patients with severe primary valve disease or prosthetic heart valves were considered to be of valvular etiology. Patients with a history of prior myocardial infarction or obstructive coronary artery disease were considered of ischemic etiology. Treatment strategies were individualized following established guidelines operating at the time patients were included in the registry.

Echocardiography

A 2-dimensional transthoracic echocardiogram was performed in all patients during index hospitalization (96±24 hours after admission) using the left lateral decubitus position by experienced sonographers. Commercially available systems were used throughout

the study. Patients were admitted to the hospitalization ward and clinically stable by the time of the examination. All images were recorded with the second harmonic at the time of end expiration. LVEF was assessed by the biplane Simpson method.

Follow-up, End points, and Ethical Concerns

The incidence of 6-month all-cause, cardiovascular, and HF-related mortality were considered to be the study end points. Cardiovascular death was considered secondary to worsening HF, acute myocardial infarction, stroke or transient ischemic attack, cardiac arrhythmias, peripheral artery disease, sudden cardiac deaths, or unknown cause of death.[19] The cause of death was considered as non-cardiovascular if a specific non-cardiovascular cause was identified. HF-related deaths were considered to be secondary to worsening HF or sudden cardiac death. As LVEF trajectories are dynamic over time,[20] we censored follow-up at 6 months following discharge to ensure appropriate associations between LVEF category and sex-related outcomes.

Survival status and the cause of death were adjudicated based on the paper-written and electronic medical records from the public healthcare system. Researchers in charge of end points adjudications were all blinded to the LVEF status.

The study was conformed to the principles outlined in the 1975 Declaration of Helsinki and was approved by the institutional, local review ethical committee.

Statistical Analysis

Continuous variables were expressed as mean±SD or median (interquartile range [IQR]), whenever appropriate. Discrete variables were summarized as percentages. Baseline characteristics were compared among categories with Pearson's chi-square and t-test for categorical or continuous variables, respectively. The association between sex and the end points was evaluated along the continuum of LVEF and across established HF categories defined by LVEF (HFrEF [≤40%], HF with mid-range EF [41%–49%], and HFpEF [≥50%]),[18] using Cox regression analyses, and the results were expressed as hazard ratios (HR) with 95% CI. Candidate covariates were chosen based on previous medical knowledge; then, a backward stepwise selection was performed. During this selection process, the linearity assumption for all continuous variables was simultaneously tested, and the variable transformed, if appropriate, with fractional polynomials. All variables listed in Table 1 were evaluated as potential covariates in the multivariable models, independently of their P value. For evaluating cardiovascular and HF mortality, Cox regression models adjusted for competing events were employed. Competing

events included non-cardiovascular death when evaluating cardiovascular-for mortality and non-HF-death when analyzing HF death. The discriminative ability of the models was assessed by Harrell's C-statistics. The variables included in the final multivariable model for all-cause mortality were: age, sex, LVEF, previous admissions for AHF, New York Heart Association (NYHA) class III/IV before admission, ischemic etiology, valvular etiology, atrial fibrillation, heart rate at admission, systolic blood pressure at admission, Charlson comorbidity index, hemoglobin, N-terminal pro-brain natriuretic peptides (NT-proBNP), blood urea nitrogen, estimated glomerular filtration fraction by the Chronic Kidney Disease Epidemiology Collaboration equation, and equivalent loop diuretic dose at discharge. Cardiovascular and HF-mortality models included the previous covariates except for hemoglobin and the estimated glomerular filtration fraction. The proportional-hazards assumption was tested based on Schoenfeld residuals. In all cases, we did not find a violation of the proportionality assumption for the interaction of sex-LVEF. The proportion of missing values of covariates included in the multivariate model was <5%. The STATA ICE module performed multiple imputations of the variables by the MICE system of chained equations. In the process, we created 50 copies of the dataset and 100 cycles of regression switching. Then, the 50 estimated values for each variable were averaged and used for filling in the missingness.

A 2-sided P value of <0.05 was considered to be statistically significant for all analyses. All survival analyses were performed using STATA 15.1 (StataCorp. 2015. Stata Statistical Software: Release 14.1. College Station, TX: StataCorp LP).

RESULTS

The mean (±SD) age of the whole sample was 74.2±11.1 years, and 2243 (46.6%) were women. The number of patients with LVEF≤40%, 41%–49%, and ≥50% were 1514 (31.5%), 690 (14.3%), and 2608 (54.2%), respectively. Baseline characteristics categorized by sex in the overall cohort are shown in Table 1. Women were older and showed more frequent HFpEF (70.5% versus 39.9%, respectively; P<0.001). Women had fewer comorbidities and a lower prevalence of ischemic heart disease but showed a more advanced NYHA class and a higher prevalence of valvular disease or atrial fibrillation. Values of NT-proBNP and carbohydrate antigen 125 were lower in women. In contrast, they presented with lower kidney function and a higher pulmonary artery systolic pressure (Table 1).

In the cohort of patients with HFpEF, women also had fewer comorbidities and less ischemic heart disease than men (Table 2). Still, they were older and more likely to suffer from previous admissions for HF.

Table 1. Baseline Characteristics By Sex in Patients Admitted for Acute Heart Failure

	Overall (n=4182)	Men (n=2569)	Women (n=2243)	P value
Demographics and medical history				
Age, y	74.2±11.1	71.9±11.8	76.8±9.7	<0.001
NYHA class III-IV, n (%)	854 (17.7)	412 (16.0)	442 (19.7)	0.001
First HF admission, n (%)	3269 (67.9)	1762 (53.9)	1507 (46,1)	0.299
HFpEF, n (%)	2608 (54.2)	1026 (39.9%)	1582 (70.5%)	<0.001
Hypertension, n (%)	3821 (79.4)	2000 (77.8)	1821 (81.2)	0.004
Diabetes, n (%)	2093 (43.5)	1184 (46.1)	909 (40.5)	<0.001
Dyslipidemia, n (%)	2510 (52.2)	1384 (53.9)	1.126 (50.2)	0.011
Current smoker, n (%)	555 (11.5)	469 (18.2)	86 (3.8)	<0.001
Peripheral artery disease, n (%)	485 (10.0)	350 (13.6)	135 (6.0)	<0.001
COPD, (%)	988 (20.5)	709 (27.6)	279 (12.4)	<0.001
Valvular heart disease, n (%)	1663 (34.6)	761 (29.6)	902 (40.2)	<0.001
Ischemic heart disease, n (%)	1615 (33.6)	1078 (41.9)	537 (23.9)	<0.001
Charlson index ≥2, n (%)	2787 (57.9)	1651 (64.3)	1.136 (50.6)	<0.001
ICD carrier, n (%)	152 (3.2)	133 (5.2)	19 (0.8)	<0.001
Physical signs				
Heart rate, bpm	96±28	95±27	97±28	0.001
SBP, mm Hg	143±31	141±31	145±31	<0.001
DBP, mm Hg	80±19	80±19	79±18	0.343
Pleural effusion, n (%)	2306 (47.9)	1220 (47.8)	1078 (48.1)	0.857
Peripheral edema, n (%)	2958 (61.5)	1596 (62.1)	1362 (60.7)	0.310
Electrocardiogram				
QRS >120 mseg, n (%)	1546 (32.1)	938 (36.5)	608 (27.1)	<0.001
Atrial fibrillation, n (%)	2226 (46.3)	1141 (44.4)	1.085 (48.4)	0.006
Laboratory data				
BUN, mg/dL	60.7±32.2	62.2±33.2	59.0±31.1	<0.001
Hemoglobin, g/dL	12.5±1.9	12.8±2.1	12.1±1.7	<0.001
Sodium, mEq/L	138±4	138±4	138±5	0.522
NT-proBNP, pg/mL*	3690 (5445)	3958 (5938)	3463 (4989)	<0.001
CA125, U/mL*	50 (90)	56 (100)	43 (78)	<0.001
Creatinine at admission, mg/dL	1.28±0.67	1.41±0.76	1.13±0.52	<0.001
eGFR, mL/min	62.4±28.1	64.3±29.9	60.2±25.7	<0.001
eGFR< 60 mL/min, n (%)	2422 (50,3)	1206 (46.9)	1216 (54.2)	<0.001
Echocardiography				
LVEF, %*	51 (26)	45 (24)	58 (19)	<0.001
DT, ms	207±55	200±57	215±53	<0.001
LAD, mm	44.3±7.5	45.1±7.1	43.3±7.7	<0.001
TAPSE, mm	18.6±3.6	18.3±3.7	18.9±3.5	<0.001
PASP, mm Hg	46±12	45±12	47±13	<0.001
PASP >45 mm HG, n (%)	2191 (45.5)	1063 (41.4)	1128 (50.3)	<0.003
Treatment at discharge				
Beta-blockers, n (%)	3286 (69.8)	1763 (70.3)	1523 (69.3)	0.466
ACEI/ARB/ARNI, n (%)	2508 (62.7)	1358 (63.5)	1150 (61.9)	0.291
MRA, n (%)	1614 (33.6)	984 (38.3)	616 (27.5)	<0.001
Furosemide dose at discharge, mg	64.3±47.0	67.1±51.9	61.2±40.5	<0.001

ACEI indicates angiotensin-converting enzyme inhibitors; ARB, antagonist receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; BUN, blood urea nitrogen; CA125, carbohydrate antigen 125, COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; DT, deceleration time; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; ICD, implantable cardioverter defibrillator; MRA, mineralocorticoid receptor antagonist; NT-proBNP, amino-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association, LAD, left atrial diameter; LVEF, left ventricular ejection fraction; PASP, pulmonary arterial systolic pressure; SBP, systolic blood pressure; and TAPSE, tricuspid annular plane systolic excursion.

* Data given as n (%), mean±SD or median (IQR).

Interestingly, sex-related differences in biomarkers became blurred in patients with HFpEF, but women consistently showed a higher prevalence of valvular heart disease, pulmonary hypertension, or renal dysfunction. In patients with either HFrEF or HF with midly reduced EF (HFmrEF), women were also older with a higher prevalence of valvular heart disease or pulmonary hypertension, but with a lower prevalence of ischemic heart disease and less burden of comorbidities. There were no sex-related significant differences in guideline-directed medical treatments, but women were less likely to receive device therapy (Table 2).

Mortality Risk Across Sex and LVEF
All-Cause Mortality

At a 6-month follow-up, 645 patients had died (13.4%), and mortality rates were 13.3% in women and 13.5% in men (P=0.822). Kaplan Meier curves showed no significant sex-related differences in all-cause mortality (log-rank test, P=0.615) (Figure 1A).

In a multivariable analysis, LVEF, as main term, was not an independent predictor of all-cause mortality (HR, 1.02; 95% CI 0.99–1.05; P=0.135, Figure S1A). Likewise, sex did not predict the risk. Sex was neutrally associated with the end point across the continuum of LVEF (women versus men; HR, 0.92; 95% CI 0.77–1.10; P=0.335) (Figure 2), and in the three HF categories, as is shown in Table 3. The interaction between sex and LVEF was not significant (P value for interaction=0.168), reflecting a non-differential prognostic effect of sex along the continuum of LVEF, as is shown in Figure 2. The C-statistic of the multivariable model for all-cause mortality was 0.77. All the covariates included in the model and their estimates are provided in Table S1.

Cardiovascular Mortality

At 6-month follow-up, 544 (11.3%) patients had died for cardiovascular causes. Rates of cardiovascular mortality were comparable between women and men (11.3 versus 11.3%, P=0.958), and no significant differences in the incidence of cardiovascular mortality were found (Figure 1B).

After multivariable adjustment, including non-cardiovascular mortality as a competing event, female sex was not an independent predictor of cardiovascular mortality (HR, 0.97; 95% CI 0.79–1.19; P=0.778). When the association between sex and 6-month cardiovascular-mortality was evaluated across the established categories of HF, sex was not associated with this end point in any of the categories (Table 3). However, we found a significant interaction between sex and the continuum of LVEF (P for interaction=0.030). Compared with men, women had a significantly lower risk of cardiovascular mortality at lower extremes of LVEF (LVEF<25%), as shown in Figure 3 and Table 4. The risk of cardiovascular mortality was progressively higher in women versus men as LVEF increased (Figure 3), but differences did not reach statistical significance (Table 4). The C-statistic for the model was 0.78. LVEF was not an independent predictor of cardiovascular mortality (P=0.755, Figure S1B). All variables included in the model and their estimates are provided in Table S2.

HF-Mortality

At 6-month follow-up, 416 (8.6%) patients had experienced an HF-related death. Rates of HF mortality were 8.6% in women and 8.7% in men, and no significant differences were found in the incidence of HF mortality, as is shown in Kaplan Meier curves (Figure 1C). In the multivariable model, including established prognosticators and non-HF mortality as a competing event, sex was not an independent predictor of the risk of HF death (women versus men: HR, 0.89; 95% CI 0.70–1.16; P=0.331). However, a differential prognostic effect of sex across LVEF status was found (P value for interaction=0.007) (Figure 4). Compared with men, women displayed a reduced risk of HF death at LVEF<43% (HR, 0.77; CI 95%=0.59–0.99), but the risk of HF mortality was progressively higher as LVEF increased (Figure 4), and differences became significant in women with HFpEF at the upper extreme of LVEF (LVEF>80%), as it is shown in Table 4.

When the effect of sex and HF-mortality was explored across LVEF categories, we found that women showed a statistical trend to an adjusted lower risk if LVEF<40% (HR, 0.69; 95% CI, 0.47–1.03, P=0.069). In patients with HFmrEF and HFpEF, sex was not related to the end point (Table 3).

As a main term, LVEF was not independently associated with the outcome (P=0.219; Figure S1C). The C-statistic for the model was 0.80. All variables included in the model and their estimates are provided in Table S3.

DISCUSSION

In this study, sex was not a determinant of 6-month all-cause mortality risk following a HF decompensation. However, we found a differential prognostic effect of sex across the LVEF spectrum for 6-month cardiovascular and HF-mortality. Thus, women had a lower risk of both outcomes at LVEF<25% and <43%, respectively. On the contrary, women equaled cardiovascular and HF death's risk of men as LVEF increased, even showing a higher risk of HF mortality at the upper extreme of LVEF (>80%). However, established HF categories based on LVEF could not discriminate sex-mortality differences in this particular context further.

Table 2. Baseline Characteristics Between Women and Men in the Different Heart Failure Categories Defined by Left Ventricular Ejection Fraction

	HFrEF			HFmrEF			HFpEF		
	Women (n=419)	Men (n=1095)	P value	Women (n=242)	Men (n=488)	P value	Women (n=1582)	Men (n=1026)	P value
Age, y	72.9±11.9	68.8±12.6	<0.001	77.2±8.8	73.2±11.0	<0.001	77.7±9	74.6±10	<0.001
NYHA class III-IV, n (%)	77 (18.4)	184 (16.8)	0.468	43 (17.8)	78 (17.1)	0.906	322 (20.3)	150 (14.6)	<0.001
First HF admission, n (%)	307 (73.3)	752 (68.7)	0.081	158 (65.3)	284 (63.4)	0.620	1042 (65.8)	726 (70.7)	0.009
Hypertension, n (%)	299 (71.4)	794 (72.5)	0.655	202 (83.5)	371 (82.8)	0.826	1320 (83.4)	835 (81.4)	0.176
Diabetes, n (%)	168 (40.1)	507 (46.3)	0.030	129 (53.3)	220 (49.1)	0.292	612 (38.7)	457 (44.5)	0.003
Dyslipidemia, n (%)	214 (51.1)	598 (54.6)	0.217	124 (51.2)	254 (56.7)	0.169	788 (49.8)	532 (51.8)	0.308
Current smoker, n (%)	43 (10.3)	243 (22.2)	<0.001	11 (4.6)	75 (16.7)	<0.001	32 (2.0)	151 (14.7)	<0.001
Peripheral artery disease, n (%)	23 (5.5)	157 (14.3)	<0.001	17 (7.0)	65 (14.5)	0.004	135 (6.0)	350 (13.6)	<0.001
COPD, (%)	55 (13.1)	268 (24.5)	<0.001	27 (11.2)	113 (25.2)	<0.001	197 (12.4)	328 (31.9)	<0.001
Valvular heart disease, n (%)	116 (27.7)	261 (23.8)	0.121	86 (35.5)	144 (32.1)	0.367	700 (44.2)	356 (34.7)	<0.001
Ischemic heart disease, n (%)	133 (31.7)	518 (47.3)	<0.001	86 (35.5)	218 (48.7)	0.001	318 (20.1)	342 (33.3)	<0.001
Charlson index ≥2, n (%)	197 (47.0)	701 (64.0)	<0.001	144 (59.5)	300 (66.9)	0.051	795 (50.2)	650 (69.3)	<0.001
ICD carrier, n (%)	13 (3.4)	103 (9.4)	<0.001	2 (0.9)	20 (4.4)	0.014	4 (0.3)	16 (1.5)	<0.001
Heart rate, bpm	100±24	98±26	0.079	100±24	94±26	0.004	96±29	92±29	<0.001
SBP, mm Hg	139±28	136±30	0.028	149±34	146±32	0.180	147±31	145±30	0.255
DBP, mm Hg	82±18	81±19	0.473	83±19	82±20	0.584	78±18	78±19	0.689
Pleural effusion, n (%)	226 (53.9)	517 (47.2)	0.019	340 (51.4)	733 (47.5)	0.091	738 (46.6)	495 (48.2)	0.425
Peripheral edema, n (%)	242 (57.8)	657 (60.0)	0.427	128 (52.9)	274 (61.2)	0.036	992 (62.7)	665 (64.8)	0.274
QRS >120 mseg, n (%)	185 (44.1)	(43.9)	0.937	91 (37.6)	167 (37.3)	0.933	332 (20.9)	290 (28.3)	<0.001
Atrial fibrillation, n (%)	128 (30.6)	397 (36.3)	0.037	84 (34.7)	109 (44.4)	0.013	873 (55.2)	545 (53.1)	0.301
BUN, mg/dL	57.6±30	61.9±35	0.029	57.9±27	65.2±35	0.007	59.5±31.9	61.2±30.6	0.199
Hemoglobin, g/dL	12.5±1.6	13.2±2.0	<0.001	12.3±1.6	12.9±1.9	0.001	11.9±1.8	12.4±2.1	<0.001
Sodium, mEq/L	138±4	138±4	0.404	139±4	138±5	0.209	138±5	138±4	0.457
NT-proBNP, pg/mL*	5787 (8525)	5120 (7984)	0.450	4412 (6083)	4840 (6634)	0.859	2978 (4025)	2949 (3970)	0.494
CA125, U/mL*	67 (102)	76 (119)	0.029	49 (79)	63 (97)	0.033	39 (70)	40 (75)	0.188
Creatinine at admission, mg/dL	1.11±0.6	1.40±0.7	<0.001	1.14±0.5	1.49±0.8	<0.001	1.13±0.5	1.39±0.8	<0.001
eGFR, mL/min	62.6±27.8	64.5±26.0	0.217	58.6±24.4	61.1±26.9	0.233	59.7±25.2	65.6±34.6	<0.001
eGFR <60 mL/min, n (%)	357 (54.0)	722 (46.8)	0.002	357 (54.0)	722 (46.8)	0.002	859 (54.3)	484 (47.1)	<0.001
LVEF, %*	33 (8)	32 (10)	0.003	45 (4)	45 (4)	0.188	62 (9)	59 (10)	<0.001
DT, ms	194±54	183±52	0.002	208±55	206±57	0.680	223±51	218±58	0.085
LAD, mm	42.5±7.4	45.2±7.1	<0.001	42.5±6.9	45.0±7.1	<0.001	43.7±7.9	45.0±7.3	<0.001
TAPSE, mm	17.4±3.6	17.1±3.6	0.061	18.1±2.9	18.4±3.8	0.336	19.4±3.5	19.6±3.4	0.221

(Continued)

Table 2. Continued

	HFrEF			HFmrEF			HFpEF		
	Women (n=419)	Men (n=1095)	P value	Women (n=242)	Men (n=488)	P value	Women (n=1582)	Men (n=1026)	P value
PASP, mm Hg	44.7±10.7	44.1±11.2	0.368	46.9±14.1	44.1±10.9	0.004	47.8±13.2	45.7±13.2	<0.001
PASP >45 mm Hg, n (%)	177 (42.2)	411 (37.5)	0.093	119 (49.2)	178 (39.7)	0.017	832 (52.6)	474 (46.2)	0.001
Beta-blockers, n (%)	323 (78.8)	833 (78.2)	0.813	169 (71.3)	317 (71.2)	0.874	1052 (66.5)	626 (61.1)	0.006
ACEI /ARB/ARNI, n (%)	264 (71.5)	659 (68.9)	0.341	138 (65.1)	220 (60.9)	0.322	931 (58.6)	596 (58.5)	0.951
MRA, n (%)	131 (55.0)	342 (57.5)	0.521	36 (35.6)	64 (30.8)	0.390	251 (16.7)	211 (19.0)	0.307
Furosemide dose at discharge, mg	66.0±36.9	71.9±55.8	0.043	61.2±37.7	65.9±51.3	0.197	59.9±41.7	62.4±47.1	0.152

ACEI indicates angiotensin-converting enzyme inhibitors; ARB, antagonist receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; BUN, blood urea nitrogen; CA125, carbohydrate antigen 125, COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; DT, deceleration time; 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; ICD, implantable cardioverter defibrillator; MRA, mineralocorticoid receptor antagonist; NT-proBNP, amino-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association, LAD, left atrial diameter; LVEF, left ventricular ejection fraction; PASP, pulmonary arterial systolic pressure; SBP, systolic blood pressure; and TAPSE, tricuspid annular plane systolic excursion.

* Data given as n (%), mean±SD or median (IQR).

General Sex-Related Differences in Patients With Heart Failure

Different studies have shown overt sex-related differences in the clinical presentation of patients with HF.[1] Women with HF are older than men, as it has been consistently reported in different studies, such as the MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) meta-analysis,[9] or the Swedish HF registry.[11] Accordingly, in the current study, women with AHF were 5 years older on average than men. Notably, women displayed more frequently HFpEF than men, as has also been described.[1,8,9,14] In the current study, including patients admitted for AHF in real-world clinical daily practice, these differences were striking, and women constituted about 70% of patients with HFpEF. These findings are in agreement with recent data from the ARIC (Atherosclerosis Risk in Communities) Community Surveillance Study from hospitalized HFpEF patients in the United States, in which women constituted 65% of the patients included in the registry.[21] In addition, women with HF have a different profile of other clinical characteristics than men. Consistently with previous databases, such as the MAGGIC meta-analysis,[9] the Swedish HF registry,[11] or the GREAT (Global Research on Acute Conditions Team) Network registry,[10] women had a lower prevalence of ischemic heart disease and other comorbidities such as vascular disease or chronic pulmonary obstructive disease. In contrast, the prevalence of hypertension, valvular disease, or renal failure was higher in women than in men, and women showed a higher burden of symptoms.

## Sex-Related Differences in Mortality in Heart Failure With a Reduced Ejection Fraction

Previous studies have consistently reported a lower risk of women with HFrEF when compared with men.[1,5,6,9,11] Despite showing more symptoms and poorer quality of life, women with HFrEF seem to have a better prognosis in terms of death. It is the case of real-world registries, such as the Swedish HF registry, in which women had a lower risk of all-cause and cardiovascular mortality, or data from clinical trials, as it was reported in the CHARM program, or in a pooled analysis from the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) and ATMOSPHERE (Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure) trials, both showing higher rates of all-cause, cardiovascular and HF-related deaths in men.[5,6] Our results are partially in line with previous studies. Compared with men, the risk of cardiovascular death in women was significantly lower when LVEF was severely impaired, and
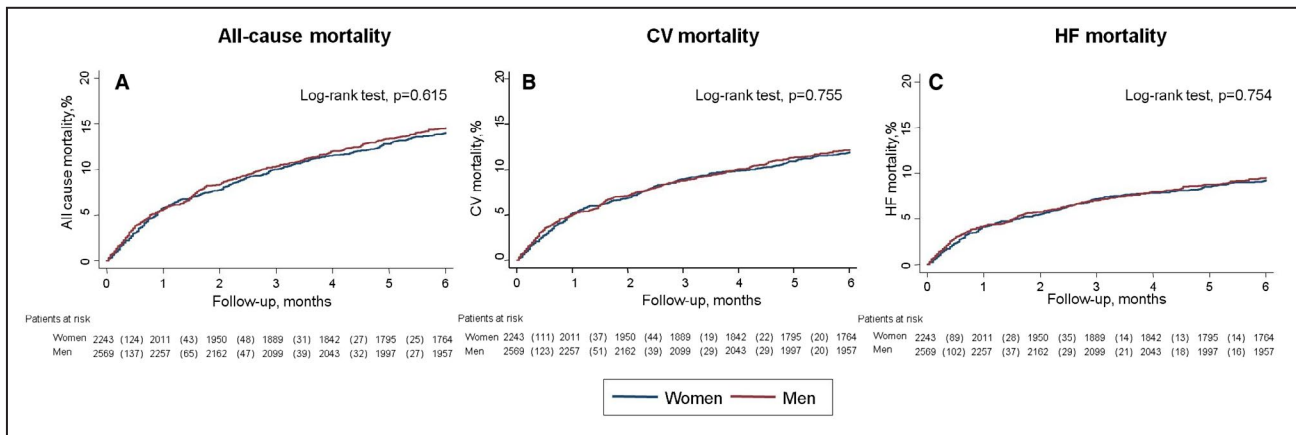
Figure 1. Kaplan-Meier curves for mortality in women versus men.
A, Cumulative incidente of all-cause mortality by sex. **B**, Cumulative incidence of cardiovascular mortality by sex. **C**, Cumulative incidence of HF mortality by sex. HF indicates heart failure.

differences were even more marked for HF mortality, with a significantly lower risk starting in patients with mildly reduced EF. However, sex was not independently associated with the risk of all-cause mortality. This is similar to a recent analysis from the ESC HF Long-Term registry in 16 345 chronic and AHF patients from 21 countries in Europe, in which sex was not an independent risk factor for mortality,[22] or to data from European patients enrolled in the large multinational GREAT registry.[10] Recently, no sex-related differences in all-cause mortality were also found in patients included in the ASCEND-HF (Acute Study of Clinical Effectiveness of Nesitide in Decompensated Heart Failure) trial.[23] Women have been historically underrepresented in trials in HF.[1] The percentage of women included in landmark trials in HFrEF is <30%. For instance, only 22%, 26%, 22%, or 24% of the

patients included in trials such as PARADIGM-HF, EMPHASIS-HF (Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms-HF), CHARM, or SHIFT (Systolic Heart Failure Treatment With the IF Inhibitor Ivabradine Trial), respectively, were women. In addition, there is a gap between the women included in landmark trials in HF and women with HF from daily clinical practice, mainly in the acute setting. Women included in trials such as CHARM or PARADIGM-HF were considerably younger, with fewer comorbidities. For instance, in our study mean age of women with LVEF<50% was 74 years, with half of the patients showing renal insufficiency or diabetes. In the study by Dewan et al, the mean age of women was 65 years, with only 12% showing renal dysfunction and 31% diabetes.[6] In an older and more comorbid cohort of women with HFrEF, as seen in
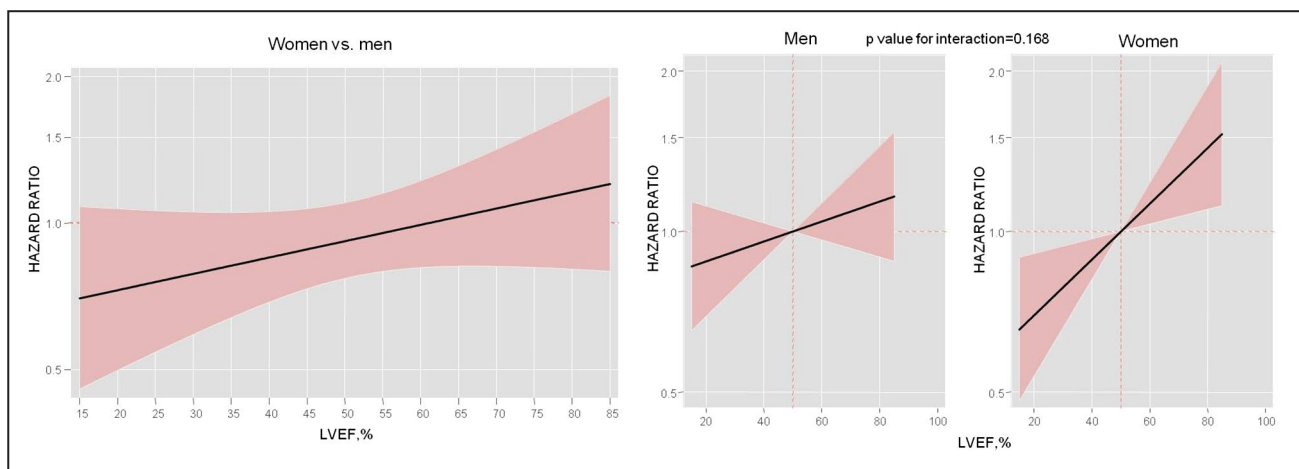
Figure 2. Hazard ratios of women versus men across left ventricular ejection status for all-cause mortality risk in the multivariable model.
Estimates of all-cause mortality risk of left ventricular ejection fraction status in men and women. The interaction between sex and left ventricular ejection was not significant (*P* for interaction=0.168). HR indicates hazard ratio; and LVEF, left ventricular ejection fraction.

Table 3. Estimates of Risk of All-Cause, Cardiovascular, and Heart Failure-Related Mortality of Women Versus Men Across LVEF Categories

	HR (95% CI)	*P* value	*P* for interaction*
All-cause mortality			
HFrEF	0.86 (0.62–1.18)	0.354	0.742*
HFmrEF	0.87 (0.57–1.34)	0.531	
HFpEF	0.98 (0.78–1.24)	0.904	
Cardiovascular mortality			
HFrEF	0.84 (0.60–1.18)	0.323	0.493*
HFmrEF	0.88 (0.55–1.41)	0.596	
HFpEF	1.07 (0.82–1.40)	0.610	
HF mortality			
HFrEF	0.69 (0.46–1.04)	0.076	0.232*
HFmrEF	0.85 (0.49–1.49)	0.577	
HFpEF	1.06 (0.78–1.44)	0.691	

CI indicates confidence interval; 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; HR, hazard ratio; and LVEF, left ventricular ejection fraction.

* Adjusted Interaction between the sex and heart failure categories defined by left ventricular ejection fraction.

Table 4. Estimates of Risk of All-Cause, Cardiovascular, and Heart Failure-Related Mortality of Women Versus Men, at Different Cut-Offs of Left Ventricular Ejection Fraction

LVEF, (%)	Hazard ratio (95% CI)		
	All-cause mortality	Cardiovascular mortality	HF mortality
15	0.78 (0.56–1.09)	0.61 (0.39–0.97)	0.45 (0.29–0.80)
20	0.79 (0.57–1.08)	0.65 (0.44–0.98)	0.50 (0.31–0.81)
25	0.80 (0.60–1.08)	0.69 (0.49–0.99)	0.54 (0.35–0.84)
30	0.81 (0.62–1.07)	0.74 (0.54–1.01)	0.60 (0.41–0.87)
35	0.84 (0.66–1.07)	0.80 (0.61–1.04)	0.67 (0.48–0.92)
40	0.86 (0.69–1.07)	0.85 (0.68–1.07)	0.73 (0.60–0.97)
45	0.88 (0.73–1.07)	0.91 (0.74–1.12)	0.81 (0.63–1.03)
50	0.91 (0.76–1.09)	0.98 (0.80–1.19)	0.89 (0.71–1.13)
55	0.94 (0.78–1.13)	1.04 (0.84–1.29)	0.94 (0.75–1.20)
60	0.97 (0.80–1.19)	1.11 (0.88–1.41)	1.09 (0.83–1.42)
65	1.01 (0.80–1.29)	1.19 (0.90–1.58)	1.20 (0.88–1.64)
70	1.06 (0.79–1.42)	1.27 (0.92–1.75)	1.32 (0.92–1.90)
75	1.12 (0.77–1.64)	1.38 (0.94–2.02)	1.49 (0.97–2.23)
80	1.17 (0.75–1.81)	1.46 (0.96–2.22)	1.61 (1.00–2.61)
85	1.23 (0.72–2.20)	1.56 (0.97–2.51)	1.78 (1.03–3.08)

HF indicates heart failure; and LVEF, left ventricular ejection fraction.

real-world practice, differences in all-cause mortality become blurred, probably reflecting a higher risk of non-cardiovascular death. Future studies should go deeper into the mechanisms involved in these sex-related differences in HFrEF and provide clues to an optimal representation of women in trials in HFrEF.

Sex-Related Differences in Heart Failure With a Preserved Ejection Fraction

Concerning HFpEF, data from previous studies also showed that women might have a better prognosis than men. It has been consistently shown in clinical trials. In a pooled analysis from CHARM-Preserved, TOPCAT-Americas, and I-Preserve, women had a 30% lower risk of cardiovascular or HF-related death than men.[8] In the recent PARAGON-HF trial, women had higher HF readmission rates, but they showed lower rates of all-cause and cardiovascular-death when compared with men. On the other hand, data from observational studies are conflicting. The risk of all-cause and cardiovascular-death was significantly lower in women in the Swedish HF registry.[11] A 14% lower 1-year all-cause mortality risk was described for women with AHF and LVEF>40% in the international GREAT registry.[10] On the contrary, Hsich et al, reported no sex-differences in the risk of in-hospital mortality in patients with AHF.[24] This is partially in line with our results, in which women with HFpEF did not have a better prognosis than men. Recently, in a multicenter registry of 871 acute HFpEF patients in Japan, female sex was even significantly associated with a higher risk

of a composite end point of all-cause mortality and HF readmission (HR, 1.54; 95% CI 1.14–2.07; *P*<0.001).[17]

As in HFrEF, there are marked differences between women with HFpEF included in clinical trials and those from real-world clinical daily practice. Unlike HFrEF, half of the patients included in trials such as TOPCAT, PARAGON-HF, or EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) were women (50%, 52%, and 45%, respectively). However, as reflected in our data, women in real-world studies are older, with a higher prevalence of comorbidities and a worst functional status than those included in landmark clinical trials. For instance, women included in clinical trials showed lower values of NT-proBNP than men.[8,14] In contrast, in our HFpEF cohort, median NT-proBNP was nearly 3000 pg/mL, and no sex-related significant differences were found in this regard.

In contrast to HFrEF, the pathophysiological mechanisms underlying a better prognosis of women versus men in HFpEF are cumbersome and do not seem to have a clear pathophysiological basis. Women have a lower prevalence than men of ischemic heart disease (20% versus 33% in our study), and this fact may help to explain a worse prognosis in men, as ischemic heart disease is a predictor of cardiovascular death in patients with HF.[25] On the contrary, women with HFpEF exhibit many different clinical and pathophysiological characteristics associated with negative outcomes in HF. They have more symptoms, a worse functional
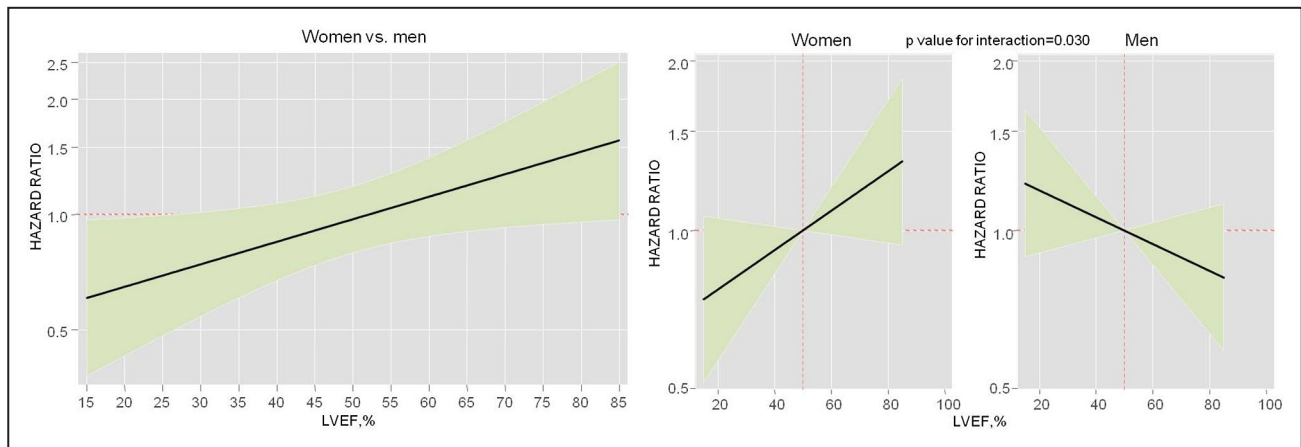
Figure 3. **Hazard ratios of women versus men across left ventricular ejection status for the risk of cardiovascular mortality in the multivariable model.**
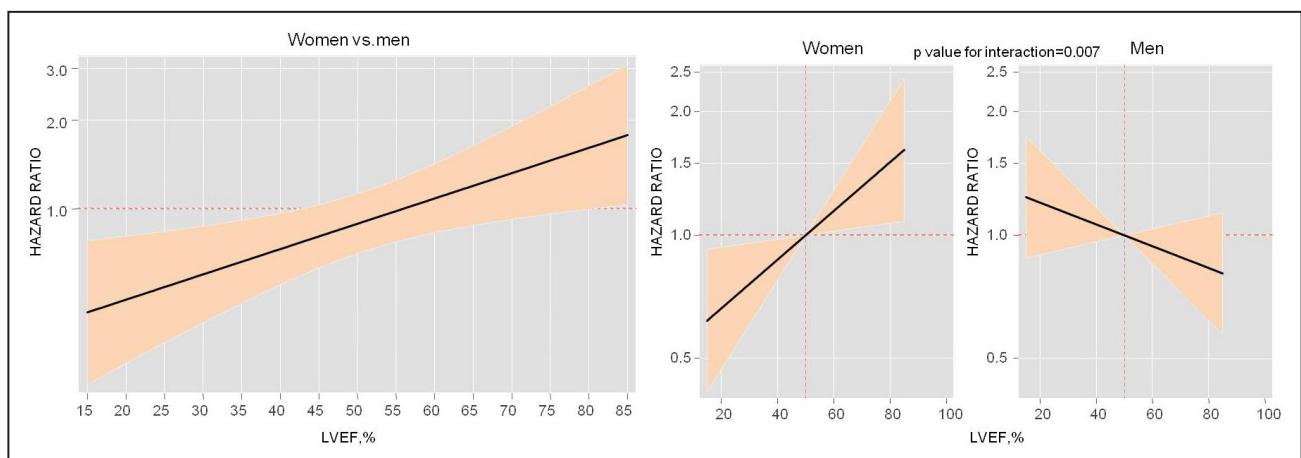Estimates of cardiovascular mortality risk of left ventricular ejection fraction status in men and women. A differential prognostic value of LVEF between women and men was found (*P* for interaction=0.030). HR indicates hazard ratio; and LVEF, left ventricular ejection fraction.

class, and more signs of congestion than men.[1,8,14] In hemodynamic studies, women showed lower systemic compliance, worse biventricular systolic and diastolic reserve, and poorer peripheral oxygen kinetics.[12,15] Other features that have a negative impact on outcomes in HFpEF, such as pulmonary hypertension or right HF, are far more prevalent in women. Women seem to have an intrinsic vulnerability to pulmonary vascular remodeling, and the risk of pulmonary arterial hypertension is four times higher in women.[26] In a recent study from our group, 75% of the patients with HFpEF who developed advanced right heart dysfunction were women.[27] In addition, other features may specifically have a negative impact on prognosis in some women with HFpEF. As we previously reported,

in patients with HFpEF following admission for AHF, diabetes conferred a higher risk of mortality in women when compared with men.[28]

Sex-Related Differences in Prognosis in Patients With Supranormal LVEF

One of the most interesting findings of the current study was that the risk of HF death was significantly higher in the upper extreme of LVEF in women versus men, as it has not been reported previously in HF. Recent data have shown that a supranormal LVEF is associated with negative outcomes in the general population, as postulated in the MESA (Multiethnic Study of Atherosclerosis) study.[29] A trend to a higher risk with

Figure 4. **Hazard ratios of women versus men across left ventricular ejection status for the risk of heart failure-related mortality in the multivariable model.**
Estimates of heart failure mortality risk of left ventricular ejection fraction status in men and women. A differential prognostic value of LVEF between women and men was found (*P* for interaction=0.007). HR indicates hazard ratio; and LVEF, left ventricular ejection fraction.

LVEF>70% has also been described in patients with a coded diagnosis of HF from a large echocardiographic database in the United States.[30] A key finding is that the risk underlying a supranormal LVEF may be higher in women versus men. In a large nationwide registry in Australia, including nearly half a million subjects referred for echocardiography, the risk of cardiovascular death started to increase at high LVEF levels (>60%–65%) in women versus men.[31] In a large cohort of patients evaluated for coronary artery disease, women in the upper extreme of LVEF had a higher risk of death than men.[32] Our results are in line with these studies but extend them to the field of HF, reporting for the first time that women with HF and supranormal LVEF may have a higher risk of HF death than men.

Our observational study does not elucidate underlying mechanisms accounting for these differences, but there are well-established differences in cardiac remodeling in women versus men.[33] A supranormal LVEF may reflect a small LV cavity, typical of hypertensive heart disease or hypertrophic cardiomyopathy. Women display smaller LV cavities than men, and a small LV cavity results in a higher LVEF.[34] Arterial stiffness is a landmark of HFpEF in elderly women, affecting subendocardial function. On the contrary, the subepicardial function remains relatively unaffected, resulting in an increased circumferential shortening and LV twist in women, driven to a maintained and even augmented LVEF over time.[33] A supranormal LVEF may also reflect a hyperdynamic state or different patient characteristics, such as anemia, hyperthyroidism, or valvular regurgitations.[35] A hyperdynamic state in women may predispose them to a cardiac vulnerability and increased metabolic demand in high-stress and overload states, such as HF. In addition, microvascular dysfunction and an increased sympathetic tone, typical adverse features in HFpEF, have also been associated with a supranormal LVEF in women, but not in men.[36]

Of note, there is controversy about what cut-off of LVEF should be considered as "normal" across different scientific societies.[37] In this study, we have evaluated the interaction between sex and the three HF categories originally established by the ESC.[18] Still, some experts advise for a different distribution of HF categories based on LVEF in women versus men.[38] For instance, the benefit of the pharmacological neurohormonal blockade may extent to a higher LVEF in women versus men.[38] In addition, current findings support different sex-related prognostic cut-offs based on LVEF. Therefore, future classifications should take into account prognostic sex-related differences across LVEF status in HF.

Limitations

First, this is an observational study in which hidden bias and residual confounders might be operating. Second, early in-hospital deaths (before echo assessment) were not included in this analysis. Third, echocardiographic studies were not reviewed by an independent core laboratory external to the study sonographers. Fourth, the attribution of causes of death in observational studies remains challenging. Fifth, our results may not be extrapolated to other ethnic populations or geographical regions. Finally, pathophysiological mechanisms underlying our findings are out of the scope of our study, and future works should confirm these findings and explore the underlying causes.

CONCLUSIONS

Following hospitalization for AHF, sex was not a determinant of the risk of all-cause mortality. However, sex-related differences in the risk of cardiovascular and HF mortality were found. Women had a lower risk of cardiovascular and HF mortality when LVEF was severely impaired (<25%) and mildly reduced (<43%), respectively. On the contrary, a higher risk of HF mortality was found in women with supranormal LVEF (>80%). Future studies should confirm these findings and evaluate the potential negative implications of a supranormal LVEF in women with HFpEF.

REFERENCES

1. Lam CSP, Arnott C, Beale AL, Chandramouli C, Hilfiker-Kleiner D, Kaye DM, Ky B, Santema BT, Sliwa K, Voors AA. Sex differences in heart failure. *Eur Heart J*. 2019;40:3859–3868. doi: 10.1093/eurheartj/ehz835

2. Ceia F, Fonseca C, Mota T, Morais H, Matias F, de Sousa A, Oliveira A, Investigators E. Prevalence of chronic heart failure in Southwestern Europe: the EPICA study. *Eur J Heart Fail*. 2002;4:531–539. doi: 10.1016/S1388-9842(02)00034-X

3. Gerber Y, Weston SA, Redfield MM, Chamberlain AM, Manemann SM, Jiang R, Killian JM, Roger VL. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA Intern Med*. 2015;175:996–1004. doi: 10.1001/jamainternmed.2015.0924

4. Ho JE, Enserro D, Brouwers FP, Kizer JR, Shah SJ, Psaty BM, Bartz TM, Santhanakrishnan R, Lee DS, Chan C, et al. Predicting heart failure with preserved and reduced ejection fraction: the International collaboration on heart failure subtypes. *Circ Heart Fail*. 2016;9. pii:e003116. doi: 10.1161/CIRCHEARTFAILURE.115.003116

5. Dewan P, Rorth R, Jhund PS, Shen L, Raparelli V, Petrie MC, Abraham WT, Desai AS, Dickstein K, Kober L, et al. Differential impact of heart failure with reduced ejection fraction on men and women. *J Am Coll Cardiol*. 2019;73:29–40. doi: 10.1016/j.jacc.2018.09.081

6. O'Meara E, Clayton T, McEntegart MB, McMurray JJV, Piña IL, Granger CB, Östergren J, Michelson EL, Solomon SD, Pocock S, et al. Sex differences in clinical characteristics and prognosis in a broad spectrum of patients with heart failure: results of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. *Circulation*. 2007;115:3111–3120. doi: 10.1161/CIRCULATIONAHA.106.673442

7. Merill M, Sweitzer NK, Lindenfeld J, Kao DP. Sex differences in outcomes and responses to spironolactone in heart failure with preserved ejection fraction. A secondary analysis of TOPCAT trial. *J Am Coll Cardiol HF*. 2019;7:228–238. doi: 10.1016/j.jchf.2019.01.003

8. Dewan P, Rørth R, Raparelli V, Campbell RT, Shen LI, Jhund PS, Petrie MC, Anand IS, Carson PE, Desai AS, et al. Sex-related differences in heart failure with preserved ejection fraction. *Circ Heart Fail*. 2019;12:e006539. doi: 10.1161/CIRCHEARTFAILURE.119.006539

9. Martínez-Sellés M, Doughty RN, Poppe K, Whalley GA, Earle N, Tribouilloy C, McMurray JJV, Swedberg K, Køber L, Berry C, et al. Gender and survival in patients with heart failure: interactions with diabetes and aetiology. Results from the MAGGIC individual patient meta-analysis. *Eur J Heart Fail*. 2012;14:473–479. doi: 10.1093/eurjhf/hfs026

10. Motiejūnaitė J, Akiyama E, Cohen-Solal A, Maggioni AP, Mueller C, Choi D-J, Kavoliūnienė A, Čelutkienė J, Parenica J, Lassus J, et al. The association of long-term outcome and biological sex in patients with acute heart failure from different geographic regions. *Eur Heart J*. 2020;41:1357–1364. doi: 10.1093/eurheartj/ehaa071

11. Stolfo D, Uijl A, Vedin O, Stromberg A, Faxen UL, Rosano GMC, Sinagra G, Dahlstrom U, Savarese G. Sex-based differences in heart failure across the ejection fraction spectrum. Phenotyping, and prognostic and therapeutic implications. *J Am Coll Cardiol HF*. 2019;7:505–515. doi: 10.1016/j.jchf.2019.03.011

12. Beale AL, Nanayakkara S, Segan L, Mariani JA, Maeder MT, van Empel V, Vizi D, Evans S, Lam CSP, Kaye DM. Sex differences in heart failure with preserved ejection fraction pathophysiology. A detailed invasive hemodynamic and echocardiographic analysis. *J Am Coll Cardiol HF*. 2019;7:239–249. doi: 10.1016/j.jchf.2019.01.004

13. Palau P, Dominguez E, Núñez J. Sex differences on peak oxygen uptake in heart failure. *ESC Heart Fail*. 2019;6:921–926. doi: 10.1002/ehf2.12483

14. McMurray JJV, Jackson AM, Lam CSP, Redfield MM, Anand IS, Ge J, Lefkowitz MP, Maggioni AP, Martinez F, Packer M, et al. Effects of sacubitril-valsartan versus valsartan in women compared with men with heart failure and preserved ejection fraction: insights from PARAGON-HF. *Circulation*. 2020;141:338–351. doi: 10.1161/CIRCULATIONAHA.119.044491

15. Lau ES, Cunningham T, Hardin KM, Liu E, Malhotra R, Nayor M, Lewis GD, Ho JE. Sex differences in cardiometabolic trails and determinants of exercise capacity in heart failure with preserved ejection fraction. *JAMA Cardiol*. 2020;5:30–37. doi: 10.1001/jamacardio.2019.4150

16. Lam CSP, Carson PE, Anand IS, Rector TS, Kuskowski M, Komajda M, McKelvie RS, McMurray JJ, Zile MR, Massie BM, et al. Sex differences in clinical characteristics and outcomes in elderly patients with heart failure and preserved ejection fraction: the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial. *Circ Heart Fail*. 2012;5:571–578. doi: 10.1161/CIRCHEARTFAILURE.112.970061

17. Sotomi Y, Hikoso S, Nakatani D, Mizuno H, Okada K, Dohl T, Kitamura T, Sunaga A, Kida H, Oeun B, et al. Sex differences in heart failure with preserved ejection. *J Am Heart Assoc*. 2021;10:e018574. doi: 10.1161/JAHA.120.018574

18. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the heart failure association of the ESC. *Eur Heart J*. 2016;37:2129–2200. doi: 10.1093/eurheartj/ehw128

19. Hicks KA, Mahaffey KW, Mehran R, Nissen SE, Wiviott SD, Dunn B, Solomon SD, Marler JR, Teerlink JR, Farb A, et al. 2017 Cardiovascular and stroke endpoints definition for clinical trials. *J Am Coll Cardiol*. 2018;71:1021–1034. doi: 10.1016/j.jacc.2017.12.048

20. Savarese G, Vedin O, D'Amario D, Uijl A, Dahlstrom U, Rosano G, Lam CSP, Lund LH. Prevalence and prognostic implications of longitudinal ejection fraction change in heart failure. *J Am Coll Cardiol HF*. 2019;7:306–317. doi: 10.1016/j.jchf.2018.11.019

21. Sharma K, Mok Y, Kwak L, Agarwal SK, Chang PP, Deswai A, Shah AM, Kitzman DW, Wruck LM, Loehr LR, et al. Predictors of mortality by sex and race in heart failure with preserved ejection fraction: ARIC community surveillance study. *J Am Heart Assoc*. 2020;9:e014669. doi: 10.1161/JAHA.119.014669

22. Lainščak M, Milinković I, Polovina M, Crespo-Leiro MG, Lund LH, Anker SD, Laroche C, Ferrari R, Coats AJS, McDonagh T, et al. Sex- and age-related differences in the management and outcomes of chronic heart failure: an analysis of patients from the ESC HFA EORP Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2020;22:92–102. doi: 10.1002/ejhf.1645

23. Blumer V, Greene SJ, Wu A, Butler J, Ezekowitz JA, Lindenfeld J, Alhanti B, Hernandez AF, O'Connor CM, Mentz RJ. Sex differences in clinical outcomes and patient-reported outcomes among patients hospitalized for heart failure. *J Am Coll Cardiol HF*. 2021;9:336–345. doi: 10.1016/j.jchf.2020.12.011

24. Hsich EM, Grau-Sepulveda MV, Hernandez AF, Peterson ED, Schwamm LH, Bhatt DL, Fonarow GC. Sex-differences in in-hospital mortality in acute decompensated heart failure with reduced and preserved ejection fraction. *Am Heart J*. 2012;163:430–437. doi: 10.1016/j.ahj.2011.12.013

25. Vledin O, Lam CSP, Koh AS, Benson L, Teng THK, Tay WT, Braun OO, Savarese G, Dahlstrom U, Lund LH. Significance of ischemic heart disease in patients with heart failure and preserved, midrange, and reduced ejection fraction. A Nationwide Study. *Circ Heart Fail*. 2017;10:e003875. doi: 10.1161/CIRCHEARTFAILURE.117.003875

26. Badesch DB, Raskob GE, Elliott CG, Krichman AM, Farber HW, Frost AE, Barst RJ, Benza RL, Liou TG, Turner M, et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL registry. *Chest*. 2010;137:376–387. doi: 10.1378/chest.09-1140

27. Santas E, De la Espriella R, Chorro FJ, Palau P, Miñana G, Heredia R, Amiguet M, Merenciano H, Sanchis J, Lupón J, et al. Right ventricular dysfunction staging system for mortality risk stratification in heart failure with preserved ejection fraction. *J Clin Med*. 2020;18:831. doi: 10.3390/jcm9030831

28. Palau P, Bertomeu-González V, Sanchis J, Soler M, de la Espriella R, Domínguez E, Santas E, Núñez JE, Chorro FJ, Miñana G, et al. Differential prognostic impact of type 2 diabetes mellitus in women and men with heart failure with preserved ejection fraction. *Rev Esp Cardiol*. 2020;73:463–470.

29. Yeboah J, Rodriguez CJ, Qureshi W, Liu S, Carr J, Lima JA, Hundley G, Herrington DM. Prognosis of low normal left ventricular ejection fraction in an asymptomatic population-based adult cohort: the multiethnic study of atherosclerosis. *J Card Fail*. 2016;22:763–768. doi: 10.1016/j.cardfail.2016.03.013

30. Wehner GJ, Jing L, Haggerty CM, Suever JD, Leader JB, Hartzel DN, Kirchner HL, Manus JNA, James N, Ayar Z, et al. Routinely reported ejection fraction and mortality in clinical practice: where does the nadir of risk lie? *Eur Heart J*. 2020;41:1249–1257. doi: 10.1093/eurheartj/ehz550

31. Stewart S, Playford D, Scalia GM, Currie P, Celermajer DS, Prior D, Codde J, Strange G. Ejection fraction and mortality: a nationwide registered based cohort study of 499,153 women and men. *Eur J Heart Fail*. 2021;23:406–416. doi: 10.1002/ejhf.2047

32. Gebhard C, Maredziak M, Messerli M, Buechel RR, Lin F, Gransar H, Achenbach S, Al-Mallah MH, Andreini D, Bax JJ, et al. Increased long-term mortality in women with high left ventricular ejection fraction: data from CONFIRM (Coronary CT Angiography EvaluatioN for Clinical Outcomes: an InteRnational Multicenter) long-term registry. *Eur Heart J Cardiovasc Imaging*. 2020;21:363–374. doi: 10.1093/ehjci/jez321

33. Oneglia A, Nelson MD, Merz CNB. Sex differences in cardiovascular aging and heart failure. *Curr Heart Fail Rep*. 2020;17:409–423. doi: 10.1007/s11897-020-00487-7

34. Stokke TM, Hasselberg NE, Smedsrud MK, Sarvari SI, Haugaa KH, Smiseth OA, Edvarsen T, Remme EW. Geometry as a confounder when

assessing ventricular systolic function: comparison between ejection fraction and strain. *J Am Coll Cardiol*. 2017;70:942–954. doi: 10.1016/j.jacc.2017.06.046

35. Olsen FJ, Solomon SD, Biering-Sorensen T. Piecing together the puzzle of sex-specific differences in left ventricular ejection fraction. *Eur J Heart Fail*. 2021;23:417–419. doi: 10.1002/ejhf.2127

36. Maredziak M, Bengs S, Portmann A, Haider A, Wijnen WJ, Warnock GI, Etter D, Froehlich S, Fiechter M, Meisel A, et al. Microvascular dysfunction and sympathetic hyperactivity in women with supra-normal left ventricular ejection fraction (snLVEF). *Eur J Nucl Med Mol Imaging*. 2020;47:3094–3106. doi: 10.1007/s00259-020-04892-x

37. Hudson S, Petit S. What is 'normal' left ventricular ejection fraction? *Heart*. 2020;106:1445–1446. doi: 10.1136/heartjnl-2020-317604

38. Lam CSP, Solomon SD. Classification of heart failure according to ejection fraction: JACC review topic of the week. *J Am Coll Cardiol*. 2021;29:3217–3225. doi: 10.1016/j.jacc.2021.04.070

SUPPLEMENTAL MATERIAL

Table S1. All the covariates and their estimates in the multivariable model for all-cause 6-month mortality risk.

	HR (95%CI)	p value
Age	1.00 (1.00-1.00)	<0.001
Female sex	0.92 (0.77-1.10)	0.355
First HF admission	0.80 (0.68-0.95)	0.013
NYHA class III-IV	1.40 (1.17-1.67)	<0.001
Valvular etiology	1.36 (1.11-1.66)	0.003
Ischemic etiology	1.22 (0.97-1.52)	0.082
Charlson index	1.03 (0.98-1.08)	0.203
Atrial fibrillation	2.17 (1.19-3.95)	0.011
Heart rate at admission	1.01 (1.00 - 1.01)	0.006

SBP at admission	2.50 (1.89-3.31)	<0.001
Hemoglobin (g/dl)	0.97 (0.93-1.02)	0.289
NT-proBNP (pg/ml)	1.53 (1.38-1.69)	<0.001
Glomerular filtration rate (ml/min)	1.00 (1.00-1.00)	0.037
BUN (mg/dl)	1.01 (1.00-1.01)	<0.001
Loop diuretic dose at discharge	1.07 (1.05-1.10)	<0.001

BUN: blood urea nitrogen; CI: confidence interval; HF: heart failure; HR: hazard ratio; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; SBP: systolic blood pressure.

Table S2. All the covariates and their estimates in the multivariable model for cardiovascular 6-month mortality risk.

	HR (95%CI)	p value
Age	1.00 (1.00-1.00)	<0.001
Female sex	0.97 (0.79-1.19)	0.778
First HF admission	0.77 (0.64-0.93)	0.007
NYHA class III-IV	1.36 (1.11-1.65)	0.003
Valvular etiology	1.59 (1.27-1.99)	<0.001
Ischemic etiology	1.24 (0.97-1.56)	0.080
Charlson index	1.01 (0.96-0-99)	0.648
Atrial fibrillation	2.39 (1.25-4.57)	0.009
Heart rate at admission	1.01 (1.00 - 1.01)	0.023
SBP at	2.77 (2.06-3.73)	<0.001

admission		
NT-proBNP (pg/ml)	2.77 (2.06-3.73)	<0.001
BUN (mg/dl)	1.01 (1.00-1.01)	<0.001
Loop diuretic dose at discharge	1.08 (1.05-1.11)	<0.001

BUN: blood urea nitrogen; CI: confidence interval; HF: heart failure; HR: hazard ratio;

NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart

Association; SBP: systolic blood pressure

Table S3. All the covariates and their estimates in the multivariable model for heart failure 6-month mortality risk.

	HR (95%CI)	p value
Age	1.00 (1.00-1.00)	<0.001
Female sex	0.89 (0.70-1.16)	0.331
First HF admission	0.80 (0.64-1.01)	0.060
NYHA class III-IV	1.38 (1.08-1.76)	0.011
Valvular etiology	1.76 (1.33-2.32)	<0.001
Ischemic etiology	1.14 (0.84-1.55)	0.404
Charlson index	2.17 (1,18-4.00)	0.013
Atrial fibrillation	2.24 (1.02-4.89)	0.043
Heart rate at admission	1.01 (0.99 - 1.01)	0.138

SBP at admission	3.10 (2.16-4.45)	<0.001
NT-proBNP (pg/ml)	1.69 (1.49-1.92)	<0.001
BUN (mg/dl)	1.01 (1.00-1.01)	<0.001
Loop diuretic dose at discharge	1.08 (1.04-1.11)	<0.001

BUN: blood urea nitrogen; CI: confidence interval; HF: heart failure; HR: hazard ratio; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; SBP: systolic blood pressure

Figure S1. Hazard ratios of the association between left ventricular ejection as a continuous variable and the risk of all-cause, cardiovascular, and heart failure mortality in the multivariable model.