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RESEARCH ARTICLE

Sex differences in patients with advanced heart failure: an analysis of the HELP-HF registry

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Abstract

Introduction Sex differences are reported in patients with heart failure (HF), but gaps remain in clinical practice and evidence, in particular, in those with advanced HF.

Methods The HELP-HF registry enrolled consecutive patients with HF and at least one high-risk 'I NEED HELP' marker, evaluated at four Italian centres between 1 January 2020 and 30 November 2021. Patients' characteristics and outcomes were compared in men vs women. The primary endpoint was the composite of all-cause mortality or first HF hospitalization.

Results A total of 1149 patients were included (mean age 75.1 ± 11.5 years, median left ventricular ejection fraction 35%). Among them, 773 patients (67.3%) were males. Males were younger, had more cardiovascular diseases and a lower left ventricular ejection fraction (32%, [interquartile range 25–45] vs 45% [interquartile range 30–55]), while females showed a higher prevalence of non-cardiac conditions, neurocognitive and depressive disorders. The 1-year rate of the primary composite endpoint was 43.2% in males and 43.1% in females (log-rank $P = .857$). Multivariable analysis confirmed the lack of a significant impact of sex on the primary endpoint (adjusted hazard ratio 1.03, 95% confidence interval 0.85–1.27, $P = .740$). No significant differences were also observed in men vs women for the individual endpoints.

Conclusions In our registry enrolling patients with markers of advanced HF, despite differences in clinical and echocardiographic characteristics, no sex-related differences in clinical outcomes were observed.

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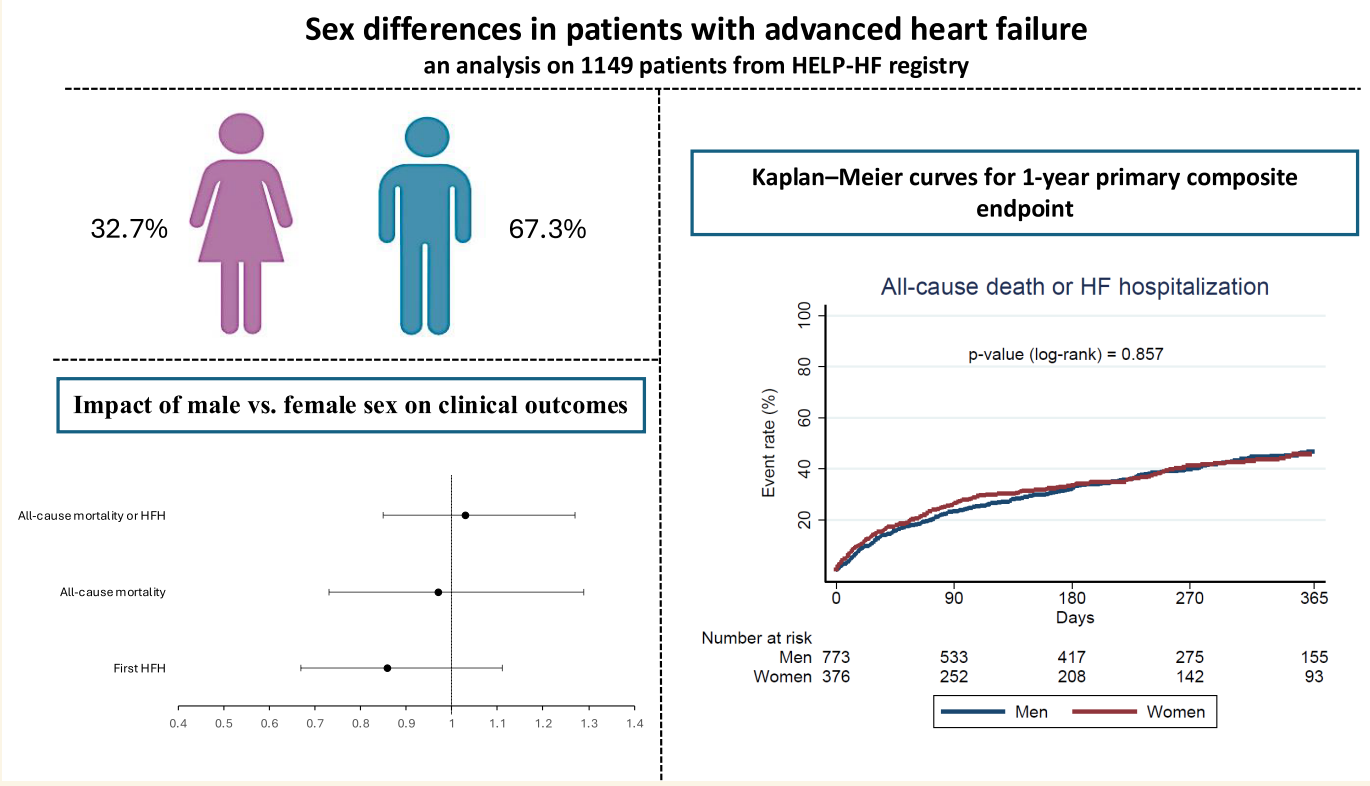
Graphical Abstract



Sex differences in advanced heart failure (HF) patients enrolled in the HELP-HF (Assessment of the I Need Help markers in Heart Failure) registry. Consecutive patients with HF who were hospitalized or evaluated as outpatients between January 2020 and November 2021 at four Italian high-volume centres and had at least one 'I NEED HELP' high-risk marker ($n = 1149$) were included in registry. Among the included patients, 773 patients (67.3%) were males, and 376 patients (32.7%) were females (upper left panel). The 1-year rate of the primary composite endpoint was 43.2% in males and 43.1% in females, without significant difference between the two groups (right panel). Multivariable analysis confirmed the lack of a significant impact of sex on the primary composite endpoint and on the two individual endpoints (lower left panel).

Keywords Sex • Advanced heart failure • HELP-HF • Differences • Mortality

Introduction

Patients with advanced heart failure (HF) (AdHF) typically have a severe cardiac dysfunction, experience refractory symptoms that are disabling for daily life, need multiple HF hospitalizations and have a poor survival, and may be candidates for long-term heart replacement therapies [i.e. heart transplantation (HTx) or left ventricular (LV) assist device [LVAD]), if indicated.[1] The overall prevalence of AdHF is expected to increase due to the overall HF burden and the efficacy of available guideline-directed medical therapy (GDMT).[1–3] Extensive sex differences exist in HF, covering all the aspects of the syndrome, from aetiology to pathophysiology and treatment.[4–10] However, major gaps remain in current clinical practice and available evidence regarding the sex-specific management of patients with HF, including those with severe HF and signs of AdHF.

The aim of our study was to assess sex differences in clinical characteristics and outcomes in a contemporary, real-world, multicentre cohort of patients with AdHF.

Methods

Study design

The observational, retrospective, multicentre HELP-HF (Assessment of the I NEED HELP markers in HF) registry[11–21] included consecutive patients who were hospitalized for acute HF or were evaluated as outpatients for chronic HF at four Italian high-volume centres between 1 January 2020 and 30 November 2021 and had at least one of the following 'I NEED HELP' high-risk markers: (i) previous or ongoing requirement for inotropes; (ii) persisting New York Heart Association (NYHA) class III or IV and/or persistently high B-type natriuretic peptide or N-terminal proBNP; (iii) end-organ dysfunction (worsening renal or liver dysfunction in the setting of HF); (iv) LV ejection fraction (EF) (LVEF) < 20%; (v) recurrent appropriate defibrillator shocks; (vi) more than one HF hospitalization in the last 12 months; (vii) persisting fluid overload and/or increasing diuretic requirement; (viii) consistently low blood pressure (systolic blood pressure <90–100 mmHg); and (ix) inability to up-titrate or need to decrease/cease prognostic medications [angiotensin-converting-enzyme inhibitor (ACE-i), β-blocker, angiotensin receptor–neprilysin inhibitor (ARNI), or

mineralocorticoid receptor antagonist (MRA)]. Institutional review board approval was waived due to the retrospective nature of this registry, involving the collection of de-identified patient data without any specific study interventions. All enrolled patients, whether inpatients or outpatients, received management and treatment according to local clinical practices and in compliance with HF guidelines.[1] Anonymized individual patient data on medical history, clinical presentation, echocardiography and laboratory findings, and clinical outcomes were collected. Congestion and perfusion status at the time of clinical presentation were assessed following established guidelines and position statements.[1,22]

Different definitions of AdHF were applied and reported, including the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) definition,[1,23] American College of Cardiology and American Heart Association stage D classification,[24] and the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) classification. Biventricular function, mitral regurgitation, and tricuspid regurgitation were assessed and graded at echocardiography using previously described methods.[1,25,26] Follow-up was performed by means of medical records (in case of rehospitalizations or outpatient clinical visits) or telephone contact.

The primary endpoint of the study was the composite of all-cause mortality or first HF hospitalization. Secondary outcomes of interest were all-cause mortality and first HF hospitalization as individual endpoints.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) or median and interquartile range (IQR), as appropriate, and compared using the unpaired Student's *t*-test or the Mann–Whitney *U* test, respectively. Categorical variables were presented as numbers and percentages and compared using the χ^2 test. All analyses were based on available data. Given the low proportion of missing values (<5% for key clinical and echocardiographic variables), no imputation of missing data was performed. Baseline characteristics, echocardiography data, laboratory data, and clinical outcomes were compared between men and women. The first occurrence of the primary composite endpoint and of all-cause mortality alone was assessed using the Kaplan–Meier method and compared between the two groups of interest using the log-rank test. The occurrence of first HF hospitalization was evaluated using the Fine-Gray method, accounting for the competing risk of mortality, and presented using the cumulative incidence function. For all endpoints, follow-up was evaluated until the date of the event or the last available follow-up. Cox proportional hazards regression analysis was performed to assess the prognostic impact of sex on the primary composite endpoint and all-cause mortality, whereas the Fine-Gray method was performed for HF hospitalization alone. Univariable and multivariable analyses were conducted to assess the impact of sex on clinical outcomes. In multivariable analyses, sex was adjusted for relevant covariates that were already included in the previously validated multivariable models.[21] In particular, for the primary composite endpoint, sex was adjusted for the following covariates: age, inpatient vs outpatient status, peripheral artery disease, prior stroke or transient ischaemic attack, history of atrial fibrillation, prior myocardial infarction, chronic obstructive pulmonary disease, HFA-ESC-defined advanced HF, NYHA class III-IV, systolic blood pressure and estimated glomerular filtration rate. The same covariates plus heart rate were included in the multivariable model for all-cause mortality.[21] For first HF hospitalization, the following covariates were included in the multivariable model: age, sex, history of atrial fibrillation, prior myocardial infarction, chronic obstructive pulmonary disease, HFA-ESC-defined advanced HF, NYHA class III-IV, LVEF < 40%, and estimated glomerular filtration rate.[21] The impact of HFA-ESC definition of AdHF on the primary endpoint was also tested in both males and females.

Results of the Cox regression analyses were reported as unadjusted or adjusted hazard ratios (HRs) with 95% confidence intervals (CIs). Results of the Fine-Gray models were reported as unadjusted or adjusted subhazard ratios (SHRs) with 95% CI.

All reported *P*-values were 2-sided, and statistical significance was set at $P < .05$. Statistical analyses were performed using STATA version 16.0 (STATA Corp., College Station, TX, USA).

Results

Baseline patient characteristics

Among 4753 patients with HF screened between January 2020 and November 2021 at the four participating centres, 1149 patients (24.3%) had at least one 'I NEED HELP' high-risk marker and were included in the registry. Among them, 773 patients (67.3%) were males, and 376 patients (32.7%) were females. At the time of enrolment, 777 patients (67.6%) were hospitalized, while 372 (32.4%) were outpatients. De-novo HF was reported in 16.3% of included patients.

Baseline characteristics are reported in *Table 1*. Overall mean age was 75.1 ± 11.5 years, and males were younger than females (73.9 ± 11.5 vs 77.5 ± 11.1, $P < .001$). Males had a higher body mass index and more cardiovascular comorbidities and risk factors, including dyslipidaemia, smoking history, ischaemic heart disease, chronic obstructive pulmonary disease (COPD), chronic kidney disease, and peripheral artery disease. Conversely, females showed a greater impairment in daily activities, more balance disorders, and a higher burden of neurocognitive and depressive disorders. Regarding GDMT, a lower proportion of women received β-blockers (71.8% vs 79.4%, $P = .004$) and ACE-i/angiotensin receptor blockers (ARB)/ARNI (44.7% vs 54.1%, $P = .003$), while no differences were observed for MRA and loop diuretics. Women also received less frequently a prior implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy with defibrillator (CRT-D) implantation ($P < .001$).

Clinical presentation and in-hospital data

Details on clinical presentation according to sex are reported in *Table 2*. Women presented more frequently with pulmonary oedema (17.8% vs 11.1%, $P = .002$), while the rate of cardiogenic shock (CS) at presentation was similar between sexes. No differences between sexes were found with respect to vital signs, congestion parameters, in-hospital diuretic treatment, inotropes/vasopressors, and mechanical circulatory support (MCS).

Echocardiographic data and laboratory data are reported in *Table 3*. Regarding echocardiographic data, male patients had a lower LVEF (32% vs 45%, $P < .001$), more dilated left ventricle (end diastolic volume 160 vs 91 mL, $P < .001$) and left atrium, and higher prevalence of right ventricular (RV) dysfunction. No difference in the prevalence of moderate-severe mitral regurgitation was observed between the two groups, whereas moderate-severe tricuspid regurgitation was more frequent in women (60.0% vs 50.3%, $P = 0.002$). Regarding laboratory data, males had higher estimated glomerular filtration rate (42.9 vs 39.6 mL/min, $P = 0.029$), haemoglobin (12.3 vs 11.7 g/dL, $P < 0.001$), and bilirubin values (0.92 vs 0.70 mg/dL, $P < 0.001$) as compared to females.

Clinical outcomes

Over a median follow-up of 260 days (IQR 105–390 days), 265 patients (23.1%) died, 308 patients (26.8%) had a first HF hospitalization, and a primary composite outcome event was observed in 496 patients (43.2%). The 1-year rate of the primary composite endpoint was 43.2% in male patients and 43.1% in female patients, without significant difference between the two groups (log-rank *P*-value = .857; *Figure 1*). Similarly, at 1-year, both individual endpoints, considered separately, did not differ between the two groups (log-rank *P*-value = .832 for mortality and Fine-Gray *P*-value = .131 for HF hospitalization) (*Figures 2* and *3*). The lack of a significant impact of sex on the primary composite endpoint and on the two individual endpoints was confirmed also in multivariable analysis (*Table 4*), with an adjusted HR of 1.03 (95% CI 0.85–1.27, $P = .740$) for the primary composite endpoint. Furthermore, the significant impact of the HFA-ESC definition of advanced HF on the primary

Table 1 Baseline characteristics according to sex

	Overall (*N* = 1149)	Males (*N* = 773)	Females (*N* = 376)	*P*-value
Age (years)	75.1 ± 11.5	73.9 ± 11.5	77.5 ± 11.1	**<.001**
BMI (kg/m²)	25.7 (22.5–28.4)	26.1 (23.3–29.6)	24.9 (22.2–29.3)	**.002**
New-onset HF	187 (16.3)	119 (15.4)	68 (18.1)	.246
Time since HF diagnosis (months)	30 (3–84)	36 (4–96)	24 (1–72)	**.007**
HF hospitalization(s) during last year	415 (36.1)	286 (37.0)	129 (34.3)	.842
Type of inclusion				
Outpatient visit	372 (32.4)	251 (32.5)	121 (32.2)	.921
Inpatient hospitalization	777 (67.6)	522 (67.5)	255 (67.8)	
Comorbidities				
Hypertension	817 (71.1)	548 (70.9)	269 (71.5)	.820
Diabetes	447 (38.9)	315 (40.8)	132 (35.1)	.066
Dyslipidaemia	609 (53.0)	428 (55.4)	181 (48.1)	**.021**
Smoking history				
Non-smoker	662 (59.2)	379 (50.5)	283 (77.1)	**<.001**
Active smoker	110 (9.84)	85 (11.3)	25 (6.8)	
Former smoker	346 (31)	287 (38.2)	59 (16.1)	
History of AF	641 (55.8)	420 (54.3)	221 (58.8)	.155
Prior CAD diagnosis	504 (43.9)	398 (51.5)	106 (28.2)	**<.001**
Prior myocardial infarction	380 (33.1)	308 (39.8)	72 (19.2)	**<.001**
Prior PCI	336 (29.2)	273 (35.3)	63 (16.8)	**<.001**
Prior CABG	171 (14.9)	147 (19.0)	24 (6.4)	**<.001**
Ischaemic cardiopathy	545 (47.4)	430 (55.6)	115 (30.6)	**<.001**
Prior valve surgery	139 (12.1)	84 (10.9)	55 (14.6)	.105
Prior percutaneous valve intervention				
TAVR	28 (2.4)	15 (1.9)	13 (3.5)	.062
Mitral TEER	49 (4.3)	39 (5.1)	10 (2.7)	
Peripheral artery disease	205 (17.8)	156 (20.2)	49 (13.0)	**.003**
Prior stroke or TIA	173 (15.1)	113 (14.6)	60 (16.0)	.551
COPD	266 (23.2)	194 (25.1)	72 (19.2)	**.025**
Chronic kidney disease	650 (56.6)	471 (60.9)	179 (47.6)	**<.001**
Depressive disorder	107 (9.3)	53 (6.9)	54 (14.4)	**<.001**
MCI or dementia	157 (13.7)	88 (11.4)	69 (18.3)	**.003**
ADL or IADL impairment	339 (31.3)	209 (28.6)	103 (37.0)	**.005**
Balance disturbances and falls	391 (36.0)	241 (32.8)	150 (42.6)	**<.001**
NYHA Class III or IV	738 (64.2)	484 (62.6)	254 (67.6)	.101
Cardiac implantable electronic devices				
Pacemaker	167 (14.5)	101 (13.1)	66 (17.6)	**<.001**
ICD	183 (15.9)	149 (19.3)	34 (9.0)	
CRT-D	168 (14.6)	136 (17.6)	32 (8.5)	
CRT-P	15 (1.3)	11 (1.4)	4 (1.1)	
Medical therapy				
β-blockers	882 (76.9)	612 (79.4)	270 (71.8)	**.004**
ACE-i or ARB or ARNI	585 (51.0)	417 (54.1)	168 (44.7)	**.003**
MRA	630 (54.9)	428 (55.5)	202 (53.7)	.568
Loop diuretics	1002 (87.4)	670 (87.0)	332 (88.3)	.162

ACEi, ACE-inhibitor; ADL, activities of daily living; AF, atrial fibrillation; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor/neprilysin inhibitor; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker; HF, heart failure; IADL, instrumental activities of daily living; ICD, implantable cardioverter-defibrillator; MCI, mild cognitive impairment; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; TAVR, transcatheter aortic valve replacement; TEER, transcatheter edge-to-edge repair; TIA, transient ischaemic attack.
Data are presented as *n* (%), mean ± SD, and median (IQR). Bold values represent significant *P*-values.

Table 2 Clinical presentation and in-hospital management according to sex

	Overall (*N* = 1149)	Males (*N* = 773)	Females (*N* = 376)	*P*-value
Clinical presentation				
Cardiogenic shock	153 (13.3)	98 (12.7)	55 (14.6)	.361
Acute pulmonary oedema	153 (13.3)	86 (11.1)	67 (17.8)	**.002**
Rales > 1/3 lung fields	490 (42.7)	318 (41.1)	172 (45.7)	.139
Orthopnea	533 (46.4)	350 (45.3)	183 (48.7)	.279
Peripheral oedema	673 (58.6)	445 (57.6)	228 (60.4)	.322
Inability to perform exercise	603 (52.5)	395 (51.1)	208 (55.3)	.179
Cardiac cachexia	42 (3.7)	24 (3.1)	18 (4.8)	.154
Forrester classification				.226
Class 1 (warm/dry)	271 (23.6)	191 (24.7)	80 (21.3)	
Class 2 (warm/wet)	716 (62.3)	477 (61.7)	239 (63.6)	
Class 3 (cold/dry)	40 (3.5)	30 (3.9)	10 (2.7)	
Class 4 (cold/wet)	122 (10.6)	75 (9.7)	47 (12.5)	
Need of ICU admission	253 (22.0)	165 (21.4)	88 (23.4)	.429
Fulfilling all 4 HFA-ESC criteria	193 (16,8)	140 (18.1)	53 (14.1)	.088
INTERMACS profile 1–3	104 (9.1)	74 (9.6)	30 (8.0)	.377
ACC/AHA stage D	185 (16.1)	126 (16.3)	59 (15.7)	.897
Vital signs				
Systolic blood pressure (mmHg)	124 ± 26	123 ± 25	126 ± 27	.980
Diastolic blood pressure (mmHg)	71 ± 15	71 ± 14	71 ± 16	.272
Mean arterial pressure (mmHg)	89 ± 17	88 ± 17	90 ± 18	.884
Heart rate (bpm)	79 ± 20	78 ± 21	79 ± 20	.835
Diuretic treatment				
IV loop diuretics	778 (67.7)	516 (66.8)	262 (69.7)	.319
Maximum furosemide dose (mg/die)	110 (0–500)	100 (0–500)	120 (0–500)	.260
Thiazide diuretics	82 (7.1)	55 (7.1)	27 (6.9)	.953
Vasoactive drugs				
Use of inotropes/vasopressors	277 (24.1)	187 (24.2)	90 (23.9)	.924
Use of vasodilators	119 (10.4)	77 (10.0)	42 (11.2)	.371
Mechanical circulatory support				
Need of temporary MCS				.099
IABP	40 (3.5)	33 (4.27)	7 (1.86)	
Impella	5 (0.4)	4 (0.52)	1 (0.27)	
VA-ECMO	3 (0.3)	3 (0.39)	0 (0.0)	
Other supports				
Need of mechanical ventilation				.102
Non-invasive	159 (13.8)	102 (13.2)	57 (15.2)	
Invasive	35 (3.1)	29 (3.8)	6 (1.6)	
Need of CRRT/ultrafiltration	45 (3.9)	29 (3.8)	16 (4.3)	.680

ACC, American College of Cardiology; AHA, American Heart Association; CRRT, continuous renal replacement therapy; HFA-ESC, Heart Failure Association of the European Society of Cardiology; IABP, intra-aortic balloon pump; ICU, intensive care unit; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; IV, intravenous; MCS, mechanical circulatory support; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.
Data are presented as *n* (%), mean ± SD and median (IQR). Bold values represent significant *P*-values.

composite endpoint was confirmed in both males (crude HR 2.19, 95% CI 1.71–2.79, $P < .001$) and females (crude HR 2.37, 95% CI 1.63–3.46, $P < .001$), with no significant interaction between such definition and sex (*P*-value for interaction = .682). Similarly, there was no significant interaction between LVEF as a continuous variable and sex with respect to the primary composite endpoint (*P*-value for interaction .287), as well as between tricuspid annular plane systolic excursion (TAPSE) as a continuous variable and sex (*P*-value for interaction .524).

Discussion

This analysis of the multicentre HELP-HF registry focuses on sex differences in patients with severe HF and signs of AdHF. As expected, significant differences in clinical characteristics and echocardiographic parameters were found between men and women. However, in-hospital management and long-term outcomes were similar in the two groups of interest, suggesting that sex may not be a primary determinant of prognosis in AdHF patients.

Table 3 Echocardiographic data and laboratory data according to sex

	Overall (*N* = 1149)	Males (*N* = 773)	Females (*N* = 376)	*P*-value
Echocardiographic data				
LVEF (%)	35 (25–50)	32 (25–45)	45 (30–55)	**<.001**
LVEF categories				**<.001**
HFrEF (LVEF <40%)	649 (56.5)	500 (64.7)	149 (39.6)	
HFmrEF (LVEF 40–49%)	172 (15.0)	107 (13.8)	65 (17.3)	
HFpEF (LVEF ≥50%)	328 (28.5)	166 (21.5)	162 (43.1)	
LV EDD (mm)	57 (50–65)	60 (52.5–66.5)	50 (45–57)	**<.001**
LV EDV (ml)	140 (92–189)	160 (115–202)	91 (70–129)	**<.001**
LV ESV (ml)	94 (49–146)	108 (69–158)	52 (27–92)	**<.001**
Left atrial diameter (mm)	49 (44–54)	50 (45–55)	46 (42–51)	**<.001**
Diastolic dysfunction (grade II-IV)	597 (68.9)	411 (70.7)	298 (66.4)	.430
Moderate or severe MR	683 (61.2)	452 (60.7)	231 (62.4)	.570
MR mechanism				**<.001**
Degenerative	253 (34,9)	134 (27,7)	119 (49,4)	
Functional	359 (49,6)	271 (56,1)	88 (36,5)	
Mixed	111 (15,3)	77 (15,9)	34 (14,1)	
RV dilatation	363 (34.4)	262 (37.1)	101 (28.9)	**.008**
RV dysfunction	482 (43.4)	345 (46.1)	137 (37.7)	**.008**
Moderate or severe TR	585 (53.5)	366 (50.3)	219 (60.0)	**.002**
Laboratory findings				
Creatinine (mg/dL)	1.48 (1.08–2.07)	1.56 (1.17–2.18)	1.28 (0.97–1.82)	**<.001**
eGFR CKD-EPI (mL/min/1.73 m^2)	41.9 (27.2–60.6)	42.9 (28.1–62.9)	39.6 (25.1–57.3)	**.029**
Urea (mg/dL)	69 (47–109)	71 (48–110)	66 (45–107)	.369
NT-proBNP (pg/mL)	5254 (2541–12 421)	5256 (2548–12 852)	5150 (2519–12 190)	.965
BNP (pg/mL)	648 (298–1248)	657 (309–1332)	579 (280–1132)	.291
Haemoglobin (g/dL)	12.0 (10.6–13.5)	12.3 (10.8–13.8)	11.7 (10.3–13)	**<.001**
Haematocrit (%)	36.8 (32.7–41.0)	37.3 (33.0–41.6)	35.6 (32.0–39.6)	**<.001**
Platelet count (10^9/L)	203 (159–259)	198 (151–251)	217 (175–277)	**<.001**
Albumin (g/dL)	3.6 (3.2–3.9)	3.6 (3.2–3.9)	3.7 (3.2–4.0)	.161
Sodium (mmol/L)	140 (137–142)	140 (137–142)	140 (138–142)	.086
Potassium (mmol/L)	4.2 (3.8–4.6)	4.2 (3.8–4.6)	4.1 (3.7–4.5)	**.004**
AST (UI/L)	25 (19–37)	25 (19–38)	27 (19–36)	.733
ALT (UI/L)	20 (14–33)	20 (14–34)	19 (14–32)	.096
Total bilirubin (mg/dL)	0.87 (0.58–1.30)	0.92 (0.60–1.40)	0.70 (0.52–1.10)	**<.001**
INR	1.26 (1.10–1.71)	1.28 (1.10–1.70)	1.20 (1.09–1.77)	.309

ALT, alanine transaminase; AST, aspartate transaminase; BNP, B-type natriuretic peptide; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HFA-ESC, Heart Failure Association of the European Society of Cardiology; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; INR, international normalized ratio; MR, mitral regurgitation; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide; RV, right ventricular; TR, tricuspid regurgitation.
Data are presented as *n* (%) and median (IQR). Bold values represent significant *P*-values.

In line with previous studies,[4,27–31] men with AdHF were younger and had a higher prevalence of ischaemic heart disease, COPD, and co-morbidities associated with macrovascular disease like obesity, smoking history, and dyslipidaemia, while women had a higher degree of functional impairment, balance disorders, and a higher rate of neurocognitive and depressive disorders, affecting quality of life (QoL). At echocardiography, women had a higher LVEF and small left ventricles, whereas men had more frequently reduced LVEF, LV dilatation, and concomitant RV dysfunction. These data confirm the known sex dimorphism in HF, where women tend to develop more frequently HF with preserved LVEF and men HF with reduced LVEF.[4,31–34] The lower QoL in females confirmed the results of the PAL-HF trial[35] and the REVIVAL registry.[36] Less use of GDMT such as β-blockers and renin angiotensin inhibitors was found in female subjects. This may reflect a historical underutilization of evidence-based therapies in women with HF, an aspect already highlighted in previous studies.[37] Possible reasons for this therapeutic disparity include a higher incidence of adverse effects in women, fewer prescriptions due inertia and poor representation of women in clinical trials.[38] Other factors including older age, comorbidities, less specialty care and more deprived socio-economic status can contribute to affect the rate of prescription.[4] Similarly, a lower implantation of ICD or CRT-D was found in female sex, as already reported in previous analyses.[4,27] In contrast, in-hospital management was similar between men and women, including the use of short-term

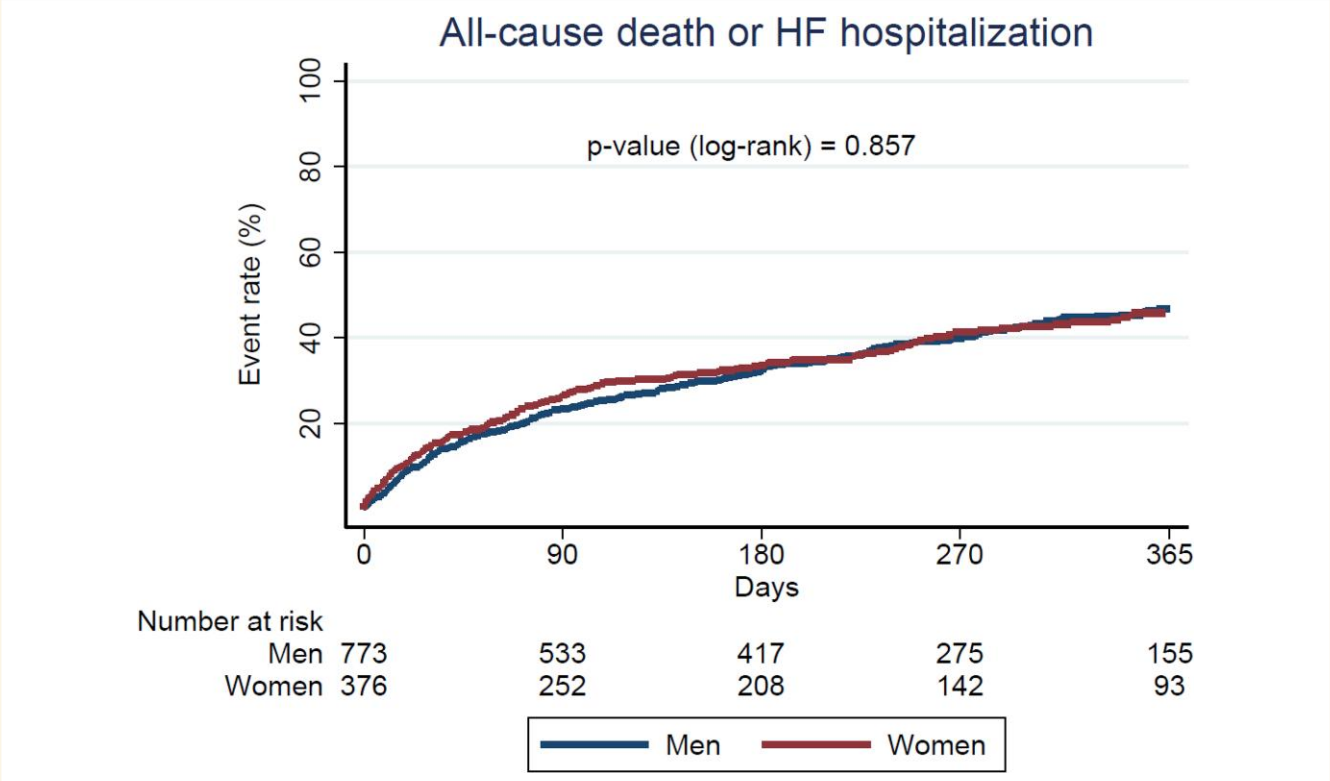


Figure 1 Primary composite endpoint stratified by sex. The figure shows Kaplan–Meier curves for 1-year primary composite endpoint of all-cause mortality or HF hospitalization in men vs women

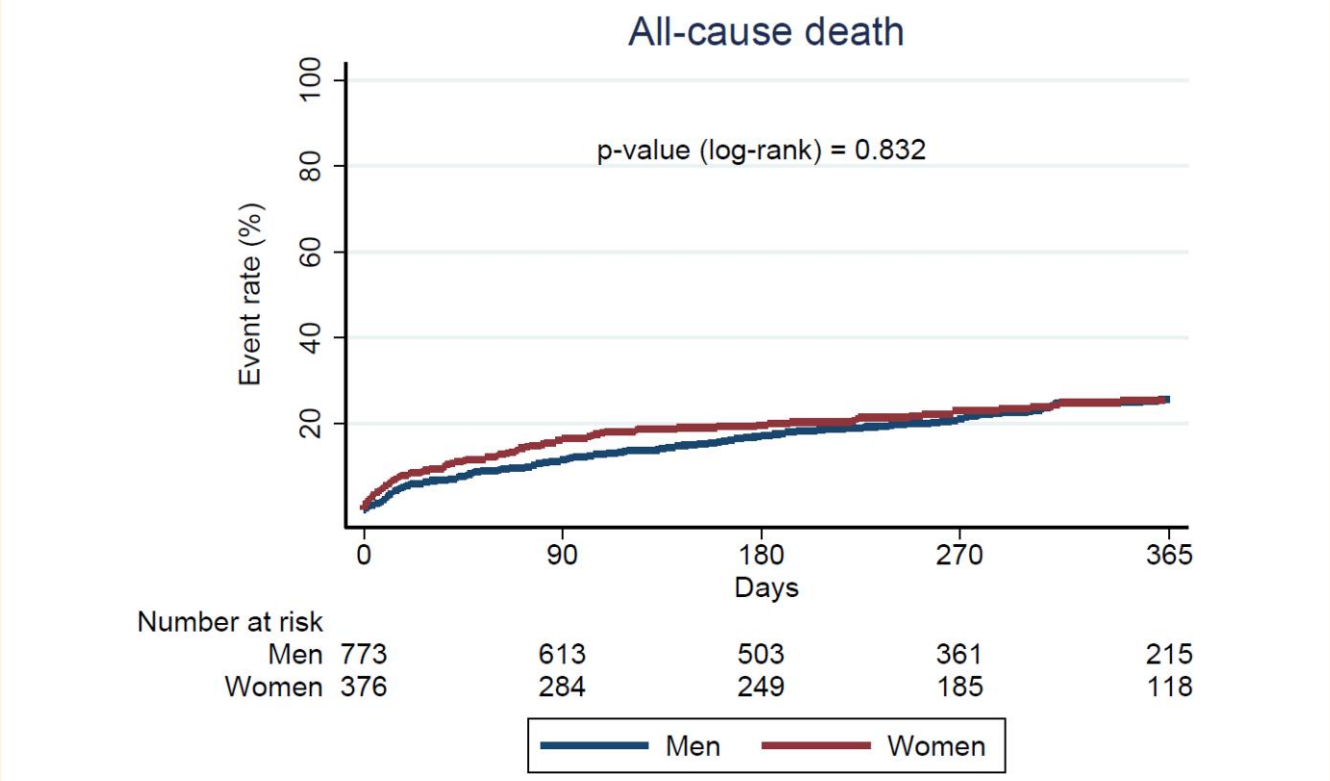


Figure 2 All-cause mortality stratified by sex. The figure shows Kaplan–Meier curves for 1-year all-cause mortality in men vs women

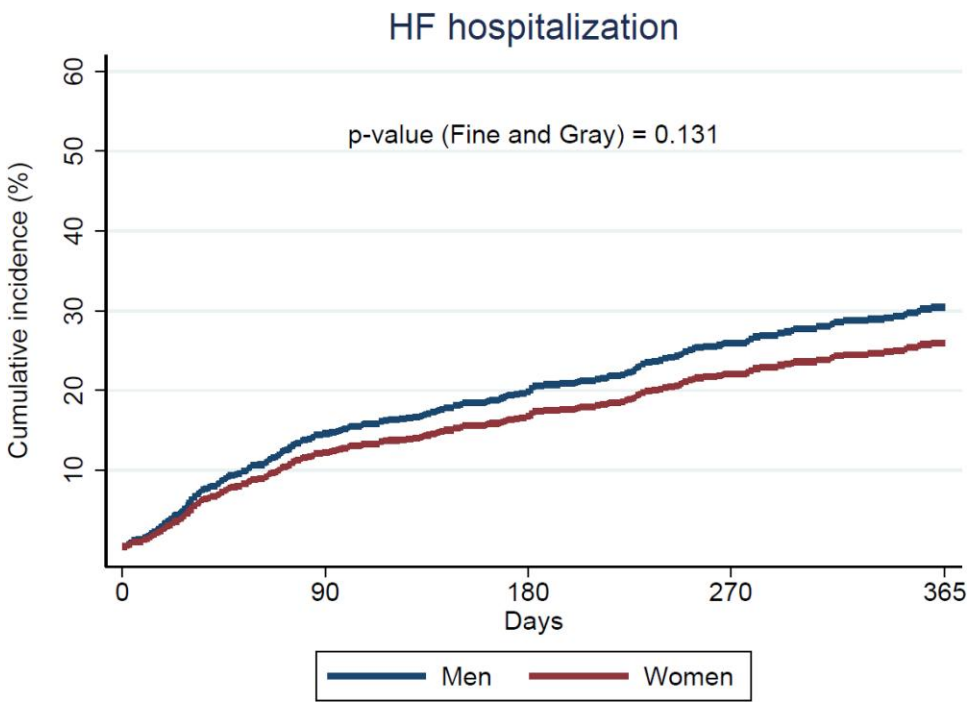


Figure 3 First HF hospitalization stratified by sex. The figure shows Kaplan–Meier curves for 1-year first HF hospitalization in men vs women

Table 4 Impact of sex differences on clinical outcomes

	All-cause death or HF hospitalization[a]		All-cause death[b]		First HF hospitalization[c]	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	SHR (95% CI)	*P*-value
Male sex vs female sex						
Univariable analysis	0.98 (0.82–1.19)	.857	1.03 (0.80–1.33)	.832	0.83 (0.65–1.06)	.130
Multivariable analysis	1.03 (0.85–1.27)	.740	0.97 (0.73–1.29)	.837	0.86 (0.67–1.11)	.257

CI, confidence interval; HFA-ESC, Heart Failure Association of the European Society of Cardiology; HF, heart failure; HR, hazard ratio; SHR, subhazard ratio.
Data are presented as HR or SHR and 95% CI.
[a]Adjusted for age, inpatient vs outpatient status, peripheral artery disease, prior stroke or transient ischaemic attack, history of atrial fibrillation, prior myocardial infarction, chronic obstructive pulmonary disease, fulfilling all 4 HFA-ESC criteria for advanced HF, New York Heart Association class III-IV, systolic blood pressure, heart rate and estimated glomerular filtration rate.
[b]Adjusted for age, inpatient vs outpatient status, peripheral artery disease, prior stroke or transient ischaemic attack, history of atrial fibrillation, prior myocardial infarction, chronic obstructive pulmonary disease, fulfilling all 4 HFA-ESC criteria for advanced HF, New York Heart Association class III-IV, systolic blood pressure and estimated glomerular filtration rate.
[c]Adjusted for age, sex, history of atrial fibrillation, prior myocardial infarction, chronic obstructive pulmonary disease, fulfilling all 4 HFA-ESC criteria for advanced HF, New York Heart Association class III-IV, left ventricular ejection fraction < 40% and estimated glomerular filtration rate.

MCS. Temporary and long-term MCS is guideline-indicated for patients with CS and AdHF. However, even in this case, they are typically underutilized in female patients.[39–43] In contrast, Sundermeyer *et al.*[44] did not find sex differences in MCS use among patients with HF-related CS, in line with our data. However, the question remains whether this result is replicable in larger cohorts and in different clinical settings. Future studies should investigate the underlying reasons for these discrepancies and whether unmeasured factors, such as clinical perception of patients' frailty, may influence treatment decisions.

In our study, no significant differences were found between sexes regarding the combined endpoint of death or HF hospitalization. Even after adjustment for relevant clinical variables, sex was not an independent predictor of clinical outcomes. These data suggest that although men and women with AdHF have different clinical profiles, their risk of adverse events seems similar. However, the worse functional status and increased presence of neurocognitive and depressive comorbidities in women may have implications for QoL and long-term management of these patients. Several studies have reported conflicting results regarding the impact of sex on outcomes in patients with AdHF. Some analyses suggested an improvement in survival in women,[28,29,45–47] attributed to a greater cardiovascular reserve, lower adverse ventricular remodelling and more favourable inflammatory profiles. However, other studies have not shown significant differences in short- and medium-term prognosis between men and women.[30,36] Possible explanations for this

apparent prognostic neutrality include the balancing effect of clinical factors such as advanced age, comorbidity and treatment response, which could mitigate any initial risk differences. In addition, the adoption of GDMT may have reduced the prognostic gap between the sexes. Our study, while confirming the absence of a significant impact of sex on medium-term outcomes, raises the need to further investigate the factors that could modulate prognosis, such as differences in care pathways, in women and men with severe HF.

Limitations

This study has some limitations. First, it has a retrospective nature, which entails the typical weaknesses associated with this type of design. To enhance the reliability of our findings, further validation in larger prospective studies is necessary. Furthermore, clinical events were reported by local investigators and not externally adjudicated, although there is little likelihood of bias in the reported outcomes, such as mortality and hospitalization due to HF. Clinical characteristics and prognosis of patients with AdHF might differ in cohorts of diverse ethnicities and races, and potential variations should be acknowledged. Moreover, although the amount of missing echocardiographic data was low and no imputation was performed, the possibility of residual bias due to incomplete data collection for specific parameters cannot be excluded. Finally, although sex-related differences in LVEF represent a relevant finding, they also constitute a limitation for the interpretation of prognostic comparisons between males and females.

Conclusions

In our analysis of the multicenter HELP-HF registry enrolling patients with AdHF, sex differences were observed in terms of clinical and echocardiographic characteristics. However, these differences did not translate into significant sex differences in the risk of mortality or HF hospitalization during follow-up. These findings highlight the need for more personalized strategies that consider the clinical characteristics of men and women with AdHF, as well as the need for future dedicated studies further exploring the impact of sex on clinical outcomes in this high-risk population.

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Author contributions

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Declarations

Disclosure of Interest

D.S. reports personal fees from Novartis, Merck, GSK, and Acceleron, outside the submitted work. M.A. reports speaker fees from Abbott Vascular and Medtronic. M. Merlo reports personal fees from Pfizer, Novartis, Novo Nordisk and Vifor pharma, outside of the present work. G.S. reports consulting fees from Novartis, Impulse Dynamics and Biotronik, and speaker and honoraria from Novartis, Bayer, AstraZeneca, Boston Scientific, Vifor Pharma, Menarini and Akcea Therapeutics, outside the submitted work. M. Metra received personal consulting honoraria of minimal amount from Abbott, Amgen, Bayer, Edwards Therapeutics, LivaNova and Vifor Pharma for participation in advisory board meetings and executive committees of clinical trials. M.P. reports personal fees from Abbott Laboratories, AstraZeneca, Boehringer Ingelheim, and Vifor Pharma, all outside the submitted work. All the other authors have nothing to disclose

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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