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Original Article

Gender-related differences in manifestations, complications, and mortality rate of systolic heart failure patients

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Abstract

***Background & Aims*:** Cardiovascular diseases (CVD) are one of the leading causes of death worldwide. Important differences in comorbidities and clinical characteristics exist between women and men with heart failure. This study aimed to explore the influence of gender on the clinical manifestations, complications, and mortality of patients with systolic heart failure.

***Materials & Methods*:** In this cross-sectional study, medical records of all patients who were hospitalized with heart failure between September 2020 and September 2022 were examined. The study gathered information on demographic characteristics, coronary risk factors, clinical symptoms, pathological features, use of selected drugs, and other comorbidities.

***Results*:** Of 1340 patients, 67.2% were men and 32.8% were women with a mean age of 70.58 ± 14.34 years. Fifty-seven (4.2%) patients had the first New York Heart Association (NYHA) class, 120 (8.9%) had the second, 341 (25.5%) had the third, and 161 (12.01%) patients had the fourth NYHA class. The mortality rate and mean ejection fraction (EF) were high in women (9.73%, 35 ± 13.27, respectively). The men had a higher glomerular filtration rate (GFR) (50.45 ± 15.43) than women (40.68 ± 13.98), which was significant ($p = 0.01$). The history of hypertension and myocardial infarction (MI) was high in men (86.36% and 33%, respectively) which were significant ($p = 0.02$, $p = 0.005$, respectively). No gender differences were found in laboratory findings ($p < 0.05$). The consumption of drugs was more common in women than in men; therefore, it was not statistically significant ($p < 0.05$).

***Conclusion*:** This study revealed that women have a significantly higher mean age and EF, drug consumption, and hospital mortality rate compared to men. Otherwise, men have a significantly higher history of hypertension, NYHU function class, and ischemic heart disease.

***Keywords*:** Complications, Gender differences, Heart failure, Mortality rate

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Introduction

Heart failure (HF) is a clinical syndrome that is characterized by the presence of symptoms and signs that indicate an increase in the retention of fluid in tissues and organs, as well as a decrease in the perfusion of tissues and organs (1). In systolic heart failure, the left

ventricle loses its ability to contract normally (2). The majority of patients who are hospitalized for HF are aged 65 years or older (3). Therefore, the increasing prevalence of HF has become one of the major health issues in developed countries (4). Since people with heart failure develop symptoms gradually, given the progressive nature of the disease characterized by a long preclinical phase, early interventions to prevent the disease are hypothetically possible (5). Early identification of clinical HF is crucial in preventing recurrences of HF and hospitalizations due to decompensation (6). There are notable differences in the epidemiology, etiology, risk factors, pathogenesis, treatment response, and prognosis of HF between women and men (7).

Gender-specific medicine has gained increasing attention in recent years due to the observed differences in the prevalence, presentation, management, and outcomes of various cardiovascular diseases between men and women (8). Sex differences in the presentation of HF may play an important role in the progression of the disease, in the development of relevant prognostic comorbidities, and even in response to therapies (9). Previous reviews have indicated significant differences in survival rates between men and women across a wide range of heart failure severity levels (10, 11). Women with heart failure tend to be older than men and are more likely to have a history of chronic hypertension before developing heart failure. Additionally, women with heart failure exhibit a different lipid profile compared to men with the same condition (12). Furthermore, there appear to be differences in the clinical manifestations of heart failure between men and women (13). However, the results of studies examining these differences between the sexes have been inconsistent, with some studies reporting contradictory results (14).

In our thorough research, no studies have investigated the impact of gender on clinical outcomes among heart failure patients in Iran. Furthermore, our country is currently facing a crisis related to the middle-aged and elderly populations, who are more susceptible to diseases associated with this stage of life, including cardiovascular diseases. This highlights the need for further research to improve our understanding and management of these conditions. The objective of this study was to explore the influence of gender on the clinical manifestations, complications, and mortality of patients with systolic heart failure. It is expected that the findings of this study will provide a deeper understanding of the disease and aid in the development of diagnostic and treatment strategies for heart failure patients.

Materials & Methods

In this cross-sectional study, medical records of all patients who were hospitalized with heart failure at Urmia Seyed-ol Shohada Hospital, Iran between September 2020 and September 2022 were examined. Census sampling was used to collect the data. New York Heart Association (NYHA) classification was used to determine the severity of heart failure. Kidney function was measured with glomerular filtration rate (GFR) by using the Modification of Diet in Renal Disease formula. The study was approved by the Ethics Committee of Urmia University of Medical Sciences with the Code of Ethics IR.UMSU.REC.1398.502. According to the approval of the Ethics Committee of Urmia University of Medical Sciences, there was no need to obtain informed consent from the patients because of the retrospective design of the study. This study was performed in line with the principles of the Declaration of Helsinki.

The study gathered information on various factors related to the patients, including their demographic characteristics such as age and sex, coronary risk factors such as BMI, diabetes mellitus (DM), hypertension, and hyperlipidemia, as well as other comorbidities such as the etiology of heart failure, renal failure based on GFR, mortality rate, readmission, and use of selected drugs. Additionally, the study collected data on the patients' symptoms such as shortness of breath, ascites, hospital mortality, ejection fraction (EF), atrial fibrillation, orthopnea, and jugular venous pressure (JVP), as well as their NYHA classification and pathological features.

The inclusion criteria included clinical signs and symptoms of HF, and a left ventricular ejection fraction

(LVEF) ≤ 45%. Exclusion criteria were significant valvular or congenital heart disease and chronic obstructive pulmonary disease (COPD).

Conditions under study

The diagnosis of HF was based on the clinical evaluation (clinical history, plus symptoms, and signs of HF) according to the 2005 European Society of Cardiology (ESC) criteria. Then, subjects with a clinical diagnosis of HF and NYHA class were checked centrally, and the diagnosis of HF was validated only when all three conditions (clinical diagnosis, NYHA class, and LV systolic dysfunction confirmed by the central echo lab) occurred. LVEF was calculated by biplane Simpsom's method.

Transthoracic echocardiography (TTE)

All patients underwent TTE by a commercially available machine (Vivid S6, GE Medical).

Statistical analysis

Descriptive statistics and baseline variables are presented as numbers and percentages, mean ± SD, or median (interquartile ranges (IQR)). A Chi-square test was used to assess differences between categorical variables, and an independent *t*-test (parametric analysis) or Mann-Whitney *U* test (non-parametric analysis) was used to test differences between numerical variables. SPSS version 21 software was used to analyze data and a p value less than 0.05 was considered significant.

Results

A total of 1340 patients were examined in this study, of which 900 (67.2%) were men and 440 (32.8%) were women. According to Table 1, 1040 (77.6%) of the 1340 studied patients, did not have atrial fibrillation (AF) rhythm, but 300 (22.4%) patients had it. Compared to men (19.67%), women (27.95%) had a higher proportion of AF rhythm; therefore, no significant difference was observed between men and women (p = 0.54). In the entire population, function class was not known in 661 (49.3%) patients. Fifty-seven (4.2%) patients had the first NYHA class, 120 (8.9%) had the second class function, 341 (25.5%) had the third class function, and 161 (12.01%) patients had the fourth class function. By comparing the class function between the two sexes, there was no significant difference between the two sexes in this regard (p = 0.33).

In terms of the number of hospitalizations, 320 (23.9%) patients had no previous history of hospitalization, 460 (34.3%), had a history of one hospitalization, 360 (26.9%) had a history of two hospitalizations, 160 (11.9%) had a history of three hospitalizations, and 40 (3%) patients had a history of four hospitalizations. Using the Chi-square test, it was determined that there is no statistically significant difference between men and women in terms of the number of previous hospitalizations (p = 0.84).

In the entire studied population, 1278 (94.37%) patients were discharged, and 62 (5.63%) patients died. Although the mortality rate in women (9.73%) was higher than in men (2.22%), there is no significant difference between the two genders in terms of mortality rate (p = 0.07) (Table 1).

Table 1. Comparison of AF rhythm, NYHA functional class, and hospitalization history between men and women with HF

Variables		Total		Male		Female		*P* value
		N	%	N	%	N	%	
AF rhythm	Yes	22.4	300	177	19.67	123	27.95	0.54*
	No	77.6	1040	723	80.33	317	72.14	
NYHA functional class	I	4.2	57	57	6.3	0	0	0.33*
	II	8.9	120	81	9	39	8.86	

Variables	Total		Male		Female		*P* value
		N	%	N	%	N	%	
	III	25.5	341	178	19.7	163	37.4	
	IV	12.01	161	141	15.6	20	4.5	
	Unknown	49.3	661	443	49.22	218	49.4	
Hospitalization history	No	23.9	320	242	26.7	78	18.2	0.84*
	One time	34.3	460	280	31.1	180	40.9	
	Two times	29.6	360	263	28.9	263	28.9	
	Three times	11.9	160	99	11.1	61	13.6	
	For times	3	40	20	1.2	20	4.5	
Mortality	No	1278	94.37	939	66.3%	339	28.07%	0.07*
	Yes	62	5.63	20	2.22	42	9.73	

Chi-square test*

As Table 2 displays, the mean EF was 30.07 ± 12.77% in the entire studied population. Considering the normality of the distribution of EF in the studied population, the independent parametric t-test was used to compare the mean EF between the two sexes. According to the test results, mean EF was higher in women (35 ± 13.27) than in men (27.66 ± 11.94), which was statistically significant ($p = 0.02$). The mean age of the patients was 70.58 ± 14.34 years, with women having a higher proportion (76.68 ± 12.85) than men (67.60 ± 14.21); therefore, there was a significant difference between the two sexes ($p = 0.01$). The mean NYHA class was 2.8 ± 0.88 among the studied patients. There was no difference between the two sexes in terms of NYHA class ($p = 0.8$). Moreover, the mean GFR was 47.44 ± 15.57 among the entire population. The men had a higher proportion (50.45 ± 15.43) than women (40.68 ± 13.98), which was statistically significant ($p = 0.01$).

Table 2. Comparison of mean EF, GFR, NYHA class, and age between the two genders

Variables	Male	Female	Total	*P* value
EF	27.66 ± 11.64	35 ± 13.27	30.07 ± 12.77	0.02*
Age	67.60 ± 14.21	76.68 ± 12.85	70.58 ± 14.34	0.01*
NYHA class	2.87 ± 1	2.91 ± 0.53	2.8 ± 0.88	0.80
GFR	50.45 ± 15.43	40.68 ± 13.98	47.44 ± 15.57	0.01*

*Independent t-test

According to Table 3, 637 (47.53%) patients had orthopnea, 200 (14.9%) had paroxysmal nocturnal dyspnea (PND), 235 (17.53%) had prominent JVP, 100 (7.5%) had ascites, and 380 (28.4%) patients had peripheral edema. According to the comparison between men and women, PND, ascites, and peripheral edema +3 and +4 were higher in men than in women. Furthermore, orthopnea, JVP, and peripheral edema +1 and +2 were

higher in female than male patients. According to the results of statistical analysis, there was no statistically significant difference between men and women in terms of any of the clinical manifestations ($p < 0.05$).

The histories of hypertension and myocardial infarction (MI) were higher in men (86.36 and 33, respectively) than in women, which were statistically significant between men and women ($p = 0.02$, $p = 0.005$, respectively). The history of diabetes was higher in men than in women, but this difference was not statistically significant ($p = 0.31$). Moreover, the mean BMI of women was higher than men, therefore this difference was not statistically significant ($p = 0.46$).

Table 3. Comparison of heart failure clinical manifestations in men and women

Variables		Male		Female		Total		*P* value
		N	%	N	%	N	%	
*Orthopnea	Yes	378	42	259	58.86	637	47.53	0.15
	No	522	58	181	41.14	703	52.47	
*PND	Yes	168	18.33	35	7.95	200	14.9	0.47
	No	735	81.97	405	92.05	1140	58.07	
*Prominent JVP	Yes	137	15.22	98	22.27	235	17.53	0.34
	No	763	84.77	342	77.72	1105	82.46	
*Ascites	Yes	86	9.5	14	3.19	100	7.5	0.25
	No	814	90.44	426	96.81	1240	92.5	
*Peripheral edema	No	658	73.11	302	68.61	960	71.64	0.80
	+1	58	6.44	42	9.54	100	7.46	
	+2	92	10.22	80	18.18	172	12.83	
	+3	56	6.22	0	0	56	4.17	
	+4	36	4	16	3.63	52	3.88	
*Diabetes history	Yes	196	21.77	68	15.45	264	19.70	0.31
	No	704	78.22	372	84.45	1076	80.30	
*Hypertension	Yes	516	57.33	380	86.36	896	66.86	0.02*
	No	384	42.67	60	13.64	444	33.13	
* MI	Yes	297	33	40	9.10	337	25.14	0.005*
	No	603	67	400	90.90	1003	74.85	
**Mean BMI (kg/m^2)		26.81 ± 5.7		28.41 ± 9.61		27.24 ± 6.89		0.46

*Chi-square Test, **Independent t-test

According to the data in Table 4, the amount of cholesterol in women was higher than in men and the amount of high-density lipoprotein (HDL), low-density lipoprotein (LDL), hemoglobin (Hb), and creatinine (Cr) was higher in men than in women. Based on statistical analysis, it was determined that none of these differences were statistically significant ($p < 0.05$).

Table 4. Comparison of laboratory findings between two genders

Variables	Mean	Female	Total	*P* value
Cholesterol Level	132.62 ± 36.95	155.46 ± 56.97	139.69 ± 44.68	0.12*
HDL (mg/dl)	36.14 ± 9.40	37.84 ± 9.47	36.70 ± 9.34	0.60*
LDL (mg/dl)	79.92 ± 21.65	72.03 ± 14.56	74.60 ± 17.31	0.18*
Hb (g/dl)	12.85 ± 2.02	11.98 ± 1.57	12.57 ± 1.92	0.06*
Cr (mg/dl)	1.81 ± 1.32	1.79 ± 0.78	1.80 ± 1.18	0.94*

Independent t-test*

Table 5 displays that 439 (32.76%) of 1340 patients, had spironolactone consumption, which was more frequent among men (35.88%) than women (26.36%), 759 (56.64%) had Furosemide consumption, 780 (58.20%) had β-blocker consumption, 561(41.86%) had angiotensin receptor blockers (ARB) consumption, 321 (23.95%) had angiotensin-converting enzyme inhibitor (ACEi) consumption, and 217 (16.19%) had Digoxin consumption. The consumption of these drugs was more common in women than in men, therefore, none of these differences were statistically significant ($p < 0.05$).

Table 5. Comparison of the type of drugs used in men and women with heart failure

Variables		Male		Female		Total		*P* value
		N	%	N	%	N	%	
Spironolactone	Yes	323	35.88	116	26.36	439	32.76	0.34*
	No	577	64.12	324	73.64	901	67.24	
Furosemide	Yes	496	55.11	263	59.78	759	56.64	0.49*
	No	404	44.89	177	40.22	581	43.36	
β-blocker	Yes	517	57.44	263	59.77	780	58.20	0.98*
	No	383	42.56	177	40.22	560	41.79	
Angiotensin receptor blockers (ARB)	Yes	343	25.59	218	49.54	561	41.86	0.24*
	No	557	61.88	222	50.45	779	58.13	
Angiotensin-converting enzyme inhibitor (ACEi)	Yes	178	19.77	143	32.5	321	23.95	0.36*
	No	722	80.23	297	67.5	1091	76.04	
Digoxin	Yes	138	15.34	79	17.95	217	16.19	0.52*
	No	762	84.66	361	82.04	1123	83.80	

*Chi-square Test

Discussion

Heart failure is a complex clinical syndrome characterized by the heart's inability to effectively circulate blood to meet the body's metabolic demands due to ventricular dysfunction (1). The lifetime risk of heart failure is comparable between men and women, with estimates of 21% for men and 20% for women at the age of 40 based on the Framingham Heart Study (FHS) (15). Various studies investigating human cardiac hypertrophy and heart failure have identified clinical associations between gender differences in cardiac growth and adaptation observed in laboratory settings. For instance, Patrizio and Marano (16) suggest that gender may influence the nature of left ventricular adaptation in patients with aortic stenosis. They observed that elderly women with severe aortic stenosis tended to have better-preserved systolic function with less ventricular dilatation and hypertrophy compared to their male counterparts. The current findings reveal significant gender disparities in the distribution of demographic characteristics, coronary risk factors (such as BMI, DM, hypertension, and hyperlipidemia), and other comorbidities.

In this investigation, female patients were admitted at an older age than their male counterparts. A comparable study conducted by Mejhert et al. (17) also reported that the mean age of women was significantly higher than that of men. The risk profile of cardiovascular disease in men increases linearly over time, and the atherosclerotic process continues to progress (1). In contrast, estrogen has a favorable impact on the cardiovascular system, which can shield women of reproductive age from atherosclerosis (7). However, the incidence of stroke among menopausal women rises

significantly, and the prevalence of hypertension in women over 75 years of age is higher than that in men (18).

Hypertension is strongly linked to cardiovascular disease and is a significant contributor to left ventricular hypertrophy, diastolic heart failure, and stroke (1). Gender differences in systolic and diastolic blood pressure (BP) have been observed (8). Young men have higher systolic BP than young women (19), and isolated systolic hypertension is the most common form of hypertension in older men (20). This study found that the prevalence of hypertension was significantly higher in men than in women. However, Cesaroni et al. (21) reported that hypertension was associated with heart failure only in women. Prior research has shown that hypertension causes more end-organ damage in women than in men (22).

Pharmacodynamics exhibit significant sex differences, resulting in varying responses to pharmacological therapies for HF (23). Studies have demonstrated that the maximum plasma concentrations of several ACE inhibitors, ARBs, and beta-blockers can be up to 2.5 times higher in women than in men, despite similar dosages (24). Consistent with the findings of this study, women experience adverse events from HF medications at a rate twice that of men (7). The higher use of digoxin in women upon admission reflects the higher prevalence of atrial fibrillation and flutter (25). Moreover, after the main trial's positive outcomes, which indicated that digoxin significantly reduced HF hospitalizations, a sex-stratified sub-analysis revealed a significantly higher risk of death in women but not in men (26).

The majority of patients in this study were classified as NYHA classes II-IV, with males and females being represented in nearly equal proportions, and the vast majority being classified as NYHA class III. In the United States, heart failure is a significant public health concern affecting over five million Americans, with an estimated 250,000 belonging to NYHA functional class IV (27). In our study, more men than women were classified as NYHA class II and IV. These findings were consistent with the study by Baumhakel et al. (28) but differed from those presented by Pop et al. (29), who reported a significant difference between the sexes regarding NYHA classes. Additionally, similar to the study by Mejhert et al. (17), our study found that the mean GFR in men was significantly higher than in women. Several theories have been proposed to explain the more rapid decline in GFR observed in females. As females age, the impact of estrogens on renal hemodynamics and structure is lost due to a gradual decline in estrogen levels even before menopause (8).

In our study, we found that women had higher cholesterol levels than men, while men had higher levels of HDL, LDL, Hb, Cr, BMI, and a history of hypertension and diabetes. It is widely accepted that menopause leads to changes in hormonal, metabolic, and lipid profiles (30). Conventional risk factors such as obesity, hypertension, and hypercholesterolemia are associated with an increased risk of developing chronic heart failure and mortality in the general population (31). However, in contrast to the general population, a higher body mass index, increased serum total cholesterol level, and higher blood pressure are strongly correlated with decreased morbidity and mortality in heart failure (32). In our study, there was no significant difference between men and women in terms of clinical symptoms, including shortness of breath, peripheral edema, ascites, orthopnea, PND, and prominent JVP. Similarly, Adams et al. (33) reported no significant difference between men and women in terms of clinical symptoms, except for orthopnea, which was significantly more common in women than in men.

The present study revealed notable variations in the occurrence of AF rhythm between sexes, with a higher incidence observed in women than in men. This finding is in contrast to previous studies that have reported a higher age-adjusted incidence of AF in men across multiple cohorts (34). The observed difference has been linked to factors such as taller stature and a higher prevalence of AF risk factors, including coronary artery disease, in men (35). However, certain AF risk factors, such as hypertension, valvular disease, and heart failure with preserved ejection fraction, may be more prevalent in women (36). The previous history of MI was

significantly higher in men than in women in this study. This contrasts with the findings of a recent study conducted in England, which involved a large sample of 1.25 million patients and 11,029 MI events (37).

In this study, the crude rates of all-cause mortality were found to be higher in female patients compared to male patients. Despite the fact that women generally have a lower incidence of cardiovascular disease (CVD) than men, various clinical studies have shown that women have a higher mortality rate and poorer prognosis following an acute CV event. The SHAPE study, which focused on HF awareness and perception in Europe, revealed concerning statistics regarding HF mortality. The study found that only 25% of men and 38% of women survive for more than 5 years after being diagnosed with HF. This indicates that women with HF have a higher survival rate compared to men, which is contrary to the findings of our study.

The study has several limitations that need to be acknowledged. Firstly, the cross-sectional design of the investigation only allowed for an examination of the gender disparities in the indications, complications, and mortality rates of HF, without establishing causality. Secondly, the study's reliance on patients' medical records may have introduced inaccuracies in the findings. Finally, the generalizability of the study's findings may be limited due to the small sample size. As a result, further research with a larger sample size is necessary to obtain more accurate and reliable outcomes.

Conclusion

Gender has a significant impact on various aspects of HF, including risk factors, pathophysiology, response to treatment, and eventual outcomes. Gender modifies the relationship between several conventional risk factors and HF. Women have a significantly higher mean age and EF, drug consumption, and hospital mortality rate compared to men. On the other hand, men have a significantly higher history of hypertension, NYHA function class, and ischemic heart disease compared to women. Understanding these differences is a key requirement for early recognition and the early strategies to prevent the disease. The results suggest that prevention policies should consider the sex-specific impact on cardiac function of modifiable cardiovascular risk factors.

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Author's Contributions

Mojgan Hajahmadi Pourrafsanjani and Alireza Rostamzadeh have given substantial contributions to the conception or the design of the manuscript. Roghaiyeh Afsargharehbagh and Mahsa Mirabi Ahar Nejani performed the experiments. Behzad Rahimi supervised the experiments and determined the title. Mojgan Hajahmadi Pourrafsanjani and Alireza Rostamzadeh wrote the article. All authors read and approved the final manuscript.

Data Availability

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

Conflict of Interest

The authors have no conflict of interest in this study.

Ethical Statement

Research involving human subjects complied with all relevant national regulations, and institutional policies is in accordance with the tenets of the Helsinki Declaration (as amended in 2013), and has been approved by the Ethics Committee of Urmia University of Medical Sciences with the code of ethics IR.UMSU.REC.1398.502

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