Gender disparities in heart failure with mid-range and preserved ejection fraction: Results from APOLLON study

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Abstract

Objective: This study aimed to examine gender-based differences in epidemiology, clinical characteristics, and management of consecutive patients with heart failure with mid-range ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF).

Methods: The APOLLON trial (A comPrehensive, ObservationaL registry of heart faiLure with mid-range and preserved ejection fractiON) is a multicenter, cross-sectional, and observational study. Consecutive patients with HFmrEF or HFpEF who were admitted to the cardiology clinics were included (NCT03026114). Herein, we performed a post-hoc analysis of data from the APOLLON trial.

Results: The study population included 1065 (mean age of 67.1±10.6 years, 54% women) patients from 11 sites in Turkey. Compared with men, women were older (68 years vs. 67 years, p<0.001), had higher body mass index (29 kg/m^2 vs. 27 kg/m^2, p<0.001), and had higher heart rate (80 bpm vs. 77.5 bpm, p<0.001). Women were more likely to have HFpEF (82% vs. 70.9%, p<0.001), and they differ from men having a higher prevalence of hypertension (78.7% vs. 73.2%, p=0.035) and atrial fibrillation (40.7% vs. 29.9%, p<0.001) but lower prevalence of coronary artery disease (29.5% vs. 54.9%, p<0.001). Women had higher N-terminal pro-B-type natriuretic peptide (691 pg/mL vs. 541 pg/mL, p=0.004), lower hemoglobin (12.7 g/dL vs. 13.8 g/dL, p<0.001), and serum ferritin (51 ng/mL vs. 64 ng/mL, p=0.001) levels, and they had worse diastolic function (E/e'=10 vs. 9, p<0.001). The main cause of heart failure (HF) in women was atrial fibrillation, while it was ischemic heart disease in men.

Conclusion: Clinical characteristics, laboratory findings, and etiological factors are significantly different in female and male patients with HFmrEF and HFpEF. This study offers a broad perspective for increased awareness about this patient profile in Turkey. *(Anatol J Cardiol 2019; 21: 242-52)*

Keywords: clinical features, differences, gender, heart failure with mid-range ejection fraction, heart failure with preserved ejection fraction

Introduction

Heart failure (HF) is a global, epidemic clinical syndrome with millions of affected people (1). Recent guidelines separate patients with HF to either reduced ejection fraction (HFrEF) (<40%), mid-range ejection fraction (HFmrEF) (40%-49%), and preserved ejection fraction (HFpEF) (>50%) (2). Nearly half of the worldwide population with HF has either HFpEF or HFmrEF (3, 4). This con-

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dition is a major public health problem because its prevalence increases at an alarming rate of 1% per year (5), with rates of cardiovascular events that are similar to those seen in HFrEF (6, 7). Despite the fact that more than half of the patients with HF in routine care are women, randomized clinical trials supporting current HF management guidelines have recruited predominantly male subjects with a lack of prospective gender-specific analyses (8). Some evidence, largely from registries, reveal important gender differences in HF etiology, risk factors, and clinical characteristics: women, compared with men, tend to be older, with non-ischemic HF etiology, and higher blood pressure, as well as more comorbidities such as renal failure and diabetes mellitus (9). Also, recent studies suggest that female patients with HFpEF show distinct characteristics and outcomes compared with men (10). Risk factors for development of HFpEF include renal failure, hypertension, and obesity in women, and ischemic heart disease, chronic obstructive pulmonary disease, and atrial fibrillation in men (11, 12).

HFmrEF is a new category of HF. Recent studies revealed that patients with HFmrEF represent a demographically and clinically diverse group with many intermediate features compared with HFrEF and HFpEF (13). According to the available data, patients with HFmrEF are younger and more predominantly male compared with those with HFpEF (14). However, data of gender-related differences in clinical characteristics and management are limited in patients with HFmrEF, and most of the available data on gender-based characteristics in such patients are obtained from developed countries. Therefore, we performed a post-hoc analysis of data from the APOLLON trial (A comPrehensive, ObservationaL registry of heart faiLure with mid-range and preserved ejection fractiON) to explore the gender-related differences in demographic characteristics, clinical profile, and management of patients with HFpEF and HFmrEF.

Methods

The APOLLON registry

Design and results of the original study have been described elsewhere (15, 16). Briefly, the APOLLON study is a multicenter and observational study conducted in Turkey (ClinicalTrials.gov identifier NCT03026114), in which patients with HFmrEF and HFpEF aged ≥18 years were enrolled in the study between March 31, 2018, and May 20, 2018. A total of 1065 patients who presented to the outpatient cardiology clinics with sign and/or symptoms of HF were enrolled in the study at 11 sites across the country (total 13 hospitals in 11 cities; 6 university hospitals, 4 training and research hospitals, and 3 secondary hospitals). All information, such as demographic characteristics, medical history, laboratory data, electrocardiography, and echocardiography data, were recorded at the time of enrollment.

Patients with a left ventricular ejection fraction (LVEF) ≥40% and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels >125 pg/mL, and patients with signs and/or symptoms of HF were included in this study. One symptom must be present at the time of screening, and one sign must have been present in the last 12 months. To determine HFpEF and HFmrEF, at least one additional echocardiographic criterion including relevant structural heart disease or diastolic dysfunction was required. Key structural alterations were accepted as a left atrial volume index (LAVI) >34 mL/m^2 or a left ventricular mass index (LVMI) ≥115 g/m^2 for males and ≥95 g/m^2 for females. Key diastolic dysfunction criteria were accepted an E/e′ ≥13 and a mean e' septal and lateral wall <9 cm/s.

Patients with an LVEF <40%; patients with significant chronic pulmonary disease; patients with primary severe heart valve disease requiring intervention or surgery; patients with any history of surgically corrected heart valve diseases (e.g., mechanical or bioprosthetic heart valves); patients with myocardial infarction, stroke, or coronary artery bypass graft surgery in the past 90 days; percutaneous coronary intervention or pacemaker implantation in the past 30 days; heart transplant recipients; known infiltrative or hypertrophic obstructive cardiomyopathy or known pericardial constriction; patients with congenital heart diseases or cor pulmonale; and pregnant patients were excluded from the study.

The APOLLON study was approved by the Local Ethics Committee, and informed consent was obtained from all patients.

Study design

Among the 1065 (mean age of 67.1±10.6 years) patients, 577 (54.2%) were female, and 488 (45.8%) were male. Using the registry data of these patients, we examined gender differences in terms of clinical characteristics and management of patients with HFmrEF and HFpEF.

Statistical analyses

Baseline continuous variables are presented as mean ± standard deviations or median, first quartile (Q1) and third quartile (Q3); depending on the distribution of the data. The categorical variables are expressed in frequencies and percentages. The Pearson's Chi-square test was used to compare categorical variables. The continuous variables were compared using the t-test or the Mann–Whitney U-test, as appropriate. Clinical characteristics of female and male patients were compared using Fisher's exact test with two-sided p-values. Analyses were performed with the statistical package SPSS 24.0 (SPSS Inc, Chicago, Illinois, USA).

Results

The baseline characteristics of the patients are listed in Table 1. Compared with men, women with HFpEF and HFmrEF were older; and they more frequently had palpitation, peripheral edema, fatigue, and reduced exercise tolerance. Female par-

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Table 1. Patient demographics, characteristics, and comorbid features for all population

	Female (n=577)	Male (n=488)	*P* value
Age, years	68 (61–76)	67 (60–74)	<0.001
Smoking	32 (5.5)	156 (32.0)	<0.001
Alcohol use	5 (0.9)	41 (8.4)	<0.001
Paroxysmal nocturnal dyspnea	217 (37.6)	150 (30.7)	0.082
Palpitation	326 (56.5)	176 (36.1)	<0.001
Reduced exercise tolerance	499 (86.5)	380 (77.9)	<0.001
Fatigue, tiredness	399 (69.2)	279 (57.2)	<0.001
Chest pain	141 (24.4)	133 (27.3)	0.295
Syncope	29 (5.0)	16 (3.3)	0.158
Dizziness	123 (21.3)	87 (17.8)	0.154
Body mass index, kg/m^2	29 (26–33)	27 (25–30)	<0.001
Systolic blood pressure, mm Hg	130 (120–145)	130 (120–145)	0.539
Diastolic blood pressure, mm Hg	80 (70–90)	80 (70–85)	0.848
Heart rate, bpm	80 (71.5–94)	77.5 (69–89)	<0.001
Pulmonary crepitations	138 (23.9)	97 (19.9)	0.113
Peripheral edema	220 (38.1)	136 (27.9)	<0.001
ECG abnormality	323 (56.0)	293 (60.0)	0.181
Cachexia	24 (4.2)	11 (2.3)	0.082
History of hospitalization for HF in the last year	123 (21.3)	98 (20.1)	0.620
Comorbidities			
Atrial fibrillation	235 (40.7)	146 (29.9)	<0.001
Hypertension	454 (78.7)	357 (73.2)	0.035
Diabetes mellitus	184 (31.9)	135 (27.7)	0.134
Anemia	204 (35.3)	168 (34.4)	0.486
Chronic kidney disease	59 (10.2)	73 (15.0)	0.19
Obstructive sleep apnea	30 (5.2)	31 (6.4)	0.420
Hyperlipidemia	120 (20.8)	144 (29.5)	0.001
Coronary artery disease	170 (29.5)	268 (54.9)	<0.001
Previous myocardial infarction	69 (12.0)	128 (26.2)	<0.001
Coronary artery by-pass grafting	57 (9.9)	98 (20.1)	<0.001
Peripheral artery disease	7 (1.2)	21 (4.3)	0.002
CVA/TIA	39 (6.8)	31 (6.4)	0.790
COPD	71 (12.3)	72 (14.8)	0.243
Hepatic failure	11 (1.9)	7 (1.4)	0.552
Depression	41 (7.1)	17 (3.5)	0.009
Malignancy	5 (0.9)	14 (2.9)	0.014
Heart failure with mid-range ejection fraction	104 (18.0)	142 (29.1)	<0.001
Heart failure with preserved ejection fraction	473 (82.0)	346 (70.9)	

COPD - chronic obstructive pulmonary disease; CVA - cerebrovascular accident; HF - heart failure; TIA - transient ischemic attack

ticipants had higher body mass index and heart rate when compared with what their male counterparts had. Women had higher prevalence of hypertension and atrial fibrillation. However, men had higher prevalence of coronary and peripheral artery disease, and hyperlipidemia. There were significantly fewer smokers and alcohol users among the women. The ratio of patients with HFpEF was significantly higher in females than in males, but the ratio of HFmrEF was more common in men than that in women. Of the 577 female, 104 (18%) had HFmrEF; whereas of the 488 male, 142 (29.1%) had HFmrEF (p<0.001). Of the 577 female, 473 patients had HFpEF (82%), but of the 488 male, 346 (70.9%) had HFpEF (p<0.001).

Table 2. Laboratory parameters

	Female (n=577)	Male (n=488)	*P* value
NT-proBNP, pg/mL	691 (285–1323)	541 (259–918)	0.004
Fasting blood glucose, mg/dL	105 (94–133)	106 (93–123)	0.326
Blood urea nitrogen, mg/dL	17 (13–24)	17 (14–22)	0.766
Serum creatinine, mg/dL	0.8 (0.7–1.0)	0.9 (0.8–1.1)	<0.001
Serum sodium, mmol/L	141 (139–143)	141 (139–143)	0.874
Serum potassium, mmol/L	4.6 (4.3–4.9)	4.6 (4.2–4.9)	0.334
Serum calcium, mg/dL	9.3 (8.9–9.7)	9.3 (8.9–9.7)	0.816
Uric acid, mg/dL	5.5 (4.5–6.8)	5.7 (4.9–6.9)	0.016
Hemoglobin, g/dL	12.7 (11.4–13.6)	13.8 (12.4–15.0)	<0.001
Leukocyte, $x10^3/\mu L$	7.8 (6.5–9.2)	7.9 (6.7–9.4)	0.538
C-reactive protein, mg/dL	3.5 (1.8–7.9)	3.2 (1.9–7.0)	0.095
Ferritin, ng/mL	51 (26–90)	64 (29–122)	0.001
TSH, µIU/mL	1.5 (0.9–2.7)	1.4 (0.9–2.2)	0.308

NT-proBNP - N-terminal pro B-type natriuretic peptide; TSH - thyrotropin-stimulating hormone

Tables 2 and 3 show the comparison of laboratory parameter and echocardiographic findings according to the gender. The NT-proBNP levels were significantly higher in women (691 pg/mL vs. 541 pg/mL, p=0.004), but hemoglobin and ferritin levels were significantly lower in women than those in men.

Compared with female patients, male patients had significantly higher interventricular septum thickness, left ventricular posterior wall thickness, left ventricular end-diastolic and end-systolic dimensions, whereas LVEF was lower (55% vs. 60%, p<0.001) in men. Women had worse diastolic function [E/e'=10 (range:8–13) vs. 9 (range:7–12), p<0.001], and they were associated with a trend toward higher prevalence of abnormal left ventricular geometry (concentric hypertrophy or eccentric hypertrophy, or concentric remodeling) and higher pulmonary artery systolic pressure compared with those in men. Women also had higher prevalence of mitral and tricuspid valvular regurgitation compared with what men had.

Beta-blockers, statins, and antiplatelets were less frequently prescribed to women. Women more often received angiotensin receptor blockers, non-dihydropyridine and dihydropyridine calcium blockers, anticoagulants, and thiazide diuretics as compared with their male counterparts (Table 4). The use of other medications was similar in the two groups.

Etiology of HF differed between both the sexes (Table 5). Female patients were more likely to have atrial fibrillation (32.4% vs. 22.1%, p<0.001), hypertension (26.3% vs. 23.8%, p<0.001), and valvular heart disease (14.6% vs. 7.4%, p<0.001) as a cause of HF. However, ischemic heart disease (42.6% vs. 21.1%, p<0.001) was the most common cause of HF in male patients.

Comparison of female and male patients with HFpEF

Table 6 shows the differences between the patients with HFpEF of different genders. Of the 819 patients with HFpEF, 473 (57.8%) were female. Compared with male patients, female had significantly higher body mass index. Prevalence of hypertension was higher in female patients with HFpEF; however, male had higher prevalence of coronary artery disease. The NT-proBNP levels were significantly higher in female than in male patients with HFpEF. Compared with men, LVEF, LAVI, and E/e' were higher in women with HFpEF. Etiology of HF was significantly different in female and male. The main etiology of HF was atrial fibrillation (33.8%) in female patients; however, the most common cause of HF was hypertension (30.1%) in male patients with HFpEF.

Comparison of female and male patients with HFmrEF

Of the 246 patients with HFmrEF, 142 (57.7%) were male. Compared with women, men were younger, had significantly lower body mass index and heart rate. There were significantly more smokers and alcohol users among the men with HFmrEF. Women had higher prevalence of atrial fibrillation. On the other hand, prevalence of coronary artery disease was higher in male patients with HFmrEF. In female patients with HFmrEF, the NT-proBNP levels (1167 pg/mL vs. 677 pg/mL, p<0.001) and E/e' value (10.1 vs. 9, p=0.009) were significantly higher, and hemoglobin levels were lower. Angiotensin-converting enzyme inhibitors were more frequently prescribed to men; however, women more often received dihydropyridine calcium blockers. The use of other medications was similar in the two groups. In patients with HFmrEF, ischemic heart disease was the most common cause of HF in both sexes (Table 7).

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Table 3. Two-dimensional transthoracic echocardiographic, Doppler data

	Female (n=577)	Male (n=488)	*P* value
LVEF, %	60 (53–62)	55 (47–60)	<0.001
e', cm/sn	7 (6–8)	7 (6–8)	0.680
E/e'	10 (8–13)	9 (7–12)	<0.001
LV diastolic dysfunction			
None	71 (12.4)	70 (14.3)	0.042
Grade 1	132 (22.8)	57 (31.3)	
Grade 2	236 (40.9)	172 (35.3)	
Grade 3	138 (23.9)	93 (19.1)	
LVED dimension, mm	48 (44–51)	49 (45–54)	<0.001
LVES dimension, mm	32 (29–36)	33 (30–39)	<0.001
IVS dimension, mm	11 (10–12)	12 (10–13)	0.007
LVPW dimension, mm	10 (10–11)	11 (10–12)	0.008
LAVI, mL/m^2	35 (30–41)	33 (29–41)	0.067
LA enlargement	300 (52.0)	224 (45.9)	0.063
LVMI, g/m^2	108 (90–128)	110 (90–130)	0.323
LV concentric hypertrophy	386 (66.9)	221 (45.3)	<0.001
PAPs, mm Hg	30 (17–38)	27 (15–35)	<0.001
Mitral regurgitation			
None	149 (25.8)	156 (32.0)	0.003
Mild	289 (50.1)	257 (52.7)	
Moderate	135 (23.4)	74 (15.2)	
Severe	4 (0.7)	1 (0.2)	
Mitral stenosis			
None	547 (95.0)	480 (98.4)	0.010
Mild	19 (3.3)	6 (1.2)	
Moderate	10 (1.7)	2 (0.4)	
Aortic stenosis			
None	554 (96.2)	475 (97.3)	0.533
Mild	15 (2.6)	8 (1.6)	
Moderate	7 (1.2)	5 (1.0)	
Aortic regurgitation			
None	420 (72.9)	386 (79.1)	0.064
Mild	137 (23.8)	90 (18.4)	
Moderate	19 (3.3)	12 (2.5)	
Tricuspid regurgitation			
None	190 (32.9)	196 (40.2)	0.003
Mild	238 (41.2)	208 (42.6)	
Moderate	123 (21.3)	73 (15.0)	
Severe	26 (4.5)	11 (2.3)	

IVS - interventricular septum; LA - left atrium; LAVI - left atrial volume index; LV - left ventricle; LVED - left ventricular end-diastolic; LVEF - left ventricle ejection fraction; LVES - left ventricular end-systolic; LVMI - left ventricular mass index; LVPW - left ventricular posterior wall; PAPs - pulmonary artery systolic pressure

Age distribution by gender in patients with HFmrEF and HFpEF

Mean age of our HFpEF cohort was 67 years, with almost 50% of the patients aged between 65 and 80 years. Temporal trend analysis showed female predominance among all age groups in patients with HFpEF (Fig. 1). On the other hand, mean age of patients with HFmrEF was 68 years, with >50% of the patients aged between 65

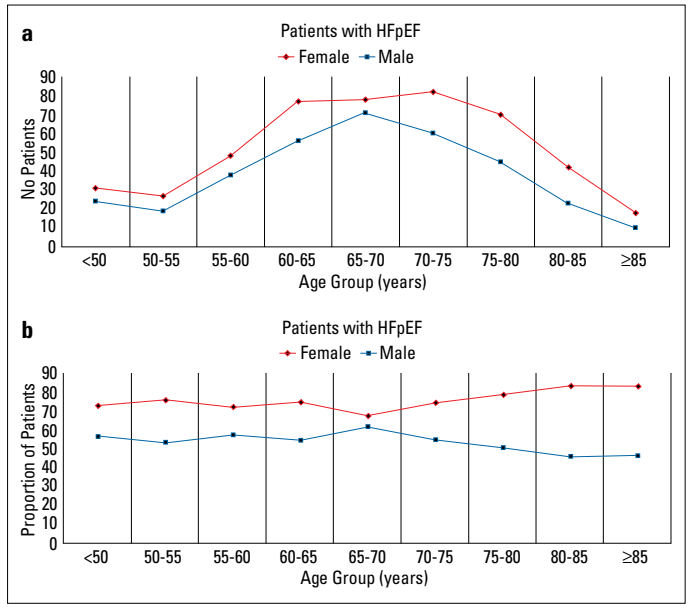

Figure 1. Age distribution by gender in patients with heart failure and preserved ejection fraction. Number of patients (a), proportion of patients (b). Temporal trend analysis showed female predominance among all age groups

HFpEF - heart failure with preserved ejection fraction

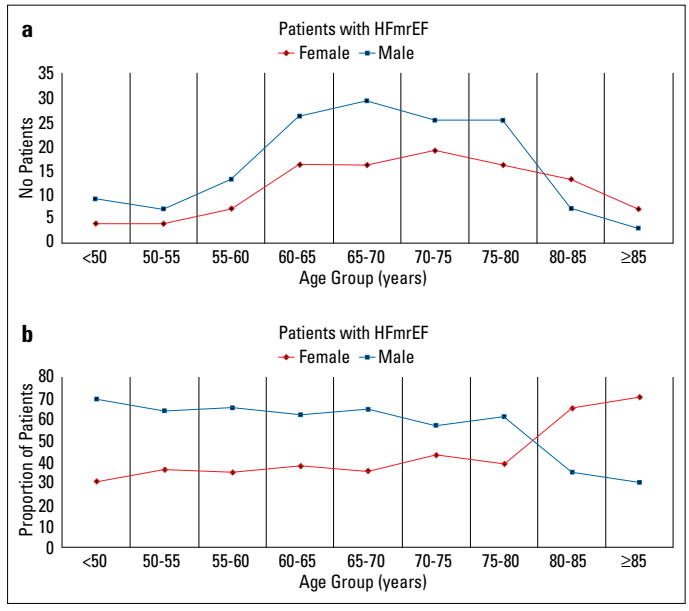

Figure 2. Age distribution by gender in patients with heart failure and mid-range ejection fraction. Number of patients (a), proportion of patients (b). The proportion of males among patients aged <80 years was higher than that of females; whereas in the elderly, the proportion of females was higher

HFmrEF - heart failure with mid-range ejection fraction

Table 4. Medications

	Female (n=577)	Male (n=488)	*P* value
Angiotensin-converting enzyme inhibitors	179 (31.0)	175 (35.9)	0.095
Angiotensin receptor blockers	173 (30.0)	119 (24.4)	0.041
Beta-blockers	318 (55.1)	306 (62.7)	0.012
Aldosterone antagonists	92 (15.9)	87 (17.8)	0.413
Ivabradine	3 (0.5)	7 (1.4)	0.200
Amiodarone	12 (2.1)	8 (1.6)	0.656
Propafenone	3 (0.5)	0 (0)	0.255
Non-dihydropyridine calcium blockers	80 (13.9)	38 (7.8)	0.002
Dihydropyridine calcium blockers	133 (23.1)	80 (16.4)	0.007
Digoxin	31 (5.4)	37 (7.6)	0.166
Statins	110 (19.1)	168 (34.4)	<0.001
Loop diuretics	202 (35.0)	146 (29.9)	0.078
Thiazide	194 (33.6)	124 (25.4)	0.004
Isosorbide	19 (3.3)	29 (5.9)	0.038
Antiaggregant	210 (36.4)	269 (55.1)	<0.001
Anticoagulant	185 (32.1)	110 (22.5)	0.001
Non-steroidal anti-inflammatory drugs	47 (8.1)	31 (6.4)	0.263
Oral antihyperglysemic	142 (24.6)	104 (21.3)	0.203
Insulin	50 (8.7)	37 (7.6)	0.575

Table 5. Etiology of heart failure

	Female (n=577)	Male (n=488)	*P* value
Ischemic	122 (21.1)	208 (42.6)	
Atrial fibrillation	187 (32.4)	108 (22.1)	
Hypertension	152 (26.3)	116 (23.8)	<0.001
Valvular disease	84 (14.6)	36(7.4)	
Other	32 (5.5)	20 (4.1)	

and 80 years. This analysis revealed male predominance among those aged <80 years in patients with HFmrEF, whereas, in older patients, percentage of females increased, and ultimately the rate of female exceeded the male ratio in HFmrEF group (Fig. 2).

Discussion

Previous epidemiological studies revealed a female predominance in the development of HFpEF (17). Fifty-five percent of patients with HFpEF were female in the Swedish Heart Failure Registry, which included over 18,000 patients with HFpEF and HFmrEF (18). However, most of these studies were clinical drug trials, and they may not reflect real-life patients with HFpEF. Moreover, to the best of our knowledge, there have been no studies evaluating gender differences in patients with HFmrEF.

In this analysis from APOLLON study, we evaluated sex differences in demographic, clinical, and laboratory parameters in a large national cohort of patients with HFmrEF and HFpEF in a real-world setting. Our results indicate that the clinical manifestations of HFmrEF and HFpEF differ widely between women and men. Women were usually older at presentation, and had a greater burden of atrial fibrillation and hypertension; on the other hand, men were more likely to have coronary and peripheral artery disease, hyperlipidemia, and malignancy compared with women. Our results also showed that signs and symptoms may also have sex-related differences: women tended to be more symptomatic for palpitations, reduced exercise tolerance, peripheral edema, and fatigue on admission. The ratio of HFmrEF was also significantly different among men and women; nearly one-fifth of the women and one-third of the men had HFmrEF in our study cohort. Another important difference concerns the management of HF; men were more likely to receive beta-blockers, statins, and antiplatelets, probably due to higher prevalence of ischemic heart disease in men, whereas women more often received anticoagulant drugs that may be secondary to the higher prevalence of atrial fibrillation in women.

Over the past decade, one of the most important findings across numerous HFpEF studies was a distinct gender distribution. Generally, women significantly outnumber men, leading to a gender ratio of approximately 2:1 in HFpEF (19, 20). In our study, 57.8% of the patients with HFpEF were female. Previous studies have shown that women with HFpEF tend toward higher LVEF,

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Table 6. Heart failure with preserved ejection fraction in female and male

	Female (n=473)	Male (n=346)	*P* value
Age, years	67 (61–75)	67 (60–74)	0.262
Smoking	29 (6.1)	100 (28.9)	<0.001
Alcohol use	26 (7.5)	3 (0.6)	<0.001
Body mass index, kg/m^2	29 (26–33)	27 (24–30)	<0.001
Heart rate, bpm	80 (70–92)	78 (70–90)	0.076
History of hospitalization for HF in the last year	92 (19.5)	60 (17.3)	0.443
Comorbidities			
Atrial fibrillation	194 (41.0)	119 (34.4)	0.054
Hypertension	377 (79.7)	246 (71.1)	0.004
Diabetes mellitus	153 (32.3)	91 (26.3)	0.062
Anemia	165 (34.9)	120 (34.6)	0.903
Chronic kidney disease	43 (9.1)	45 (13.0)	0.074
Obstructive sleep apnea	26 (5.5)	29 (8.4)	0.103
Coronary artery disease	116 (24.5)	155 (44.8)	<0.001
Previous myocardial infarction	31 (6.6)	48 (13.9)	<0.001
Laboratory data			
NT-proBNP, pg/mL	574 (263–1060)	483 (224–865)	0.021
Blood urea nitrogen, mg/dL	17 (13–22)	17 (13–22)	0.666
Serum creatinine, mg/dL	0.8 (0.7–1)	0.9 (0.8–1.1)	<0.001
Serum potassium, mmol/L	4.6 (4.3–5.0)	4.5 (4.2–5.0)	0.817
Haemoglobin, g/dL	12.7 (11.4–13.5)	13.8 (12.3–15.0)	<0.001
Ferritin, ng/mL	51 (25–88)	63 (28–132)	0.003
Echocardiography			
LVEF, %	60 (55–65)	59 (55–62)	<0.001
E/e'	9.8 (8.0–12.4)	9.0 (7.1–12.0)	0.002
LV diastolic dysfunction			
None	57 (12.1)	47 (13.5)	0.054
Grade 1	114 (24.1)	111 (32.1)	
Grade 2	192 (40.6)	119 (34.5)	
Grade 3	110 (23.2)	69 (19.9)	
LVED dimension, mm	48 (44–51)	47 (44–52)	0.168
LVES dimension, mm	31 (28–35)	32 (29–36)	0.033
LAVI, mL/m^2	35 (30–40)	33 (28–38)	0.029
Medications			
Angiotensin-converting enzyme inhibitors	151 (31.9)	114 (32.9)	0.757
Angiotensin receptor blockers	142 (30.0)	86 (24.9)	0.103
Beta-blockers	246 (52.0)	206 (59.5)	0.032
Aldosterone antagonists	70 (14.8)	50 (14.5)	0.889
Nondihydropyridine calcium blockers	70 (14.8)	32 (9.2)	0.17
Dihydropyridine calcium blockers	112 (23.7)	67 (19.4)	0.140
Digoxin	22 (4.7)	28 (8.1)	0.042
Isosorbide	16 (3.4)	15 (4.3)	0.480

Table 6. Cont

	Female (n=473)	Male (n=346)	*P* value
Loop diuretics	157 (33.2)	93 (26.9)	0.053
Thiazide	163 (34.5)	77 (22.3)	<0.001
Etiology of heart failure			
Ischemic	76 (16.1)	98 (28.3)	<0.001
Atrial fibrillation	160 (33.8)	96 (27.7)	
Hypertension	142 (30.0)	104 (30.1)	
Valvular disease	74 (15.6)	31 (9.0)	
Other	21 (4.4)	17 (4.9)	

HF - heart failure; LAVI - left atrial volume index; LV - left ventricle; LVED - left ventricular end-diastolic; LVEF - left ventricle ejection fraction; LVES - left ventricular end-systolic; NT-proBNP - N-terminal pro B-type natriuretic peptide

less often active or former smokers, had worse diastolic function and less comorbid conditions as compared with men (20, 21). In line with these data, in our cohort, women were less often active or former smokers, had higher LVEF, had worse diastolic function, and had higher prevalence of hypertension and atrial fibrillation. Deswal and Bozkurt (10) analyzed 719 patients with HFpEF and found that compared with men, women with HFpEF were older and more frequently had a history of diabetes or hypertension, history of myocardial infarctions, and ischemic causes of HF were less frequent in women than in men. At the time of enrollment, women appeared to have greater clinical severity of HF, as evidenced by more women with New York Heart Association (NYHA) class III or IV and fewer women with NYHA class I functional status, a greater proportion of women with a history of orthopnea and resting dyspnea, chest X-ray findings of vascular congestion, and examination findings of rales and edema, as well as more women receiving diuretics (10). Similar to the previous data, the APOLLON study showed that female patients with HFpEF were more symptomatic (palpitations, reduced exercise tolerance, peripheral edema, and fatigue), and they more often received diuretics on admission. In the APOLLON study, ischemic heart disease and ischemic etiology of HF were less frequent in females than in males with HFpEF. Recent findings from studies investigating HFpEF pathophysiology, mechanisms, and sex effects on cardiovascular aging have identified some potential contributors to the sex discrepancy (22, 23). Extent of concentric ventricular remodeling is enhanced in women, and this may be associated with worse diastolic function in the aged female heart (24). In our study, although LVEF was higher in women with HFpEF, women were more symptomatic and had higher NT-proBNP levels compared with men probably due to worse diastolic function, higher LAVI and pulmonary artery systolic pressure, and more frequent LV concentric hypertrophy.

The 2016 European Society of Cardiology HF guidelines recognized HFmrEF as an entity distinct from HFrEF and HFpEF (2). Clinical characteristics of HFmrEF were found to be intermediate between those of HFrEF and HFpEF (25). Some authors suggest that HFmrEF has a phenotype closer to HFpEF (13), whereas other authors consider it closer to HFrEF (26). Recent studies have shown that patients with HFmrEF were younger, more often male, and had more frequent ischemic heart disease compared with HFpEF (27). Even though patients with HFmrEF have higher readmission rates than patients with HFpEF and mortality rates comparable to HFrEF and HFpEF (28), HFmrEF remains insufficiently characterized compared with the other groups. In addition, there are limited data regarding the effect of gender in patients with HFmrEF. Swedish Heart Failure Registry included 9019 patients with HFmrEF, and 60.8% of these patients were male (18). Kapoor et al. (29) analyzed the factors potentially contributing to the HF hospitalization among 99,825 HF admissions from 305 hospitals in the Get With The Guidelines-HF (GWTG-HF) database; and among the 12,819 patients with HFmrEF, 51.5% were male. The APOLLON study has shown that prevalence of male was 57.7% in patients with HFmrEF. Previous studies revealed that there might be differences in sex distribution by age in patients with HF (30). Stein et al. (31) studied all consecutive 5228 males and 4107 females hospitalized patients with HF, aged 50 or older. Although there was no separate evaluation for HFmrEF and HFpEF in this study, the proportion of males among patients aged <75 years was significantly higher than that of females, whereas in the elderly the proportion was similar in both genders (31). We analyzed gender distribution by age groups for HFmrEF and HFpEF groups. In our study, female gender was higher among all age groups in patients with HFpEF. However, male gender was higher in patients with HFmrEF aged <80 years, and female gender was higher in octogenarian patients with HFmrEF. In patients with HFmrEF, men smoked more, and were younger, had higher prevalence of coronary artery disease, had lower prevalence of atrial fibrillation, had better diastolic function, and had lower NT-proBNP levels. Ischemic heart disease was the main cause of HF in men and women with HFmrEF.

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Table 7. Heart failure with mid-range ejection fraction in female and male

	Female (n=104)	Male (n=142)	*P* value
Age, years	71 (62–79)	67 (62–74)	0.004
Smoking	3 (2.9)	56 (39.4)	<0.001
Alcohol use	2 (1.9)	15 (10.6)	0.009
Body mass index, kg/m^2	29 (27–32)	27 (25–31)	0.003
Heart rate, bpm	83 (74–97)	76 (68–86)	<0.001
History of hospitalization for HF in the last year	31 (29.8)	38 (26.8)	0.599
Comorbidities			
Atrial fibrillation	41 (39.4)	27 (19.0)	<0.001
Hypertension	77 (74.0)	111 (78.2)	0.451
Diabetes mellitus	31 (29.8)	44 (31.0)	0.843
Anemia	39 (37.5)	48 (33.8)	0.173
Chronic kidney disease	16 (15.4)	28 (19.7)	0.381
Obstructive sleep apnea	4 (3.8)	2 (1.4)	0.245
Coronary artery disease	54 (51.9)	113 (79.6)	<0.001
Previous myocardial infarction	38 (36.5)	80 (56.3)	0.002
Laboratory data			
NT-proBNP, pg/mL	1167 (592–2114)	677 (368–1305)	<0.001
Blood urea nitrogen, mg/dL	19.5 (15–27.7)	17.0 (14.0–22.2)	0.028
Serum creatinine, mg/dL	0.8 (0.7–1.1)	0.9 (0.8–1.1)	<0.001
Serum potassium, mmol/L	4.6 (4.3–4.9)	4.6 (4.3–4.9)	0.886
Haemoglobin, g/dL	12.6 (11.4–13.6)	13.8 (12.4–15.0)	<0.001
Ferritin, ng/mL	62 (27–99)	66 (34–112)	0.393
Echocardiography			
LVEF, %	45 (41–45)	45 (40–45)	0.461
E/e'	10.1 (8.1–13.1)	9.0 (7.0–11.4)	0.009
LV diastolic dysfunction			
None	14 (13.4)	23 (16.3)	0.032
Grade 1	18 (17.4)	42 (29.5)	
Grade 2	44 (42.3)	53 (37.3)	
Grade 3	28 (26.9)	24 (16.9)	
LVED dimension, mm	50.5 (45.0–53.7)	53.0 (49.0–57.0)	0.001
LVES dimension, mm	35.0 (30.2–41.0)	39.0 (33.0–45.0)	0.005
LAVI, mL/m^2	35 (31–42)	35 (30–43)	0.592
Medications			
Angiotensin-converting enzyme inhibitors	28 (26.9)	61 (43.0)	0.010
Angiotensin receptor blockers	31 (29.8)	33 (23.2)	0.246
Beta-blockers	72 (69.2)	100 (70.4)	0.840
Aldosterone antagonists	22 (21.2)	37 (26.1)	0.374
Nondihydropyridine calcium blockers	10 (9.6)	6 (4.2)	0.090
Dihydropyridine calcium blockers	21 (20.2)	13 (9.2)	0.013
Digoxin	9 (8.7)	9 (6.3)	0.491
Isosorbide	3 (2.9)	14 (9.9)	0.041

Table 7. Cont

	Female (n=104)	Male (n=142)	*P* value
Loop diuretics	45 (43.3)	53 (37.3)	0.347
Thiazide	31 (29.8)	47 (33.1)	0.584
Etiology of heart failure			
Ischemic	46 (44.2)	110 (77.5)	<0.001
Atrial fibrillation	27 (26.0)	12 (8.5)	
Hypertension	10 (9.6)	12 (8.5)	
Valvular disease	10 (9.6)	5 (3.5)	
Other	11 (10.6)	3 (2.1)	

HF - heart failure; LAVI - left atrial volume index; LV - left ventricle; LVED - left ventricular end-diastolic; LVEF - left ventricle ejection fraction; LVES - left ventricular end-systolic; NT-proBNP - N-terminal pro B-type natriuretic peptide

This study provides contemporary data on gender differences in clinical features and management of patients with HFmrEF and HFpEF who participated in the APOLLON study. Several baseline clinical and echocardiographic features were found to differ significantly between women and men. Female subjects were older compared with males. There were gender differences in comorbidity status. Some were as expected, for example, coronary artery disease, and hyperlipidemia were more common among men, and hypertension and atrial fibrillation disease were more common in women. Our study also showed that gender discrepancies in HFmrEF and HFpEF management may exist in our country. The presence of this gender difference in the epidemiology and management of HFmrEF and HFpEF should be investigated in prospective studies to reveal whether these differences have consequences for outcome. Therefore, we need prospective clinical trials evaluating the management and prognosis of HFmrEF and HFpEF in both sexes throughout the country.

Study limitations

This study is a post-hoc analysis of the APOLLON registry. The main limitations of this study are its observational nature and lack of follow-up data. We assessed the associations between gender and HFmrEF or HFpEF, but we cannot demonstrate causality. The limitation of the "clinician-judged HF" diagnosis in the APOLLON registry is also acknowledged. Another limitation is that the coverage of the study is limited to outpatient cardiology clinics; hospitalized patients are not included in this study.

Conclusion

In this large real-world survey, we demonstrated that clinical manifestations of HFmrEF and HFpEF differed widely between women and men. Patients with HFpEF are predominantly women, and patients with HFmrEF are predominantly men. Female patients with HFpEF are more symptomatic, have higher body mass index, have higher NT-proBNP levels, have worse diastolic function, and have higher prevalence of hypertension. The main etiology of HF is atrial fibrillation in these patients. Male patients with HFmrEF are younger, have higher prevalence of coronary artery disease, have more dilated left ventricle, and have better diastolic function. To the best of our knowledge, this is the first study to analyze gender differences in patients with HFmrEF. The results of this multicenter study have presented a broad perspective on gender in patients with HFmrEF and HFpEF in Turkey.

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