ESC HEART FAILURE
ESC Heart Failure 2018; **5**: 1159–1164
Published online 3 September 2018 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12347

ORIGINAL RESEARCH ARTICLE

Gender differences in Egyptian patients hospitalized with heart failure: insights from the European Society of Cardiology Heart Failure Long-Term Registry

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Abstract

Aims This analysis evaluates gender differences in the Egyptian cohort of patients hospitalized for acute heart failure (AHF) in the European Society of Cardiology Heart Failure Long-Term Registry.

Methods and results From April 2011 to September 2014, 1634 patients hospitalized with AHF were enrolled by 20 hospitals all over Egypt. Of these patients, 1112 (68%) patients were male and 522 (32%) were female. Women presented with a higher admission systolic blood pressure and resting heart rate. Compared with men, women had a higher body mass index (32.5 ± 9.0 vs. 29.3 ± 4.9, $P < 0.001$), more frequent atrial fibrillation (34.7% vs. 22.4%, $P < 0.001$), and anaemia defined by haemoglobin < 12 g/dL (83.1% vs. 58.4%, $P < 0.001$). Women were more likely to present with heart failure with preserved ejection fraction (29.7% vs. 10.6%, $P < 0.001$). Women had more frequent diabetes mellitus (48.1% vs. 41.6%, $P < 0.05$) and hypertension (48.7% vs. 39.3%, $P < 0.001$) than had men, whereas smoking was rare among them (8.8% vs. 82.9%, $P < 0.005$). There was no significant difference in the primary aetiology of heart failure between both sexes. ACE inhibitors, beta-blockers, mineralocorticoid receptor antagonists, antiplatelets, statins, and nitrates were less frequently prescribed to women, whereas they more often received digoxin, amiodarone, anticoagulants, and calcium channel blockers. There was no significant difference in in-hospital (5.7% vs. 4.6%, $P = 0.39$) and 1 year mortality (27.9% vs. 25.9%, $P = 0.48$) between women and men, respectively.

Conclusions Men and women with AHF differ significantly in baseline clinical characteristics and management but not in adverse outcomes. These findings emphasize the importance of individualized management and need for more comprehensive recruitment of women in clinical trials.

Keywords Heart failure; Gender differences; Egypt

Received: 11 April 2018; Accepted: 18 July 2018
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Introduction

Heart failure (HF) is a heavy medical and societal burden. The prevalence of HF is ~1–2% of the adult population in developed countries, rising to ≥10% among people > 70 years of age.[1,2] Projections show that the prevalence of HF in the USA will increase 46% from 2012 to 2030, resulting in >8 million people ≥ 18 years of age with HF.[3]

Women, compared with men, with cardiovascular disease have distinct clinical manifestations and outcome. Women

less often undergo preventive measures and are underdiagnosed, undertreated, and understudied.[4] Knowledge on relevant gender-specific risk factors for HF can assist with appropriate targeted preventative interventions, diagnosis, and therapeutics for each gender.

The purpose of this study is to evaluate the gender-related differences in patients hospitalized for acute decompensated HF (ADHF) with respect to the demographics, underlying aetiology, co-morbidities, and type of HF, as well as management and clinical course.

Methods

The present study uses data from the European Society of Cardiology Heart Failure Long-term Registry 'ESC-HF Long-term Registry', which has been reported in detail elsewhere.[5,6] Briefly, this is a prospective, multi-centre, observational study of patients presenting to 211 cardiology centres of 21 European and Mediterranean countries, which are members of the ESC. The ESC Heart Failure Association endorsed the study, which was conducted by an ad hoc Executive Committee. Twenty hospitals, representing diverse geographic regions of Egypt (Mediterranean coast, Nile delta, Cairo, Upper Egypt, and Suez Canal region), voluntarily participated in this registry. Site selection was aimed to target a sample of hospitals of different levels of complexity, admitting patients with ADHF. Nine participating centres were university hospitals. Seven centres had neither catheterization laboratories nor cardiac surgery facilities. The EURObservational Research Programme (EORP) department at the European Heart House co-ordinated the project operationally, provided support to the participating centres, and guarded the methodological aspects of the survey. Moreover, study sites were monitored on a random basis by an auditor, named by the Executive Committee, who checked compliance with the protocol and reviewed consecutiveness and quality of data. The database was set up at the European Heart House according to the requirements defined by the appointed Executive Committee, with the support of the EORP department.

Patient population

The study population included all patients with HF admitted for acute, pre-existing, or new-onset HF in participating centres during the enrolment period. To facilitate consecutive enrolment, patients were enrolled in the registry on a 1 day/week basis and followed up for at least once a year. Later on during the registry, the 1 day/week policy was changed to 5 days per season, as recommended by the steering committee of the registry. Acute HF (AHF) was defined as either new-onset HF or decompensation of chronic, established HF with symptoms sufficient to warrant hospitalization. There were no specific exclusion criteria, with the exception of age that should be >18 years. Data were collected in the period from April 2011 to September 2014. The aim of this registry was to describe the demographic and clinical characteristics of patients admitted with acute HF who were being taken care of by the participating centres. Specific attention was focused on clinically relevant co-morbidities, which frequently were associated with HF and impact patient outcomes. It was also aimed to describe the diagnostic and therapeutic approaches undertaken in the routine practice of physicians during the hospital phase for ADHF and to assess the in-hospital outcomes of patients with HF.

Ethical considerations

The survey was approved by each local institutional review board according to the rules of each participating centre. The study complies with the Declaration of Helsinki. No data were collected before detailed information was given to the patient, and a signed informed consent was obtained.

Statistical analysis

Descriptive statistics were used to summarize the data. For categorical variables, frequencies and percentages were reported, and differences between groups were analysed using the χ^2 test. For continuous variables, the mean and standard deviation were used to summarize the data, while analysis was performed using Student's *t*-test. Statistical analysis was performed by IBM SPSS for MAC, version 23. All tests were bilateral, and a *P* value of 0.05 or less was the limit of statistical significance.

Results

From April 2011 to September 2014, 1634 patients hospitalized with AHF were enrolled by all participating centres: 1112 (68%) patients were male and 522 (32%) were female. The baseline characteristics are reported in *Table 1*. Analysis of demographic and clinical characteristics of men and women revealed several significant differences. Women presented with a higher admission systolic blood pressure (SBP) and resting heart rate; New York Heart Association class and pulmonary rales were less severe than those of men. Women had a higher body mass index (MI) than had men (32.5 ± 9.0 vs. 29.3 ± 4.9, $P < 0.001$), and 66% of women were by definition obese (BMI > 30 kg/m^2). Women had more frequent atrial fibrillation (34.7% vs. 22.4%, $P < 0.001$) and anaemia, as defined by haemoglobin < 12.0 g/dL (83.1% vs. 58.4% $P < 0.001$), than had men. Women were more likely to present with HF with preserved ejection fraction (HFpEF) than were men (29.7% vs. 10.6%, $P < 0.001$). *Table 2* depicts history, cardiovascular risk factors, and aetiology of HF. Both

Table 1 Baseline characteristics of male and female patients

Characteristic	Men $n = 1112$	Women $n = 522$	*P* value
Demographics and clinical features			
Age (year)	60.5 ± 11.9	60.3 ± 13.3	0.80
BMI (kg/m^2)	29.3 ± 4.9 ($n = 1094$)	32.5 ± 9.0 ($n = 514$)	<0.001
BMI ≥ 30 kg/m^2	435 (42.7%)	315 (66%)	<0.001
NYHA			
Class III	635 (62%)	271 (55.3%)	
Class IV	389 (38%)	219 (44.7%)	0.01
Pulmonary rales	996 (89.6%)	424 (81.5%)	<0.001
SBP (mm/Hg)	130 ± 31	138 ± 35	<0.001
HR (b.p.m.)	101 ± 21	107 ± 25	<0.001
Ejection fraction (%)	36.7 ± 11.2 ($n = 801$)	42.5 ± 13.6 ($n = 408$)	<0.001
Ejection fraction			<0.001
<40 reduced	572 (71.4%)	224 (54.9%)	
40–49 mid-range	144 (18%)	63 (15.4%)	
≥50 preserved	85 (10.6%)	121 (29.7%)	
Atrial fibrillation	237 (22.4%)	170 (34.7%)	<0.001
Haemoglobin g/dL	11.9 ± 2.2 ($n = 1046$)	11.0 ± 1.9 ($n = 483$)	<0.001
Haemoglobin <12 g/dL	536 (58.4%)	364 (83.1%)	<0.001

b.p.m., beats per minute; BMI, body mass index; HR, heart rate; NYHA, New York Heart Association; SBP, systolic blood pressure.

Table 2 History, cardiovascular risk factors, and primary aetiology of heart failure

	Men $n = 1112$	Women $n = 522$	*P* value
History of previous HF	690 (63.4%)	295 (57.3%)	<0.002
HF status			
New onset	403 (36.3%)	215 (41.3%)	0.06
Worsening	707 (63.7%)	305 (58.7%)	
Smoker	921 (82.9%)	46 (8.8%)	<0.001
Diabetes mellitus	463 (41.6%)	251 (48.1%)	<0.05
Hypertension	437 (39.3%)	254 (48.7%)	<0.001
Renal dysfunction	321 (29.9%)	144 (28.6%)	0.63
Hepatic dysfunction	117 (10.5%)	33 (6.3%)	0.006
PAD	63 (5.7%)	22 (4.2%)	0.23
COPD	191 (17.2%)	41 (7.9%)	<0.001
Stroke/TIA	79 (7.1%)	46 (8.8%)	0.23
Primary aetiology			
Ischaemic	706 (65.1%)	333 (64.8%)	0.09
Dilated cardiomyopathy	195 (18%)	81 (15.8%)	
Valvular	97 (8.9%)	47 (9.1%)	
Hypertension	33 (3%)	30 (5.8%)	
Other	53 (4.9%)	23 (4.5%)	

COPD, chronic obstructive pulmonary disease; HF, heart failure; PAD, peripheral arterial disease; TIA, transient ischaemic attack.

Table 3 Hospital presentation, precipitating factors, and mortality

	Men $n = 1112$	Women $n = 522$	*P* value
Hospital presentation			
ACS/HF	228 (20.5%)	90 (17.3%)	<0.001
ADHF	640 (57.6%)	253 (48.7%)	
Pulmonary oedema	133 (12%)	77 (14.8%)	
Cardiogenic shock	37 (3.3%)	23 (4.4%)	
Hypertensive HF	37 (3.3%)	40 (7.7%)	
Right HF	36 (3.2%)	37 (7.1%)	
Precipitating factors for HF			
Myocardial ischaemia	475 (42.8%)	208 (40.0%)	0.31
ACS	293 (26.4%)	120 (23.1%)	0.18
Atrial fibrillation	160 (14.4%)	150 (28.8%)	<0.001
Infection	335 (30.2%)	159 (30.6%)	0.86
Uncontrolled hypertension	216 (19.4%)	170 (32.7%)	<0.001
Renal dysfunction	148 (13.3%)	83 (16.0%)	0.17
Anaemia	210 (18.9%)	184 (35.4%)	<0.001
Non-compliance	89 (8.0%)	47 (9.0%)	0.50
Mortality			
In-hospital	50 (4.6%)	29 (5.7%)	0.39
1 year	218 (25.9%)	109 (27.9%)	0.48

ACS/HF, acute coronary syndrome/heart failure; ADHF, acute decompensated heart failure.

men and women were more commonly admitted with worsening chronic HF; however, new-onset acute HF was more frequently seen in women. Concerning cardiovascular risk factors, smoking was a rarity among women; however, diabetes mellitus and hypertension were more often seen in women. Chronic obstructive pulmonary disease (COPD) and hepatic dysfunction prevalence was significantly higher in men. There was no significant difference in the primary aetiology of HF between both sexes.

Table 3 depicts mode of hospital presentation, precipitating factors for HF, and mortality. Men tended to present with acute coronary syndrome/HF and ADHF, whereas women were more likely to present with pulmonary oedema, hypertensive HF, and right HF. Significant precipitating risk factors for HF requiring hospital admission in women were atrial fibrillation (28.8%), uncontrolled hypertension (32.7%), and anaemia (35.4%). There was no significant difference in in-hospital and 1 year mortality between both sexes. Admission and discharge medications are listed in *Table 4*. Angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, mineralocorticoid receptor antagonists, antiplatelets, statins, and nitrates were less frequently prescribed to women, whereas they more often received digoxin, amiodarone, anticoagulants, and calcium channel blockers.

DOI: 10.1002/ehf2.12347

Table 4 Medication on admission to hospital and at discharge

Variable	Admission medications			Discharge medications		
	Men	Women	*P* value	Men	Women	*P* value
ACE-I	1173 (75.4%)	541 (71%)	0.03	826 (77.6%)	363 (73.5%)	0.08
ARBs	222 (14.3%)	93 (12.3%)	0.19	111 (10.4%)	48 (9.7%)	0.71
Beta-blockers	946 (60.8%)	453 (59.4%)	0.56	699 (65.6%)	299 (60.6%)	0.06
MRAs	1202 (77.2%)	534 (70%)	<0.001	773 (72.7%)	307 (61.9%)	<0.001
Diuretics	1224 (78.8%)	592 (77.8%)	0.59	901 (80.1%)	369 (69%)	<0.001
Digitalis	572 (36.8%)	326 (42.8%)	0.01	365 (34.3%)	198 (39.9%)	0.04
Statins	1091 (70.2%)	428 (56.1%)	0.001	780 (73.4%)	322 (64.8%)	0.001
Antiplatelets	1236 (79.5%)	472 (61.9%)	0.001	887 (83.4%)	340 (68.5%)	0.001
Anticoagulants	676 (43.5%)	429 (56.2%)	0.001	284 (26.7%)	225 (45.5%)	0.001
Amiodarone	164 (10.5%)	134 (17.6%)	0.001	94 (8.8%)	82 (16.6%)	0.001
Nitrates	968 (62.3%)	403 (52.8%)	0.001	594 (55.9%)	197 (39.7%)	0.001
Ca^{++} channel blockers	105 (6.8%)	74 (9.7%)	0.01	70 (6.6%)	60 (12.1%)	0.001
Ivabradine	85 (8%)	30 (6%)	0.16	85 (8%)	28 (5.6%)	0.12

ACE-I, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; MRAs, mineralocorticoid receptor antagonists

Discussion

Baseline characteristics

This study demonstrates significant differences in baseline characteristics, cardiovascular risk factors, and management of men and women presenting with AHF. Women presented with a higher admission SBP and resting heart rate. One of the major differences between men and women presenting with HF was obesity. Women admitted with HF were more frequently obese than were men. Higher prevalence of obesity in women with HF was previously reported in the Saudi HEARTS study.[7] El-Zanaty and Way[8] reported in a survey carried out in Egypt in 2008 that obesity in women increased directly with age, from a level of 10% among women aged 15–19 years to 65% or more among women in the 45–59 year age groups. Obesity has been consistently associated with left ventricular hypertrophy and dilatation, which are known precursors of HF.[9] Kenchaiah *et al*. reported from the Framingham Heart Study cohort that compared with women who had a normal BMI, overweight women had a 50% greater risk of HF, and obese women had twice the risk of HF.[10] Atrial fibrillation was another frequent feature among women presenting with HF. This may be related to the increased prevalence of hypertension among women in our registry. Moreover, atrial fibrillation was a common precipitating trigger for HF in our female population. A high prevalence of atrial fibrillation among women was reported in the EuroHeart Failure Survey II.[11] This was attributed to the older age and more prevalent hypertension in those women.

Women were more likely to present with HFpEF than were men. This is in accordance with the majority of studies[11–13] that revealed higher prevalence of HFpEF in women. In the New York heart failure registry,[14] up to 73% of patients hospitalized for HF with a normal ejection fraction were female. The authors attributed the higher prevalence of HFpEF in women to hypertension and old age. In our registry, women had higher prevalence of hypertension, but they were not older than their male counterparts.

The majority of female patients in our registry had anaemia (haemoglobin $<$ 12.0 g/dL). Fox *et al*.[15] reported anaemia in 56% of women but only in 33% of men. In a systemic review and meta-analysis by Groenveld *et al*.,[16] anaemia was associated with an increased risk of mortality in both systolic and diastolic HF. There was no difference in underlying aetiology of HF between men and women in our registry. This is in variance with many other studies[11,13,17] where men more often had coronary artery disease than had women.

Cardiovascular risk factors

One major difference between men and women was history of smoking, which was quite uncommon among Egyptian women. In contrast, most of our male patients were smokers. This was reflected by a higher prevalence of COPD and more frequent hospital presentation with acute HF associated with acute coronary syndrome in men. The World Health Organization global status report on non-communicable diseases showed an age-adjusted prevalence of daily tobacco smoking in Egypt in adults aged 15 years or older of 37.2% in men and 0.6% in women.[18] Women more frequently suffered from diabetes mellitus and hypertension. This is compatible with other studies that reported similar findings.[11,17,19] The Framingham study was the first epidemiological study to demonstrate an increased risk of congestive HF in patients with diabetes mellitus. The estimated increase in the incidences of HF for young diabetic men and women, compared with non-diabetic men and women, were four-fold and eight-fold, respectively.[20] The proportion of subjects with diabetes was 23% in CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study),[21] 25% in SOLVD (Studies of Left Ventricular Dysfunction),[22] and 20% in V-HeFT II (Vasodilator Heart Failure Trial II).[23] Thus, the prevalence of diabetes mellitus

in the Egyptian cohort of HF patients was disturbingly high. Levy *et al*.[24] studied the relative and population-attributable risks of hypertension in the original Framingham Heart Study and Framingham Offspring Study participants for the development of congestive HF. Multivariable analyses revealed that hypertension had a high population-attributable risk for HF, accounting for 39% of cases in men and 59% in women.

Ibrahim *et al*.[25] reported an estimated prevalence of hypertension in Egypt of 26.3%. Hypertension prevalence increased progressively with age, from 7.8% in those who are 25–34 years to 56.6% in those who are 75 years or older. Hypertension was slightly more common in women than in men (26.9% vs. 25.7%, respectively).

Treatment and outcomes

The higher use of digoxin, warfarin, and amiodarone in women reflects the higher prevalence of atrial fibrillation. The more frequent use of nitrates, statins, and antiplatelets in men was due to more frequent hospital presentation with AHF secondary to acute coronary syndrome. Female patients received less often ACE inhibitors, aldosterone antagonists, and beta-blockers. The same observation was made by other investigators in previous reports.[26,27] The rate of prescription of ACE inhibitors and beta-blockers tended to increase at discharge from hospital in both sexes, but still men and women were undertreated with beta-blockers.

Our study revealed no difference in in-hospital and 1 year mortality between men and women. Our results are compatible with those of EuroHeart Failure Survey II by Nieminen *et al*.,[11] who found similar in-hospital and 1 year mortality in both genders. Women overall have been shown to have better survival than have men.[28,29] However, women with ischaemic heart disease resulting in left ventricular dysfunction may have a mortality similar to that of men with ischaemic disease.[30,31]

Conclusions

This study revealed significant sex differences in clinical presentation, risk profile, and hospital therapies in patients presenting with AHF. Despite these findings, however, we identified no significant sex-based differences in short-term and long-term outcomes. The clinical implications for gender differences in HF impact risk factor screening and targeting gender-specific interventions.

Limitations

There are several limitations of this registry. First, the diagnosis of HF was made by each centre's practicing physician and was not validated centrally. Second, patients enrolled in the registry did not include those patients with HF admitted to other facilities in the hospital. Third, brain natriuretic peptide testing was not included in the diagnosis of HF, because it was performed in a minority of our patients. Fourth, coronary arteriography was not performed or was not available to rule in/out coronary artery disease in a large fraction of patients. Moreover, we did not record re-admission rates in our patients.

Conflict of interest

None declared.

Funding

This survey was funded by the European Society of Cardiology. Each participating national cardiology society was given a grant of €10 000 to help with the organizational needs of national network implementation. The following companies supported the EURObservational Research Programme. Gold-level support: Abbott Vascular (US), Bayer Pharma, BMS/Pfizer, Boehringer Ingelheim International, Daiichi Sankyo Europe, Menarini International, Novartis Pharma, and Laboratoires Servier. Silver-level support: Amgen. Bronze-level support: Boston Scientific International, MSD/Merck & Co, and Sanofi-Aventis Group. Special thanks are due to Laboratoires Servier, Egypt, for their sincere support during the whole period of the survey in Egypt.

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