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Gender Differences in Mechanical Circulatory Support, Heart Transplantation, and Survival Among Patients with Advanced Heart Failure

İleri Düzey Kalp Yetersizliği Hastalarında Mekanik Dolaşım Desteği, Kalp Nakli ve Yaşam Süresi Açısından Cinsiyet Farklılıkları

ABSTRACT

Objective: Despite growing awareness of sex-based disparities in heart failure (HF), their impact on clinical outcomes in advanced stages remains poorly understood, largely due to confounding in observational data. This study aimed to assess the independent effect of biological sex on clinical outcomes in advanced HF.

Method: In this retrospective cohort study, 522 patients with advanced HF (85.2% male) evaluated between 2021 and 2024 underwent comprehensive assessments, including echocardiography, cardiopulmonary exercise testing, and cardiac catheterization. Covariate balance was achieved using inverse probability weighting (IPW) based on propensity scores. Primary outcomes included left ventricular assist device (LVAD) implantation, heart transplantation, all-cause mortality, and a composite of these events. Cox proportional hazards models were applied, with a median follow-up of 864 days.

Results: At baseline, male patients were older (54.0 vs. 49.5 years; P = 0.025), had higher rates of ischemic etiology (49.9% vs. 22.7%; P < 0.001), larger cardiac dimensions, and superior exercise capacity. Following IPW adjustment, female sex was associated with a significantly lower risk of LVAD implantation (hazard ratio [HR]: 0.13; 95% confidence interval [CI]: 0.04–0.40; P < 0.001). In contrast, no significant sex-related difference was found in all-cause mortality (HR: 0.75; 95% CI: 0.36–1.58; P = 0.43). The composite outcome showed a non-significant trend toward better outcomes in women (HR: 0.53; 95% CI: 0.26–1.06; P = 0.076). These findings should be interpreted in the context of the relatively small female cohort (14.8%).

Conclusion: In patients with advanced HF, female sex was associated with a lower likelihood of LVAD implantation without an effect on overall mortality. These findings suggest that advanced HF may follow distinct pathophysiological trajectories in women and men, underscoring the importance of sex-informed clinical decision-making frameworks to optimize management and outcomes.

Keywords: Advanced heart failure, sex differences, left ventricular assist device, mechanical circulatory support, inverse probability weighting, propensity score

ÖZET

Amaç: İleri düzey kalp yetersizliği (KY) yönetiminde ve sonuçlarında cinsiyete dayalı farklılıklar tam olarak anlaşılamamıştır. Bu çalışma, biyolojik cinsiyetin mekanik dolaşım desteği (LVAD) uygulanması, kalp nakli ve mortalite üzerindeki bağımsız etkisini değerlendirmeyi amaçlamıştır.

Yöntem: 522 ileri KY hastasından oluşan (%85,2'si erkek) retrospektif bir kohort analiz edilmiştir. Klinik, ekokardiyografik, hemodinamik ve laboratuvar verileri cinsiyete göre karşılaştırılmıştır. Birincil birleşik sonlanım; LVAD implantasyonu, kalp nakli veya tüm nedenlere bağlı ölüm olarak belirlenmiştir. Kafa karıştırıcı etkenleri ayarlamak için eğilim skoru kullanılarak ters olasılık ağırlıklı (IPW) analiz ve çok değişkenli Cox regresyon modelleri uygulanmıştır.

Bulgular: Başlangıçta, erkek hastalar daha yaşlıydı (54,0 yaşa karşı 49,5 yaş; P = 0,025), iskemik etiyoloji oranları daha yüksekti (49,9%'a karşı 22,7%; P < 0,001), kalp boyutları daha büyüktü ve egzersiz kapasiteleri daha üstündü. IPW ayarlamasından sonra, kadın cinsiyeti LVAD implantasyonu riskinde anlamlı olarak daha düşük bir riskle ilişkiliydi (HR: 0,13; %95 GA: 0,04–0,40; P < 0,001). Buna karşın, tüm nedenlere bağlı mortalitede cinsiyetle ilişkili önemli bir fark bulunmamıştır (HR: 0,75; %95 GA: 0,36–1,58; P = 0,43). Bileşik sonuç, kadınlarda daha iyi sonuçlara doğru anlamlı olmayan bir eğilim gösterdi (HR: 0,53; %95 GA: 0,26–1,06; P = 0,076). Sonuçların yorumlanması, nispeten küçük kadın kohortu (%14,8) bağlamında değerlendirilmelidir.

ORIGINAL ARTICLE
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Sonuç: İleri düzeyde kalp yetmezliği olan hastalarda, kadın cinsiyeti genel mortaliteyi etkilemeksizin LVAD implantasyonu ihtiyacının daha düşük olmasıyla ilişkilendirilmiştir. Bu bulgular, ileri düzeyde kalp yetmezliğinin kadınlarda ve erkeklerde farklı patofizyolojik seyir izleyebileceğini göstermekte ve tedaviyi ve sonuçları optimize etmek için cinsiyete dayalı klinik karar verme çerçevelerinin önemini vurgulamaktadır.

Anahtar Kelimeler: İleri kalp yetmezliği, ters olasılık ağırlıklandırması, sol ventrikül destek cihazı, mekanik dolaşım desteği, eğilim skoru, cinsiyet farklılıkları

Heart failure (HF) represents a major global health burden, affecting over 64 million individuals worldwide and contributing substantially to morbidity and mortality.[1] Despite significant advances in both pharmacologic and device-based therapies, a considerable proportion of patients progress to advanced HF, characterized by persistent symptoms, frequent hospitalizations, and markedly reduced quality of life.[2]

Advanced HF is typically defined as New York Heart Association (NYHA) Class III-IV or American College of Cardiology/American Heart Association (ACC/AHA) Stage D, where conventional treatment options fail to provide adequate relief.[2] At this critical stage, mechanical circulatory support (MCS), particularly left ventricular assist devices (LVADs), is frequently employed either as a bridge to transplantation or recovery or as destination therapy.[3,4] Although LVAD therapy has improved survival and quality of life, growing evidence suggests that sex-based disparities may influence access to these therapies and the outcomes they produce.

Prior studies have highlighted potential sex differences in HF etiology, clinical phenotype, hemodynamics, and treatment response.[5,6] Women are more likely to exhibit non-ischemic causes, HF with preserved ejection fraction (HFpEF), and different patterns of ventricular remodeling, while men are more often diagnosed at a younger age with ischemic HF and undergo invasive interventions more frequently.[7,8] Despite this, women remain underrepresented in advanced HF therapies such as LVAD implantation.[9–11] These disparities likely reflect not only clinical heterogeneity but also biological variation, health system factors, and decision-making biases.

Understanding these disparities is complicated by confounding factors common to observational research. Traditional multivariable modeling often fails to fully adjust for numerous sex-related clinical and demographic differences. In this context, inverse probability weighting (IPW) using propensity scores offers a more robust framework by achieving covariate balance between comparison groups.[12,13]

Therefore, the objective of this study was to determine the independent impact of biological sex on clinical outcomes—including LVAD implantation, mortality, and heart transplantation—in patients with advanced HF by applying IPW methodology. This approach aims to clarify the role of sex in clinical progression and risk stratification, with the potential to inform more equitable and personalized HF management strategies. Specifically, we hypothesized that sex-related differences in cardiovascular pathophysiology, including variations in neurohormonal activation, inflammatory responses, and metabolic adaptation, may influence the trajectory toward mechanical circulatory support requirements.

ABBREVIATIONS

ACC/AHA	American College of Cardiology/American Heart Association
ACE	Angiotensin-converting enzyme
BIOSTAT-CHF	BIOlogy Study to TAilored Treatment in Chronic Heart Failure
BMI	Body Mass Index
BNP	B-type natriuretic peptide
CPET	Cardiopulmonary exercise testing
HF	Heart failure
HFpEF	HF with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
IPW	Inverse probability weighting
LVAD	Left ventricular assist device
LVEDD	Left ventricular end-diastolic dimension
LVEF	Left ventricular ejection fraction
LVESD	Left ventricular end-systolic dimension
MCAR	Missing completely at random
MCS	Mechanical circulatory support
MET	Metabolic equivalent
NYHA	New York Heart Association
PASP	Pulmonary artery systolic pressure
RER	Respiratory exchange ratio
RHC	Right heart catheterization
SMD	Standardized mean difference
TAPSE	Tricuspid annular plane systolic excursion
TSH	Thyroid-stimulating hormone

Materials and Methods

Study Population

This retrospective cohort study included patients with advanced HF who were admitted to the heart transplantation outpatient clinic between 2021 and 2024. All patients underwent comprehensive clinical evaluation, including echocardiographic examination, cardiopulmonary exercise testing (CPET), and right heart catheterization (RHC). Clinical, laboratory, echocardiographic, and hemodynamic data were obtained within a maximum of two weeks from the CPET date to ensure temporal consistency of measurements.

Inclusion criteria comprised patients with advanced HF (predominantly New York Heart Association Class III-IV or ACC/AHA Stage D) who had complete clinical, echocardiographic, exercise testing, and hemodynamic evaluation. Patients with

left ventricular ejection fraction (LVEF) >25%, severe lung disease, or contraindications to CPET or RHC were excluded from the study. To ensure accurate assessment of exercise capacity, patients with a peak respiratory exchange ratio (RER) < 1.05, indicating submaximal effort, were excluded from the analysis, as such values are associated with poor reproducibility of peak VO_2 in multicenter trials.[14] Demographics, clinical characteristics, and laboratory results were retrieved from electronic hospital records.

The study was approved by the Koşuyolu High Specialization Training and Research Hospital Ethics Committee (Approval Number: 2025/12/1199, Date: 22.07.2025), and conducted in accordance with the Declaration of Helsinki. All patients provided informed consent for the procedures and data collection.

Clinical Data Collection

Comprehensive clinical evaluation included documentation of cardiovascular risk factors, comorbidities, medication history, and functional status. Body Mass Index (BMI) was calculated as weight in kilograms divided by height in meters squared. Smoking history, diabetes mellitus, hypertension, hyperlipidemia, and previous cardiovascular interventions were systematically recorded. Heart failure etiology was classified as ischemic or non-ischemic based on clinical history, imaging findings, and coronary angiography when available.

Echocardiographic Assessment

Transthoracic echocardiography was performed by a single experienced cardiology echocardiographer using EPIQ CVx v9.0.5 with an X5-1 transducer (Philips Medical Systems, Andover, MA, USA) to minimize inter-observer variability. LVEF was measured using the biplane method of disk summation (modified Simpson's rule). The left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD), and left atrial dimension were measured in the parasternal long-axis view.

Doppler echocardiography was performed in accordance with current American Society of Echocardiography guidelines.[15] Tricuspid annular plane systolic excursion (TAPSE) was measured using M-mode imaging in the apical four-chamber view. The severity of tricuspid regurgitation was assessed using color Doppler and graded as mild, moderate, or severe. Echocardiographic estimation of pulmonary artery systolic pressure (PASP) was determined by summing the peak velocity of tricuspid regurgitation (calculated using the Bernoulli equation) and the estimated central venous pressure, derived from inferior vena cava diameter and collapsibility.

Cardiopulmonary Exercise Testing

Maximal CPET was performed using a continuous, incremental treadmill protocol based on individualized ramp design, conducted on a JAEGER Vyntus CPX system (Vyaire Medical, Germany). Oxygen uptake was measured breath-by-breath using an automated system, with data collected at rest, during graded exercise, and throughout a two-minute recovery period.

Exercise capacity was expressed in metabolic equivalents (METs), calculated by dividing the VO_2max value by 3.5 mL/kg/min. VO_2, VCO_2, and respiratory exchange ratio (RER = VCO_2/VO_2) were computed and averaged every 10 seconds. Maximal effort was defined as achieving an RER greater than 1.05. Peak VO_2 was defined as the highest 10-second averaged VO_2 during the final stage of exercise testing. Blood pressure was measured before testing, every three minutes during exercise, and during the recovery phase.

Right Heart Catheterization

Right heart catheterization was performed using a 7Fr balloon-tipped Swan–Ganz catheter (Edwards Lifesciences, Irvine, CA, USA) or a pigtail catheter introduced through the right jugular or femoral vein. Hemodynamic measurements included right atrial pressure, right ventricular pressure, pulmonary artery pressure, and pulmonary capillary wedge pressure. Cardiac output was estimated using the indirect Fick method. Stroke volume was calculated as cardiac output divided by heart rate. Systemic vascular resistance was calculated using standard hemodynamic formulas.

All pressure tracings were visually inspected for physiological accuracy, and end-expiratory pressure values were recorded to minimize respiratory variation effects. Measurements were obtained after hemodynamic stabilization and averaged over multiple cardiac cycles.

Laboratory Assessment

Blood samples were obtained in the fasting state within two weeks of hemodynamic evaluation. Laboratory parameters included complete blood count (hemoglobin, hematocrit), comprehensive metabolic panel (creatinine, electrolytes), lipid profile (total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], triglycerides), liver function tests, thyroid-stimulating hormone (TSH), and B-type natriuretic peptide (BNP) or N-terminal pro-BNP, when available.

Clinical Outcomes

The primary outcomes of interest were: (1) LVAD implantation, (2) heart transplantation, (3) all-cause mortality, and (4) a composite outcome defined as the occurrence of any of the above events. Patients were followed from the date of initial evaluation until the occurrence of an endpoint, loss to follow-up, or study closure. Follow-up data were obtained through electronic medical records, outpatient clinic visits, and telephone contact when necessary.

Statistical Analysis

Baseline characteristics were reported as means ± standard deviations (SD) for continuous variables and as counts with percentages for categorical variables. Comparisons between men and women were made using t-tests or chi-square tests, as appropriate.

To address potential confounding by indication and achieve balance in baseline characteristics between men and women, we employed IPW using propensity scores. The propensity score represented the probability of being female conditional on observed baseline covariates. We compared propensity scores derived from logistic regression and gradient boosting machine (GBM) algorithms based on their ability to balance clinical covariates between men and women, assessed by standardized mean differences after weighting. The logistic regression-based IPW was selected because it provided superior covariate balance and more stable weights. The propensity score model included cardiovascular risk factors, comorbidities, demographic variables,

laboratory parameters, echocardiographic measurements, hemodynamic variables, and exercise testing results. Variables were selected based on: (1) differences observed between groups in unadjusted analyses, (2) clinical importance based on expert judgment, and (3) established associations with heart failure outcomes in the literature. IPWs were calculated as 1/propensity score for women and 1/(1–propensity score) for men. Extreme weights were trimmed at the 1st and 99th percentiles to stabilize estimates, resulting in 49 patients being trimmed. Standardized mean differences were used to evaluate the balance of patient characteristics following weighting, with values < 0.2 considered indicative of adequate balance.

Cox proportional hazards regression models were employed to assess the association between sex and clinical outcomes. Using the IPWs, weighted Cox proportional hazards models were fitted. To implement a doubly robust approach, the same covariates used in propensity score estimation were included in the multivariable model, providing protection against misspecification of either the propensity score model or the outcome model. Additionally, a weighted ridge-penalized Cox model was fitted, with all covariates except the sex variable subject to penalization, allowing for regularized coefficient estimation while preserving the unpenalized effect of sex. A traditional multivariable Cox model without weighting was also fitted for comparison.

The proportional hazards assumption was tested using Schoenfeld residuals and was not found to be violated for the primary analyses. Hazard ratios with 95% confidence intervals were calculated for all models. Due to the retrospective design, no a priori sample size calculation was performed; however, post hoc power analyses for LVAD implantation and the composite outcome were conducted and are provided in the Appendix 1.

Overall, 7.9% of the dataset contained missing values. Missing data were assumed to be missing completely at random (MCAR) and were imputed using the missForest algorithm.

The Kaplan-Meier method was used to visualize the cumulative incidence of outcomes, including the composite endpoint and LVAD implantation separately, stratified by sex. Comparisons were made using the log-rank test. Time-to-event analyses were conducted with patients censored at the time of last follow-up or study closure.

All statistical analyses were performed using R 4.4.1 software (R Foundation for Statistical Computing, Vienna, Austria) with the following packages: "WeightIt," "survey," "survival," "survminer," "ggplot2," "cobalt," "tableone," "naniar," "missForest," and "powerSurvEpi." A two-tailed P value <0.05 was considered statistically significant.

Results

A total of 522 patients diagnosed with advanced HF were included in the study. Of the participants, 85.2% were male (n = 445) and 14.8% were female (n = 77). When evaluated by sex, significant differences were identified in demographic characteristics, body composition, heart failure etiology, comorbidities, hemodynamic parameters, and laboratory findings (Table 1).

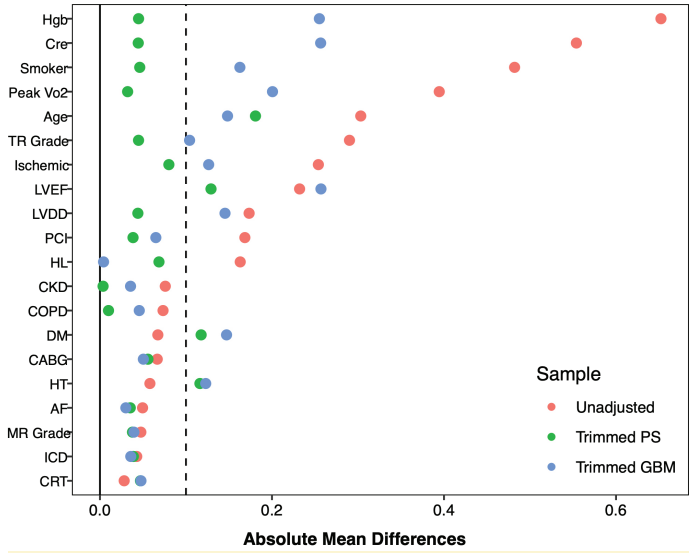

Figure 1. Covariate balance assessment before and after propensity score weighting. Standardized mean differences (SMD) for key covariates comparing patients by sex with advanced heart failure. Red dots represent unadjusted differences showing substantial imbalances between groups. Green dots show results after propensity score weighting (trimmed PS), and blue dots show results after gradient boosting machine weighting (trimmed GBM). The solid vertical line at 0.0 represents perfect balance, while the dashed vertical line at 0.2 indicates the threshold for adequate balance. All covariates achieved SMD < 0.2 after propensity score weighting, demonstrating successful covariate balance and supporting the validity of causal inference analyses.

Male patients were older than female patients (median age: 54.0 [interquartile range [IQR]: 44.0–59.0] vs. 49.5 [IQR: 41.0–58.0]; P = 0.025), taller (172 vs. 158 cm; P < 0.001), and heavier (80 vs. 69.5 kg; P < 0.001), but there was no difference in BMI (P = 0.155). Ischemic etiology (49.9% vs. 22.7%; P < 0.001), history of PCI (39.0% vs. 22.1%; P = 0.004), hyperlipidemia (42.4% vs. 26.0%; P = 0.007), and smoking (78.0% vs. 29.9%; P < 0.001) were more frequent in men.

Echocardiographic evaluation revealed significantly larger left ventricular and atrial dimensions in men: LVEDD (6.90 vs. 6.05 cm; P < 0.001), LVESD (6.00 vs. 5.40 cm; P < 0.001), and left atrium (LA) (4.70 vs. 4.25 cm; P < 0.001). LVEF values were similar (P = 0.066). Tricuspid regurgitation was more prominent in women (P < 0.001) (Table 2).

Invasive hemodynamic measurements showed higher stroke volume (41.0 vs. 36.8 mL; P = 0.001) and cardiac output (3.40 vs. 2.90 L/min; P < 0.001) in men, while women had higher systemic vascular resistance (25.90 vs. 22.05 Wood units; P < 0.001) and aortic systolic pressure (120 vs. 112 mmHg; P = 0.009) (Table 2).

Laboratory evaluation demonstrated significantly higher hemoglobin (14.1 vs. 12.7 g/dL; P < 0.001), hematocrit (43.1% vs. 40.1%; P < 0.001), and creatinine (1.03 vs. 0.81 mg/dL; P < 0.001) levels in men. Women had higher HDL cholesterol (43.0 vs. 38.2 mg/dL; P = 0.031) and TSH (2.45 vs. 1.84 mIU/L; P = 0.020) levels (Table 1).

Table 1. Baseline clinical characteristics, laboratory assessment and outcomes stratified by sex

Variable	Overall	Male	Female	P
Demographic and follow-up data				
Follow-up (days)	864.50 (517.25–1461.00)	830.00 (507.00–1482.00)	1018.00 (529.00–1281.00)	0.328
Age (years)	53.00 (44.00–59.00)	54.00 (44.00–59.00)	49.50 (41.00–58.00)	0.0254
Height (cm)	170.00 (165.00–176.00)	172.00 (168.00–178.00)	158.00 (153.75–162.00)	<0.001
Weight (kg)	79.00 (70.00–90.00)	80.00 (71.00–91.00)	69.50 (59.00–80.00)	<0.001
BMI (kg/m²)	27.00 (24.00–30.00)	27.00 (24.00–30.00)	28.00 (23.75–33.00)	0.155
Comorbidities				
Ischemic	231 (45.8)	214 (49.9)	17 (22.7)	<0.001
PCI	191 (36.5)	174 (39)	17 (22.1)	0.004
CABG	57 (10.9)	53 (11.9)	4 (5.2)	0.082
HT	185 (35.4)	154 (34.5)	31 (40.3)	0.331
DM	173 (33.1)	152 (34.1)	21 (27.3)	0.241
AF	97 (18.5)	86 (19.3)	11 (14.3)	0.298
HL	209 (40)	189 (42.4)	20 (26)	0.007
CKD	102 (19.5)	92 (20.6)	10 (13)	0.118
CVD	42 (8)	38 (8.5)	4 (5.2)	0.321
PAD	26 (5)	24 (5.4)	2 (2.6)	0.299
Smoker	371 (70.9)	348 (78)	23 (29.9)	<0.001
COPD	60 (11.5)	56 (12.6)	4 (5.2)	0.061
Laboratory parameters				
Urea (mg/dL)	43.00 (34.35–55.95)	43.80 (35.10–56.95)	40.00 (31.10–48.30)	0.00672
Cre (mg/dL)	1.00 (0.83–1.20)	1.03 (0.86–1.23)	0.81 (0.70–0.96)	<0.001
AST (U/L)	20.60 (15.60–27.20)	20.95 (15.70–27.33)	19.20 (14.80–26.60)	0.336
ALT (U/L)	20.65 (14.22–30.95)	21.10 (14.90–32.10)	16.70 (13.00–25.30)	0.00448
Total Bil (mg/dL)	0.75 (0.50–1.20)	0.79 (0.52–1.28)	0.60 (0.41–0.94)	0.00154
Direct Bil (mg/dL)	0.30 (0.19–0.54)	0.32 (0.20–0.55)	0.26 (0.17–0.36)	0.0159
Pro-BNP (pg/mL)	2232.00 (1000.00–4411.00)	2236.50 (998.00–4384.75)	2022.00 (1081.00–4835.00)	0.659
Trig (mg/dL)	122.00 (88.05–172.30)	121.15 (86.80–175.07)	126.25 (97.43–160.57)	0.715
LDL (mg/dL)	92.30 (65.30–121.83)	92.06 (64.98–121.76)	93.59 (78.31–122.30)	0.692
HDL (mg/dL)	38.80 (32.02–48.32)	38.20 (31.95–47.70)	43.00 (35.80–51.45)	0.0305
Sodium (mEq/L)	138.00 (136.00–140.00)	138.00 (136.00–140.00)	139.00 (137.00–141.00)	0.0381
Potassium (mEq/L)	4.49 (0.52)	4.48 (0.52)	4.55 (0.48)	0.275
Total prot (g/dL)	71.00 (67.00–75.00)	72.00 (67.00–75.00)	71.00 (68.00–75.00)	0.813
Alb (g/dL)	44.00 (41.00–47.00)	44.00 (40.00–47.00)	44.00 (41.75–46.00)	0.914
LDH (U/L)	216.00 (185.00–265.00)	213.00 (185.00–263.00)	221.00 (195.00–276.50)	0.0949
GFR (mL/min/1.73m²)	82.00 (66.00–98.00)	82.00 (66.00–98.00)	84.78 (69.00–103.00)	0.393
TSH (mIU/L)	1.92 (1.23–3.09)	1.84 (1.22–2.98)	2.45 (1.55–4.19)	0.0203
INR	1.18 (1.06–1.40)	1.19 (1.06–1.38)	1.17 (1.06–1.43)	0.84
Hgb (g/dL)	13.90 (12.50–15.10)	14.10 (12.70–15.30)	12.70 (11.80–13.90)	<0.001
Hct (%)	42.66 (5.54)	43.11 (5.52)	40.11 (4.93)	<0.001
PLT (×10³/μL)	249.00 (205.00–291.00)	245.50 (205.00–288.00)	260.00 (205.00–328.00)	0.137
Neu (×10³/μL)	5.07 (4.04–6.26)	5.07 (4.10–6.27)	5.12 (3.62–6.21)	0.396
Lym (×10³/μL)	1.93 (1.42–2.52)	1.92 (1.41–2.50)	1.94 (1.53–2.53)	0.725
Devices and outcomes				
ICD	128 (24.5)	112 (25.1)	16 (20.8)	0.414
CRT	33 (6.3)	30 (6.7)	3 (3.9)	0.346
LVAD	66 (12.6)	60 (13.5)	6 (7.8)	0.165
TX	4 (0.8)	3 (0.7)	1 (1.3)	0.473
Death	113 (21.6)	97 (21.8)	16 (20.8)	0.841

AF, Atrial fibrillation; Alb, Albumin; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BMI, Body mass index; Bil, Bilirubin; CABG, Coronary artery bypass grafting; CKD, Chronic kidney disease; Cre, Creatinine; COPD, Chronic obstructive pulmonary disease; CRT, Cardiac resynchronization therapy; CVD, Cerebrovascular disease; DM, Diabetes mellitus; GFR, Glomerular filtration rate; HL, Hyperlipidemia; Hct, Hematocrit; Hgb, Hemoglobin; HT, Hypertension; ICD, Implantable cardioverter defibrillator; INR, International normalized ratio; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; Lym, Lymphocyte count; LVAD, Left ventricular assist device; Neu, Neutrophil count; PCI, Percutaneous coronary intervention; PLT, Platelet count; Pro-BNP, Pro-B-type natriuretic peptide; TX, Heart transplantation; Trig, Triglycerides; TSH, Thyroid-stimulating hormone; WBC, White blood cell count; LDH, Lactate dehydrogenase.

Table 2. Echocardiographic assessment, invasive hemodynamic parameters and Cardiopulmonary Exercise Testing parameters stratified by sex

Variable	Overall	Male	Female	P
Echocardiography parameters				
LVEF (%)	22.00 (20.00–25.00)	22.00 (20.00–25.00)	24.00 (20.00–25.00)	0.0656
LVEDD (mm)	6.70 (6.20–7.40)	6.90 (6.30–7.40)	6.05 (5.80–6.62)	<0.001
LVESD (mm)	5.90 (5.40–6.60)	6.00 (5.50–6.60)	5.40 (4.80–6.00)	<0.001
LA (mm)	4.60 (4.30–5.00)	4.70 (4.34–5.00)	4.25 (3.98–4.60)	<0.001
LVDD				0.027
0		1 (0.2)	0 (0)	
1		86 (20.2)	14 (20.3)	
2		82 (19.3)	24 (34.8)	
3		256 (60.2)	31 (44.)	
Echo-PASP (mm Hg)	40.00 (30.00–53.00)	40.00 (30.00–55.00)	36.00 (25.00–50.00)	0.341
TAPSE (mm)	1.60 (1.36–2.00)	1.62 (1.36–2.00)	1.60 (1.33–2.00)	0.7
IVC (mm)	1.90 (1.60–2.20)	1.90 (1.60–2.20)	1.80 (1.50–2.10)	0.0346
Plethorea (0/1)	132 (27.0)	108 (25.9)	24 (33.8)	
MR grade				0.960
0		1 (0.2)	0 (0)	
1		156 (36.1)	26 (36.1)	
2		181 (41.9)	29 (40.3)	
3		94 (21.8)	17 (23.6)	
TR grade				<0.001
1		246 (55.8)	40 (52.6)	
2		141 (32)	13 (17.1)	
3		54 (12.2)	22 (28.9)	
4		0 (0)	1 (1.3)	
AVR (0/1)	9 (1.7)	8 (1.8)	1 (1.3)	0.757
MVR (0/1)	19 (3.7)	15 (3.4)	4 (5.3)	0.428
Invasive hemodynamic parameters				
Aort Sys (mmHg)	113.00 (100.00–129.50)	112.00 (99.00–128.00)	120.00 (110.00–142.00)	0.00921
Aort Dia (mmHg)	70.00 (62.00–79.00)	70.00 (62.00–78.00)	71.00 (67.00–84.00)	0.0842
Aort Mean (mmHg)	86.00 (78.00–96.00)	85.00 (76.25–95.00)	88.00 (82.00–104.00)	0.0099
LVEDP (mmHg)	24.00 (15.00–28.00)	24.00 (16.00–28.00)	22.00 (12.00–27.00)	0.0746
Cath_PASP (mmHg)	50.00 (35.00–63.00)	50.00 (35.00–64.00)	45.00 (36.00–59.00)	0.155
Cath_PADP (mmHg)	23.00 (14.00–29.00)	23.00 (14.00–30.00)	20.00 (13.00–28.00)	0.0684
Cath_PAMP (mmHg)	33.00 (22.00–42.00)	34.00 (23.00–42.00)	31.00 (21.00–40.00)	0.149
RVSP (mmHg)	48.00 (36.00–62.00)	49.00 (36.00–62.00)	45.00 (35.00–58.00)	0.137
RAP (mmHg)	8.00 (5.00–13.50)	8.00 (5.00–13.00)	8.00 (6.00–14.00)	0.425
TPG (mmHg)	9.00 (5.00–14.00)	8.00 (5.00–14.00)	9.00 (5.00–13.00)	0.998
TSG (mmHg)	76.00 (66.00–87.00)	75.00 (66.00–86.00)	80.00 (72.00–90.00)	0.0216
SV (mL)	40.02 (32.31–51.00)	41.00 (33.20–52.00)	36.80 (28.25–43.85)	0.00141
SVI (mL/m²)	20.80 (17.12–25.66)	21.00 (17.50–25.85)	19.00 (16.15–24.60)	0.204
CO (L/min)	3.32 (2.80–4.12)	3.40 (2.84–4.20)	2.90 (2.44–3.62)	<0.001
CI (L/min/m²)	1.70 (1.50–2.06)	1.70 (1.50–2.07)	1.64 (1.39–2.01)	0.23
PVR (Wood units)	2.45 (1.36–4.30)	2.38 (1.33–4.29)	2.98 (1.75–4.32)	0.211
SVR (Wood units)	22.80 (18.96–27.00)	22.05 (18.00–26.40)	25.90 (22.27–32.15)	<0.001
RVSWI (g·m/m²)	6.55 (4.68–9.12)	6.70 (4.79–9.20)	5.80 (4.00–8.00)	0.0349

Table 2 (cont). Echocardiographic assessment, invasive hemodynamic parameters and Cardiopulmonary Exercise Testing parameters stratified by sex

Variable	Overall	Male	Female	P
Cardiopulmonary exercise test				
Duration (minutes)	6.58 (4.18–9.30)	7.02 (4.39–9.32)	5.57 (2.56–8.52)	0.0178
Load (watts)	90.00 (45.00–140.00)	100.00 (50.00–150.00)	65.00 (26.25–115.00)	<0.001
VE (L/min)	46.00 (38.00–54.00)	48.00 (41.00–56.00)	35.00 (30.00–40.75)	<0.001
VO_2 (mL/min)	1072.00 (801.50–1370.00)	1111.00 (834.00–1445.00)	850.50 (660.00–1104.25)	<0.001
Peak VO_2 (mL/min/kg)	13.60 (10.40–16.95)	13.90 (10.60–17.10)	12.05 (9.43–14.70)	0.00157
Pred percent (%)	29.00 (25.13–33.88)	29.50 (26.17–34.52)	23.75 (19.50–28.88)	<0.001
RER (unitless)	1.03 (0.98–1.08)	1.03 (0.98–1.08)	1.03 (0.98–1.09)	0.905
METS (unitless)	3.90 (3.00–4.80)	4.00 (3.00–4.90)	3.45 (2.70–4.20)	0.00195
HR (bpm)	116.99 (25.60)	116.95 (26.06)	117.24 (23.14)	0.928
HRR (bpm)	53.00 (39.75–70.25)	53.00 (39.00–70.00)	55.00 (41.00–73.00)	0.605
Peak Sat (%)	98.00 (95.00–99.00)	98.00 (95.00–99.00)	98.00 (94.00–98.00)	0.124
$VECO_2$ (unitless)	38.04 (31.50–52.34)	37.95 (31.38–51.10)	38.52 (33.09–81.00)	0.236
VO_2WS (mL/min/kg)	3.60 (2.02–5.27)	3.66 (2.14–5.20)	2.93 (1.46–6.87)	0.633
HRO_2WS (bpm)	2.21 (0.99–3.30)	2.21 (0.99–3.30)	2.13 (1.07–3.24)	0.842
MECKI score	15.36 (5.68–31.83)	18.42 (7.28–32.12)	7.94 (4.97–13.33)	0.231

Aort Sys/Dia/Mean, aortic systolic/diastolic/mean pressure; AVR, Aortic valve replacement; Bil, Bilirubin; Cath_PASP/PADP/PAMP, Catheter-derived pulmonary artery systolic/diastolic/mean pressure; CI, Cardiac index; CO, Cardiac output; Echo-PASP, Echocardiographic pulmonary artery systolic pressure; HR, Heart rate; HRO_2WS, Heart rate at anaerobic threshold; HRR, Heart rate reserve; IVC, Inferior vena cava diameter; LA, Left atrial dimension; LVDD, Left ventricular diastolic dysfunction (0, normal, 1, mild, 2, moderate, 3, severe); LVEF, Left ventricular ejection fraction; LVEDD, Left ventricular end-diastolic dimension; LVEDP, Left ventricular end-diastolic pressure; LVESD, Left ventricular end-systolic dimension; MECKI, Metabolic Exercise Test data combined with Cardiac and Kidney Indexes; METS, Metabolic equivalents; MR, Mitral regurgitation (0, none, 1, mild, 2, moderate, 3, severe); MVR, Mitral valve replacement; Peak Sat, Peak oxygen saturation; Peak VO_2, Peak oxygen consumption normalized to body weight; Pred Percent, Predicted percentage of normal peak VO_2; PVR, Pulmonary vascular resistance; RAP, Right atrial pressure; RER, Respiratory exchange ratio; RVSP, Right ventricular systolic pressure; RVSWI, Right ventricular stroke work index; SV, Stroke volume; SVI, Stroke volume index; SVR, Systemic vascular resistance; TAPSE, Tricuspid annular plane systolic excursion; TPG, Transpulmonary gradient; TR, Tricuspid regurgitation (1, mild, 2, moderate, 3, severe, 4, torrential); TSG, Total systemic gradient; VE, Minute ventilation; $VECO_2$, Ventilatory equivalent for carbon dioxide; VO_2, Absolute oxygen consumption; VO_2WS, Oxygen consumption at anaerobic threshold.

Regarding functional capacity, men exhibited higher values across all parameters compared to women: exercise duration (7.02 vs. 5.57 minutes; P = 0.018), maximum workload (100 vs. 65 watts; P < 0.001), peak VO_2 (13.9 vs. 12.05 mL/min/kg; P = 0.002), and METs value (4.0 vs. 3.45; P = 0.002) (Table 2).

To isolate the independent effect of sex on clinical outcomes, IPW was applied. The propensity score model was comprehensively constructed to include demographic data, comorbidities, laboratory findings, and echocardiographic and hemodynamic parameters. After weighting, standardized mean difference (SMD) values < 0.2 were achieved for all covariates, indicating successful balancing between female and male groups (Appendix 2). Figure 1 demonstrates the elimination of significant imbalances present before weighting (red dots) and the achievement of excellent balance after IPW (green dots).

The median follow-up period was 864 days (approximately 28.8 months). During this period, 66 patients (12.6%) underwent LVAD implantation, 113 patients (21.6%) died, and 4 patients (0.8%) received heart transplantation. The composite outcome (LVAD, transplantation, or death) occurred in a total of 161 patients (30.8%). Although female patients had a lower absolute incidence of these events, the differences were not statistically significant.

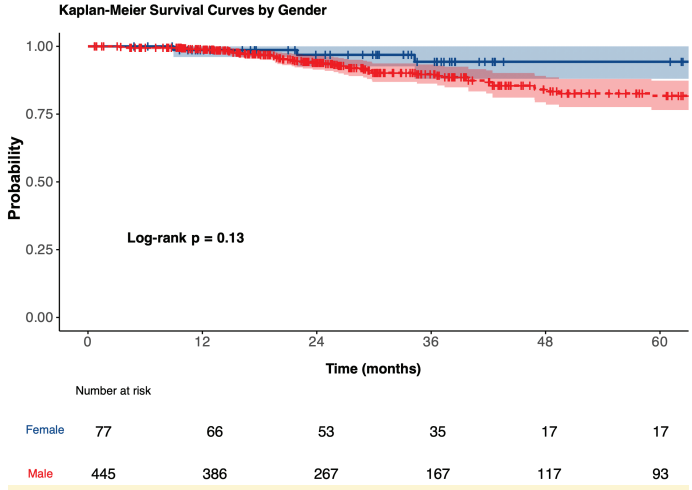

Figure 2. Kaplan-Meier curves for left ventricular assist device-free (LVAD-free) survival by sex. Kaplan-Meier survival curves showing the cumulative probability of remaining free from left ventricular assist device (LVAD) implantation over a 60-month follow-up period, stratified by sex. Female patients demonstrated a consistently lower risk of LVAD implantation compared to male patients, although the difference did not reach statistical significance (log-rank P = 0.13). The number at risk at each time point is displayed below the plot.

Table 3. Cox proportional hazards models for lvad implantation risk by sex

Model	Info	Gender HR	P	Concordance	LR df	LR p value
1	Weighted and adjusted (double robust)	0.125 (0.039-0.398)	<0.001	0.812	21	<0.001
2	Unweighted and adjusted	0.226 (0.082-0.614)	0.004	0.804	21	<0.001
3	Unweighted univariate	0.532 (0.082-0.614)	0.141	0.538	1	0.10
4	Weighted univariate	0.196 (0.064-0.591)	0.004	0.556	1	0.005
5	Weighted and penalized	0.128 (0.040-0.400)	<0.001	0.812	20.45	<0.001

HR, Hazard ratio; LVAD, Left ventricular assist device; LR df, Degrees of freedom for likelihood ratio test; LR p value, P-value for overall model significance via likelihood ratio test.

Table 4. Cox proportional hazards models for composite outcome by sex

Model	Info	Gender HR	P value	Concordance	LR df	LR p value
1	Weighted and adjusted (double robust)	0.527 (0.259-1.069)	0.076	0.716	21	<0.001
2	Unweighted and adjusted	0.501 (0.288-0.872)	0.014	0.707	21	<0.001
3	Unweighted univariate	0.759 (0.475-1.212)	0.248	0.515	1	0.2
4	Weighted univariate	0.604 (0.291-1.252	0.175	0.53	1	0.07
5	Weighted and penalized	0.532 (0.263-1.073)	0.078	0.717	20	<0.001

HR, Hazard ratio; LR df, Degrees of freedom for likelihood ratio test; LR p value, P-value for overall model significance via likelihood ratio test.

Table 5. Cox proportional hazards models for all-cause mortality risk by sex

Model	Info	Gender HR	P value	Concordance	LR df	LR p value
1	Weighted and adjusted (double robust)	0.75 (0.366-1.533)	0.43	0.719	21	<0.001
2	Unweighted and adjusted	0.69 (0.364-1.293)	0.25	0.707	21	<0.001
3	Unweighted univariate	0.92 (0.544-1.571)	0.77	0.504	1	0.8
4	Weighted univariate	0.82 (0.370-1.800)	0.62	0.52	1	0.5
5	Weighted and penalized	0.75 (0.368-1.536)	0.43	0.72	21	<0.001

Model Descriptions: ●Model 1 (Weighted and adjusted - double robust): Inverse probability weighted Cox model with all covariates included, providing protection against misspecification of either propensity score or outcome model. ●Model 2 (Unweighted and adjusted): Traditional multivariable Cox model including all baseline covariates without propensity score weighting. ●Model 3 (Unweighted univariate): Simple univariate Cox model with sex as the only predictor. ●Model 4 (Weighted univariate): Inverse probability weighted Cox model with sex as the only predictor. ●Model 5 (Weighted and penalized): Ridge penalized Cox model with inverse probability weighting, where all covariates except sex were subject to L2 regularization. Statistical Measures: HR, hazard ratio for female vs. male sex; P value, statistical significance of the sex coefficient; Concordance, C-index measuring model's discriminative ability (0.5 = no discrimination, 1.0 = perfect discrimination); LR df, Degrees of freedom for likelihood ratio test; LR p value, P-value for overall model significance via likelihood ratio test.

A notable finding was the consistent association between female sex and lower observed LVAD implantation rates. Kaplan-Meier analyses showed better LVAD-free survival in female patients, although this difference did not reach statistical significance (Figure 2, log-rank P = 0.13). In the IPW-weighted, doubly robust model, LVAD requirement was lower in women (hazard ratio [HR]: 0.13; P < 0.001). This finding demonstrated consistency across all analyses, including penalized and traditional multivariable Cox models (Table 3).

In multivariable Cox regression analysis, female sex was associated with a lower risk for the composite outcome (HR: 0.50; 95% confidence interval [CI]: 0.29–0.87; P = 0.015). However, after IPW weighting, this association weakened and approached the significance threshold (HR: 0.53; 95% CI: 0.26–1.06; P = 0.076) (Table 4). Kaplan-Meier curves also showed a trend toward better event-free survival in female patients, but this difference was not significant (Figure 3, log-rank P = 0.25).

No significant difference was found between sexes regarding all-cause mortality. IPW-adjusted models showed a slightly lower risk in women (e.g., doubly robust model: HR: 0.75; P = 0.43), but this difference was not statistically significant (Table 5). Due to the very low number of heart transplantation events (n = 4), we did not analyze transplantation separately and instead focused on LVAD implantation and the composite outcome (LVAD, transplantation, or death). Female patients appeared to remain stable for longer periods and required less invasive treatment. Risk tables supported this trend. The protective effect was not observed for outcomes other than LVAD (mortality and transplantation).

In conclusion, when all measurable clinical and hemodynamic variables were balanced, female sex did not have an independent effect on mortality in advanced heart failure. However, female patients had lower observed LVAD implantation rates; this association is hypothesis-generating and should not be interpreted as evidence of causal clinical superiority.

Figure 4 provides a visual summary of the observed lower LVAD implantation rates in female patients, while showing no significant effect on mortality or composite outcomes. The consistent results obtained across five different Cox regression models reinforce the validity and reliability of these findings (Appendix 3).

Discussion

This study evaluated the effect of biological sex on clinical outcomes in patients with advanced HF using IPW. After achieving excellent covariate balance across 522 patients (all SMD < 0.2), female sex was associated with lower observed LVAD implantation rates; however, this represents an observational association and should not be interpreted as evidence of clinical superiority. Alternative explanations, including referral bias, provider decision-making, and systemic barriers, may contribute to this finding.

These findings are consistent with the growing literature suggesting sex-specific pathophysiological mechanisms.[6,8] Women demonstrate enhanced lipid metabolism and fatty acid utilization, which may contribute to more efficient myocardial energy use under stress.[6] In contrast, men exhibit more prominent neuroinflammatory activation and maladaptive cytokine signaling, potentially accelerating progression toward mechanical circulatory support.[6] Additionally, estrogen's beneficial effects on endothelial function and calcium handling,[8,16] along with greater parasympathetic tone and a predisposition to HFpEF phenotypes, may contribute to a more favorable hemodynamic trajectory in women.[5,16]

The lower prevalence of ischemic etiology among women (22.7% vs. 49.9%) and more preserved ventricular-arterial coupling offer further physiological explanations.[5,17] The association between female sex and lower LVAD utilization observed in this study is hypothesis-generating and should not be overinterpreted as causal. In unadjusted analyses, female sex was associated with a lower risk of the composite outcome (HR: 0.50; P = 0.015), but this effect attenuated after IPW adjustment (HR: 0.53; P = 0.076), indicating that the lower composite event rate was primarily driven by lower LVAD utilization rather than differences in mortality. The small number of female patients (n = 77, 14.8%) limits statistical power and precision, as reflected in the attenuation of the composite outcome after IPW adjustment (HR: 0.53, P = 0.076), highlighting the potential for type II error.

Interestingly, despite lower use of LVADs, women showed comparable long-term survival to men. This finding mirrors that of Gruen et al.,[10] who reported higher complication rates—including bleeding, stroke, and device malfunction—in female LVAD recipients. Similarly, Hsich et al.(18) found that women on transplant waitlists, particularly those with UNOS 1A/1B status, had higher mortality risk, suggesting that women may progress more gradually, potentially reaching similar clinical stages as men. Studies by Rubinstein,[19] Rose,[11] and Steinberg[20] also indicate that systemic barriers in referral and decision-making may contribute to sex-based disparities in access to advanced therapies. Thus, the lower LVAD implantation rate in women may reflect a combination of biological differences, disease trajectory, and systemic factors, rather than inherent clinical advantage. Further supporting this, Diaz-Arocutipa et al.[21] reported that women in acute cardiogenic shock were 23% less likely to receive mechanical circulatory support and experienced higher mortality when devices were implanted—highlighting context-specific sex differences in pathophysiologic response.

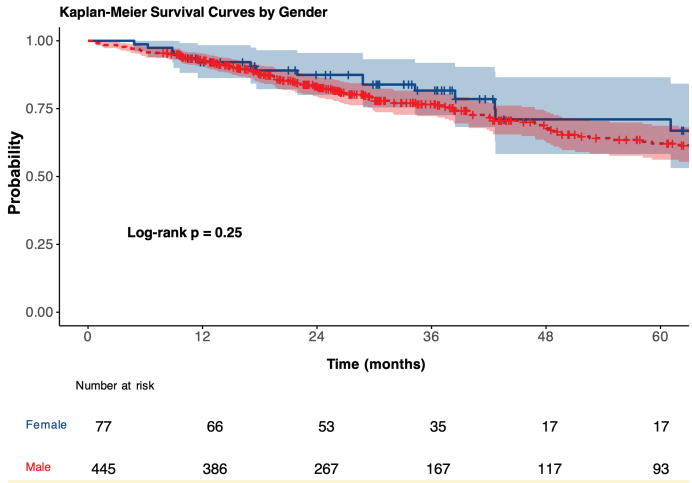

Figure 3. Kaplan-Meier curves for freedom from composite outcome (LVAD, transplantation, or death) by sex. Kaplan-Meier curves depicting the probability of remaining free from the composite outcome of left ventricular assist device (LVAD) implantation, heart transplantation, or all-cause death over a 60-month follow-up period, stratified by sex. Although female patients exhibited a trend toward better event-free survival, the difference was not statistically significant (log-rank P = 0.25). Risk tables display the number of patients at risk in each group at specified time points.

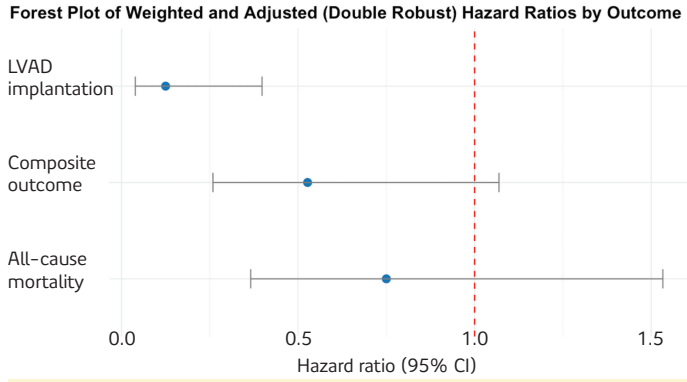

Figure 4. Forest plot of weighted and adjusted (doubly robust) hazard ratios by outcome. Forest plot of hazard ratios (HRs) for female sex in advanced heart failure. Shown are HRs (95% CI) for LVAD implantation, composite outcome (LVAD, heart transplantation, or death), and all-cause mortality, derived from IPW-weighted and doubly robust Cox models. HR < 1 indicates lower risk for female patients. Female sex was consistently associated with reduced LVAD implantation, with no significant effect on mortality or the composite outcome.

Pharmacological data also reinforce these disparities. In the BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF) trial, women achieved similar therapeutic benefit with lower doses of angiotensin-converting enzyme (ACE) inhibitors and beta-blockers, yet treatment strategies are still primarily based on male-centric dosing thresholds.[22] This cautious approach may partially explain the reduced LVAD use observed in women. The long-standing underrepresentation of women in cardiovascular trials further amplifies these issues.

Whitelaw et al.[23] found that in more than 70% of heart failure studies, women were underrepresented relative to disease prevalence, hindering the development of sex-specific clinical guidelines. By applying IPW methodology, this study helps bridge that gap, isolating the effect of sex on outcomes that previous studies lacked the statistical power to detect.[13]

The biological mechanisms underlying these differences likely reflect complex interactions among hormonal regulation, metabolic efficiency, and inflammatory tone. While enhanced lipid metabolism may help women maintain cardiac function, it may also create distinct anticoagulation-related complication profiles in the context of device therapy. Conversely, more active inflammatory profiles in men may influence their physiological response to LVAD implantation.[6,8,16]

Our methodological approach—incorporating five analytic models and rigorous IPW implementation—ensured consistent and robust findings, with all models showing a consistent association between female sex and lower observed LVAD implantation rates.[12,13] The single-center design enhanced internal validity, and standardized protocols helped reduce confounding.

Future studies should aim to clarify whether reduced LVAD use in women reflects undertreatment, differences in disease progression, or both. Integrating hormonal, genetic, and inflammatory parameters into risk stratification and device therapy selection may facilitate more personalized and equitable care. Aligning these strategies with current echocardiographic guidelines and evidence-based management frameworks will help optimize outcomes for all patients with advanced heart failure.

Limitations

Several constraints warrant consideration. The observational design limits causal inferences, while unmeasured confounders, including hormonal levels, genetic polymorphisms, and epigenetic modifications, influence outcomes. The low female representation (14.8%) constrains statistical power for subgroup analyses, and the single-center design limits external generalizability.

Selection bias in referral patterns also affects interpretation, as women receive advanced HF evaluation at different disease stages. Unmeasured socioeconomic factors—such as insurance coverage, social support, and caregiver availability—may differentially impact treatment decisions. Furthermore, the ethnically homogeneous Turkish population limits generalizability to other demographic groups with different genetic backgrounds and cardiovascular risk profiles. Evidence from other cohorts suggests that survival and HF progression may vary across ethnic groups; a Danish registry study comparing immigrants with native Danish patients with heart failure with reduced ejection fraction (HFrEF) found differences in comorbidities and outcomes that diminished after age- and sex-matching.[24] Therefore, the findings should be interpreted with caution when applied outside this setting. Our binary approach focused solely on biological sex, without evaluating gender identity, sexual orientation, or the broader gender spectrum. Limited LGBTI+ representation obscures health patterns relevant to these populations. Social determinants, including socioeconomic status, educational attainment, and cultural factors, were not systematically assessed. Additionally, patient-reported quality-of-life outcomes were not included in this study, which could have provided additional context for LVAD decision-making.

Conclusion

Female sex was associated with a significant reduction in LVAD requirement in advanced HF without demonstrating differences in overall mortality. These findings indicate that heart failure may progress through distinct pathophysiological pathways in women, highlighting the importance of developing tailored clinical evaluation approaches. For female patients, mechanical support decisions should incorporate comprehensive evaluations that account for unique complication profiles and pathophysiological differences, thereby contributing to improved patient safety and optimized clinical outcomes. Prospective multicenter studies are warranted to further validate these observations and guide clinical practice.

Ethics Committee Approval: Ethics committee approval was obtained from Koşuyolu High Specialization Training and Research Hospital (Approval Number: 2025/12/1199, Date: 22.07.2025).

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Appendix 1

Post-hoc Power Analysis

Post-hoc power analysis was performed using the powerSurvEpi R package.[1] For LVAD implantation, based on 66 events among 522 patients and a hazard ratio of 0.125, the study had nearly 100% power to detect sex differences. For the composite outcome of LVAD implantation, heart transplantation, or death, based on 165 events and a hazard ratio of 0.527, the post-hoc power was 86.1%, indicating sufficient sensitivity to detect sex-related effects. Mortality alone had fewer events, resulting in lower power, which explains why sex differences were not statistically significant for this endpoint.

Missing Data Handling

Dataset and Missingness Overview

The analysis dataset comprised 522 patients with advanced heart failure and approximately 50 clinical, laboratory, echocardiographic, hemodynamic, and exercise testing variables. Overall, 7.9% of the data were missing. The pattern of missing data across patients and variables was visualized using a heatmap, where red indicates missing values and blue indicates observed values.

Assumption

Missing values were assumed to be missing completely at random (MCAR), based on the distribution and lack of systematic patterns in observed data.

Imputation Method

Imputation was performed using the MissForest algorithm (from the missForest R package). MissForest is a non-parametric method based on random forests that can handle mixed-type data (continuous and categorical variables) and accounts for non-linear relationships.[2] This approach iteratively predicts missing values for each variable using other observed variables until convergence is achieved.

References

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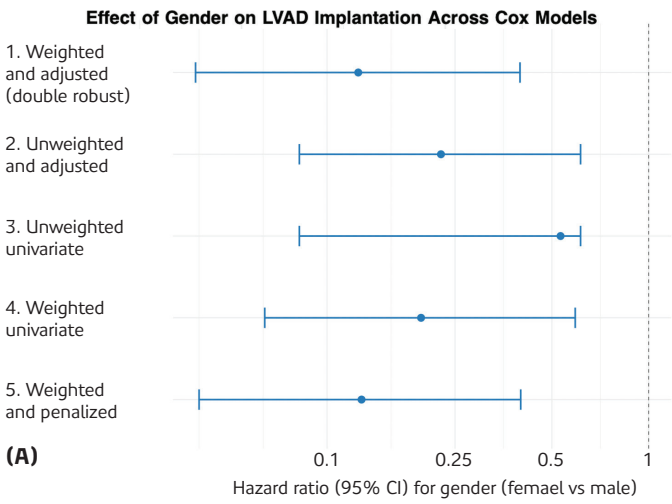
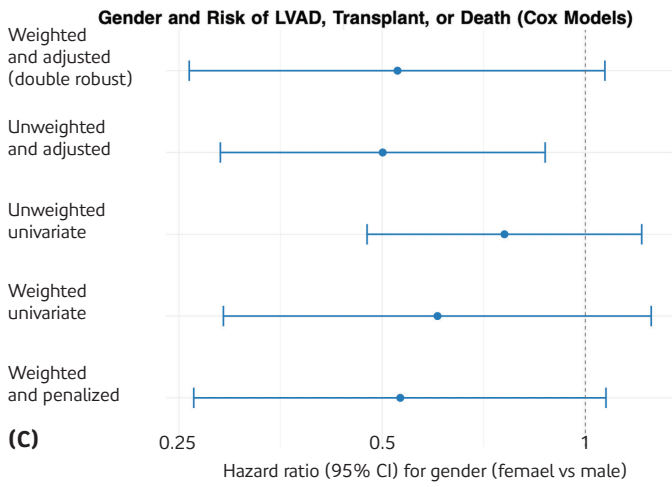
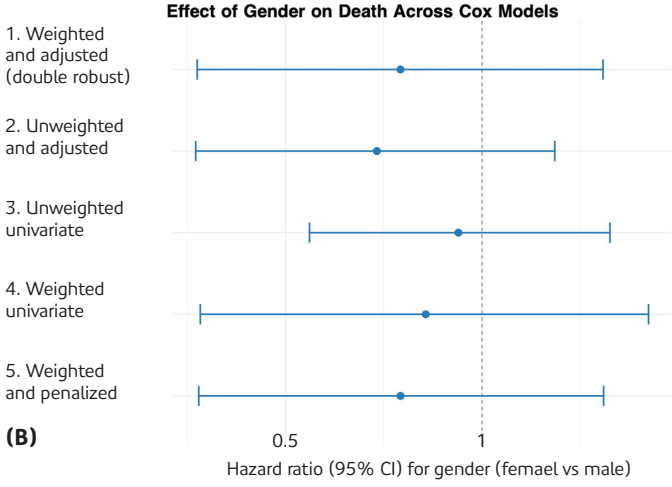
Appendix 2. Standardized mean differences (smd) of covariates by sex after inverse probability weighting

Covariate	Type	Adjusted SMD
Age	Continu-ous	-0.181
Ischemic	Binary	-0.080
LVEF	Continu-ous	0.129
MR grade	Continu-ous	-0.038
TR grade	Continu-ous	0.045
LVDD	Continu-ous	-0.044
Creatinine	Continu-ous	-0.045
Hemoglobin	Continu-ous	-0.045
Peak VO_2	Continu-ous	-0.032
Hypertension	Binary	0.116
Diabetes mellitus	Binary	-0.118
Atrial fibrillation	Binary	0.035
Hyperlipidemia	Binary	0.069
Chronic kidney disease	Binary	-0.004
Smoker	Binary	-0.046
COPD	Binary	-0.010
PCI	Binary	-0.039
CABG	Binary	-0.056
ICD	Binary	0.039
CRT	Binary	-0.047

LVEF, Left ventricular ejection fraction; MR, Mitral regurgitation; TR, Tricuspid regurgitation; LVDD, Left ventricular diastolic dysfunction; Peak VO_2, Peak oxygen consumption; COPD, Chronic obstructive pulmonary disease; PCI, Percutaneous coronary intervention; CABG, Coronary artery bypass grafting; ICD, Implantable cardioverter defibrillator; CRT, Cardiac resynchronization therapy. Interpretation: ●SMD < 0.1: Negligible difference (excellent balance). ●SMD 0.1–0.2: Small difference (adequate balance). ●SMD > 0.2: Meaningful imbalance (inadequate balance).







Appendix 3. Forest plot demonstrating the effect of female sex on clinical outcomes across different Cox regression models. Forest plot panels display hazard ratios (HRs) and 95% confidence intervals for the effect of female sex (vs. male) on (A) LVAD implantation, (B) all-cause mortality, and (C) the composite outcome (LVAD, transplantation, or death), evaluated across five Cox regression models: unweighted univariate, unweighted multivariable, weighted univariate, weighted multivariable (doubly robust), and weighted penalized models. Panel A illustrates a consistently significant inverse association between female sex and LVAD implantation risk across all models. Panel B shows no significant association between sex and mortality. Panel C suggests a nonsignificant trend toward lower composite event risk in female patients. These consistent findings across diverse modeling approaches reinforce the robustness of the observed sex-based difference in LVAD implantation.