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# Gender-Related Differences in Patients with Acute Heart Failure: Observation from the Journey Heart Failure—Turkish Population Study

## ABSTRACT

**Background:** Gender-related clinical variations in patients with acute heart failure have been described in previous studies. However, there is still a lack of research on gender differences in patients hospitalized for acute heart failure in Türkiye. The aim of this study is to compare the clinical features, in-hospital approaches, and outcomes of male and female patients hospitalized for acute heart failure.

**Methods:** Differences in clinical characteristics, medication prescription, hospital management, and outcomes between males and females with acute heart failure were investigated from the Journey Heart Failure—Turkish Population study.

**Results:** Nine hundred eighteen patients (57.2%) were men and 688 (42.8%) were women. Women were older than men (70.48 ± 13.20 years vs. 65.87 ± 12.82 years; $P < .001$). The frequency of comorbidities such as hypertension (72.7% vs. 62.4%, $P < .001$), diabetes (46.5% vs. 38.5%, $P = .001$), atrial fibrillation (46.5% vs. 33.4%, $P < .001$), New York Heart Association class III-IV symptoms (80.6% vs. 71.2%, $P = .001$), and dyspnea in the rest (73.8% vs. 68.3%, $P = .044$) were more common in women on admission. Male patients were more frequently hospitalized with reduced left ventricular ejection fraction (51.0% vs. 72.4%, $P < .001$). In-hospital mortality was higher among female patients (9.3% vs. 6.4%, $P = .022$). Higher New York Heart Association class, lower estimated glomerular filtration rate, higher N-terminal pro-B type natriuretic peptide on admission, and mechanical ventilation usage were the independent parameters of in-hospital mortality, whereas the female gender was not.

**Conclusion:** Our study clearly demonstrated the diversity in presentation, management, and in-hospital outcomes of acute heart failure between male and female patients. Although left ventricular systolic functions were better in female patients, in-hospital mortality was higher. Recognizing these differences in the management of heart failure in different sexes will serve better results in clinical practice.

**Keywords:** Heart failure, acute heart failure, gender differences

ORIGINAL INVESTIGATION

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## INTRODUCTION

Acute heart failure (AHF) is mostly defined as decompensation of pre-existing heart failure (HF) or new-onset HF requiring emergency treatment and/or hospitalization.[1] It is a frequent reason for hospital admission, especially in elderly patients.[2]

Universal guidelines recommend similar therapeutic approaches to both men and women in the treatment of AHF.[3] However, despite the fact that more than half of HF patients in real life are women, significant randomized controlled clinical studies on the management of HF in female patients are not sufficient.[4] Previous large-scale regional or national observational studies and registries have documented gender differences in clinical characteristics, management, and outcomes of AHF patients.[5-9]

Characteristics of patients hospitalized for AHF may vary by region in terms of periodic management patterns, outcomes, demographics, and regional or national health policies. Türkiye is a country with a relatively younger population with a 2.9% prevalence of HF.[10]

In a recent study from Türkiye, gender-related clinical and management differences were demonstrated in patients with chronic HF (CHF) with reduced ejection fraction (EF) (HFrEF).[11] In another observational study, gender disparities were found in HF with mid-range EF (HFmrEF) and preserved EF (HFpEF).[12] However, there is still no large-scale prospective clinical trial offering gender comparison in patients hospitalized for AHF.

The Journey HF—TR study provided data that analyzed gender disparities in demographic information, medical histories, medications, symptoms and signs, AHF classifications, precipitating factors, in-hospital management, in-hospital outcomes, and discharge findings in patients presenting with AHF.

The aim of this study is to compare the clinical characteristics, in-hospital management, and results of male and female patients hospitalized for AHF with the data of this study.

## METHODS

### Study Protocol

Study population, methodology, and primary results pooled from the Journey HF—TR study have been reported in detail previously.[13] In summary, the Journey HF—TR study was conducted between September 2015 and September 2016 as a prospective and observational study in which 37 centers participated in Türkiye.

The diagnosis of AHF was made and classified according to the guidelines of the European Society of Cardiology, based on the presence of HF signs and symptoms, evidence of cardiac dysfunction, and the need for treatment.[1] Diagnosis of AHF included acute decompensated chronic heart failure (ADCHF) and new-onset (de novo) AHF (DNAHF). Acute decompensated chronic heart failure was defined as the worsening of HF in previously diagnosed or hospitalized patients with HF. De novo acute heart failure was defined as AHF in patients without a history of HF.[1] Other definitions were made according to the Journey HF—TR study.

Patients with AHF included in the study were divided into 2 groups according to their gender. Demographics, medical histories, drugs, symptoms, physical examination, chest x-ray, electrocardiographic, echocardiographic and laboratory findings, AHF classifications, precipitating factors, in-hospital management parameters and outcomes, and discharge medications and parameters were compared between the 2 groups.

The study was approved by the Local Ethics Committee and all patients gave their informed consent.

### Statistical Analysis

Kolmogorov–Smirnov test was used to identify whether the distribution of continuous variables was normal or not. Continuous variables were expressed as mean ± SD if normally distributed and as median and interquartile range if abnormally distributed. Continuous variables were compared by the independent *t*-test or Mann–Whitney *U* test according to the results of normality tests. The categorical variables were expressed as numbers (n) and percentages (%) and compared by the chi-square or Fisher's exact test. A value of $P < .05$ was considered statistically significant. Binary logistic regression analyses were used to identify independent predictors for in-hospital mortality. Variables with *P*-values <.1 and variables that are known to have predictive value were entered into the multivariate analysis. The Statistical Package for the Social Sciences (SPSS) software (SPSS Inc., Chicago, Ill, USA) for Windows, version 22.0 was used for the statistical analyses.

## RESULTS

### Baseline Medical History, Medication, and Symptoms

The mean age of the study population was 67.8 ± 13 years. Of 1606 patients admitted to The Journey HF—TR study with AHF, 918 (57.2%) were male and 688 (42.8%) were female. Female patients were older than males (70.48 ± 13.20 vs. 65.87 ± 12.82; $P < .001$) (Table 1).

In the medical history, in female patients, frequencies of comorbidities such as hypertension (72.7% vs. 62.4%, $P < .001$), diabetes mellitus (DM) (46.5% vs. 38.5%, $P = .001$), and atrial fibrillation (AF) (46.5% vs. 33.4%, $P < .001$) were more common, while current smoking (9.9% vs. 37.9%, $P < .001$), coronary artery disease (CAD) (49.7% vs. 67.0%, $P < .001$), peripheral artery disease (PAD) (4.0 vs. 8.1%, $P = .005$), and previous device therapy (11.5% vs. 19.5%, $P < .001$) were less common compared to male patients (Table 1).

When drug history was compared between the groups, in male patients, acetylsalicylic acid (ASA) (57.1% vs. 65.3%, $P = .002$), statin (20.9% vs. 27.5%, $P = .002$), mineralocorticoid receptor antagonist (MRA) (35.5% vs. 40.5%, $P = .026$), and diuretic use (67.8% vs. 73.6%, $P = .012$) were higher. Oral antidiabetic usage was higher in women (23% vs.19%, $P = .046$) (Table 1).

When symptomatic states at hospital admission were compared between the 2 groups, while New York Heart Association (NYHA) class I-II symptoms were detected as more common in males (19.6% vs. 28.9%, $P < .001$), NYHA class III-IV symptoms (80.6% vs. 71.2%, $P < .001$) and dyspnea in the rest (73.8% vs. 68.3%, $P = .044$) were more common in female patients (Table 1).

## HIGHLIGHTS

- There are gender-related clinical variations in patients with acute heart failure.
- The occurrence, presentation, management, and in-hospital mortality rates of acute heart failure differ between male and female patients.
- In-hospital mortality is higher in females despite better left ventricular function.
- Monitoring of female patients with a recent heart failure attack for the presence of arrhythmia might be important to reduce future hospitalization rates.
- Recognizing these differences in the treatment of heart failure in different sexes will serve better outcomes in clinical practice.

**Table 1. Comparison of Medical History, Medication, and Symptoms on Admission**

| Parameters | Female (n = 688) | Male (n = 918) | *P* |
|---|---|---|---|
| ***Medical history*** | | | |
| Age, mean ±SD | **70.48±13.20** | 65.87±12.82 | **<.001** |
| Hypertension, n (%) | **500 (72.7)** | 573 (62.4) | **<.001** |
| Diabetes mellitus, n (%) | **320 (46.5)** | 353 (38.5) | **.001** |
| Hyperlipidemia, n (%) | 182 (26.5) | 273 (29.7) | .163 |
| Smoking, n (%) | 68 (9.9) | **348 (37.9)** | **<.001** |
| Atrial fibrillation, n (%) | **320 (46.5)** | 307 (33.4) | **<.001** |
| VT/VF/CPA n (%) | 45 (6.6) | 72 (7.8) | .331 |
| Bradyarrhythmia n (%) | 24 (3.5) | 36 (3.9) | .670 |
| CAD, n (%) | 342 (49.7) | **615 (67.0)** | **<.001** |
| PAD, n (%) | 28 (4.0) | **74 (8.1)** | **.001** |
| Previous CVD, n (%) | 83 (12.1) | 92 (10.0) | .183 |
| CRF, n (%) | 184 (26.7) | 269 (29.3) | .281 |
| VTE, n (%) | 28 (4.0) | 45 (4.9) | .512 |
| Anemia, n (%) | 349 (50.7) | 423 (46.1) | .191 |
| Prior device therapy, n (%) | 79 (11.5) | **179 (19.5)** | **<.001** |
| ***Medication*** | | | |
| ASA, n (%) | 393 (57.1) | **599 (65.3)** | **.002** |
| RAAS Blockers, n (%) | 412 (59.9) | 598 (65.1) | .504 |
| Beta Blockers, n (%) | 479 (69.6) | 661 (72.0) | .250 |
| MRA, n (%) | 244 (35.5) | **372 (40.5)** | **.026** |
| Diuretic, n (%) | 466 (67.8) | **676 (73.6)** | **.012** |
| Digoxin, n (%) | 147 (21.4) | 186 (20.3) | .291 |
| Ivabradine, n (%) | 39 (5.7) | 69 (7.5) | .091 |
| Statin, n (%) | 144 (20.9) | **252 (27.5)** | **.002** |
| OAD n (%) | **158 (23.1)** | 175 (19) | **.046** |
| Insulin n (%) | 141 (20.6) | 178 (19.4) | .544 |
| ***Symptoms*** | | | |
| NYHA I-II, n (%) | 135 (19.6) | **264 (28.9)** | **<.001** |
| NYHA III-IV, n (%) | **553 (80.6)** | 654 (71.2) | **<.001** |
| Dyspnea on rest, n (%) | **508 (73.8)** | 627 (68.3) | **.044** |
| Dyspnea on exercise, n (%) | 643 (93.7) | 858 (93.5) | .743 |
| Orthopnea, n (%) | 542 (78.8) | 694 (75.6) | .245 |
| PND, n (%) | 430 (62.5) | 547 (59.6) | .486 |
| Angina, n (%) | 177 (25.7) | 242 (26.4) | .833 |
| Anxiety, n (%) | 343 (49.9) | 431 (46.9) | .456 |
| Fatigue, n (%) | 586 (85.1) | 766 (83.4) | .927 |

ASA, acetylsalicylic acid; CAD, coronary artery disease; CPA, cardiopulmonary arrest; CRF, Chronic renal failure; CVD, cerebrovascular disease; Device therapy, cardiac resynchronization therapy or implantable cardioverter defibrillator or pacemaker; MRA, mineralocorticoid receptor antagonist; n, number; NYHA, New York Heart Association; OAD, oral antidiabetic; PAD, Peripheral arterial disease; PND, paroxysmal nocturnal dyspnea; RAAS, renin-angiotens in-aldosterone system; VF, ventricular fibrillation; VT, ventricular tachycardia; VTE, venous thromboembolism. The proportionally high values and *P* values of the analyzes reaching statistical significance are indicated in bold.

## Baseline Physical Examination, Chest X-ray, Electrocardiographic, Echocardiographic, and Laboratory Findings

While mean systolic blood pressure (SBP) (129.6 ± 30.5 mm Hg vs. 126.1 ± 31.1 mm Hg, $P = .02$) and heart rate (95.9 ± 24.1 bpm vs. 92.4 ± 23.1 bpm, $P = .002$) were higher, $O_2$ saturation (89.41 ± 10.0% vs. 90.5 ± 8.3%, $P = .007$) was lower in female patients (Table 2).

The mean QRS duration was longer in male patients (101.76 ± 30.35 ms in females and 110.07 ± 39.70 ms in males, $P < .001$) (Table 2).

Left ventricular (LV) end-diastolic diameter was higher (44.65 ± 20.64 mm in females vs. 47.56 ± 23.08 mm in males, $P < .001$) and LV ejection fraction (EF) was lower in male patients (35.95 ± 15.13% in women vs. 30.35 ± 12.78% in men $P < .001$). Moderate-to-severe mitral regurgitation (54.8% vs. 46.8% $P = .010$), moderate-to-severe tricuspid regurgitation (50.7% vs. 41.6%, $P = .001$), and pulmonary hypertension (60.5% vs. 55.2%, $P = .021$) rates were higher in female patients (Table 2).

Serum fasting blood glucose level [123 (97-180) mg/dL vs. 115 (96-157) mg/dL, $P = .004$] was higher in female patients. Blood urea nitrogen (BUN) level [38 (24-60) mg/dL vs. 34 (23-54) mg/dL, $P = .032$] and serum creatinine level [1.12 (0.81-1.7) mg/dL vs. 1.2 (0.9-1.69) mg/dL, $P = .001$] were found to be higher in female patients, while mean estimated glomerular filtration rate (eGFR) [46 (26-68) mL/min/1.73 $m^2$ vs. 52 (25.75-76) mL/min/1.73 $m^2$, $P = .001$] was lower (Table 2).

## Acute Heart Failure Classifications and Precipitating Factors

While the proportion of patients with HFrEF (51.0% vs. 72.4%, $P < .001$) was higher in men than in women, the proportion of patients with HFmrEF (23.7% in women vs. 16.2% in men, $P < .001$) and HFpEF (25.3% in females vs. 11.4% in males, $P < .001$) were higher in females than males (Table 3). Among the precipitating factors, the rate of arrhythmia was higher in the female patient group than in the male patient group (28.8% vs. 22.3%, $P < .001$) (Table 3).

## In-Hospital Management Parameters and Outcomes

Female patients needed more mechanical ventilation (MV) support than male patients (10% vs. 6.1%, $P = .010$). Inotropic agent support, in-hospital device therapy, and percutaneous coronary intervention (PCI)/coronary artery bypass surgery (CABG) were higher in the male patient group compared to female patient group, respectively (16.3% in women vs. 21.9% in men, $P = .010$; 4.2% in women, 7.6% in men, $P = .004$; 7.5% in women vs. 12.1% in men, $P = .005$) (Table 4).

Median length of stay (LOS) in-hospital was higher in the men (5 days, 95% CI 3-7 days in women vs. 5 days, 95% CI 3-8 days in men, $P < .001$). The women had a higher in-hospital mortality rate than the men (9.3% vs. 6.4%, $P = .022$) (Table 5). Although the mortality rate was higher in women compared with men, female gender was not associated with in-hospital mortality in multivariate analysis. New York Heart Association class, eGFR, invasive mechanic ventilation, and N-terminal pro-B type natriuretic peptide (NT-ProBNP) on

**Table 2. Comparison of Baseline Physical Examination, Chest X-ray, ECG, and Echocardiographic Findings on Admission**

| Parameters | Female (n = 688) | Male (n = 918) | *P* |
|---|---|---|---|
| ***Physical examination*** | | | |
| SBP (mm Hg), mean ± SD | **129.6 ± 30.5** | 126.1 ± 31.1 | **.002** |
| DBP (mm Hg), mean ± SD | 105.23 ± 38.02 | 106.50 ± 32.66 | .067 |
| Heart rate (bpm), mean ± SD | **95.9 ± 24.1** | 92.4 ± 23.1 | **.002** |
| $O_2$ saturation (%), mean ± SD | 89.41 ± 1.0 | **90.5 ± 8.3** | **.007** |
| Crackles, n (%) | 484 (70.3) | 658 (71.6) | .411 |
| S3 gallop, n (%) | 312 (45.3) | 461 (50.2) | .148 |
| Elevated JVP, n (%) | 247 (35.9) | 315 (34.3) | .627 |
| AD and ascites n (%) | 191 (27.8) | 265 (28.9) | .192 |
| Hepatojugular reflux, n (%) | 227 (33.0) | 276 (30.0) | .223 |
| Peripheral edema, n (%) | 463 (67.3) | 597 (65.0) | .418 |
| ***Chest x-ray*** | | | |
| Cardiomegaly, n (%) | 548 (79.7) | 705 (76.8) | .056 |
| Alveolar edema, n (%) | 293 (42.6) | 385 (41.9) | .222 |
| Pulmonary congestion, n (%) | 446 (64.8) | 598 (65.1) | .425 |
| Pleural effusion, n (%) | 353 (51.3) | 467 (50.9) | .902 |
| ***ECG on admission*** | | | |
| Sinus rhythm, n (%) | 382 (55.5) | 565 (61.5) | .524 |
| Atrial fibrillation/flutter, n (%) | 236 (34.3) | 337 (36.7) | .312 |
| LBBB pattern, n (%) | 130 (18.9) | 200 (21.8) | .206 |
| QRS duration (ms), mean ±SD | 101.76 ± 30.35 | **110.07 ± 39.70** | **<.001** |
| ***Echocardiographic findings*** | | | |
| LA (mm), mean ± SD | 37.21 ± 17.43 | 36.90 ± 18.75 | .681 |
| LVEDD (mm), mean ± SD | 44.65 ± 20.64 | **47.56 ± 23.08** | **<.001** |
| EF (%), mean ± SD | **35.95 ± 15.13** | 30.35 ± 12.78 | **<.001** |
| RVEDD (mm), mean ± SD | 29.6 ± 15.6 | 29.1 ± 16.2 | .576 |
| Moderate-to-severe MR, n (%) | **360 (54.8)** | 415 (46.8) | **.010** |
| Moderate-to-severe TR, n (%) | **348 (50.7)** | 382 (41.6) | **.001** |
| Moderate-to-severe AS, n (%) | 45 (6.5) | 46 (5.2) | .103 |
| Moderate-to-severe AR, n (%) | 45 (6.5) | 71 (8.0) | .509 |
| Pulmonary hypertension, n (%) | **395 (60.5)** | 485 (55.2) | **.021** |
| ***Laboratory findings*** | | | |
| NT-ProBNP (pg/mL), med. (IQR) | 41.5 (920-11.536.75) | 3379 (934.5-8342.5) | .055 |
| FBG (mg/dL), med. (IQR) | **123 (97-180)** | 115 (96-157) | **.004** |
| BUN (mg/dL), med. (IQR) | **38 (24-60)** | 34 (23-54) | **.023** |
| S. creatinine (mg/dL), med. (IQR) | **1.12 (0.81-1.7)** | 1.2 (0.9-1.69) | **.016** |
| eGFR (mL/min/1.73 $m^2$), med. (IQR) | 46 (26-68) | **52 (25.75-76)** | **.001** |
| Uric acid (mg/dL), med. (IQR) | 7.9 (5.8-10.1) | 7.5 (5.9-10.0) | .418 |
| AST (U/L), med. (IQR) | 24 (17-41) | **26 (19-40.75)** | **.014** |
| ALT (U/L), med. (IQR) | 20 (13-35) | **22.93 (14-37)** | **.015** |
| Albumin (g/L), med. (IQR) | 3.6 (3.1-4.1) | 3.6 (3.2-4.4) | .742 |
| Total bil. (mg/dL), med. (IQR) | 0.85 (0.5-1.5) | 0.9 (0.547-1.5) | .695 |
| Leukocyte (×$10^3$/μL), med. (IQR) | 8760 (6800-11.400) | 8600 (6590-10.700) | .058 |
| Hemoglobin (g/dL), mean ± SD | 11.74±1.99 | **12.51±2.19** | **<.001** |
| Hematocrit (%), mean ± SD | 36.47±6.17 | **38.90±7.01** | **<.001** |
| TSH (μIU/mL), med. (IQR) | 1.65 (0.73.2) | 1.59 (0.86-3.12) | .988 |

AD, abdominal distension; ALT, alanine aminotransferase; AS, aortic stenosis; AST, aspartate aminotransferase; AY, aortic regurgitation; BUN, blood urea nitrogen; DBP, diastolic blood pressure; EF, ejection fraction; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; IQR, interquartile range; JVP, jugular venous pressure; LA, left atrium; LVEDD, Left ventricular end-diastolic diameter; MR, mitral regurgitation; med., median; n, number; NT-ProBNP, N-terminal pro-B type natriuretic peptide; PHT, pulmonary hypertension; RVEDD, right ventricular end-diastolic diameter; S., serum; SBP, systolic blood pressure; Total bil., total bilirubin; TR, tricuspid regurgitation; TSH, thyrotropin-stimulating hormone. The proportionally or quantitatively high values and *P* values of the analyzes that reached statistical significance between the two groups are shown in bold.

**Table 3. Comparison of Acute Heart Failure Classifications and Precipitating Factors between the 2 Groups**

| Parameters | Female (n = 688) | Male (n = 918) | *P* |
|---|---|---|---|
| ***De novo AHF/ADCHF*** | | | |
| *De novo*, n (%) | 125 (18.2) | 148 (16.1) | .263 |
| ADCHF, n (%) | 563 (81,8) | 770 (83,9) | .523 |
| ***Clinical classification*** | | | |
| Decompensated HF, n (%) | 441 (67.5) | 605 (68.5) | .639 |
| Pulmonary edema, n (%) | 219 (31.8) | 286 (31.1) | .921 |
| Cardiogenic shock, n (%) | 28 (4.1) | 36 (3.9) | .965 |
| Hypertensive HF, n (%) | 114 (16.6) | 121 (13.2) | .105 |
| Right HF, n (%) | 191 (27.8) | 228 (24.8) | .371 |
| ***Classification according to EF*** | | | |
| HFrEF, n (%) | 351 (51.0) | **664 (72.4)** | **<.001** |
| HFmrEF, n (%) | **163 (23.7)** | 149 (16.2) | **<.001** |
| HFpEF, n (%) | **174 (25.3)** | 105 (11.4) | **<.001** |
| ***Precipitating factors*** | | | |
| ACS, n (%) | 105 (15.3) | 131 (14.3) | .163 |
| Infection, n (%) | 202 (29.4) | 268 (29,2) | .493 |
| Arrhythmia, n (%) | **198 (28.8)** | 205 (22.3) | **.002** |
| Renal dysfunction, n (%) | 154 (22.4) | 215 (23.4) | .337 |
| NWM, n (%) | 185 (26.9) | 222 (24.2) | .111 |

ACS, acute coronary syndrome; ADCHF, acute decompensated chronic heart failure; AHF, acute heart failure; EF, ejection fraction; HF, heart failure; HFmrEF, heart failure with mid-range EF; HFpEF, heart failure with preserved EF; HFrEF, heart failure with reduced EF; NWM, noncompliance with medication. The proportionally high values and *P* values of the analyzes reaching statistical significance are indicated in bold.

**Table 4. Comparison of in-Hospital Management Parameters and Outcomes between the Sex Groups**

| Parameters | Female (n = 688) | Male (n = 918) | *P* |
|---|---|---|---|
| ***In-hospital management*** | | | |
| Invasive monitorization, n (%) | 116 (16.9) | 144 (15.7) | .384 |
| Mechanical ventilation, n (%) | **69 (10.0)** | 56 (6.1) | **.010** |
| Non-invasive ventilation, n (%) | 112 (16.3) | 150 (16.3) | .458 |
| UF/HD, n (%) | 41 (6.0) | 43 (4.7) | .355 |
| IV diuretic, n (%) | 106 (15.4) | 138 (15.0) | .408 |
| TPAID (min), median (IQR) | 25 (10-60) | 25 (10-45) | .515 |
| IV diuretic duration (day), median (IQR) | 3 (2-5) | 3 (2-5.75) | .226 |
| ≥1 g/day diuretic infusion dosage, n (%) | 24 (3.5) | 26 (2.8) | .826 |
| Vasodilator, n (%) | 190 (27.6) | 285 (31.0) | .083 |
| Inotropic agent, n (%) | 112 (16.3) | **201 (21.9)** | **.010** |
| Device therapy, n (%) | 29 (4.2) | **70 (7.6)** | **.004** |
| PCI/CABG | 51(7.5) | 111(12.1) | .005 |
| ***In-hospital outcomes*** | | | |
| Weight differences (kg), mean ± SD | 5.57 ± 8.47 | 5.45 ± 8.57 | .171 |
| LOSIC (days), median (IQR) | 3 (2-5) | 3 (2-5) | .082 |
| LOS (days), median (IQR) | 5 (3-7) | **5 (3-8)** | **<.001** |
| In-hospital mortality, n (%) | **63 (9.3)** | 58 (6.4) | **.022** |

HD, hemodialyses; IV, intravenous; IV diuretic dur., IV diuretic duration; LOS, length of stay in hospital; LOSIC, length of stay in intensive care; PCI/CABG, percutaneous coronary intervention/coronary artery bypass surgery; TPAID, time passed from admission to initiation of IV diuretic therapy; UF, ultrafiltration. The proportionally or quantitatively high values and *P* values of the analyzes that reached statistical significance between the two groups are shown in bold.

admission were independent predictors of in-hospital mortality in the multivariate analysis (Table 6).

Binary logistic regression analyses for independent predictors of in-hospital mortality in both female and male patients are presented in Tables 7 and 8.

## Discharge Parameters and Medication

While the use of ASA (54.0% in women vs. 58.9% in men, *P* = .046) and statins (21.0% in women vs. 27.5% in men, *P* = .002) were higher in men, MRA (60.6% in women vs. 59.4% in men, *P* = .026) and diuretic use (84.3% in women vs. 78.3% in men, *P* = .016) were higher in female patients (Table 5).

**Table 5. Comparison of Discharge Parameters and Medications between the Sex Groups**

| Variables | Female (n = 688) | Male (n = 918) | *P* |
|---|---|---|---|
| ***Discharge medication*** | | | |
| ASA, n (%) | 372 (54.0) | **541 (58.9)** | **.046** |
| RAAS Blockers, n (%) | 580 (84.3) | 719 (78.3) | .504 |
| Beta Blockers, n (%) | 585 (85,1) | 810 (88,2) | .213 |
| MRA, n (%) | **417 (60.6)** | 545 (59.4) | **.026** |
| Diuretic, n (%) | **580 (84.3)** | 719 (78.3) | **.016** |
| Digoxin, n (%) | 145 (21.1) | 186 (20.3) | .378 |
| Ivabradine, n (%) | 74 (10.8) | 124 (13.5) | .054 |
| Statin, n (%) | 144 (21.0) | **252 (27.5)** | **.002** |
| ***Discharge findings*** | | | |
| NYHA III-IV, n (%) | 97 (14.1) | 125 (13.6) | .577 |
| SBP (mm Hg), mean ± SD | **129.6 ± 30.5** | 126.1 ± 31.1 | **.002** |
| DBP (mm Hg), mean ± SD | 105.23 ± 38.02 | 106.50 ± 32.66 | .067 |
| Heart rate (bpm), mean ± SD | 71.26 ± 24.28 | 71.71 ± 22.79 | .300 |
| GFR (mL/min/1.73 $m^2$), mean ± SD | 54.12 ± 25.94 | **62.73 ± 26.19** | **<.001** |
| NT-ProBNP (pg/mL), median (IQR) | 1065 (380-3700) | 862.5 (255-3150) | .081 |

ASA, acetylsalicylic acid; CABG, coronary artery bypass surgery; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HD, hemodialyses; IV, intravenous; LOSIC, length of stay in intensive care; LOS, length of stay; MRA, mineralocorticoid receptor antagonist; NT-ProBNP, N-terminal pro-B type natriuretic peptide; NYHA, New York Heart Association; PCI, Percutaneous coronary intervention; RAAS, renin-angiotensin-aldoste rone system; SBP, systolic blood pressure; TPAID, time passed from admission to initiation of iv diuretic therapy; UF, ultrafiltration. The proportionally or quantitatively high values and *P* values of the analyzes that reached statistical significance between the two groups are shown in bold.

**Table 6. Binary Logistic Regression Analysis for Predictors of In-Hospital Mortality in All Population**

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| **Variables** | **OR 95% CI** | ***P*** | **OR 95% CI** | ***P*** |
| Male gender | .671 (.463-.973) | .036 | | |
| NYHA | 1.878 (1.440-2.448) | <.001 | 2.758 (1.382-5.504) | **.004** |
| Hypertension | .580 (.400-.843) | .004 | | |
| Hyperlipidemia | .600 (.379-.951) | .030 | | |
| LOSIC (days) | 1.101 (1.070-1.133) | <.001 | | |
| VT/VF/CPA | 2.598 (1.528-4.418) | <.001 | | |
| Cardiogenic shock | 6.319 (3.590-11.123) | <.001 | | |
| Denova HF | .551 (.305-.995) | .048 | | |
| Pulmonary edema | 1.773 (1.218-2.579) | .003 | | |
| Anemia | 2.743 (1.295-6.092) | .013 | | |
| Mechanic ventilation | 22.593 (14.598-34.965) | <.001 | 31.136 (10.989-88.220) | **<.001** |
| Inotropic agent | 5.450 (3.724-7.976) | <.001 | | |
| B-blockers | 1.278 (.842-1.940) | .249 | | |
| RAAS Blockers, n (%) | .711 (.500-1.011) | .058 | | |
| Ivabradine | 1.951 (1.075 -3.539) | .028 | | |
| Hemoglobin | .903 (.827-.986) | .023 | | |
| eGFR | .972 (.963-.982) | <.001 | .979 (.962-.997) | **.021** |
| BUN | 1.012 (1.008-1.016) | <.001 | | |
| NT-Pro BNP | 1.000 (1.000-1.000) | .065 | 1.000 (1.000-1.000) | **.038** |
| SBP | .979 (.971-.986) | <.001 | | |

BUN, blood urea nitrogen; CI, confidence interval; CPA, cardiopulmonary arrest; eGFR, estimated glomerular filtration rate; HF, heart failure; LOSIC, length of stay in intensive care; NT-ProBNP, N-terminal pro-B type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure; VF, ventricular fibrillation; VT, ventricular tachycardia. The *P* values reaching statistical significance in multivariate analysis are indicated in bold.

**Table 7. Binary Logistic Regression Analysis for Predictors of In-Hospital Mortality in Female**

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| **Variables** | **OR 95% CI** | ***P*** | **OR 95% CI** | ***P*** |
| NYHA | 1.554 (1.074-2.249) | .019 | 1.667 (1.053-2.639) | **.029** |
| Hypertension | .956 (.539-1.696) | .878 | | |
| Hyperlipidemia | .693 (.367-1.306) | .256 | | |
| LOSIC (days) | 1.077 (1.039-1.117) | <.001 | | |
| VT/VF/CPA | 4.084 (1.990-8.382) | <.001 | | |
| Cardiogenic shock | 6.163 (2.719-14.015) | <.001 | | |
| Denova HF | .611 (.283-1.315) | .208 | | |
| Pulmonary edema | 1.653 (.978-2.793) | .061 | | |
| Anemia | 1.097 (.645-1.868) | .732 | | |
| Mechanic ventilation | 22.753 (12.416-41.697) | <.001 | 21.481 (9.577-48.182) | **<.001** |
| Inotropic agent | 5.757 (3.344-9.910) | <.001 | 3.002 (1.386-6.505) | **.005** |
| B-blockers | 1.095 (.625-1.917) | .752 | | |
| ACE/ARB | .544 (.331-.895) | .017 | .430 (.234-.789) | **.006** |
| Ivabradine | 2.786 (1.219-6.367) | .015 | | |
| Hemoglobin | .990 (.861-1.138) | .891 | | |
| eGFR | .985 (.975-.995) | .003 | .984 (.972-.997) | **.016** |
| BUN | 1.008(1.004-1.013) | <.001 | | |
| NT-Pro BNP | 1.000 (1.000-1.000) | .469 | | |
| SBP | .986 (.977-.995) | .002 | | |

BUN, blood urea nitrogen; CI, confidence interval; CPA, cardiopulmonary arrest; eGFR, estimated glomerular filtration rate; HF, heart failure; LOSIC, length of stay in intensive care; NT-ProBNP, N-terminal pro-B type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure; VF, ventricular fibrillation; VT, ventricular tachycardia. The *P* values reaching statistical significance in multivariate analysis are indicated in bold.

**Table 8. Binary Logistic Regression Analysis for Predictors of In-Hospital Mortality in Male**

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| **Variables** | **OR 95% CI** | ***P*** | **OR 95% CI** | ***P*** |
| NYHA | 2.621 (1.752-3.920) | <.001 | | |
| Hypertension | .318 (.183-.554) | <.001 | | |
| Hyperlipidemia | .533(.272-1.045) | .067 | | |
| LOSIC (days) | 1.132(1.083-1.183) | <.001 | | |
| VT/VF/CPA | 1.677 (.731-3.841) | .222 | | |
| Cardiogenic shock | 6.562 (2.993-14.391) | <.001 | | |
| Denova HF | .463 (.182-1.179) | .106 | | |
| Pulmonary edema | 1.901 (1.110-3.256) | .019 | | |
| Anemia | 3.137 (1.636-6.017) | .001 | | |
| Mechanic ventilation | 21.250 (11.233-40.201) | <.001 | 36.459 (7.187-184.953) | **<.001** |
| Inotropic agent | 5.874 (3.390-10.178) | <.001 | | |
| B-blockers | 1.564 (.831-2.942) | .165 | | |
| ACE/ARB | .943 (.567-1.567) | .819 | | |
| Ivabradine | 1.483 (.612-3.591) | .382 | | |
| Hemoglobin | .810 (.710-.924) | .002 | | |
| eGFR | .995 (.986-1.004) | .248 | | |
| BUN | 1.017 (1.011-1.024) | <.001 | 1.025 (1.015-1.045) | **.012** |
| NT-Pro BNP | 1.000 (1.000-1.000) | <.001 | | |
| SBP | .965 (.953-.978) | <.001 | | |

BUN, blood urea nitrogen; CI, confidence interval; CPA, cardiopulmonary arrest; eGFR, estimated glomerular filtration rate; HF, heart failure; LOSIC, length of stay in intensive care; NT-ProBNP, N-terminal pro-B type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure; VF, ventricular fibrillation; VT, ventricular tachycardia. The *P* values reaching statistical significance in multivariate analysis are indicated in bold.

The proportion of NYHA class III-IV patients at discharge was similar between the 2 groups (14.1% in females vs. 13.6% in males, $P$ = .577). The mean SBP at discharge was higher in the female patient group (129.6 ± 30.5 vs. 126.1 ± 31.1, $P$ = .002). The difference in mean heart rates between the 2 groups lost significance at discharge (71.26 ± 24.28 bpm vs. 71.71 ± 22.79 bpm, $P$ = .300). The mean eGFR level was lower in females than in male patients (54.12 ± 25.94 ml/min/1.73 $m^2$ vs. 62.73 ± 26.19 mL/min/1.73 $m^2$, $P$ < .001).

## DISCUSSION

The Journey HF—TR study is the largest scaled AHF study in Türkiye.[13] Recent observations from the Journey HF—TR study revealed gender-related differences in medical history, medications, symptoms and signs, HF classifications, precipitating factors, hospital management, hospital outcomes, discharge parameters, and medications. Although the female gender was not an independent predictor of in-hospital mortality, the mortality rate was higher in women. However, higher NYHA class, lower eGFR, higher NT-ProBNP on admission, and MV support were the independent predictive parameters of in-hospital mortality in the AHF population. Higher NHYA class, less use of Renin-angiotensin-aldosterone system (RAAS) blockers on admission, lower eGFR, MV, and inotrope use were independent predictors of in-hospital mortality in female patients, whereas higher BUN level and MV were independent predictors of in-hospital mortality in male patients.

In the current study, women were represented by 42.8%, similar to several studies and even better than several large HF studies.[6,14,15] Knowledge gap still seems to exist about female patients with HF. Despite an estimated population prevalence of HF of 47%, a study comparing randomized trials cited in guidelines endorsed by the American College of Cardiology/American Heart Association for the diagnosis and management of AF, unstable angina/non-ST-segment elevation myocardial infarction, and HF showed that female representation was 29% in HF guideline citations.[16,17] Although an increasing trend was observed in the inclusion of the female gender in HF studies following the 1980s, landmark studies that served as a level of evidence for guideline recommendations underrepresented the female HF population.[18] It seems that there still exists a need for new trials focusing on female patients with HF to better specify the underlying reasons, precipitating factors, and outcomes in women with HF. Despite being a cross-sectional one, this study underlined the gender differences in AHF. Our study seems important because it contains the largest data on gender comparison in AHF in this region, and women constitute a significant proportion of the study population.

The mean age of the current study population (67.8 ± 13 years) was younger compared to the several observational studies. Characteristics of the study population, management pattern, and national and regional health policies on HF may contribute to it. Besides, developing technologies, the availability of biomarkers used in the emergency services, and the increased knowledge of physicians about AHF might have increased the success in the diagnosis of it. Consistent with previous reports, women with AHF were older than men in the present study.[4,5,8,14,19] Late presentation of HF in women might have played a role in the worse functional status of women during admission. Age-associated decline in the intensity level of physical activity might have contributed to the late notification of the symptoms.

Despite the higher mortality rate of women in our recent study, there was no gender difference on in-hospital mortality in gender analyses of previous large-scale AHF studies such as EuroHeart Failure Survey II (EHFS II),[4] Acute Decompensated HF National Registry (ADHERE),[5] and ALARM-HF Study.[19]

Patients with uncontrolled hypertension (SBP >160/90 mm Hg) have a 1.6-fold greater risk of HF than those with SBP >120/90 mm Hg. Although men in the Framingham study had a similar prevalence of hypertension to women, hypertensive women were 1.5 times more likely to have HF than men.[20-23] In the current study, the rate of hypertension[5,14] and mean SBP[5,14,19] were higher in female patients similar to some of the AHF studies in the literature.

It is certainly known that DM is associated with an increased risk of HF and the risk of premature death even after diagnosis.[23-25] In a meta-analysis by Ohkuma et al[26] compiled on 47 cohorts of more than 12 million people, DM is shown to be a stronger risk factor for HF in women than in men. There are studies reporting that the duration of prediabetes is up to 2 years in women compared to men and therefore they are exposed to high glycemia for a longer period of time.[27] As the duration of prediabetes increases, LV systolic and diastolic functions are adversely affected. Even after diagnosis, female patients have poor glycemic control than male patients.[28-30] In our study, supporting all these studies, females with HF were more likely to have diabetes. Similarly, serum fasting glucose level was higher in female patients. Some of the previous studies on gender comparison in AHF also had data consistent with our study.[14,19]

As found in some previous studies, AF and AHF coexistence was higher,[4,5,8,19] anemia frequency was higher,[4,5,14,19] and prior device implantation history[4,5] was lower in women in the recent study. MRA and diuretic[5] use frequency were lower. Women were more symptomatic,[5] mean heart rate[19] was higher, and mean oxygen saturation was lower. Valvular heart disease[4,14,19] and pulmonary hypertension were more common in women. In-hospital interventions such as device therapy and revascularization were performed less frequently in women.[4,14,19]

In a previous study, it has been shown that MV was an independent predictive parameter for in-hospital mortality in patients with AHF.[31] In those patients, MV increased the risk of mortality by 15 times in that study.[31] MV was related to mortality in another study involving approximately 40 000 HF patients.[32] In line with the study results above, in the recent study, MV was an independent risk factor for in-hospital mortality in the whole population, also in women and men with AHF separately. The higher MV rate may contribute to the higher mortality rate in women.

Many studies have shown the relationship between inotropic agent usage and increased mortality.[33,34] In ADHERE Registry, inotropic support was higher in men, and patients treated with inotropes had higher mortality.[5] Female gender was a predictor of inotrope usage and inotrope usage was a risk factor for in-hospital mortality in one study on positive inotropic agent use in AHF patients.[34] In our study, the rate of inotropic agent support was higher in men as in ADHERE Registry but the use of inotropic agents was an independent predictor of in-hospital mortality in women.

In the current study, women had worse renal function tests. The prevalence of kidney disease is high among hospitalized adults with HF regardless of the mechanism, and the presence of it is associated with worse outcomes as found in our study.[35-37] Despite the low eGFR and high in-hospital mortality relationship, many evidence-based drugs including MRAs, angiontensin-converting enzyme inhibitors/angiotensin II receptor blockers/angiotensin receptor—neprilysin inhibitors therapies were not optimally used in these patients, and this may contribute to greater in-hospital mortality.[38] Glomerular filtration rate was lower in women, and lower eGFR was an independent mortality predictor in AHF patients and the female subgroup in our study. A previous study conducted in AHF patients revealed that one of the independent predictors of RAAS blocker discontinuation was worsening renal function and the use of RAAS blocker at admission was associated with less inpatient mortality.[39] In a recent study, less RAAS blocker usage was an independent risk factor for in-hospital mortality in the female group. Blood urea nitrogen level was higher in women also; however, higher level of it was found to be a predictor of mortality only in males.

The Acute Decompensated Heart Failure Syndromes (ATTEND) registry showed that the in-hospital mortality rate was significantly higher in patients with high NYHA class, and the relationship between NYHA class and mortality was stronger, especially in elderly and female patients.[40] In our study, women had higher NYHA class, there was a significant association between higher NYHA class and inpatient mortality of AHF patients and female subgroup.

Age-stratified cutoff levels of NT-proBNP for AHF diagnosis were as follows: 450 pg/mL for age <50; 900 pg/mL for ages 50-75; and 1800 pg/mL for age >75. The specificity decreased with increasing age.[41] In the current study, female patients had slightly higher NT-proBNP levels on admission but similar discharge levels despite having better renal functions. The increasing age and renal dysfunction contribute to an increase in NT-proBNP levels due to diminished renal clearance of the peptide.[41,42] The female patients had a modestly lower eGFR level compared to the males at discharge; however, their peptide levels were higher despite being statistically non-significant. It has been shown that BNP level at admission was an independent predictor of in-hospital mortality in AHF patients as found in our study.[43] All of the factors listed above may have contributed to the higher mortality rate in women in the presented study.

Length of stay in intensive care (LOSIC) was similar between the 2 groups as in gender comparisons of EHFS II,[4] ADHERE,[5] and ALARM-HF Trials.[19] Length of stay was higher in the men than women unlike the trials[4,5,19] The higher detection of in-hospital mortality rate of the women may have contributed to the longer duration of hospitalization in men. In addition, more revascularization procedures (PCI/CABG) which may be associated with a higher incidence of CAD, and more device implantations which may be associated with lower mean EF may also have contributed to prolonged service hospitalization in males. This may be a subject of a different study.

A study investigating precipitating factors of HF exacerbation with a 54% proportion of women participants displayed respiratory infections (28%), non-compliance with dietary recommendations (27%), and non-compliance with pharmacological treatment (23%) as the most frequent reasons of decompensation of HF.[44] Similarly, infections were in the first place among the precipitants of AHF in both genders in our study. Arrhythmias were the second-line trigger in women and precipitated AHF more frequently in women than in men. The present trial showed that arrhythmias might also trigger decompensation of the patients and more commonly in females as in EHFS II Study.[4] Although the recent ACC/AHA guideline for the management of HF has not specified any recommendation, looking for signs of arrhythmias in ECG and even searching them with Holter ECG might be of clinical concern, especially, for female patients with a recent HF exacerbation.[45]

Heart failure with preserved EF was shown to be more common in women than in men.[46] Women are more prone to have lower LV end-diastolic volumes at similar LV end-diastolic pressures compared to men suggesting that impaired diastolic functions might explain the paradox of women having more frequent HF symptoms despite a better preserved LV systolic function.[3,47] We also observed a smaller LV end-diastolic diameter and better LV systolic function in women. Despite these parameters, women were more symptomatic. One explanation for this finding might also be the higher frequency of valvular pathologies and pulmonary hypertension observed in the current study.

## Study Limitations

Despite presenting important findings, this study has a few limitations that need to be addressed. First, the current study was an observational study. Second, patients enrolled in the study were limited to those recruited by study cardiologists; therefore, the results cannot be generalized to the whole population. Third, long-term follow-up of patients was not provided. Monitoring not only in-hospital mortality but also long-term survival could provide valuable information regarding gender differences in patient follow-up. Fourth, since this study was conducted before the widespread use of sodium-glucose cotransporter-2 inhibitors, it is difficult to give information about the effect of these drugs on mortality. Fifth, as each participating center did not have coronary angiography (CAG) laboratory, CAG might be underused and the ischemic etiology might be underestimated,

consequently the low rates of angiography may lead to the undertreatment of CAD in this group.

## CONCLUSION

In the current study, diversity in the precipitation, presentation, management, and in-hospital outcome of AHF between male and female patients was clearly established. In-hospital mortality was higher among women although they had better LV systolic functions. More careful management of female patients with HF in the outpatient settings seems necessary to avoid hospitalization. Precipitating factors also differed between genders. Understanding this gender difference might serve better outcomes in clinical practice.

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