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

**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/m² vs. 27 kg/m², 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. 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. 77.5 bpm, 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
Gender disparities in HFmrEF and HFpEF

Methods

The APOLLON registry

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-
Participants 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 HFmrEF 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 1. Patient demographics, characteristics, and comorbid features for all population |
|---------------------------------|---------------|----------------|
|                                  | Female (n=577) | Male (n=488)  |
| Age, years                       | 68 (61–76)    | 67 (60–74)    |
| Smoking                          | 32 (5.5)      | 156 (32.0)    |
| Alcohol use                      | 5 (0.9)       | 41 (8.4)      |
| Paroxysmal nocturnal dyspnea     | 217 (37.6)    | 150 (30.7)    |
| Palpitation                      | 326 (56.5)    | 176 (36.1)    |
| Reduced exercise tolerance       | 499 (86.5)    | 380 (77.9)    |
| Fatigue, tiredness               | 399 (69.2)    | 279 (57.2)    |
| Chest pain                       | 141 (24.4)    | 133 (27.3)    |
| Syncope                          | 29 (5.0)      | 16 (3.3)      |
| Dizziness                        | 123 (21.3)    | 87 (17.8)     |
| Body mass index, kg/m²           | 29 (26–33)    | 27 (25–30)    |
| Systolic blood pressure, mm Hg   | 130 (120–145) | 130 (120–145) |
| Diastolic blood pressure, mm Hg  | 80 (70–90)    | 80 (70–85)    |
| Heart rate, bpm                  | 80 (71.5–94)  | 77.5 (69–89)  |
| Pulmonary crepitations           | 138 (23.9)    | 97 (19.9)     |
| Peripheral edema                 | 220 (38.1)    | 136 (27.9)    |
| ECG abnormality                  | 323 (56.0)    | 293 (60.0)    |
| Cachexia                         | 24 (4.2)      | 11 (2.3)      |
| History of hospitalization for HF in the last year | 123 (21.3) | 98 (20.1)    |

| Comorbidities                    |               |               |
|----------------------------------|---------------|---------------|
| Atrial fibrillation              | 235 (40.7)    | 146 (29.9)    |
| Hypertension                     | 454 (78.7)    | 357 (73.2)    |
| Diabetes mellitus                | 184 (31.9)    | 135 (27.7)    |
| Anemia                           | 204 (35.3)    | 168 (34.4)    |
| Chronic kidney disease           | 59 (10.2)     | 73 (15.0)     |
| Obstructive sleep apnea          | 30 (5.2)      | 31 (6.4)      |
| Hyperlipidemia                   | 120 (20.8)    | 144 (29.5)    |
| Coronary artery disease          | 170 (29.5)    | 268 (54.9)    |
| Previous myocardial infarction   | 69 (12.0)     | 128 (26.2)    |
| Coronary artery by-pass grafting | 57 (9.9)      | 98 (20.1)     |
| Peripheral artery disease        | 7 (1.2)       | 21 (4.3)      |
| CVA/TIA                          | 39 (6.8)      | 31 (6.4)      |
| COPD                             | 71 (12.3)     | 72 (14.8)     |
| Hepatic failure                  | 11 (1.9)      | 7 (1.4)       |
| Depression                       | 41 (7.1)      | 17 (3.5)      |
| Malignancy                       | 5 (0.9)       | 14 (2.9)      |
| Heart failure with mid-range ejection fraction | 104 (18.0) | 142 (29.1)    |
| 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
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.

Comparison of female and male patients with HFrEF

Of the 246 patients with HFrEF, 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 HFrEF. Women had higher prevalence of 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 HFrEF. 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 HfmrEF

Comparison of female and male patients with HfmrEF

Table 2. Laboratory parameters

| Parameter                        | 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, x10^9/µL              | 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, µU/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
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 and 80 years.

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**

|                      | Female | Male | P value |
|----------------------|--------|------|---------|
| 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) |         |

|                      | Female (n=488) | Male (n=488) | P value |
|----------------------|----------------|--------------|---------|
| 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/m²          | 35 (30–41)     | 33 (29–41)   | 0.067   |
| LA enlargement       | 300 (52.0)     | 224 (45.9)   | 0.063   |
| LVMI, g/m²           | 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**

|                      | Female | Male | P value |
|----------------------|--------|------|---------|
| None                 | 149 (25.8) | 156 (32.0) | 0.003   |
| Mild                 | 547 (95.0) | 480 (98.4) | 0.010   |
| Moderate             | 135 (23.4) | 74 (15.2) |         |
| Severe               | 4 (0.7) | 1 (0.2) |         |

**Mitral stenosis**

|                      | Female (n=488) | Male (n=488) | P value |
|----------------------|----------------|--------------|---------|
| None                 | 554 (96.2)     | 475 (97.3)   | 0.533   |
| Mild                 | 15 (2.6)       | 8 (1.6)      |         |
| Moderate             | 7 (1.2)        | 5 (1.0)      |         |

**Aortic stenosis**

|                      | Female (n=488) | Male (n=488) | P value |
|----------------------|----------------|--------------|---------|
| 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**

|                      | Female (n=488) | Male (n=488) | P value |
|----------------------|----------------|--------------|---------|
| 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**

|                      | Female (n=488) | Male (n=488) | P value |
|----------------------|----------------|--------------|---------|
| 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

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
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 APOLLO 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 antithrombotic agents 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, 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).

### 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   |
| Iverapride | 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   |
| Antiagregant | 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 anthyperglysemic | 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) | <0.001 |
| Atrial fibrillation | 187 (32.4) | 108 (22.1) | 0.263   |
| Hypertension | 152 (26.3) | 116 (23.8) | <0.001 |
| Valvular disease | 84 (14.6) | 36 (7.4) | 0.203   |
| Other | 32 (5.5) | 20 (4.1) | 0.575   |
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/m² | 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**

|                         | Female (n=473) | Male (n=346) | P value |
|-------------------------|----------------|-------------|---------|
| 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**

|                        | Female (n=473) | Male (n=346) | P value |
|------------------------|----------------|-------------|---------|
| 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**

|                        | Female (n=473) | Male (n=346) | P value |
|------------------------|----------------|-------------|---------|
| 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**

|                        | Female (n=473) | Male (n=346) | P value |
|------------------------|----------------|-------------|---------|
| 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/m²            | 35 (30–40)     | 33 (28–38)  | 0.029   |

**Medications**

|                               | Female (n=473) | Male (n=346) | P value |
|-------------------------------|----------------|-------------|---------|
| 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   |
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 HFrEF and found that compared with men, women with HFrEF 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 HFrEF 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 HFrEF. Recent findings from studies investigating HFrEF 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 HFrEF, 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 HFrEF as an entity distinct from HFrEF and HFrEF (2). Clinical characteristics of HFrEF were found to be intermediate between those of HFrEF and HFrEF (25). Some authors suggest that HFrEF has a phenotype closer to HFrEF (13), whereas other authors consider it closer to HFrEF (26). Recent studies have shown that patients with HFrEF were younger, more often male, and had more frequent ischemic heart disease compared with HFrEF (27). Even though patients with HFrEF have higher readmission rates than patients with HFrEF and mortality rates comparable to HFrEF and HFrEF (28), HFrEF remains insufficiently characterized compared with the other groups. In addition, there are limited data regarding the effect of gender in patients with HFrEF. Swedish Heart Failure Registry included 9019 patients with HFrEF, 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 HFrEF, 51.5% were male. The APOLLON study has shown that prevalence of male was 57.7% in patients with HFrEF. 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 HFrEF and HFrEF 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 HFrEF and HFrEF groups. In our study, female gender was higher among all age groups in patients with HFrEF. However, male gender was higher in patients with HFrEF aged <80 years, and female gender was higher in octogenarian patients with HFrEF. In patients with HFrEF, 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 HFrEF.

| Etiology of heart failure | Female (n=473) | Male (n=346) | P value |
|--------------------------|----------------|--------------|---------|
| Ischemic                 | 160 (33.8)     | 96 (27.7)    | <0.001  |
| Atrial fibrillation      | 142 (30.0)     | 104 (30.1)   |         |
| Hypertension             | 74 (15.6)      | 31 (9.0)     |         |
| Valvular disease         | 21 (4.4)       | 17 (4.9)     |         |
| Other                    | 249            | 119          |         |

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
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/m²   | 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 (28.8) | 38 (26.8) | 0.599   |

**Comorbidities**

- Atrial fibrillation: 41 (39.4) vs. 27 (19.0), <0.001
- Hypertension: 77 (74.0) vs. 111 (78.2), 0.451
- Diabetes mellitus: 31 (29.8) vs. 44 (31.0), 0.843
- Anemia: 39 (37.5) vs. 48 (33.8), 0.173
- Chronic kidney disease: 16 (15.4) vs. 28 (19.7), 0.381
- Obstructive sleep apnea: 4 (3.8) vs. 2 (1.4), 0.245
- Coronary artery disease: 54 (51.9) vs. 113 (79.6), <0.001
- Previous myocardial infarction: 38 (36.5) vs. 80 (56.3), 0.002

**Laboratory data**

- NT-proBNP, pg/mL: 1167 (592–2114) vs. 677 (368–1305), <0.001
- Blood urea nitrogen, mg/dL: 19.5 (15–27.7) vs. 17.0 (14.0–22.2), 0.028
- Serum creatinine, mg/dL: 0.8 (0.7–1.1) vs. 0.9 (0.8–1.1), <0.001
- Serum potassium, mmol/L: 4.6 (4.3–4.9) vs. 4.6 (4.3–4.9), 0.886
- Haemoglobin, g/dL: 12.6 (11.4–13.6) vs. 13.8 (12.4–15.0), <0.001
- Ferritin, ng/mL: 62 (27–99) vs. 66 (34–112), 0.393

**Echocardiography**

- LVEF, %: 45 (41–45) vs. 45 (40–45), 0.461
- E/e’: 10.1 (8.1–13.1) vs. 9.0 (7.0–11.4), 0.009

**LV diastolic dysfunction**

- None: 14 (13.4) vs. 23 (16.3), 0.032
- Grade 1: 18 (17.4) vs. 42 (29.5)
- Grade 2: 44 (42.3) vs. 53 (37.3)
- Grade 3: 28 (26.9) vs. 24 (16.9)
- LVED dimension, mm: 50.5 (45.0–53.7) vs. 53.0 (49.0–57.0), 0.001
- LVES dimension, mm: 35.0 (30.2–41.0) vs. 39.0 (33.0–45.0), 0.005
- LAVI, mL/m²: 35 (31–42) vs. 35 (30–43), 0.592

**Medications**

- Angiotensin-converting enzyme inhibitors: 28 (26.9) vs. 61 (43.0), 0.010
- Angiotensin receptor blockers: 31 (29.8) vs. 33 (23.2), 0.246
- Beta-blockers: 72 (69.2) vs. 100 (70.4), 0.840
- Aldosterone antagonists: 22 (21.2) vs. 37 (26.1), 0.374
- Nondihydropyridine calcium blockers: 10 (9.6) vs. 6 (4.2), 0.090
- Dihydropyridine calcium blockers: 21 (20.2) vs. 13 (9.2), 0.013
- Digoxin: 9 (8.7) vs. 9 (6.3), 0.491
- Isosorbide: 3 (2.9) vs. 14 (9.9), 0.041
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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| Table 7. Cont | Female | Male | P value |
|--------------|--------|------|---------|
|              | (n=104)| (n=142)|         |
| Loop diuretics | 45 (43.3) | 53 (37.3) | 0.347 |
| Thiazide     | 31 (29.8) | 47 (33.1) | 0.584 |
| Etiology of heart failure | | | <0.001 |
| Ischemic        | 46 (44.2) | 110 (77.5) |         |
| 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
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