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Gender Differences in Mortality After Left Ventricular Assist Device Implant: A Causal Mediation Analysis Approach

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We used the International Society for Heart and Lung Transplantation (ISHLT) Registry for Mechanically Assisted Circulatory Support (IMACS) database to examine 1) gender differences in post-left ventricular assist device (LVAD) mortality in the contemporary era and 2) preimplant clinical factors that might mediate any observed differences. Adults who received continuous-flow (CF)-LVAD from January 2013 to September 2017 (n = 9,565, age: 56.2 ± 13.2 years, 21.6% female, 31.1% centrifugal pumps) were analyzed. An inverse probability weighted Cox proportional hazards model was used to estimate association of female gender with all-cause mortality, adjusting for known covariates. Causal mediation analysis was performed to test plausible preimplant mediators mechanistically underlying any association between female gender and mortality. Females had higher mortality after LVAD (adjusted hazard ratio [HR]: 1.36; $p < 0.0001$), with significant gender × time interaction ($p = 0.02$). An early period of increased risk was identified, with females experiencing a higher risk of mortality during the first 4 months after implant (adjusted HR: 1.74; $p < 0.0001$), but not after (adjusted HR: 1.18; $p = 0.16$). More severe tricuspid regurgitation and smaller left ventricular end-diastolic diameter at baseline mediated ≈21.9% of the increased early hazard of death in females; however, most of the underlying mechanisms remain unexplained. Therefore, females have increased mortality only in the first 4 months after LVAD implantation, partially driven by worsening right ventricular dysfunction and LV-LVAD size mismatch. *ASAIO Journal* 2020; XX:00–00.

Key Words: left ventricular assist device, heart failure, gender, disparity, mortality

Due to the constant shortage of donor organs available for heart transplantation (HT), surgical treatment of end-stage heart failure (HF) with a left ventricular assist device (LVAD) is used to bridge patients to HT (BTT) and as destination therapy (DT) for patients who are not suitable HT candidates. While LVADs are associated with improved survival, health-related quality of life and functional capacity compared with medical therapy alone[1]; important gender disparities in post-LVAD outcomes exist.[2]

The contemporary post-2013 LVAD era is characterized by higher overall survival for LVAD recipients,[3] as well as improved LVAD utilization in females due to the advent of smaller pumps.[2] While prior analyses of the Interagency Registry for Mechanical Circulatory Support (INTERMACS) and European Registry for Patients with Mechanical Circulatory Support (EUROMACS) have shown that females are at higher risk for post-LVAD mortality,[3,4] the majority of patients in these studies were implanted before 2013. Therefore, whether these differences persist in the contemporary era is unknown.[3,4] Additionally, there is a paucity of data on the underlying mechanisms for the observed differences,[3,4] compounded by the fact that most large multicenter LVAD trials lack sufficient numbers of females to draw strong conclusions.[1]

While several epidemiological studies iterate gender differences in HF development, pathophysiology, and outcomes;

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there are large critical gaps in knowledge of the underlying mechanisms.[5] Multiple gender-related attributes could account for the higher risk of mortality for women with HF, including genetic susceptibility, immunologic phenomena, drug pharmacokinetics, hormonal milieu, psychosocial risk factors, and cardiac structure. However, none of these factors have been explored as potential mechanisms of worse post-LVAD outcomes in females. We used the International Society for Heart and Lung Transplantation (ISHLT) Mechanically Assisted Circulatory Support (IMACS) database to 1) confirm any gender differences in post-LVAD mortality in the contemporary era and 2) determine which preimplant clinical factors might mediate any observed gender differences in mortality after LVAD.

METHODS

Database

Deidentified patient-level data were obtained from the IMACS Registry, which collects data from patients undergoing durable LVAD support in 35 countries across the globe. Sources of data include 4 large collectives: INTERMACS (The United States), EUROMACS (Europe), Japanese Registry for Mechanical Assisted Circulatory Support (Japan), and the United Kingdom Registry. In addition, 24 hospitals from Australia, Brazil, Colombia, Spain, Finland, Greece, Hong Kong, Ireland, Israel, Italy, Republic of Korea, New Zealand, Saudi Arabia, Singapore, Slovakia, Sweden, and Turkey provide data directly to the Registry. Data are uploaded yearly and merged into the registry for analysis. Single-country, single-collective, device brand, and race data are not available for analysis. This article was reviewed and approved by the IMACS Steering Committee and considered exempt from review by the Emory University Institutional Review Board.

Study Participants

Adults (≥18 years) who received continuous-flow (CF) LVAD from January 9, 2013, to September 30, 2017, were included in the study (n = 15,498). Among the 15,498 subjects, n = 5,933 had missing data in at least one covariate of interest. We performed analyses in both the complete-case analytic cohort (n = 9,565) as the primary results and the entire data set using multiple imputations (see below).

Outcomes

The primary outcome of interest was all-cause mortality. Primary cause of death is reported as collected in the IMACS database. Time to death was calculated from date of LVAD implantation, with patients censored at the time of transplantation and explant. The last date of follow-up was October 31, 2017.

Statistical Analysis

Baseline characteristics were summarized as mean ± standard deviation, median (interquartile range [IQR]), or as number (%), and the differences between males and females, as well as between the complete-case analytic cohort and those with missing data, were examined using two sample *t* test for normally distributed continuous variables, Mann–Whitney *U* test for non-normally distributed continuous variables, and χ^2 test for categorical variables.

Inverse probability weighting. Baseline covariates included in the logistic regression model for propensity scores were chosen based on prior literature examining gender differences in post-LVAD outcomes[2,6,7] and included age, body surface area (BSA), etiology of HF (ischemic *versus* nonischemic), pump type (centrifugal *versus* axial flow), cardiogenic shock at implant (INTERMACS profiles 1 and 2 *versus* profiles 3–7), serum sodium, blood urea nitrogen (BUN), total bilirubin, international normalized ratio (INR), hemoglobin, Modified End-Stage Liver Disease (MELD) score,[8] HeartMate II Risk Score (HMRS; calculated without modification for implant center volume[9] categorized as low [HMRS < 1.58], medium [1.58 ≤ HMRS ≤ 2.48], or high [HMRS > 2.48][9] risk), pulmonary artery diastolic pressure (PADP), and cardiac index (CI). Standardized mean differences in the covariates were computed for the weighted cohort to ensure balanced distribution of baseline covariates.[10] A difference of <0.10 was considered to be negligible.[11]

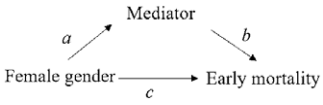
Survival analyses. Cox proportional hazards models were used to examine the association between gender and all-cause mortality. To control for potential confounding, we used doubly robust estimation based on the inverse probability weights as mentioned above.[12] Covariates included in the model were the aforementioned variables, and estimated glomerular filtration rate (eGFR; categorized according to chronic kidney disease [CKD] stage),[13] as well as gender × follow-up time interaction to examine time-varying hazard ratios (HRs). Restricted cubic splines were used to approximate the underlying hazard function to account for nonlinearity and guide the identification of a sensible landmark time. As a sensitivity analysis, a cause-specific Cox model was used to account for competing risk events (*i.e.*, transplantation) for BTT LVAD patients.[14]

Imputation of missing data. To minimize potential selection bias from missing data,[15] we performed multiple imputation (with 5 imputations) using the entire dataset (n = 15,498) as a sensitivity analysis to evaluate the robustness of our findings with regards to survival outcomes. Missing data were imputed using Multivariate Imputation by Chained Equations (MICE), followed by the aforementioned analysis procedure.[15] Values for MELD score,[8] HMRS,[9] and eGFR[13] were calculated from the imputed contributing covariates.[8,9,13] Final results were aggregated using Rubin's rules.[16]

Causal mediation analysis. Causal mediation analysis was used to examine whether the effect of gender on all-cause early mortality was mediated *via* plausible nontraditional preimplant mediators of increased mortality that were significantly different between genders.[17] Mediators were chosen based on prior literature hypothesizing reasons for observed gender disparities in HF outcomes.[5,18,19] An accelerated failure time (AFT) model with Weibull distribution was fitted in the weighted cohort, adjusting for all aforementioned covariates.[20] Mediators tested included "diagnosis and referral strategies": time since cardiac diagnosis (> or ≤2 years); "preimplant medical/device management": cardiac resynchronization therapy (CRT), implantable cardioverter-defibrillator (ICD), beta-blocker, angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB), aldosterone antagonist, inotropes, and amiodarone; "preimplant transthoracic echocardiogram data": moderate to severe mitral regurgitation (MR), tricuspid regurgitation (TR), aortic regurgitation (AR), LV end-diastolic diameter (LVEDD), and qualitative right ventricular (RV) function (reported as normal, mild, moderate, or severe reduction in RV function); "baseline

inflammatory markers": platelet count, uric acid, and lymphocyte count (%); "psychosocial and socioeconomic data": education level, working for income status, marital status, history of depression, and other major psychiatric diagnosis; and "comorbidities": history of solid organ cancer, lymphoma or leukemia, and recent pulmonary embolus (PE).

The effect of female gender on mortality was decomposed into its indirect effect (path ab in the figure below, mediated effect of female gender on mortality), direct effect (path c, nonmediated effect of female gender on mortality), and total effect (path ab + path c).[17] Proportion mediated was defined as the proportion of the total effect mediated *via* the mediator.[17] Bonferroni correction was applied to account for multiple testing as a result of 20 candidate mediators. The mediation analysis was conducted based on the analytic cohort.



All tests were 2 sided, and p value <0.05 was considered statistically significant. SAS version 9.4 (SAS Institute, Inc., Cary, NC) and R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria) were used to perform statistical analyses.

RESULTS

Baseline Characteristics

Baseline characteristics of the analytic cohort (n = 9,565) are described in **Table 1**. Females were younger, had a smaller BSA, and were more likely to have a nonischemic HF etiology. They were more likely to have a centrifugal pump implanted. Additionally, they were more likely to have more advanced stages of CKD but had lower BUN at baseline. Females had lower MELD scores and HMRS than their male counterparts. After inverse probability weighting, males and females were well balanced with regards to pertinent aforementioned covariates with standardized mean differences <0.10 for covariates (**Table 2**).

Survival Analysis

Over a median follow-up of 13.3 months [IQR: 5.6–25.6 months], there were 2,287 (23.9%) deaths. Females experienced a 36% increased risk of mortality (adjusted HR: 1.36; 95% CI: 1.21–1.53; $p < 0.0001$) after LVAD implantation in a fully adjusted survival analysis. Gender × time interaction was significant ($p = 0.02$); the restricted cubic spline analysis revealed an early hazard of death for females after LVAD implantation (**Figure 1**). Females experienced a 74% increased risk of mortality during the first 4 months after implant (adjusted HR: 1.74; 95% CI: 1.47–2.06; $p < 0.0001$; **Figure 2**) but not after (adjusted HR: 1.18; 95% CI: 0.96–1.31; $p = 0.16$).

To verify the findings, a sensitivity analysis was performed on the entire cohort of 15,498 patients using multiple imputation on the patients with missing data (n = 5,933). Due to the large sample size, there were statistically significant differences in preimplant demographics, biochemical, risk score, and hemodynamic data between the analytic cohort (n = 9,565) and patients who were excluded for missing data (n = 5,933); however, the values were numerically similar (Table 1, Supplemental Digital Content, http://links.lww.com/ASAIO/A551) with the exception of more centrifugal pumps (43.6% *vs.* 31.1%; $p < 0.001$) and INTERMACS 1–2 patients (18.7% *vs.* 13.4%; $p < 0.001$) in the excluded cohort. Even in the larger

Table 1. Baseline Characteristics of Male and Female CF-LVAD Recipients in the Analytic Cohort

	Male (n = 7,499)	Female (n = 2,066)	*p* Value
Age at implant, years	56.87 (12.96)	53.93 (13.61)	<0.001
Body surface area, m^2	2.11 (0.31)	1.88 (0.30)	<0.001
BMI, kg/m^2	28.17 (6.70)	28.23 (7.49)	0.72
Centrifugal pump	2,248 (30.0%)	724 (35.0%)	<0.001
Device strategy			
Bridge to transplant	3,924 (52.3%)	1,116 (54.0%)	0.17
Destination therapy	3,539 (47.2%)	937 (45.4%)	
Bridge to recovery	31 (0.4%)	13 (0.6%)	
Ischemic heart failure etiology	3,290 (43.9%)	475 (23.0%)	<0.001
Cardiogenic shock at implant (INTERMACS 1 and 2)	1,002 (13.4%)	280 (13.6%)	0.82
Continent			
Americas	6,893 (91.9%)	1,902 (92.1%)	0.006
Asia Pacific	325 (4.3%)	111 (5.4%)	
Europe	281 (3.7%)	53 (2.6%)	
Major infection during index hospitalization preimplant	386 (5.2%)	130 (6.3%)	0.03
Mechanical ventilation during index hospitalization preimplant	746 (10.0%)	199 (9.6%)	0.67
Serum sodium, meq/L	134.84 (4.66)	135.43 (4.50)	<0.001
BUN, mg/dl	30.08 (19.38)	26.18 (18.57)	<0.001
Total bilirubin, mg/dl	1.36 (1.47)	1.13 (1.09)	<0.001
Stages of CKD			
1–2	3,953 (52.7%)	948 (45.9%)	<0.001
3A	1,822 (24.3%)	489 (23.7%)	
3B	1,310 (17.5%)	444 (21.5%)	
4–5	414 (5.5%)	185 (9.0%)	
Albumin, gm/dl	3.46 (0.67)	3.44 (0.67)	0.21
AST, U/L	53.85 (225.80)	56.12 (223.05)	0.69
ALT, U/L	61.80 (213.36)	57.66 (222.63)	0.44
WBC, $\times 10^3/\mu l$	9.53 (65.42)	8.16 (3.94)	0.34
Hemoglobin, gm/dl	11.55 (2.40)	10.73 (1.88)	<0.001
INR	1.32 (0.39)	1.29 (0.43)	0.001
MELD score	12.00 (5.54)	9.18 (5.84)	<0.001
Heart Mate 2 Risk Score category			
Low risk	3,897 (52.0%)	1,339 (64.8%)	<0.001
Medium risk	2,573 (34.3%)	536 (25.9%)	
High risk	1,029 (13.7%)	191 (9.2%)	
RA pressure, mm Hg	12.83 (8.15)	12.63 (8.44)	0.37
PA diastolic pressure, mm Hg	25.24 (9.00)	24.26 (8.57)	<0.001
Cardiac index, $L/min/m^2$	2.05 (0.66)	2.00 (0.69)	0.007
Follow-up time, months	12.5 (5.2–24.1)	12.4 (4.9–24.9)	0.90

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BUN, blood urea nitrogen; CF, continuous flow; CKD, chronic kidney disease; INR, international normalized ratio; INTERMACS, Interagency Registry for Mechanical Circulatory Support; LVAD, left ventricular assist device; MELD, Model for End-Stage Liver Disease; PA, pulmonary artery; RA, right atrial; WBC, white blood cell count.

Table 2. Standardized Difference Between Males and Females for Weighted Covariates in the Analytic Cohort

Baseline Characteristics	Standardized Difference
Age	−0.054
Pump type	−0.023
Body surface area	−0.010
Heart failure etiology	0.004
Cardiogenic shock at implant (INTERMACS 1 and 2 *vs.* profiles 3–7)	0.009
BUN	0.069
Serum sodium	0.007
Total bilirubin	0.002
INR	−0.007
Hemoglobin	−0.099
MELD score	0.043
HeartMate II Risk Score Category	
Low	−0.003
Medium	−0.006
High	0.009
PA diastolic pressure	0.023
Cardiac index	0.007

BUN, blood urea nitrogen; INR, international normalized ratio; INTERMACS, Interagency Registry for Mechanical Circulatory Support; MELD, Model for End-Stage Liver Disease; PA, pulmonary artery.

cohort of 15,498 patients, the findings were similar, with females having an increased risk of mortality (adjusted HR: 1.39; 95% CI: 1.27–1.53; $p < 0.0001$; Table 2, Supplemental Digital Content, http://links.lww.com/ASAIO/A551).

Survival among BTT LVAD patients. Among BTT LVAD patients (n = 5,036), there were 875 (17.3%) deaths and 1,781 (35.4%) transplant events during a median follow-up of 12.0 months [IQR: 5.4–24.0 months]. Over the duration of follow-up, females had a higher risk of death (adjusted HR: 1.30; 95% CI: 1.07–1.59; $p = 0.009$), even after accounting for the competing risk of transplantation. Gender × time interaction was significant ($p < 0.0001$), with females experiencing an increased risk of mortality during the first 4 months after implant (adjusted HR: 1.63; 95% CI: 1.20–2.23; $p = 0.002$) but not after (adjusted HR: 1.42; 95% CI: 0.88–1.49; $p = 0.32$).

Cause of Death

The primary causes of death by gender in the first 4 months after implant are noted in **Table 3**. Females experienced an increased risk of early mortality due to neurologic dysfunction (adjusted HR: 2.62; 95% CI: 1.80–3.81; $p = 0.006$) after LVAD implantation in the fully adjusted survival analysis.

Causal Mediation Analysis

To study the reasons for the observed gender differences in early mortality, multiple aforementioned preimplant variables were evaluated as plausible mediators (**Table 4**). Females were more likely to have carried their primary cardiac diagnosis for less than 2 years at the time of implant. They were less likely to have received device therapy and amiodarone but more likely to be on aldosterone antagonist therapy and inotropes preimplant. Females had a smaller LVEDD, worse MR and TR, but better qualitative RV function before implant. Markers of inflammation were worse in females: they had higher platelet and lymphocyte counts and lower uric acid than their male counterparts. Additionally, they were more likely to have a history of cancer and a recent PE. They were more likely to carry a diagnosis of severe depression or another major psychiatric disorder, more likely to be single and less likely to have worked for income despite similar levels of education preimplant.

Variables that were significantly different between genders were individually added to the model for causal mediation analysis (**Table 5**; Table 3, Supplemental Digital Content 1, http://links.lww.com/ASAIO/A551). After correction for multiple testing, LVEDD and the presence of moderate to severe TR

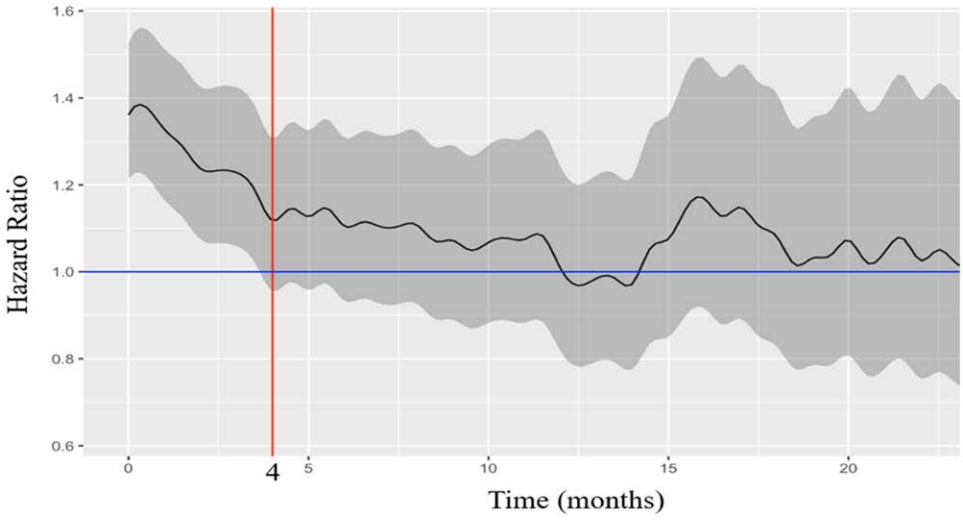


Figure 1. Restricted cubic spline depicting adjusted mortality hazard ratio with 95% CI (gray-shaded area) for female gender over time, adjusted for age, BSA, etiology of HF, pump type, presence of cardiogenic shock at implant (INTERMACS profiles 1 and 2 *vs.* profiles 3–7), serum sodium, BUN, total bilirubin, INR, hemoglobin, CKD stage, MELD score, HMRS, PADP, and CI. Female gender is associated with a higher risk of mortality in the first 4 months postimplant, but not after. BSA, body surface area; BUN, blood urea nitrogen; CI, cardiac index; CKD, chronic kidney disease; HF, heart failure; HMRS, HeartMate II Risk Score; INR, international normalized ratio; INTERMACS, Interagency Registry for Mechanical Circulatory Support; MELD, Model for End-Stage Liver Disease; PADP, pulmonary artery diastolic pressure.

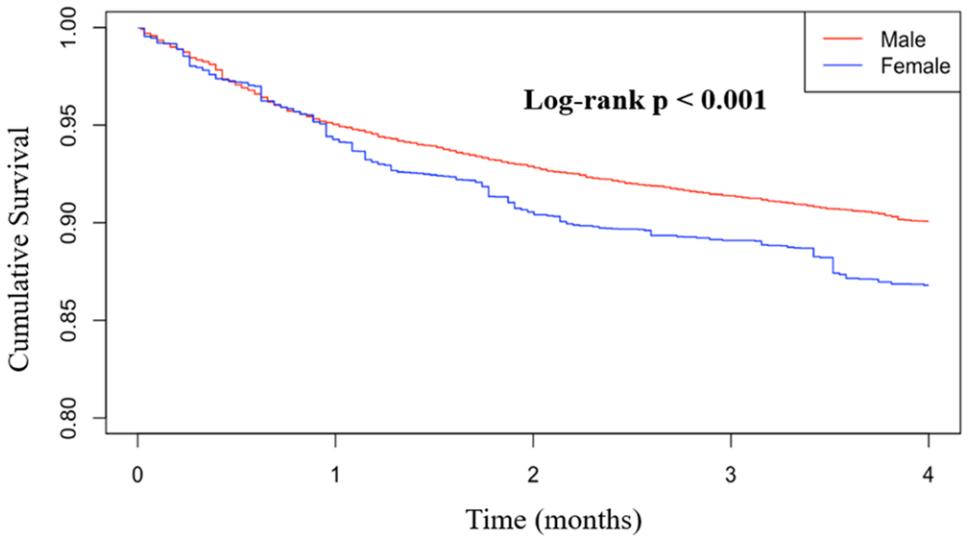


Figure 2. Inverse probability weighted Kaplan–Meier survival curves for early (4 month) mortality in males (n = 7,499) *vs.* females (n = 2,066). There were 9.7% deaths in males *vs.* 12.8% deaths in females in the first 4 months after implant ($p < 0.001$). After adjustment for covariates, female gender was associated with a significantly higher risk of early mortality in the first 4 months after LVAD implant (adjusted HR, 1.74; 95% CI, 1.47–2.06). CI, cardiac index; HR, hazard ratio; LVAD, left ventricular assist device.

Table 3. Primary Cause of Death in the First 4 Months Postimplant in Males and Females in the Analytic Cohort (n = 9,565)

Primary Cause of Death	Male n = 729	Female n = 205	*p* Value	*p* Value for Overall Difference
Right ventricular failure	33 (4.5%)	11 (5.4%)	0.62	0.03
Major bleeding	22 (3.0%)	10 (4.9%)	0.20	
Cardiac arrhythmia	8 (1.1%)	3 (1.5%)	0.67	
Major infection	47 (6.5%)	6 (2.9%)	0.05	
Device malfunction	6 (0.8%)	1 (0.5%)	0.62	
Neurologic dysfunction	122 (16.8%)	51 (25.0%)	0.008	
Multisystem organ failure	217 (29.8%)	42 (20.6%)	0.009	
Withdrawal of support	85 (11.7%)	27 (13.2%)	0.56	
Others	189 (25.9%)	54 (26.3%)	0.99	

mediated ≈21.9% of the increased mortality associated with female gender in the first 4 months post-LVAD implantation.

DISCUSSION

In this analysis of the largest multinational registry of LVAD implants in the contemporary era, we determined that 1) females experience higher mortality than males after LVAD implantation, even after accounting for traditional correlates of postimplant mortality; 2) an early hazard phase of increased mortality exists, with females experiencing a higher risk of mortality during the first 4 months after implant but not after; and 3) two novel variables mediate ≈21.9% of the increased early hazard of mortality in females: smaller LVEDD and increased TR at baseline. Although prior analyses have also demonstrated increased risk for females after LVAD implantation, our analysis is novel because we have identified at least two variables that underlie the observed association between female gender and increased mortality.

Gender Differences in Post-LVAD Mortality

There is conflicting evidence on gender disparities in post-LVAD mortality. The 8th annual INTERMACS report, including data on >20,000 patients implanted between 2006 and 2016, reported a 47% increased risk of early mortality for females in the first 3 months after implant, consistent with our findings.[3] The report also detailed improved overall survival for LVAD recipients after 2013[3]; however, gender-specific mortality data were only reported for the cohort from 2008 to 2016, which includes patients supported with older generation pumps not currently used. Indeed, there continues to be an increase in the number of women supported in the modern era. [2] A smaller EUROMACS registry analysis of 966 patients implanted between 2011 and 2014 found that females are at higher risk of mortality for up to 3 years after LVAD implantation.[4] However, neither registry analysis described the reasons for increased mortality in females.[3,4] Contrary to these analyses, studies by Birks *et al.*[21] and Bogaev *et al.*[6] reported no difference in post-LVAD survival between males and females. However, these studies included a smaller number of patients enrolled in LVAD clinical trials, who may not be completely representative of "real-world" patients. Similarly, Hsich *et al.*[7] found no gender differences in mortality in an INTERMACS registry study of 1,936 patients. However, this study reported data on patients implanted between 2006 and 2010 and may not be reflective of trends in the contemporary era. Our study is novel and adds to the existing literature because it is the largest description of gender differences in the contemporary CF-LVAD era and includes data from multiple international sites as well as 24 sites that report data to the IMACS registry. In spite of improved overall survival for LVAD patients in the contemporary era, [3] we still identified a higher risk of death for female patients.

Table 4. Gender Differences in Candidate Mediators of Increased Mortality in the Analytic Cohort

	Male (n = 7,499)	Female (n = 2,066)	*p* Value
Time since cardiac diagnosis: >2 years	5,716 (78.6%)	1,473 (73.2%)	<0.001
Preimplant medical/device therapy			
ICD	5,770 (82.3%)	1,512 (78.4%)	<0.001
CRT	2,197 (32.2%)	520 (27.5%)	<0.001
ACE inhibitor/ARB	4,016 (61.9%)	1,122 (63.3%)	0.29
β-blocker	5,869 (80.4%)	1,584 (78.8%)	0.10
Aldosterone antagonist	4,393 (61.4%)	1,317 (66.2%)	<0.001
Inotropes	2,843 (38.7%)	849 (42.1%)	0.007
Amiodarone	3,576 (50.4%)	811 (41.6%)	<0.001
Preimplant echocardiographic data			
Moderate to severe MR	4,098 (57.6%)	1,264 (64.0%)	<0.001
Moderate to severe TR	2,885 (40.8%)	978 (49.7%)	<0.001
Moderate to severe AR	282 (4.3%)	69 (3.8%)	0.37
LVEDD, cm	6.98 (1.12)	6.56 (1.03)	<0.001
Qualitative RV function			
Normal	1,439 (24.1%)	516 (31.1%)	
Mildly reduced	1,766 (29.6%)	468 (28.2%)	<0.001
Moderately reduced	1,922 (32.2%)	476 (28.7%)	
Severely reduced	838 (14.1%)	201 (12.1%)	
Preimplant inflammatory markers			
Lymphocyte count, %	17.64 (9.24)	20.34 (11.77)	<0.001
Platelet count, $\times 10^3/\mu l$	189.77 (80.68)	204.12 (89.98)	<0.001
Uric acid, mg/dl	8.41 (3.00)	8.14 (3.08)	0.01
Psychosocial and socioeconomic			
Severe depression	152 (2.1%)	89 (4.5%)	<0.001
Other major psychiatric disorder	130 (1.8%)	51 (2.6%)	0.03
Education level			
None	15 (0.3%)	3 (0.2%)	
Primary education	185 (3.4%)	49 (3.2%)	
Secondary education	2,653 (48.0%)	758 (48.7%)	0.90
College education	2,669 (48.3%)	748 (48.0%)	
Marital status			
Married or domestic partner	4,963 (67.7%)	1,052 (52.6%)	<0.001
Single, divorced, separated, or widowed	2,365 (32.3%)	949 (47.4%)	
Working for income	1,342 (19.9%)	264 (14.1%)	<0.001
Comorbidities			
Solid organ cancer	301 (4.0%)	162 (7.9%)	<0.001
Recent pulmonary embolism	108 (1.5%)	42 (2.1%)	0.05
Lymphoma or leukemia	89 (1.2%)	36 (1.8%)	0.04

ACE, angiotensin-converting enzyme; AR, aortic regurgitation; ARB, angiotensin II receptor blocker; β-blocker, beta blocker; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; LVEDD, left ventricular end-diastolic diameter; MR, mitral regurgitation; RV, right ventricular; TR, tricuspid regurgitation.

Table 5. Mediation Analysis Results Reported as Percentage Proportion of Hazard Mediated

	Proportion Mediated		
Mediator	Proportion Mediated (%)	95% CI	*p* Value*
Time since cardiac diagnosis <2 years	–0.31%	–2.48% to 1.00%	0.48
Preimplant medical/device therapy			
ICD	–0.31%	–3.25% to 2.00%	0.76
CRT	–0.93%	–3.00% to 0.00%	0.14
Aldosterone antagonist	1.27%	–0.00% to 4.00%	0.07
Inotropes	0.06%	–1.12% to 1.00%	0.98
Amiodarone	1.32%	–1.71% to 5.00%	0.35
Preimplant echocardiographic data			
Moderate to severe MR	–2.00%	–4.88% to 0.00%	0.05
Moderate to severe TR‡	4.78%	1.70% to 9.00%	0.002†
LV end-diastolic diameter, cm‡	17.10%	10.76% to 28.00%	<0.0001†
Qualitative RV function	0.28%	–0.94% to 1.00%	0.91
Preimplant Inflammatory markers			
Platelet count, $\times 10^3/\mu l$	–1.42%	–3.72% to 0.00%	0.01
Uric Acid, mg/dl	–2.59%	–8.53% to 1.00%	0.17
Lymphocyte count, %	–2.06%	–7.52% to 0.00%	0.09
Psychosocial and socioeconomic			
Severe depression	0.05%	–2.60% to 1.00%	0.91
Other major psychiatric disorder	0.02%	–1.17% to 2.00%	0.90
Marital status	1.19%	–2.90% to 6.00%	0.53
Working for income	1.79%	–0.18% to 6.00%	0.08
Comorbidities			
Solid organ cancer	1.16%	0.14% to 3.00%	0.03
Recent pulmonary embolism	–1.29%	–14.0% to 2.00%	0.38
Lymphoma or leukemia	0.009%	–0.51% to 1.00%	0.90

Mediation analysis results are reported as percentage proportion of hazard mediated: the proportion of the total hazard of mortality associated with female gender that is mediated *via* each mediator of interest. Negative values indicate that the mediator is protective in females. All models are adjusted for age, BSA, etiology of HF, pump type, presence of cardiogenic shock at implant (INTERMACS profiles 1 and 2 *vs.* profiles 3–7), serum sodium, BUN, total bilirubin, INR, hemoglobin, CKD stage, MELD score, HMRS, PADP, and CI.

*A raw *p* value <0.0025 meets Bonferroni-corrected *p* value significance.

†Bonferroni-corrected *p* value significant.

‡Moderate to severe tricuspid regurgitation mediated 4.75% (95% CI: 1.30%–10.00%; $p = 0.02$) and LV end-diastolic diameter mediated 12.52% (95% CI: 4.62%–27.00%; $p < 0.0001$) of the increased hazard of early mortality coded due to neurologic dysfunction in females.

BSA, body surface area; BUN, blood urea nitrogen; CI, cardiac index; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; HMRS, HeartMate II Risk Score; ICD, implantable cardioverter-defibrillator; INR, international normalized ratio; INTERMACS, Interagency Registry for Mechanical Circulatory Support; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; MELD, Model for End-Stage Liver Disease; MR, mitral regurgitation; PA, pulmonary artery; RV, right ventricular; TR, tricuspid regurgitation.

Mediators of Gender Differences in Early Mortality

A key finding in our study is the identification of a distinctly higher risk of mortality for females in the first 4 months after implant, highlighting a window of opportunity for perioperative interventions that may help mitigate the observed gender disparities. Females are known to have higher perioperative mortality after cardiothoracic surgery, with the Society for Thoracic Surgeon's adult cardiac surgery short-term risk calculator assigning a higher perioperative risk for female gender regardless of the type of cardiothoracic surgical procedure being performed.[22] Although potential explanations have included older age and more comorbid conditions, late referrals, atypical disease presentations, and anatomical considerations may also influence the disparate clinical outcomes.

Our study is the first to comprehensively explore mediators of the increased risk associated with female gender. In this study, the results of a causal mediation analysis demonstrated that smaller LVEDD and more severe TR mediated ≈21.9% of the increased early hazard of death. Previous studies have

similarly demonstrated an association of these variables with increased risk of postimplant mortality after LVAD implantation, although none have described differences by gender. Topilsky *et al*.[23] studied preimplant echocardiographic parameters in 83 CF-LVAD patients and demonstrated that a smaller LVEDD (<63 mm) was associated with a higher 30 day risk of mortality after LVAD implantation. Similarly, in an analysis of the INTERMACS registry, Shah *et al*.[24] found a 11% increased hazard of postimplant death for each centimeter decrease in LVEDD. Prior analyses in non-LVAD populations have described important cardiac structural differences based on gender: females have a smaller LV mass, relative wall thickness and LVEDD,[25,26] and more TR.[27] There may be multiple adverse physiologic consequences of LVAD implantation into a smaller LV. In addition to making the surgery more technically challenging, high LVAD pump speeds relative to LV size may increase the risk of "suction" events by shifting the interventricular septum to the left, worsening RV failure, and diminishing LV cavity size.[23] The presence of moderate to severe TR preimplant also portends worse survival post-LVAD: increased RV volume from increased cardiac output post-LVAD, tethering of valve leaflets to the leftward shifted septum, and volume resuscitation perioperatively further worsen preexisting TR and may precipitate postoperative RV failure.[28] Our study confirms the collective findings of these reports but, more importantly, for the first time, highlights that these factors mediate observed gender disparities in post-LVAD morbidity and mortality.

Importantly, although we were able to analyze 20 plausible mediators collected in IMACS, ≈78.1% of the increased risk associated with female gender was not explained by our causal mediation analyses. Females are diagnosed and referred for advanced HF therapies later in the course of their disease, which may be due to atypical disease presentations and implicit bias on the part of providers. [2,18,19] Additionally, females are less likely to be prescribed guideline-directed device and medical therapy[18] for HF, possibly accounting for the higher INTERMACS profiles in females at presentation.[2,19] Psychosocial and socioeconomic determinants of cardiovascular health have a greater impact on females than on males.[19] Fewer females live with spouses or work for income, resulting in females being more likely to experience cost-related issues with health insurance and medications.[19] Depression is also more prevalent in females and is a significant predictor of adverse Cardiovascular (CV) outcomes.[29] Inflammatory biomarkers are worse in females and are significant predictors of CV events.[30] While prior small studies in the LVAD population have demonstrated that these psychosocial and socioeconomic factors[16] and inflammation[31,32] predict adverse outcomes post-LVAD, none have studied whether these risk factors mediate worse outcomes in females. Although we were able to include these variables in our mediation models, they were not significant mediators of the observed worse survival in women. Thus, there may be additional unmeasured confounders not collected in the IMACS or other registries that may account for this substantial unexplained hazard.

There are multiple limitations of our study that are worth noting. First, the study itself is retrospective, and the decision to implant an LVAD is not randomized. However, the inverse probability weighting strategy helped to balance covariates that may be associated with differences in choice of treatment between men and women. Furthermore, we report a high E-value (Supplemental Digital Content, http://links.lww.com/ASAIO/A551), indicating that only the presence of very strong unmeasured confounders associated with both female gender and mortality with an effect estimate of 2.29 (lower limit E-value = 1.94) could explain away the observed association of female gender with mortality. Second, although IMACS is an expansive database, participation in the database is voluntary, and whether the data are truly representative of all LVAD implanting sites is unknown. IMACS also relies on accurate data entry by participating hospitals, and other variables that might influence outcomes, such as geographical region, implant center, race/ethnicity, anticoagulation, and device brand, were not available in the IMACS registry. There may be subjective differences in coding primary cause of death across participating centers. In addition, the IMACS registry does not include any patients with the HeartMate 3 (Abbott, North Chicago, IL) LVAD. However, a recent analysis of BTT patients from the United Network for Organ Sharing (UNOS) Database that included 365 HeartMate 3 (Abbott) patients showed that female gender was associated with higher waitlist mortality even after accounting for device type.[2] Although we have studied transthoracic echocardiographic parameters as potential mediators of increased mortality for females, some parameters such as qualitative RV function are known to have poor reproducibility.[28] Finally, as with any large database study, there was significant data missingness, resulting in the inclusion of 9,565 patients in our final analyses. However, we do not expect that the exclusion of patients with missing data biased our results because we were able to confirm our findings in a sensitivity analysis of the entire dataset of 15,498 (Table 2, Supplemental Digital Content 1, http://links.lww.com/ASAIO/A551).

In conclusion, the largest contemporary evaluation of CF-LVAD implants confirms that females continue to experience worse mortality after implant, with a distinct early phase of highest risk in the first 4 months after implantation. Causal mediation analysis demonstrates that this is partially explained by a smaller LVEDD and higher TR. Future research should examine whether novel perioperative interventions, lower LVAD pump speeds, and tricuspid valve repair will improve outcomes in women. Additionally, registries should collect additional information that might help determine what other confounders mediate the residual risk in women. A similar approach with a focus on elucidating the underlying mechanisms is necessary to bridge gender disparities in HF outcomes.

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