

Original Article

Gender disparities and cardiovascular/transplant associated outcomes of heart transplant: national readmission database transplant cohort

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Abstract: Objective: There has been an exponential increase in heart transplantation volumes over the last decade due to advancements in the treatment of refractory heart failure (HF). However, the data regarding gender disparities in transplant outcomes are variable and limited. We aim to evaluate the gender-based outcomes of HF patients undergoing cardiac transplant. Methods: The national readmission database (NRD) for 2016 to 2020 was queried to assess the outcomes after cardiac transplant. The cohorts were divided by gender, and statistical analysis was performed using Stata v. 18. Results: 91,358 hospitalizations for post-heart transplant patients occurred during the study period. 62,435 (69%) patients were males, while 28,923 (31%) were females. In the propensity-matched (PSM) analysis, males had higher rates of congestive heart failure (26.7% vs. 22.9%, $P<0.001$) and vasculopathy (0.4% vs. 0.2%, $P=0.004$), while females had higher rates of acute kidney injury (34.6% vs. 33.2%, $P=0.012$). There was no significant difference in in-hospital mortality between the groups (2.06% vs. 1.77%, $P=0.072$). Median length of stay was 4 days in both groups, with a statistically significant overall difference ($P=0.017$), and total hospital charges were higher in males (\$46,122 vs. \$41,969, $P<0.001$). Conclusion: In cardiac transplant recipients, females had lower adjusted odds of in-hospital mortality in multivariable analysis (aOR 0.83, 95% CI 0.70-0.98; $P=0.034$), although this difference was not statistically significant in the propensity-matched analysis. Females had higher rates of AKI, while males more commonly developed HF and vasculopathy.

Keywords: Cardiac transplant, heart failure, nationwide readmission database, gender disparities, women's health

Introduction

Approximately 6.7 million Americans over 20 years of age have heart failure (HF), and the prevalence is expected to rise to 8.5 million Americans by 2030 [1]. The lifetime risk for developing HF is around 24% [2]. Despite achieving a significant leap in the treatment of end-stage heart disease, a considerable number of patients facing refractory heart failure, progressive angina, or uncontrolled ventricu-

lar arrhythmias cannot achieve stabilization through medical, interventional, or surgical approaches, resulting in substantial morbidity and mortality. Heart transplantation remains the gold standard treatment for end-stage heart disease, offering an improved quality of life and higher survival rate for patients refractory to optimal treatments [3, 4].

Consequently, the volume of heart transplants increased by 67.4% from 2010 to 2021. How-

ever, the more frequent transplant recipients in 2021 were the elderly white male population, and only a third of the transplants were allocated to women [2, 5]. Risk factors predictive of post-transplant mortality include recipient characteristics such as age, prior cardiac surgery, etiology (congenital and amyloidosis), diabetes, and hospitalization at the time of transplantation. Donor risk factors include donor-heart ischemic time, heart transplant sex-mismatch, hepatitis C status, insulin-dependent diabetes, and age [6]. The gender disparities have been noted in clinicopathological variabilities and treatment recommendations for HF patients. Recent statistics indicate higher mortality in women on the transplant list than in men [7, 8]. Post-transplant median survival for men is 11.4 years and for women 12.2 years, based on the International Society for Heart and Lung Transplant (ISHLT) data [9]. However, conflicting results have been reported in previous studies, which noted a higher rejection rate in females [1, 3, 4].

The causal mechanisms underlying these gender differences are unclear and warrant investigation. Most prior studies have focused on the gender disparities in donor and recipient characteristics. Our study aims to delineate and highlight transplant outcomes between men and women to understand this dilemma better.

Methods

Data source

The Nationwide Readmission Database (NRD) is an all-payer inpatient database in the United States. The data is obtained from 97% of the US population, including 48 states and the District of Columbia. NRD is maintained by the Agency for Healthcare Research and Quality (AHRQ) [10]. It is a nationally representative administrative database of the United States comprising annual discharge and readmission records of around 7 million hospital stays. This database contains de-identified information for each hospitalization, including demographics, admission status, comorbidities, discharge diagnoses, procedures, insurance payer, and hospitalization cost. However, patients admitted under observation status, long-term non-acute care hospitals, short-term rehabilitation hospitals, psychiatric hospitals, and alcohol or

chemical dependency units are omitted. Our study cohorts were derived from the NRD database from 2016 to 2020. Since NRD uses de-identified hospital data with prior ethical committee approval, no additional institutional review board (IRB) approval was required for the present analysis.

Study design and population

International Classification of Diseases, Tenth Edition, Clinical Modification Procedural Codes (ICD-10-PCS) were used to select patients with a history of cardiac transplant. ICD-10-CM codes used to identify the study population and primary and secondary outcomes are included in [Table S1](#).

We identified adult patients (age ≥ 18 years) with a history of cardiac transplantation using the ICD-10-CM diagnosis code Z94.1 between 2016 and 2020. All-cause hospitalizations during this period were included.

Exclusion criteria included: 1. Patients younger than 18 years, 2. Hospitalizations with missing key demographic data (age or sex), 3. Admissions from facilities not included in the NRD (e.g., rehabilitation hospitals, psychiatric hospitals, long-term non-acute care facilities), and 4. Hospitalizations lacking valid patient linkage numbers required for readmission analysis. Admissions involving cardiac transplantation during the same hospitalization were not included, as the Z94.1 code identifies transplant status rather than transplant procedure. Patients were stratified into two groups based on biological sex: men and women. We analyzed baseline patient characteristics (i.e., age, sex, and patient comorbidities) and hospital characteristics (including bed size, teaching status, and urban-rural designation).

Study outcomes

The primary outcome was in-hospital mortality, defined as death during the index hospitalization as recorded in NRD discharge disposition variables. Secondary outcomes included acute kidney injury (AKI), congestive heart failure (CHF), stroke, transplant rejection, transplant infection, and cardiac allograft vasculopathy. These outcomes were identified using ICD-10-CM diagnosis codes detailed in [Table S1](#), and their definitions are provided in [Table S2](#). All outcomes were assessed during the index hos-

pitalization unless otherwise specified. Resource utilization measures included length of stay (days), total hospital charges, and hospitalization costs. Cost estimates were adjusted for national inflation. Readmission outcomes were evaluated at 30, 90, and 180 days using validated NRD patient linkage variables.

Statistical analysis

Descriptive statistics were used to summarize continuous and categorical variables. Histograms assessed Gaussian normality and Kernel Density to determine whether the population was normally distributed ([Figure S1](#)). Our data were negatively skewed, with a leptokurtic histogram; the median with interquartile range (P25-P75) was used for continuous variables. Binary data were compared using Pearson's χ^2 test. Non-parametric trend analyses used the Jonckheere-Terpstra test or the Cochran-Armitage test after fitting the test. An unadjusted analysis of cardiovascular outcomes was performed using the Chi-Square test on an unmatched cohort. Two methodologies were used: multivariate logistic regression using the melogit model to rule out confounding factors and estimate measures of association (odds ratios, ORs) for cardiovascular outcomes, and propensity score matching to limit further confounding. A Propensity Score Matching-2 (PSM-2) model using nearest-neighbor matching was applied. PSM scores were plotted as box plots to compare the crude and matched cohorts. Pearson's χ^2 test was applied to the PSM-2 matched cohort to compare outcomes. Inverse probability weighting (IPW) matching was used to create the graphical box plot of propensity scores ([Figure S2](#)). Covariates included in the multivariate regression and PSM are listed in [Tables S3](#) and [S4](#). Yearly trend and readmission analyses were also performed using inferential statistics from Pearson's chi-square. All statistical tests were two-sided, and a p -value <0.05 was considered statistically significant. Confidence intervals were calculated at the 95% level. Kaplan-Meier survival curves displayed mortality over time ([Figure S3](#)). The total cost was adjusted for both national inflation and insurance adjustments for out-of-pocket costs. All analyses were conducted using appropriate stratifying, clustering, and weighting samples provided by the Healthcare Cost and Utilization Project regulations. STATA v.18 software (Stata Corp, College Station, TX) was used

for all statistical analyses [11]. We used Bio-Render for the central illustration [12].

Results

Baseline characteristics and comorbidities

Among 91,358 cardiac transplant recipients hospitalized between 2016 and 2020, 62,435 (68.34%) were men, and 28,923 (31.66%) were women. There was no difference in age between men and women (63 vs. 54, $P=0.620$). Men had a higher prevalence of hyperlipidemia (53.1% vs. 43.2%, $P<0.001$), hypertension (58.7% vs. 46.7%, $P<0.001$), and smoking (31.3% vs. 18.2%, $P<0.001$). Obesity was reported in 11.4% of men and 12.7% of women ($P=0.007$). The rates of immunocompromised state (1.4% vs. 1.5%, $P=0.630$) and liver disease (2.2% vs. 2.0%, $P=0.178$) were similar between the two groups. Other baseline characteristics are presented in [Table 1](#).

Overall resource utilization

There was a statistically significant difference in median length of hospitalization [4 days (IQR: 5) vs. 4 days (IQR: 5), $P=0.017$], although the median length of stay was 4 days in both groups. Total charges [\$46,122 (IQR: 66,867) vs. \$41,969 (IQR: 58,657), $P<0.001$] were higher in males ([Table 2](#)).

Yearly readmission trends of resource utilization over 30 to 180 days

Between 2016-2020, hospitalization costs significantly increased in both males (within 30 days: \$12,269 vs. \$10,688, p -trend <0.001 ; within 90 days: \$13,135 vs. \$11,762, p -trend <0.001 ; and within 180 days: \$13,232 vs. \$11,762, p -trend <0.001) and females (within 30 days: \$12,471 vs. \$9,874, p -trend <0.001 ; within 90 days: \$12,949 vs. \$9,934, p -trend <0.001 ; and within 180 days: \$12,457 vs. \$10,384, p -trend <0.005). Length-of-stay trends were significant for males at 30, 90, and 180 days ($P=0.0473$, $P=0.0149$, and $P=0.0450$, respectively) and for females at 90 days ($P=0.0342$), but not at 30 or 180 days ($P=0.0560$ and $P=0.5165$, respectively) ([Tables S5](#), [S6](#) and [S7](#)).

Univariate and multivariate matched analysis

Women had lower odds of in-hospital mortality (uOR 0.66, 95% CI 0.56-0.78), AKI (uOR 0.87,

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Table 1. Baseline characteristics and comorbidities

Baseline Characteristics	Male (n=62,435) (69%)	Female (n=28,923) (31%)	P-Value
Calendar Year			0.7924
2016	12,608.3 (20.2%)	5606.6 (19.4%)	
2017	12,798 (20.5%)	5755.82 (20.0%)	
2018	12592.2 (20.2%)	6025.49 (21.0%)	
2019	13040.9 (21%)	6150.76 (21.3%)	
2020	11395.4 (18.2%)	5384.43 (18.6%)	
Mean Age (Years)	63 (21)	54 (41)	0.62
Payer Type			<0.001
Medicare	39,005 (62.5%)	14,460.1 (50.0%)	
Medicaid	6,882.59 (11.0%)	6,185.92 (21.4%)	
Private	14,477.2 (23.21%)	7,392.2 (25.6%)	
Self-pay	440.57 (0.7%)	249.56 (0.9%)	
No charge	39 (0.1%)	17 (0.1%)	
other	1508.65 (2.4%)	598.56 (2.1%)	
Hospital Bed Size			0.368
Small	4,381.18 (7%)	1,887.25 (6.5%)	
Medium	9,937.78 (15.9%)	4,999.95 (17.3%)	
Large	48,115.8 (77.1%)	22,035.9 (76.2%)	
Location/teaching status of hospital			<0.005
Large metropolitan	45,824 (73.4%)	22,131.5 (76.5%)	
Small metropolitan	15,055 (24.1%)	6,219.53 (21.5%)	
micropolitan	1,125.33 (1.8%)	417.28 (1.4%)	
Not metropolitan	430.45 (0.7%)	154.79 (0.5%)	
Teaching status of urban hospitals			<0.001
Metropolitan	5,619.4 (9.0%)	1,965.18 (6.8%)	
Metropolitan	55,259.6 (88.5%)	26,385.8 (91.2%)	
non-metropolitan	1,555.79 (2.5%)	572.07 (2.0%)	
Day of Admission			0.2566
Mon-Fri	50,258.3 (80.5%)	23,130.1 (80.0%)	
Sat/Sun	12,169.7 (19.5%)	5,791.53 (20.0%)	
Transfer flag indicating same-day events			0.0168
Not a transfer	58,980.3 (94.5%)	27,560.7 (95.3%)	
Two discharges from different hospitals	1,320.87 (2.1%)	550.38 (1.9%)	
Same day stay involving two discharges from different hospitals	679.31 (1.1%)	282.12 (1.0%)	
Same day stay involving two discharges at the same hospital	1,050.8 (1.7%)	362.48 (1.3%)	
Same day stay involving three or more discharges at the same or different hospitals	403.55 (0.6%)	167.44 (0.6%)	
Median household Income			<0.001
1 (\$1-\$49,999)	15,216.6 (24.4%)	8,371 (28.9%)	
2 (\$50,000-\$64,999)	16,816.2 (26.9%)	8,147.43 (28.2%)	
3 (\$65,000-\$85,999)	15,992.3 (25.6%)	6,913.01 (23.9%)	
4 (\$86,000+)	13,707.2 (22.0%)	5,168.91 (17.9%)	
A combined record involving rehab transfer			<0.001
Non transferred	61,391.8 (98.3%)	28,611 (98.9%)	
Transferred	1,042.96 (1.7%)	312.13 (1.1%)	
Patient's state is the same state as the hospital			0.2659
Non Resident	7,275.99 (11.7%)	3,199.39 (11.1%)	
Resident	55,158.8 (88.3%)	25,723.7 (88.9%)	
Ownership of hospital			<0.005
Government, nonfederal	7,628.93 (12.2%)	4,066.97 (14.1%)	
Private, non-profit	51,554.5 (82.6%)	23,657.1 (81.8%)	
Private, invest-own	3,251.33 (5.2%)	1,199.08 (4.1%)	

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Comorbidities			
HLD	33,170.6 (53.1%)	12,491 (43.2%)	<0.001
HTN	36,670.7 (58.7%)	13,517.8 (46.7%)	<0.001
Obesity	7,099.01 (11.4%)	3,668.37 (12.7%)	0.0071
Smoker	19,558.2 (31.3%)	5,287.56 (18.3%)	<0.001
Prior MI	7,045.48 (11.3%)	1,733.77 (6.0%)	<0.001
Prior PCI	3,268.67 (5.2%)	1,035.4 (3.6%)	<0.001
Prior CABG	3,985.15 (6.4%)	721.20 (2.5%)	<0.001
OSA	11,154.3 (17.9%)	2,984.5 (10.3%)	<0.001
Pulm disease	7,402.1 (11.9%)	2,405.78 (8.3%)	<0.001
Immunocompromised	879.65 (1.4%)	430.93 (1.5%)	0.6304
Hypothyroidism	8,702.38 (13.9%)	5,007.4 (17.3%)	<0.001
Anemia	4,131.27 (6.6%)	2,432.13 (8.4%)	<0.001
PNA	5,793 (9.3%)	2,343.01 (8.1%)	0.0014
Liver disease	1,384.25 (2.2%)	572.32 (2.0%)	0.1776

Table 2. Resource utilization: Adjusted charges for length of stay and total cost

Resource utilization	Male Median (IQR)	Female Median (IQR)	P-Value
LOS	4 (5)	4 (5)	0.017
Total cost	11345 (15,388)	10687 (13841)	<0.001
Adjusted charges	46122 (66,867)	41969 (58657)	<0.001

LOS=length of stay, IQR=interquartile range.

95% CI 0.82-0.92), stroke (uOR 0.59, 95% CI 0.43-0.80), and HF (uOR 0.82, 95% CI 0.76-0.89), but higher odds of failure/rejection (uOR 1.30, 95% CI 1.10-1.54). There was no difference in transplant infection (uOR 0.97, 95% CI 0.40-2.30) or vasculopathy (uOR 0.69, 95% CI 0.41-1.14) (**Table 3**).

After adjustment for baseline comorbidities, in-hospital mortality remained lower in women (aOR 0.83, 95% CI 0.70-0.98; $P=0.034$), while failure/rejection (aOR 1.24, 95% CI 1.04-1.47; $P=0.012$) was higher in women. There was no significant adjusted difference in AKI, stroke, HF, transplant infection, or vasculopathy (**Table 3** and **Figure S4**).

Propensity-matched outcomes

In the PSM2-matched analysis, the two groups did not differ in in-hospital mortality (2.06% vs. 1.77%, $P=0.072$). AKI was higher in women (34.6% vs. 33.2%, $P=0.012$), whereas CHF (26.7% vs. 22.9%, $P<0.001$) and vasculopathy (0.40% vs. 0.21%, $P=0.004$) were higher in men (**Figures 1 and 2; Table 4**). Among patients who were readmitted, males accounted for 67.5% of readmissions within 30 days, 68.0% within 90 days, and 67.59% within 180 days,

compared with 32.4%, 32.3%, and 32.40% for females, respectively ($P=0.0473$, $P=0.0149$, and $P=0.0450$, respectively) (**Table S8**).

Yearly trends of adverse outcomes

Between 2016 and 2020, males with cardiac transplant had a significant increase in deaths (3.44% vs. 2.67%, $p\text{-trend}=0.038$) and heart failure rates (27.38% vs. 23.02%, $p\text{-trend}<0.01$). Females had a significant increase in heart failure rates (23.30% vs. 20.31%, $p\text{-trend}=0.004$) and AKI (38.74% vs. 30.54%, $p\text{-trend}<0.01$) (**Figures 3 and 4; Table 5**). The yearly mortality trend in females was not statistically significant ($p\text{-trend}=0.070$).

Discussion

In our extensive retrospective study using the NRD, we identified 91,358 all-cause hospitalizations among patients with a history of cardiac transplant from 2016 to 2020. The primary objective was to assess gender-based disparities in the clinical outcomes of these hospitalizations.

The key findings of our study are as follows: (1) Female patients with a history of cardiac transplant had lower adjusted odds of mortality in multivariable analysis, although this difference was not statistically significant in the propensity-matched analysis. (2) Females were more prone to AKI, while males more commonly developed CHF and vasculopathy. (3) Males demonstrated significantly higher resource uti-

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Table 3. Adjusted and unadjusted outcomes on regression analysis in gender-based heart transplant patients

Outcome	ULR				MLR			
	uOR	Lower CI	Upper CI	P-value	aOR	Lower CI	Upper CI	P-value
In-hospital mortality	0.66	0.56	0.78	<0.001	0.83	0.70	0.98	0.034
AKI	0.87	0.82	0.92	<0.001	1.00	0.95	1.06	0.839
Acute stroke	0.59	0.43	0.80	<0.001	0.75	0.55	1.03	0.081
HF	0.82	0.76	0.89	<0.001	1.00	0.94	1.07	0.89
Failure rejection	1.30	1.10	1.54	<0.001	1.24	1.04	1.47	0.012
Transplant infection	0.97	0.40	2.3	0.953	0.94	0.39	2.29	0.907
Vasculopathy	0.69	0.41	1.14	0.153	0.85	0.52	1.39	0.52

Abbreviations: uOR: unadjusted odds ratio; CI: confidence interval; ULR: univariate regression; MLR: multivariate regression; aOR: adjusted odds ratio; AKI: acute kidney injury; HF: heart failure.

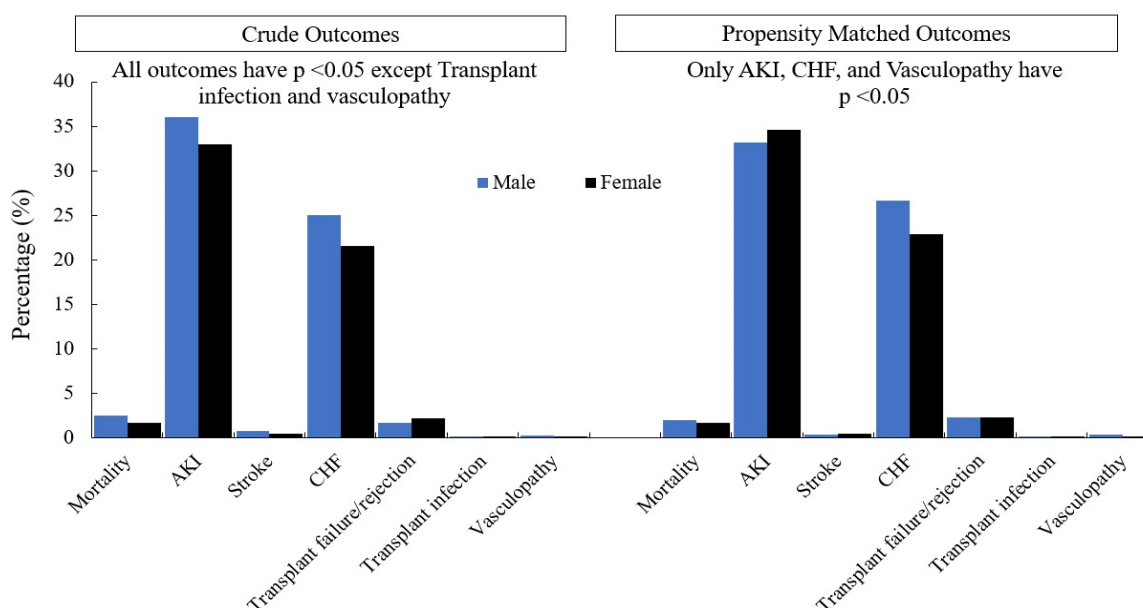


Figure 1. Crude and Propensity-matched outcomes. Abbreviations: AKI: acute kidney injury; CHF: congestive heart failure.

lization, including total hospital charges, than females.

Although pre-transplant survival in advanced heart failure tends to be worse in females as compared to males, likely due to lower organ allocation and higher waitlist mortality in United Network for Organ Sharing (UNOS) status 1A and 1B [13], post-transplant survival appears to be better [9]. Our study found lower adjusted odds of in-hospital mortality among female cardiac transplant recipients in multivariable analysis; however, this difference was not statistically significant in the propensity-matched analysis. The mortality association should therefore be interpreted in the context of the

different analytical approaches. This difference may be related to the lower burden of some comorbidities among females. Complications following a heart transplant may vary depending on the time elapsed since transplantation. These complications can be related to the graft itself or may indicate systemic dysfunction, potentially due to the side effects of immunosuppressive medications and the progression of pre-existing conditions [14].

Previous studies, such as The NEW HEART study, have reported a higher incidence of transplant rejections in females [8]. The elevated rejection rate, in part, was attributed to increased sensitization in females. Sensitization is a

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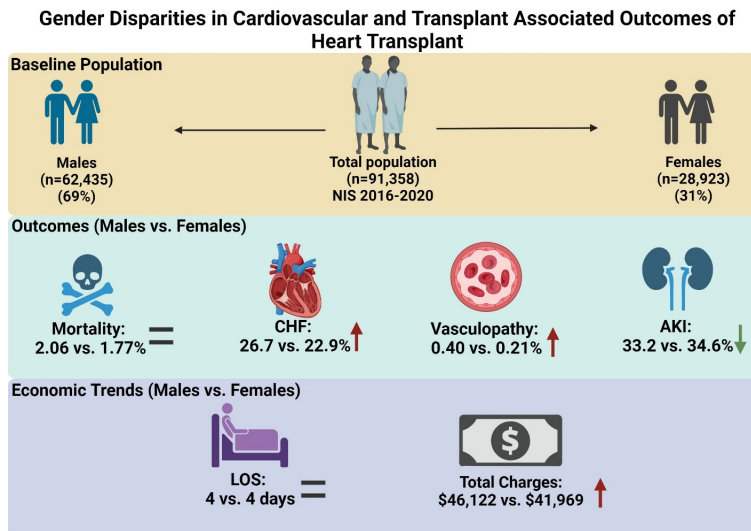


Figure 2. Central illustration. Abbreviations: = : no significant difference; ↑: higher rates in males; ↓: lower rates in males; CHF: congestive heart failure; AKI: acute kidney injury; LOS: length of stay.

process in which antibodies form against the human leukocyte antigen (HLA), potentially arising from prior pregnancies, consequently increasing the risk of post-transplant rejection [15]. Another large cohort study involving 8,160 cardiac transplants by Nwakanma et al. also reported similar outcomes [16]. Graft rejection itself is a predictor for the development of acute heart failure. Reperfusion injury and procurement-related damage to the donor's heart may lead to massive release of free radicals and inflammatory responses, leading to myocardial damage, leading to systolic and or diastolic dysfunction of both ventricles [14]. Moreover, primary graft failure is a well-recognized complication that results in severe mechanical dysfunction requiring inotropic agents or mechanical circulatory support (MCS) and is not due to graft rejection [17, 18]. The development of heart failure, either triggered by graft rejection or primary graft failure, may require the use of MCS modalities, contribute to the development of AKI, extend the Intensive Care Unit (ICU) stay, and increase resource utilization, thereby complicating the hospital course [19]. Our study revealed a similar rate of transplant rejection in men and women, but significantly higher rates of CHF were seen in men. This opens the discussion of current theories and encourages future studies to examine rejection rates further.

Several pre-operative risk factors associated with the development of AKI include diabetes,

chronic kidney disease (CKD), and older age [20-24]. These factors are usually lower in females. However, our study reveals a higher rate of AKI in females. The increased incidence of AKI in females is likely linked to the higher rates of cardiac dysfunction observed post-cardiac transplant in females.

The functions of the heart and kidney are intricately interconnected. Dysfunction of one organ system can profoundly impact the other, giving rise to what is termed "cardiorenal syndromes" [19]. Kidney dysfunction can develop secondary to reduced renal blood flow, renin-angiotensin-aldosterone system (RAAS)-induced renal vasoconstriction, renal hypoxia, and acute tubular necrosis [19]. Also, worsening renal function can develop due to elevated right atrial pressure, as demonstrated in ADHERE and ESCAPE trials [25-28]. Prolonged ICU stay is itself a contributor to AKI through mechanisms such as acute tubular necrosis, interstitial nephritis, abdominal compartment syndrome, and urinary retention [29, 30]. AKI has been well recognized as an independent predictor of prolonged hospital stay [31, 32]. Despite this, the median hospitalization length was 4 days in both males and females in our study, although the overall distribution differed statistically. Total costs were significantly higher in males, for reasons that remain unidentified. Recent registry and meta-analytic data continue to demonstrate sex-specific differences in heart transplantation outcomes, although these associations vary by donor sex, recipient age, and clinical context [33-35].

Limitations

Before interpreting our findings, we must acknowledge several limitations in our study. The identification of hospitalizations with post-cardiac transplant status relied on the "Z94.1" ICD-10-CM code, which lacks information about the timing of the transplant. Moreover, the analysis likely did not include acute complications during the transplant procedure, as those admissions would not be coded with

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Table 4. Crude and propensity matched in-hospital outcomes of gender-based heart transplant

Outcomes	Crude Outcomes			Propensity Match Outcomes		
	Male	Female	P value	Male	Female	P value
	N=62,435	N=28,923		N=14,469	N=14,469	
	N (%)	N (%)		N (%)	N (%)	
Inpatient Mortality	1,539 (2.5%)	479 (1.7%)	<0.001	298 (2.06%)	256 (1.77%)	0.072
AKI	22,480 (36%)	9,553 (33%)	<0.001	4,804 (33.2%)	5,006 (34.6%)	0.012
Stroke	497 (0.8%)	137 (0.5%)	0.001	64 (0.44%)	75 (0.52%)	0.350
CHF	15,593 (25%)	6,242 (21.6%)	<0.001	3,868 (26.7%)	3,304 (22.9%)	<0.001
Transplant failure/rejection	1,066 (1.7%)	643 (2.2 %)	0.001	332 (2.29%)	336 (2.32%)	0.876
Transplant infection	42 (0.1%)	19 (0.1%)	0.953	NR (0.03%)	11 (0.1%)	0.071
Vasculopathy	158 (0.3 %)	51 (0.2%)	0.151	57 (0.4%)	30 (0.21%)	0.004

Abbreviations: CHF: Congestive Heart Failure; AKI: Acute kidney injury; NR: not reportable due to data suppression.

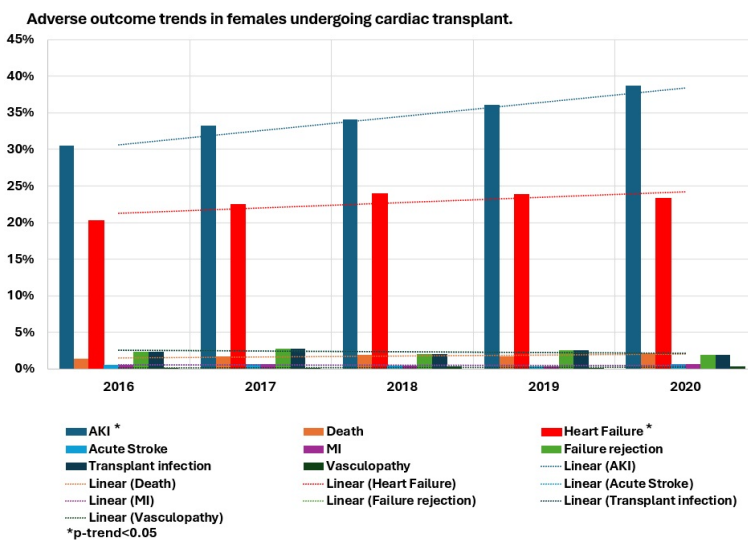


Figure 3. Trends of adverse outcomes in females.

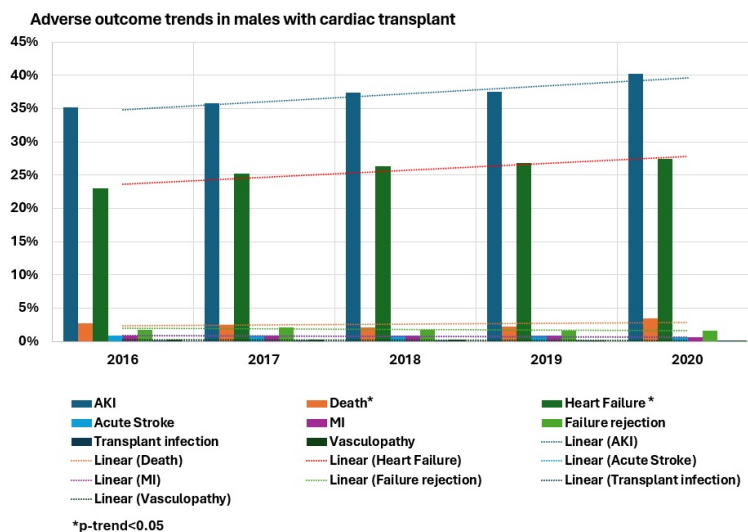


Figure 4. Trends of adverse outcomes in males.

“Z94.1”. Our data, which depends on ICD codes, is susceptible to human error. The presence of confounding bias stemming from unmeasured variables may have influenced the study outcomes.

It is important to note that our observational study can establish associations, but causality cannot be definitively established. NRD lacks information on medication compliance, so an important data element affecting outcomes is missing. Our ability to assess only in-hospital outcomes of post-cardiac transplant hospitalizations, coupled with the lack of data on emergency and out-of-hospital cardiac events, further restricts the scope of our investigation. Despite these limitations, the strength of our study lies in the size of the database, which enables us to derive nationwide estimates and partially mitigate potential constraints.

Conclusion

Our study indicates that female cardiac transplant recipients had lower adjusted odds of in-hospital mortality in multivariable analysis, although the mortality difference was not statistically significant in the

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Table 5. Overall outcomes in the years 2016-2020

Variables	Sex		Calendar year					p-trend
			2016	2017	2018	2019	2020	
Transplant	Male	Count	12608	12798	12592	13041	11395	
% within a Calendar year			69.22%	68.98%	67.63%	67.95%	67.91%	
	Female	Count	5607	5756	6026	6151	5384	
% within a Calendar year			30.78%	31.02%	32.37%	32.05%	32.09%	
Death	Males	Count	167	165	137	158	212	0.038
% within a Calendar year			2.67%	2.48%	2.06%	2.29%	3.44%	
	Females	Count	36	49	56	52	59	0.070
% within a Calendar year			1.38%	1.72%	1.91%	1.67%	2.14%	
AKI	Males	Count	2204	2393	2498	2593	2484	0.289
% within a Calendar year			35.18%	35.78%	37.38%	37.52%	40.18%	
	Females	Count	817	962	1015	1127	1083	<0.01
% within a Calendar year			30.54%	33.21%	34.05%	36.13%	38.74%	
Heart Failure	Males	Count	1442	1685	1757	1850	1693	<0.01
% within a Calendar year			23.02%	25.20%	26.30%	26.77%	27.38%	
	Females	Count	543	652	714	743	651	0.004
% within a Calendar year			20.31%	22.52%	23.94%	23.83%	23.30%	
Acute Stroke	Males	Count	53	59	56	58	36	0.105
% within a Calendar year			0.86%	0.89%	0.84%	0.84%	0.59%	
	Females	Count	14	17	14	9	17	0.593
% within a Calendar year			0.56%	0.62%	0.50%	0.32%	0.61%	
MI	Males	Count	53	59	55	57	36	0.105
% within a Calendar year			0.86%	0.89%	0.83%	0.83%	0.59%	
	Females	Count	14	17	14	9	17	0.593
% within a Calendar year			0.56%	0.62%	0.50%	0.32%	0.61%	
Failure rejection	Males	Count	111	140	113	110	98	0.085
% within a Calendar year			1.78%	2.10%	1.70%	1.60%	1.60%	
	Females	Count	62	79	59	79	52	0.221
% within a Calendar year			2.32%	2.75%	2.01%	2.56%	1.89%	
Transplant infection	Males	Count	2	4	4	5	2	0.995
% within a Calendar year			0.04%	0.06%	0.07%	0.08%	0.03%	
	Females	Count	0	4	3	2	2	0.720
% within a Calendar year			0%	0.13%	0.10%	0.06%	0.07%	
Vasculopathy	Males	Count	14	15	19	12	10	0.355
% within a Calendar year			0.23%	0.23%	0.29%	0.18%	0.17%	
	Females	Count	3	5	10	3	9	0.234
% within a Calendar year			0.11%	0.17%	0.33%	0.09%	0.32%	

propensity-matched analysis. Females had higher AKI rates, while men had higher CHF and vasculopathy rates. Men had higher hospitalization-related costs. Further studies are needed to establish causality, reduce complications, and optimize post-cardiac transplant care.

Disclosure of conflict of interest

None.

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Gender-based cardiac transplant outcomes

Table S1. ICD-10 codes for cohort identification and comorbidities

Study variables	ICD-10 Code
Post Procedural Bleeding	I97418, I9742, I97618, I97620, I97638, I97631, I97621, I9742, I97418, I97411, I97611, I97410, I97610, I97630, I97410
Vascular Complications	S15, S25, S35, S55, S65, S75, S85, T817, T8183XA, T8183XS, I770, I97621, I97630, I97631, I97638
AKI	N170, N171, N172, N178, N179, N1
Cardiogenic Shock	R570
Prior MI, PCI, and CABG	I252, Z955, Z951
Obesity	E66, Z683, Z684, R939, Z6854, 09921
Coronary Artery Disease	I2510, I25111, I25118, I25119, I252, I253, I254, I2541, I2542, I255, I256, I257, I2570, I25700, I25701, I25708, I25709, I2571, I25710, I25711, I25718, I25719, I2572, I25720, I25721, I25728, I25729, I2573, I25730, I25731, I25738, I25739, I2575, I25750, I25751, I25758, I25759, I2576, I25760, I25761, I25768, I25769, I2579, I25790, I25791, I25798, I25799, I258, I2581, I25810, I25811, I25812, I2582, I2583, I2584, I2589, I259
Hypertension	I10, I1150, I1151, I1152, I1158, I1159
Diabetes Mellitus	E08-E13 family
Alcohol use	F101, F1010, F1011, F1012, F10120, F10121, F10129, F1014, F1015, F10150, F10151, F10159, F1018, F10180, F10181, F10182, F10188, F1019, F102, F1020, F1021, F1022, F10220, F10221, F10229, F1023, F10230, F10231, F10232, F10239, F1024, F1025, F10250, F10251, F10259, F1026, F1027, F1028, F10280, F10281, F10282, F10288, F1029, F10920, F10921, F10929, F1094, F1095, F10950, F10951, F10959, F1096, F1097, F1098, F10980, F10981, F10982, F10988, F1099
Atrial fibrillation/flutter	I48 family
Heart failure	I50, I501, I502, I5020, I5021, I5022, I5023, I503, I5030, I5031, I5032, I5033, I504, I5040, I5041, I5042, I5043, I508, I5081, I50810, I50811, I50812, I50813, I50814, I5082, I5083, I5084, I5089, I509
Chronic obstructive pulmonary disease	J449
Smoker	F17, Z87.891
Chronic kidney disease stage ≥ 3	N183, N184, N185, E082, E132, I12, I13
ESRD	N186, Z992, Z4931, Z4901
Anemia	D50, D51, D52, D53, D55, D56, D57, D58, D59, D60, D61, D62, D63, D64, D46.0, D46.1, D46.2, D46.4, 099.0
Obstructive sleep apnea	G47.33
History of stroke	I69.3, Z86.73
Peripheral vascular disease	E08.5, E09.5, E10.5, E11.5, E13.5, I73, T82.856, Z98.62, Z95.820, I25.2, I25.83

All codes are available at "<https://www.icd10data.com/>".

Gender-based cardiac transplant outcomes

Table S2. Definition of major outcomes

Outcomes	Definition
Mortality	All causes of death, including cardiovascular causes such as sudden cardiac death, death due to acute myocardial infarction, heart failure or cardiogenic shock, and non-cardiovascular causes.
AKI	Any acute kidney injury in transplant patients during the hospital stay.
Cardiogenic Shock	Shock resulting from primary failure of the heart in its pumping function, as in myocardial infarction, severe cardiomyopathy, mechanical obstruction, or compression of the heart.
Post Procedural Bleeding	Any major bleeding or hematoma during or after the procedure.
Vasculopathy	Generalized or systemic disease that affects blood vessels, leading to structural and functional abnormalities.
Transplant Failure/Rejection	Any cardiac transplant failure or rejection during index of hospitalization.
LOS	The entire length of stay the patient spent in the hospital during the admission.
Cost of hospitalization	The total adjusted amount that hospitals billed for their services for the duration of hospitalization.

Abbreviations: LOS: Length of Stay; AKI: Acute Kidney Injury.

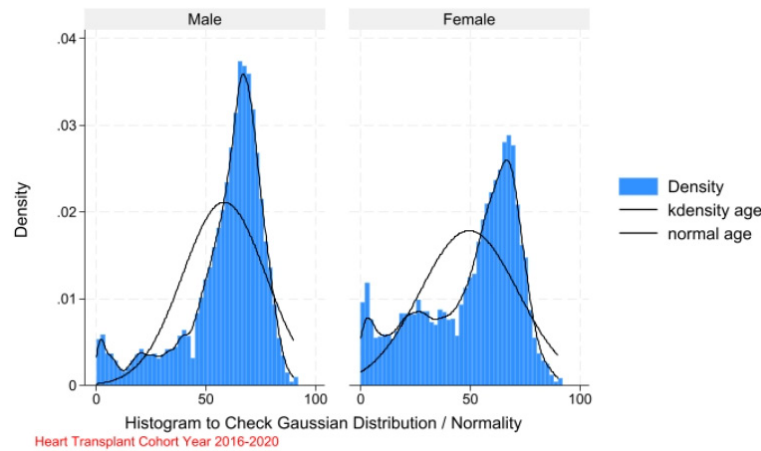


Figure S1. Distribution of data with histogram analysis.

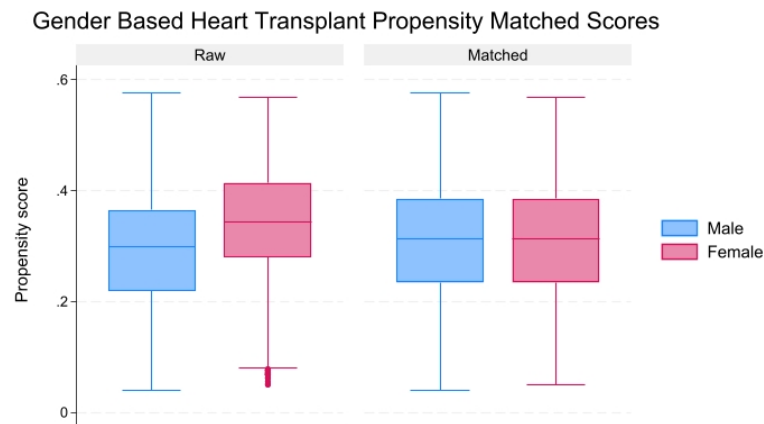


Figure S2. Graphical box plot for propensity scores.

Gender-based cardiac transplant outcomes

Table S3. Variables used for PSM2 matching

Variables included in Propensity Matching
Died during hospitalization
AKI
Stroke
CHF
Transplant failure/rejection
Transplant infection
Vasculopathy
Abbreviations: AKI: Acute kidney injury; CHF: Congestive heart failure.

Table S4. Variables used for multivariate regression

Variables included in Multivariate Regression Analysis
Died during hospitalization
AKI
Stroke
CHF
Transplant failure/rejection
Transplant infection
Vasculopathy
Abbreviations: AKI: Acute kidney injury; CHF: Congestive heart failure.

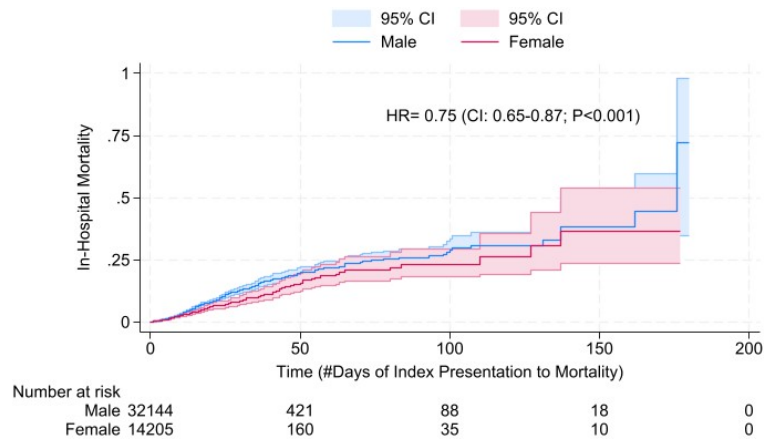


Figure S3. Kaplan-Meier survival estimates.

Table S5. Resource utilization within 30 days per calendar year

Year	Total cost yearly trend		Length of stay yearly trend	
	Male Median (IQR)	Female Median (IQR)	Male Median (IQR)	Female Median (IQR)
2016	10688 (11,974)	9874 (11,193)	4 (4)	4 (4)
2017	9998 (12,512)	9674 (11,372)	4 (5)	4 (4)
2018	10975 (13,488)	11142 (13,633)	4 (5)	4 (4)
2019	11638 (14,408)	12007 (15,709)	4 (5)	4 (5)
2020	12269 (15,191)	12471 (15,926)	4 (4)	4 (4)
P-value	<0.001	<0.001	0.0473	0.0560

Gender-based cardiac transplant outcomes

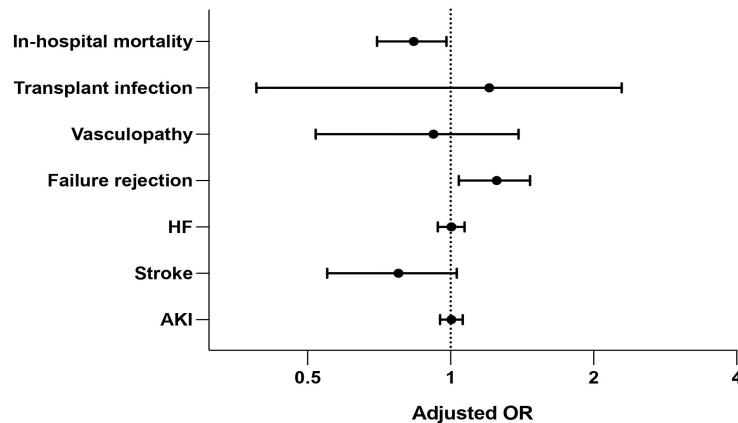
Table S6. Resource utilization within 90 days per calendar year

Year	Total cost yearly trend		Length of stay yearly trend	
	Male Median (IQR)	Female Median (IQR)	Male Median (IQR)	Female Median (IQR)
2016	11762 (13,800)	9934 (13,386)	4 (5)	4 (5)
2017	10929 (16,188)	10359 (12,975)	4 (6)	4 (5)
2018	12101 (15,653)	10628 (13,745)	5 (5)	4 (5)
2019	12897 (17,093)	11854 (15,688)	5 (6)	4 (5)
2020	13135 (17,386)	12949 (18,119)	4 (5)	5 (5)
P-value	<0.001	<0.001	0.0149	0.0342

Table S7. Resource utilization within 180 days per calendar year

Year	Total cost yearly trend		Length of stay yearly trend	
	Male Median (IQR)	Female Median (IQR)	Male Median (IQR)	Female Median (IQR)
2016	11762 (13,782)	10384 (13,616)	4 (5)	4 (5)
2017	10427 (14,878)	10153 (12,729)	4 (5)	4 (5)
2018	12116 (16,984)	10266 (12,216)	4 (6)	4 (5)
2019	12568 (16,789)	11341 (15,272)	5 (5)	4 (5)
2020	13232 (17,593)	12457 (18,402)	5 (5)	4 (5)
P-value	<0.001	<0.005	0.0450	0.5165

Adjusted outcomes of Multivariate regression analysis for gender-based heart transplant patients



Abbreviations: AKI: acute kidney injury; HF: heart failure;

Figure S4. Multivariate regression.

Table S8. Readmission in propensity-matched cohort

Readmission interval	Male	Female	P-value
Total readmissions	N=15,517	N=15,517	
Within 30 days	10,483 (67.5%)	5,033 (32.4%)	0.0473
Total readmissions	N=25,251	N=25,251	
Within 90 days	17,091 (68.0%)	8,161 (32.3%)	0.0149
Total readmissions	N=22,674	N=22,674	
Within 180 days	15,327 (67.59%)	7,347 (32.40%)	0.0450