Original Article

Sex Differences in Mortality Based on United Network for Organ Sharing Status While Awaiting Heart Transplantation

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Background—There are sex differences in mortality while awaiting heart transplantation, and the reason remains unclear.

Methods and Results—We included all adults in the Scientific Registry of Transplant Recipients placed on the heart transplant active waitlist from 2004 to 2015. The primary end point was all-cause mortality. Multivariable Cox proportional hazards models were performed to evaluate survival by United Network for Organ Sharing (UNOS) status at the time of listing. Random survival forest was used to identify sex interactions for the competing risk of death and transplantation. There were 33 069 patients (25% women) awaiting heart transplantation. This cohort included 7681 UNOS status 1A (26% women), 13 027 UNOS status 1B (25% women), and 12 361 UNOS status 2 (26% women). During a median follow-up of 4.3 months, 1351 women and 4052 men died. After adjusting for >20 risk factors, female sex was associated with a significant risk of death among UNOS status 1A (adjusted hazard ratio, 1.14; 95% confidence interval, 1.01–1.29) and UNOS status 1B (adjusted hazard ratio, 1.17; 95% confidence interval, 1.05–1.30). In contrast, female sex was significantly protective for time to death among UNOS status 2 (adjusted hazard ratio, 0.85; 95% confidence interval, 0.76–0.95). Sex differences in probability of transplantation were present for every UNOS status, and >20 sex interactions were identified for mortality and transplantation.

Conclusions—When stratified by initial UNOS status, women had a higher mortality than men as UNOS status 1 and a lower mortality as UNOS status 2. With >20 sex interactions for mortality and transplantation, further evaluation is warranted to form a more equitable allocation system. (***Circ Heart Fail*. 2017;10:e003635. DOI: 10.1161/CIRCHEARTFAILURE.116.003635.)**

Key Words: dilated cardiomyopathy ■ heart failure ■ heart-assist devices ■ sex ■ survival ■ transplantation

Women have a higher mortality rate than men while awaiting orthotopic heart transplantation, and the reason remains unclear. In 1 small European study (58 women and 260 men), women had a higher risk of death/deterioration (hazard ratio, 2.3; 95% confidence interval, 1.04–5.12; P=0.04) even after adjusting for age, Heart Failure Survival Score, serum creatinine, inpatient status, cardiac index, low vocational level, smoking, and low emotional support at the time of transplant listing.[1] In the United States, the higher risk of death in women occurred despite shorter waiting times for heart transplantation according to Scientific Registry of Transplant Recipients (SRTR) data from 1999 to 2008.[2]

See Clinical Perspective

Timing of advanced heart failure care is important; yet, there are many uncertainties when making decisions to list a woman for heart transplantation. How long will she wait until transplantation or will she die on the waiting list? Does the initial United Network for Organ Sharing (UNOS) status influence the outcome, and did this change after the U.S. Food and Drug Administration (FDA) approval of smaller left ventricular assist devices that fit in women? Finally, what pre-listing characteristics affect waitlist survival more in women than in men, and do these also influence time to transplantation? These questions and more need further investigation.

Therefore, to better advise women who are contemplating heart transplantation, the aims of this study are to (1) evaluate sex differences in waitlist survival and time to transplantation based on initial UNOS status using patient characteristics at the time of listing, (2) determine whether sex differences in waitlist survival or time to transplantation have changed over the years, and (3) identify factors associated with waitlist mortality and timing of transplantation that are different for women than for men.

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Methods

Scientific Registry of Transplant Recipients

This study used data from the SRTR. The SRTR database includes data on all donors, wait-listed candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network, and has been described elsewhere. The Health Resources and Services Administration provides oversight to the activities of the Organ Procurement and Transplantation Network and SRTR contractors. Human error collecting data are minimized by edit checks, validation of data at the time of entry, and internal verification when there are outliers.[3] The study was approved by the Institutional Review Board at the Cleveland Clinic, and informed consent was waived because all data were obtained for routine care and deidentified by SRTR before submission to the investigators.

Patient Population and UNOS Status

We included all adult patients in the SRTR database placed on the active waiting list for heart transplantation from January 1, 2004, to August 31, 2015. We excluded inactive adult candidates (UNOS status 7 patients at the time of initial listing: 375 women and 1053 men) and patients aged <18 years because UNOS criteria for pediatrics differs from adults and the donor pools are distinguished by age.[4]

Data were evaluated by UNOS status at the time of initial wait listing. UNOS status 1A (high priority) included patients requiring total artificial heart, extracorporeal membrane oxygenation, ventricular assist device with device complications, ventricular assist devices without complications for a total of 30 days, intra-aortic balloon pump, mechanical ventilation, multiple inotropes with hemodynamic monitoring, single high-dose inotrope with hemodynamic monitoring, or an exemption for critical illness such as ventricular tachycardia. UNOS status 1B (next highest status) included patients on continuous intravenous dose inotrope support and stable ventricular assist devices. UNOS status 2 included all other patients and is the least urgent status for patients actively waiting heart transplantation.

Outcome Measures

The aims of this study were to (1) evaluate sex differences in waitlist survival and time to transplantation based on initial UNOS status using patient characteristics at time of listing, (2) determine whether sex differences in waitlist survival or time to transplantation have changed over the years, and (3) identify factors associated with waitlist mortality and timing of transplantation that are different for women than for men.

Statistical Analysis

All-cause mortality was assessed as a right-censored time to death with follow-up censored at the time of heart transplantation. This analysis was based on intent-to-treat such that deaths after removal from the waiting list were included in the primary analysis. SRTR mortality data were maintained by transplant centers and verified with the complete Social Security Death Master File recently available through a specific waiver granted to the SRTR.

Sex-specific baseline characteristics were reported according to UNOS status at the time of listing for heart transplantation. Continuous variables were expressed as medians with interquartile ranges. Categorical variables were expressed as number of patients with frequency except if patient number <10 absolute values were not provided to protect the identity of the cohort as per SRTR policy. Sex-specific survival analysis was performed for UNOS status 1A, 1B, and 2 patients in 3 eras (2004–2008, 2009–2011, and 2012–2015) using the Kaplan–Meier method with censoring for heart transplantation. These eras were chosen for historical consideration. FDA approval of HeartMate II, a small device that could be implanted in most women, occurred in April 2008.[5] Before this time, there were limited devices available for bridging smaller women to transplantation. The era between 2009 and 2011 included the usage of HeartMate II. The era 2012 to 2015 included data granted to SRTR with a special waiver for the complete updated Death Master File. This era also included FDA approval on November 20, 2012, of HeartWare,[6] another device that could be implanted in smaller patients.

Cox proportional hazard models were created for each UNOS status to explore the association between female sex and time to death. Each model was adjusted for continuous and categorical baseline characteristics at the time of listing. Continuous variables included year, age, body mass index, estimated glomerular filtration rate calculated by the Modification of Diet in Renal Disease equation, pulmonary artery mean, pulmonary capillary wedge pressure mean, total albumin, and cardiac index. Categorical variables included the type of ventricular assist device (total artificial heart, left ventricular assist device [LVAD], right ventricular assist device±LVAD, unspecified mechanical circulatory device), extracorporeal membrane oxygenation, intra-aortic balloon pump, inotropes, mechanical ventilator, diabetes mellitus, dialysis, race (white, black, Hispanic, Asian, and other), cerebral vascular accident, history of tobacco, inotropes, insurance (private, Medicare, Medicaid, and other), cardiac diagnosis (dilated cardiomyopathy, ischemic cardiomyopathy, congenital heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy, valvular cardiomyopathy, and other), ABO blood type, antiarrhythmic, hypertension, malignancy, peripheral vascular disease, and implantable cardioverter-defibrillator. Variables with a high proportion of missing data were excluded from the analysis. These included peak oxygen consumption (>30% missingness), peripheral vascular disease (21% missingness), and antiarrhythmic (25% missing). Multiple imputation was used for the remaining missing data and performed with SAS (v.9.4., Cary, NC) using Proc MI to generate 5 imputed data sets to use in the Cox proportional hazard models. We did not include outcomes, time, or cumulative hazard in the imputation, assuming that these were not systematically different for the primary explanatory variables. However, estimates were similar when log survival and death were added to the imputation. The MI procedure assumes that data are from a multivariable normal distribution using the Markov chain Monte Carlo method. Proc MIANALYZE was then used to generate parameter estimates and SEs for statistical inference.

Random survival forest (RSF) analysis machine learning methodology[7,8] was used for a competing risk analysis for the competing risk of death on the waitlist and transplantation. Missing data were preimputed using missForest[9] imputation methodology, a special type of random forest[7] strategy. No outcome information was utilized in the imputation. This preimputed data, comprised variables mentioned above, and peak oxygen consumption were used for the RSF analysis. However, to estimate sex interactions, the data were expanded to include all pairwise interactions of sex with each of the original 29 independent variables. For categorical variables, 1 interaction for each level of the variable was created. Contrasts were not utilized (ie, baseline values were not used). This yielded a total of 97 independent variables, including the original 29 variables.

The data were stratified by UNOS category. For each category, 3 separate RSF competing risk forests were fit, with each forest composed of 1000 random competing risk trees. Trees were constructed from independently drawn bootstrap data. On average, each tree was grown from 63% of the data (in-sample bootstrapped data); the remaining unused data (37%), referred to as out-of-bag data, was used to calculate out-of-bag cross-validated survival for each patient and variable importance (VIMP) measures for each of the 97 independent variables.[10] Different survival splitting rules were used by the 3 separate RSF competing risk forests. In the first, trees were grown using a composite (equally weighted) generalized log-rank splitting rule. This yields an analysis most suitable for estimation of the cumulative incidence function. Trees for the remaining 2 forests were grown using a modified Gray splitting rule, with each weighted in favor of 1 of the 2 competing risks. These are most suitable for the analysis of the cause-specific hazard and for identifying cause-specific risk factors.

VIMP estimates the difference in prediction error for an RSF with and without a variable. Positive values indicate variables that are predictive, adjusting for all other variables. To derive valid SEs and confidence regions for the estimated VIMP, thereby allowing us to identify statistically significant VIMP, each RSF procedure was repeatedly subsampled.

Table 1. Sex Differences in Baseline Characteristics While Awaiting Heart Transplantation

	UNOS Status 1A		UNOS Status 1B		UNOS Status 2	
	Female	Male	Female	Male	Female	Male
Variable	n=1965	n=5716	n=3226	n=9801	n=3197	n=9164
Age, y, median (Q1, Q3)	51 (37, 59)	55 (45, 62)	53 (40, 60)	56 (46, 62)	51 (39, 59)	57 (48, 62)
Race, n (%)						
White	1150 (59)	3802 (67)	1802 (56)	6433 (66)	2156 (67)	6999 (76)
Black	558 (28)	1157 (20)	1069 (33)	2252 (23)	674 (21)	1246 (14)
Hispanic	176 (9)	467 (8)	243 (8)	781 (8)	253 (8)	594 (6)
Asian	58 (3)	234 (4)	73 (2)	256 (3)	71 (2)	213 (2)
Other	23 (1)	56 (1)	39 (1)	79 (1)	43 (1)	112 (1)
BMI, median (Q1, Q3)	25 (22, 29)	27 (24, 30)	26 (23, 31)	27 (24, 31)	27(23, 31)	28 (25, 31)
ABO blood type, n (%)						
A	731 (37)	2207 (39)	1162 (36)	3651 (37)	1172(37)	3685 (40)
B	321 (16)	840 (15)	441 (14)	1361 (14)	401 (13)	1090 (12)
O	826 (42)	2361 (41)	1464 (45)	4357 (44)	1498 (47)	3992 (44)
AB	87 (4)	308 (5)	159 (5)	432 (4)	126 (4)	397 (4)
Diagnosis, n (%)						
Dilated	1185 (60)	2634 (46)	2120 (66)	4877 (50)	1655 (52)	3245(35)
Ischemic	400 (20)	2459 (43)	631 (20)	4058 (41)	586 (18)	4325 (47)
Congenital	35 (2)	91 (2)	114 (4)	184 (2)	268 (8)	352 (4)
Hypertrophic	48 (2)	71 (1)	68 (2)	128 (1)	153 (5)	209 (2)
Restrictive	62 (3)	104 (2)	86 (3)	168 (2)	162 (5)	329 (4)
Valvular	50 (3)	79 (1)	82 (3)	132 (1)	96 (3)	173 (2)
Other	185 (9)	278 (5)	125 (4)	254 (3)	277 (9)	531 (6)
ICD, n (%)	1096 (56)	3815 (67)	2356 (73)	7729 (79)	2187 (68)	7028 (77)
eGFR mL/min per 1.73 m^2, median (Q1, Q3)	65 (47, 89)	67 (49, 89)	66 (48, 85)	67 (51, 86)	63 (48, 82)	65 (51, 81)
Serum albumin g/dL, median (Q1, Q3)	3.3 (2.9, 3.8)	3.4 (3.0, 3.9)	3.7 (3.3, 4.1)	3.7 (3.2, 4.1)	4.0 (3.6, 4.4)	4.0 (3.6, 4.3)
Mean PAP mm Hg, median (Q1, Q3)	30 (23, 37)	32 (24, 39)	29 (23, 36)	31 (24, 38)	26 (20, 33)	28 (21, 35)
PCWP mm Hg, median (Q1, Q3)	20 (14, 26)	22 (15, 28)	20 (14, 25)	21 (15, 27)	17 (12, 23)	19 (13, 25)
CI L/min, median (Q1, Q3)	2.1 (1.6, 2.5)	2.1 (1.7, 2.6)	2.0 (1.7, 2.5)	2.1 (1.7, 2.5)	2.2 (1.8, 2.6)	2.1 (1.8, 2.5)
PVO_2 mL/kg per min, median (Q1, Q3)	10 (8, 13)	11 (9, 14)	11 (9, 13)	12 (9, 14)	11 (9, 14)	12 (10, 14)
Ventilator, n (%)	219 (11)	439 (8)	41 (1)	101 (1)	12 (0)	59 (1)
Inotrope, n (%)	906 (46)	2403 (42)	1691 (52)	4880 (50)	157 (5)	531 (6)
LVAD, n (%)	447 (23)	1675 (29)	655 (20)	2660 (27)	72 (2)	241 (3)
RVAD±LVAD, MCS unspecified, n (%)	229 (12)	579 (10)	114 (4)	321 (3)	16 (1)	79 (1)
TAH	18 (1)	86 (2)	*	32 (0)	*	13 (0)
ECMO	121 (6)	200 (4)	*	*	*	*
IABP	300 (15)	966 (17)	57 (2)	167 (2)	33 (1)	97 (1)

BMI indicates body mass index; CI, cardiac index; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; IABP, intra-aortic balloon pump; ICD, implantable cardioverter-defibrillator; LVAD, left ventricular assist device; MCS, mechanical circulatory support; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVO_2, peak oxygen consumption; Q1 and Q3, 25th and 75th percentiles; RVAD, right ventricular assist device; TAH, total artificial heart; and UNOS, United Network for Organ Sharing.

*Frequency ≤10 patients.

We drew a random sample of size n/10 without replacement. Subsampled data were fit using the same RSF strategy described above, and the resulting VIMP was stored. The procedure was repeated 1000 times independently. The 1000 values were then used to construct confidence regions using subsampling methodology.[10] All RSF calculations were based on randomForestSRC R-software[11] under default competing risk settings.

Results

Sex Differences at Time of Waitlist

Baseline characteristics of 33 069 adult patients with heart failure (25% women) on the active heart transplant waiting list are shown in Table 1 (see Table I in the Data Supplement

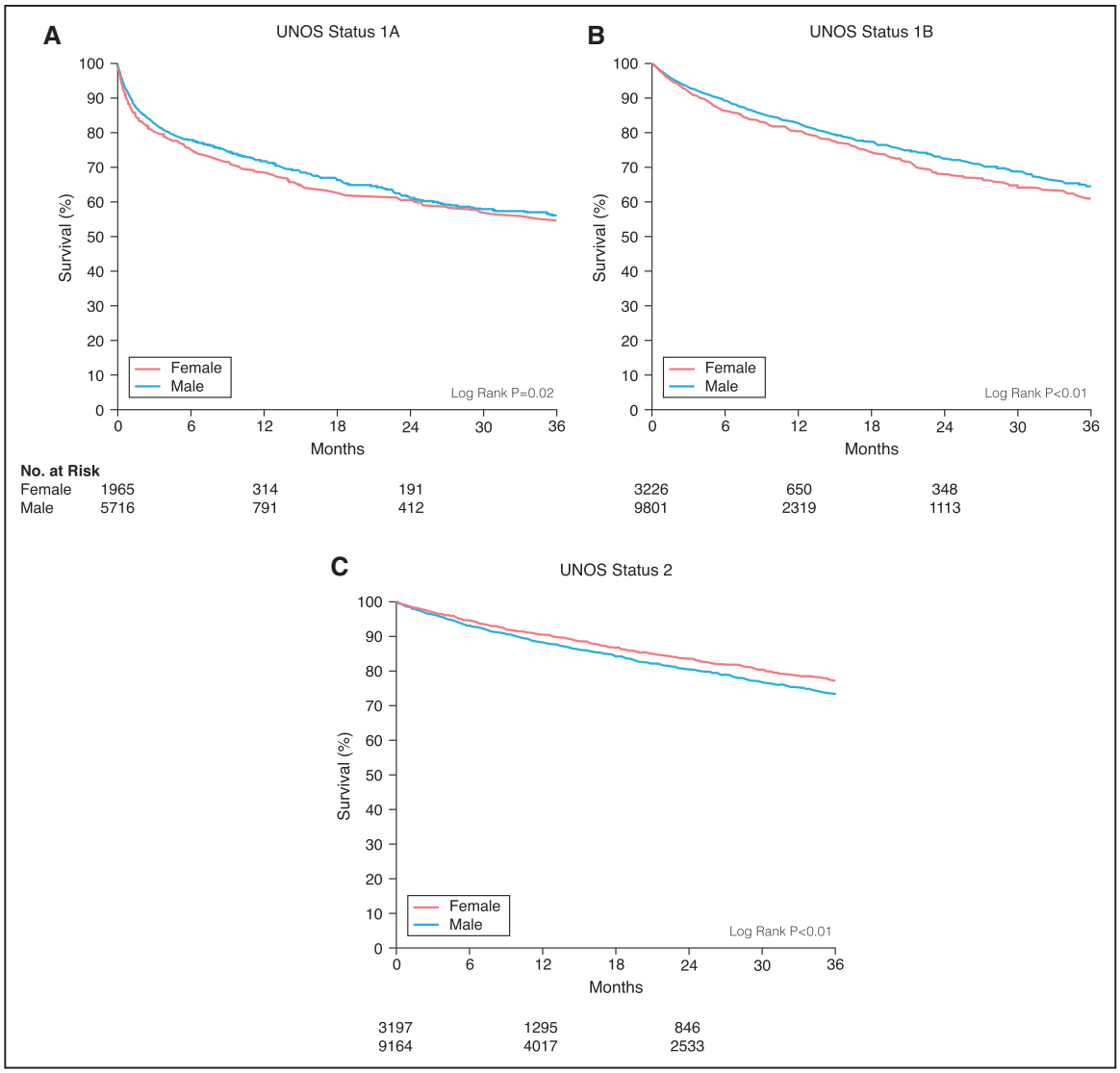

Figure 1. Sex differences in survival in patients with heart failure awaiting transplantation. Sex-specific Kaplan–Meier survival curves were generated for patients initially listed as (**A**) United Network for Organ Sharing (UNOS) status 1A, (**B**) UNOS status 1B, and (**C**) UNOS status 2.

for expanded list of baseline characteristics). This cohort included 7681 UNOS status 1A (26% women), 13 027 UNOS status 1B (25% women), and 12 361 UNOS status 2 (26% women). The majority of patients were men, white, >50 years of age, blood type O, and with private insurance. Compared with men, women were younger, had slightly lower body mass index, and higher frequency of dilated cardiomyopathy. They were less likely to have an ischemic cardiomyopathy, antiarrhythmic therapy, or an implantable cardioverter defibrillator than men.

Among UNOS status 1A patients, women were more likely than men to require a ventilator, inotropes, or extracorporeal membrane oxygenation support and less likely to have a total artificial heart, LVAD support, intra-aortic balloon pump, or implantable cardioverter defibrillator. About 50% of the UNOS status 1B patients were on inotropes at the time of listing with slightly more usage among women than among men. About 25% of the UNOS status 1B patients had a LVAD that was more likely in men than in women. Among UNOS status 2 patients, women compared with men had lower peak Vo_2 values and worse estimated glomerular filtration rate.

Sex Differences in Waitlist Mortality and Transplantation

There were 1351 women and 4052 men who died during a median follow-up of 4.3 months. Unadjusted Kaplan–Meier survival revealed women who were initially listed as UNOS status 1A and 1B were more likely to die on the waitlist than men and less likely if listed as UNOS status 2 (Figure 1). When looking at different eras, unadjusted Kaplan–Meier waitlist survival for UNOS status 1A and B candidates was better after 2008. Among UNOS status 1A candidates, women had a higher mortality than men from 2004 to 2011. Between 2012 and 2015, survival was better for women but slightly worse for men resulting in no sex difference in mortality during this time period (Figure 2A). Among patients initially listed as UNOS status 1B, women had a worse survival than men in 2004 to 2008 and 2012 to 2015 but no sex differences in survival

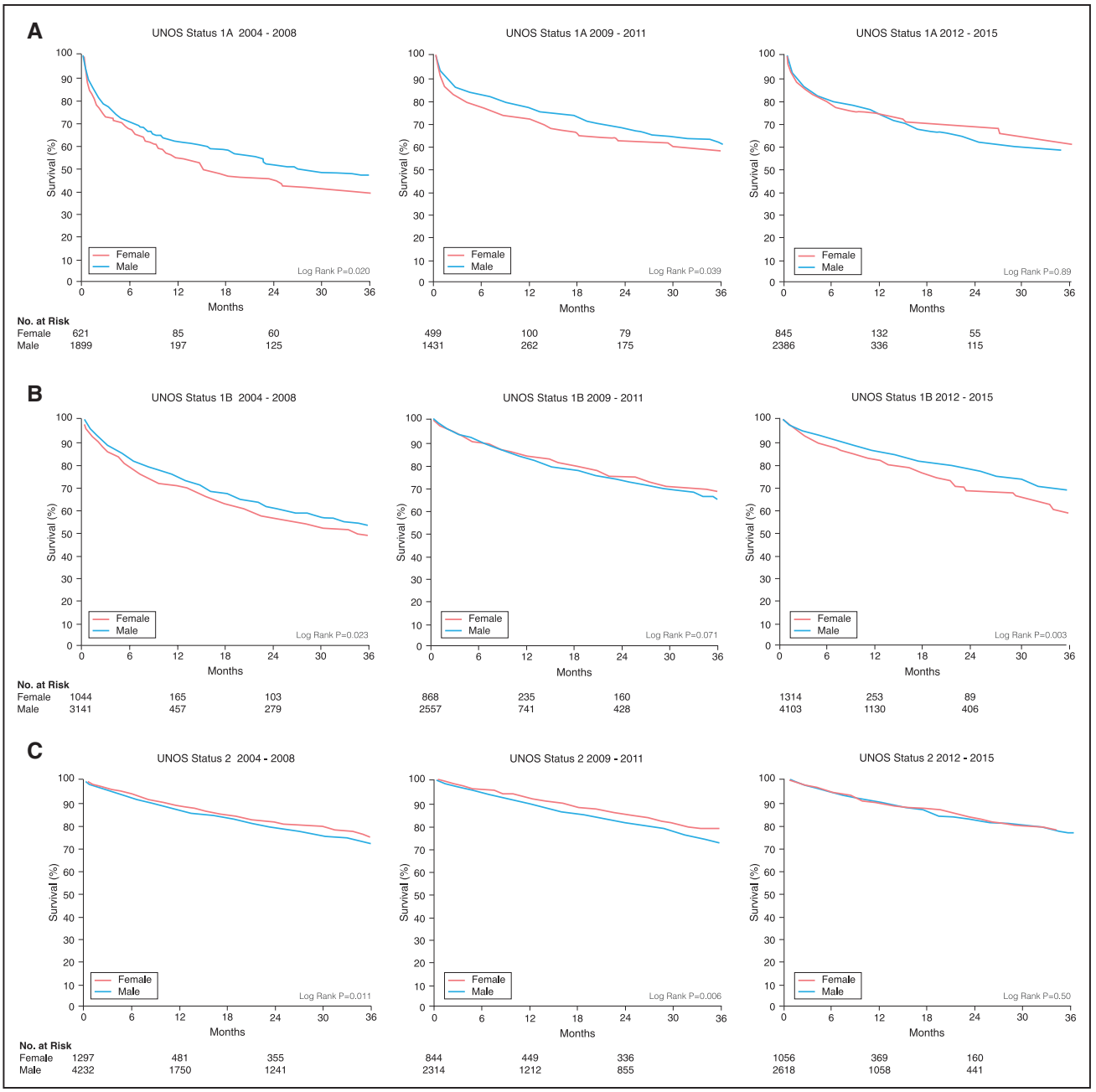

Figure 2. Sex differences in survival in patients with heart failure awaiting transplantation during 3 time periods. Sex-specific Kaplan–Meier survival curves were generated for patients initially listed as (**A**) United Network for Organ Sharing (UNOS) status 1A, (**B**) UNOS status 1B, and (**C**) UNOS status 2 during 3 time periods: 2004 to 2008, 2009 to 2011, and 2012 to 2015. All data were censored for heart transplantation.

between 2009 and 2011 (Figure 2B). Among UNOS status 2 patients, men had a higher mortality than women between 2004 and 2011 and similar survival as women between 2012 and 2015 (Figure 2C).

Cox regression of time until death revealed female sex was associated with a significant risk of death among UNOS status 1A and 1B after multivariable risk adjustment (Table 2). In contrast, female sex was protective for time to death among UNOS status 2 patients in both unadjusted and risk-adjusted models.

RSF competing risk analysis revealed women were less likely than men to be transplanted as UNOS status 1A and more likely than men as UNOS status 1B and 2 (Figure 3). When evaluating heart transplantation over time, there were many sex differences (Figure IA in the Data Supplement). For UNOS status 1A, the probability of heart transplantation was higher in men than in women until 2011. Between 2012 and 2015, there no longer was a significant sex difference. For UNOS status 1B, there was no substantial sex difference until 2012 to 2015 when the probability of transplantation in women significantly exceeded that in men (Figure IB in the Data Supplement). For UNOS status 2, the probability of transplantation was higher in women than in men in 2004 to 2008 and 2012 to 2015 (Figure IC in the Data Supplement).

Table 2. Female Sex and Mortality While Awaiting Heart Transplantation: Cox Proportional Hazards Analyses

	HR (95% CI)		
	UNOS Status 1A	UNOS Status 1B	UNOS Status 2
Female deaths (total at risk)	410 (1965)	508 (3226)	473 (3197)
Male deaths (total at risk)	1004 (5716)	1405 (9801)	1714 (9164)
Unadjusted	1.15* (1.10–1.21)	1.20* (1.15–1.26)	0.83* (0.79–0.87)
Multivariable adjusted	1.14* (1.01–1.29)	1.17* (1.05–1.30)	0.85* (0.76–0.95)

Multivariable adjusted for the following variables: sex, age, race, body mass index, insurance, initial year on waitlist for heart transplantation, ABO blood type, cardiac diagnosis (dilated, ischemic, congenital, hypertrophic, restrictive, valvular, and other), defibrillator, dialysis at listing, diabetes mellitus, hypertension, tobacco usage, malignancy, previous cerebral vascular accident, estimated glomerular filtration rate, serum albumin, mean pulmonary arterial pressure, pulmonary capillary wedge pressure, cardiac index, mechanical ventilator, inotrope usage, left ventricular assist device, right ventricular assist device, total artificial heart, intra-aortic balloon pump, extracorporeal membrane oxygenation. CI indicates confidence interval; HR, hazard ratio; and UNOS, United Network for Organ Sharing.

*HRs represent female:male comparison.

Sex Differences in Waitlist Risk Factors

There were many sex interactions with risk factors for death and heart transplantation (Figure 4A and 4B). Among patients initially listed as UNOS status 1A, the most important sex interactions associated with death were renal function, serum albumin, age, peak oxygen consumption, cardiac index, pulmonary artery pressure, pulmonary capillary wedge pressure, LVAD, and inotropes. Among patients initially listed as UNOS status 1B or 2, sex interactions associated with death were similar to UNOS status 1A but varied in magnitude and order of importance with a few exceptions. There were no sex interactions associated with renal function, LVAD, or inotrope for UNOS status 2, but there was a sex interaction with Medicare and body mass index.

For transplantation among patients initially listed as UNOS status 1A, there were 3 sex interactions: 2004 to 2008, serum albumin, and age. For UNOS status 1B, there were many sex interactions that included body mass index, 2004 to 2008, 2012 to 2015, blood type O, age, peak oxygen consumption, renal function, serum albumin, and hemodynamic variables. Sex interactions associated with transplantation for patients initially listed as UNOS status 2 were similar to those for patients listed as UNOS status 1B but varied in magnitude of importance.

Discussion

In a large, national transplant registry, we found sex differences in mortality while awaiting heart transplantation, sex differences in time to transplantation, and many sex interactions for risk of death and transplantation when patients were stratified by UNOS status at the time of initial wait listing. Female sex was associated with a higher risk of death among patients initially listed as UNOS status 1A and 1B and lower risk of death compared with men initially listed as UNOS status 2 even after adjustment for >20 possible confounding variables. Rate of heart transplantation was lower in women than in men listed as UNOS status 1A and higher in women than in men listed as UNOS status 1B or 2. There were many sex interactions for death and heart transplantation that varied with UNOS status and had not been described previously. More research is needed to understand the mechanism of these findings in hopes of providing more equitable therapy for both women and men with advanced heart failure.

Sex differences in survival on the national heart transplant waiting list have been present and known for many years, but few studies have addressed this issue.[1,12,13] Our analysis provides some insight and demonstrates changes in outcome over time. For women and men initially listed as UNOS status 1A or 2, the sex disparity in waitlist survival resolved between 2012 and 2015. During that time period, there was no change in advanced heart failure medication but there was FDA approval of small continuous flow devices that could successfully bridge patients to transplantation and be implanted in most women and men (FDA approved HeartMate II in 2008 and HeartWare in 2012).[5,6] For patients

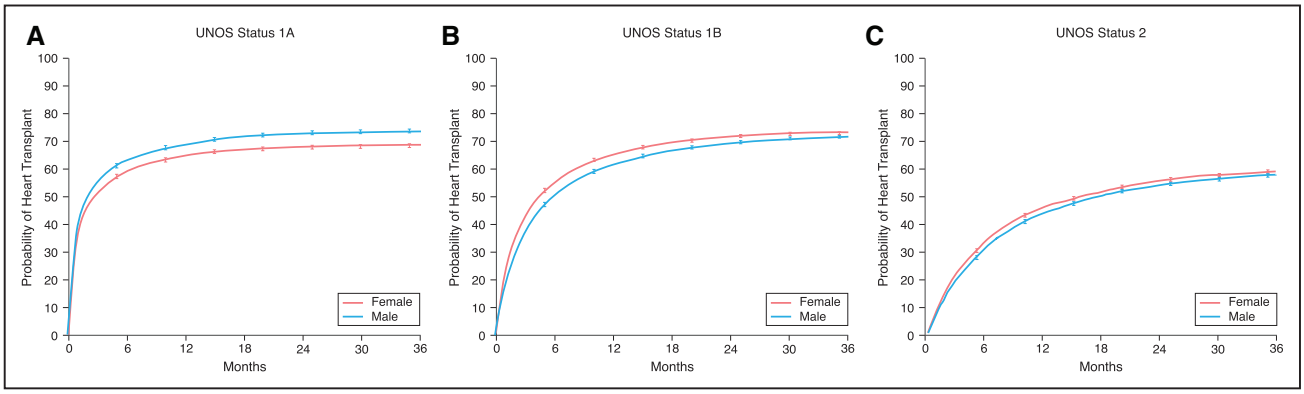

Figure 3. Sex differences in heart transplantation based on United Network for Organ Sharing (UNOS) status. Sex-specific cumulative incidence curves were generated for patients initially listed as (**A**) UNOS status 1A, (**B**) UNOS status 1B, and (**C**) UNOS status 2. Figures show uncertainty in estimators of ±2 SEs, where SEs were estimated using subsampling.

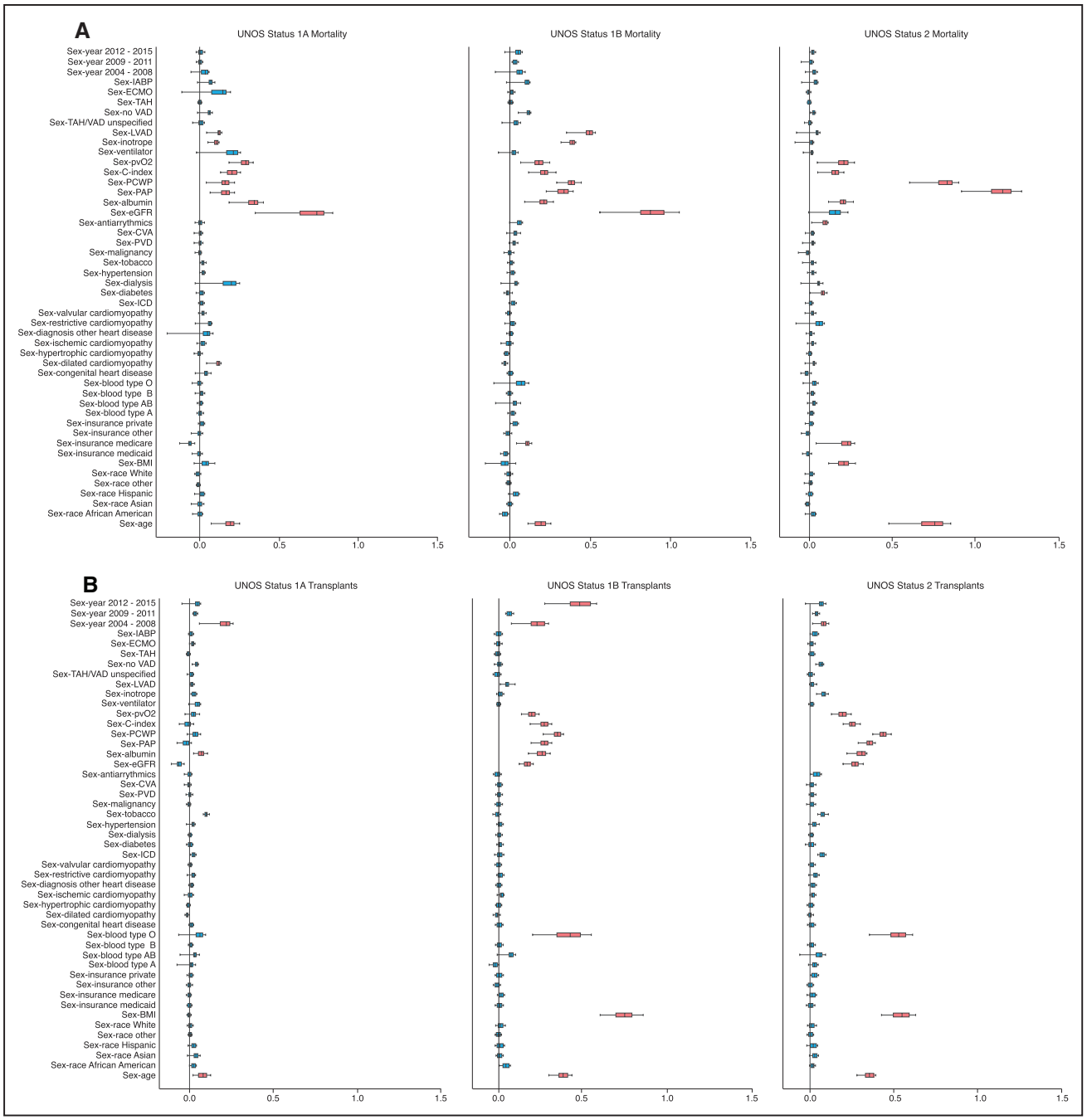

Figure 4. Sex interactions for risk of death and heart transplantation. Variable importance (VIMP) of sex interactions for risk of death (**A**) and heart transplantation (**B**) are depicted based on initially listing as United Network for Organ Sharing (UNOS) status 1A, 1B, or 2. Sex by covariate represents female:male by covariate. Boxes encompass median (line) and 25th and 75th percentile confidence limits, and whiskers 95% confidence limits. Black vertical line at 0.0 VIMP represents the point at which an interaction does not contribute predictive power to the model. Thus, blue boxes indicate interactions noncontributory and red boxes indicate interactions contributing to predictive power. BMI indicates body mass index; CVA, cerebral vascular accident; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; IABP, intra-aortic balloon pump; ICD, implantable cardioverter defibrillator; LVAD, left ventricular assist device; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVD, peripheral vascular disease; PVO_2, peak oxygen consumption; TAH, total artificial heart; and VAD, ventricular assist device.

initially listed as UNOS status 1B, the sex disparity in survival increased after 2011 with men surviving better than women despite a faster rate of heart transplantation in women than in men. The reason remains unclear and is concerning because UNOS status 1B patients are deemed in urgent need of transplantation because they failed conventional therapy and required either inotropes or mechanical circulatory support to survive. Although it is tempting to consider sex differences in the bioavailability of inotropes, this would not explain any changes in mortality over time because inotrope support did not change over this study period. Could sex differences in survival among UNOS status 1B simply reflect

a higher percentage of women bridged to transplantation on inotropes than men after 2011? Possible but in 2012 to 2015, the percent of women listed as UNOS status 1B with inotropes was similar to men (45% women and 40% men). What about mechanical circulatory support? We do not know whether there were any sex differences in survival or in complications with the most recent generation of devices because the last Intragency Registry for Mechanically Assisted Circulatory Support analysis assessing sex differences with LVADs involved patients with devices implanted between 2006 and 2010.[14] Therefore, the reason why sex differences in outcome still exist remains unknown but likely lies within the complex interplay of sex with many variables related to waitlist mortality and transplantation.

We have identified >20 factors that importantly interact with sex to affect waitlist prognosis. This is astonishing when you consider that women and men are listed based on criteria that are not sex specific and factors affecting transplantation are not supposed to favor one sex over another. Although some sex interactions were unique for a given UNOS status, urgent heart transplantation (UNOS status 1A and 1B) shared many sex interactions for death not previously known such as renal function, serum albumin, hemodynamics parameters, LVAD, and inotropes. Renal function was the most important sex interaction and is concerning given its significance for predicting survival in heart failure.[15,16] Serum albumin is a biomarker for liver function and nutritional state. It has not been included in most heart failure risk models[17,18] but has been found to be a predictor of death in heart failure,[19–22] congenital heart disease,[23] and in patients undergoing LVAD implantation.[24,25] Hemodynamic parameters are often used to determine candidacy for inotrope or mechanical circulatory support and not known to have any sex interaction. They are deemed valuable despite the lack of added prognostic significance to the noninvasive Heart Failure Survival Score,[17] an advanced heart failure survival model limited by a small derivation cohort (n=268) and the inclusion of ambulatory patients before LVADs. Sex interactions for survival with LVADs and inotropes are worrisome because these variables are used to define urgent transplantation. They have not been found previously, and previous literature suggested a similar survival for women and men with LVAD although a higher risk of stroke in women.[14] Finally, sex interactions with peak oxygen consumption[26] and age[27] have been published previously yet have not changed criteria for listing patients for transplantation.

There were many sex interactions for transplantation. Limited data exist on variables associated with higher rate of heart transplantation. However, sex is known to be a factor necessary to optimize matching of donor and recipient[28] along with body mass index, blood type, and other immune factors (allosensitization). In our analysis, we showed a lower rate of heart transplantation in women compared with men initially listed as UNOS status 1A and a higher rate of transplantation in women compared with men initially listed as UNOS status 1B or 2. Among UNOS 1A patients, there were few sex interactions for heart transplantation. However, many sex interactions for heart transplantation were identified among patients initially listed as UNOS status 1B and 2. Although the importance of the sex interactions varied, UNOS status 1B and 2 shared sex interactions for blood type O, age, body mass index, hemodynamics, serum albumin, peak oxygen consumption and renal function. None of these, to the best of our knowledge, have been described previously, and all raise concern on inequality with transplantation.

The UNOS Thoracic Organ Transplantation Committee proposed in 2016 a new heart transplant allocation system with more tiers to define urgency given known disparity in survival among certain subgroups.[29,30] How will these changes affect women? It remains unclear because the additional tiers mainly define urgency for existing criteria and do not include sex differences. What should we do to reduce sex differences in waitlist mortality? More research is needed before we can include sex differences in the UNOS allocation system or guideline therapy. For instance, which woman listed for urgent transplantation is at highest risk of death? This is important because not all women can be given priority over men who are critically ill. The answer remains unknown and is likely complex. Further research is needed and should focus on how devices and other therapy affect women differently than men and what comorbidities further modify the risk of death and the rate of transplantation. Only with knowledge on population differences are we able to improve our allocation system and provide more equitable distribution of organs.

Limitations

The SRTR database is a large national database that is subject to human error during data entry. This remains a potential problem for all databases but is minimized in SRTR by edit checks, validation of data at time of entry, and internal verification when there are outliers. Data quality specialists resolve these potential problems by reviewing the data and verifying discrepant data with the involved transplant center. Transplant centers are routinely audited by UNOS and Centers for Medicare and Medicaid Services, which further improve the quality of the database. Despite these attempts, there are data that cannot be used because of lack of standardization until recently (ie, panel of reactive antibody), missing data, and possible database errors. Missing data can be imputed if percent is low and will not alter significantly the analysis. Data with high level of missingness are often removed from a standard multiregression analysis. Therefore, we could not use peak oxygen consumption (>30% missing) with the Cox proportional hazard analysis but was able to use it with RSF analysis, a machine learning statistical methods that performs excellently even with heavy missingness (up to 75%) and when missing data are not missing completely at random. Other limitations worthy of discussion are possible database errors in entry of clinical information. The baseline characteristics for UNOS status 2 included a small percent of patients on mechanical ventilation, inotropes, or mechanical circulatory support. These seem to be errors because the level of medical support does not match the severity of illness for an ambulatory UNOS status 2 candidate. However, centers may list at a lower UNOS status than clinically indicated so it remains unknown whether these are actual database errors or patients intentionally labeled at lower status to prevent

heart transplantation while ill. Nonetheless, the low percent of possible errors in UNOS status would not be expected to alter our analysis significantly. Finally, despite the fact that the SRTR database is the best database available to study patients awaiting transplantation, it only captures information at given time points and does not require updating data unless the change affects the UNOS status of the patient. A full set of characteristics is obtained at the time of listing and at the time of transplantation. If time-varying covariables were known and available while patients remained on a waitlist, more data could be used to predict events and better understand the reasons for an event.

Conclusions

In a large national registry, we found sex differences in survival while awaiting heart transplantation, sex differences in transplantation, and many sex interactions for risk of death and transplantation when data were evaluated by UNOS status at the time of initial transplant wait listing. Outcomes have changed over time with resolution of sex disparities in waitlist survival among patients initially listed as UNOS status 1A and 2 but have increased since 2011 among patients initially listed as UNOS status 1B. The reasons remain unknown but are concerning because women initially listed as UNOS status 1B had a higher risk of death despite a faster rate of transplantation.

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Disclosures

None.

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CLINICAL PERSPECTIVE

For almost a decade, women have had a higher mortality rate on the national heart transplant waitlist and the cause remains unclear. To further evaluate, we utilized the scientific registry of transplant recipients with >30 000 patients (25% women) and stratified the cohort based on sex and United Network for Organ Sharing (UNOS) status at time of listing. Women had a higher mortality than men at the most urgent UNOS status (1A and 1B) even after adjusting for >20 risk factors including mechanical circulatory support and inotropes. These sex differences resolved over time for UNOS status 1A but worsened for UNOS status 1B despite a higher rate of transplantation for women than men listed as UNOS status 1B. The reasons remain unclear but likely are because of the complex interplay of sex with many variables related to waitlist mortality and transplantation. In fact, with machine learning statistics, we identified >20 sex interactions for mortality and transplantation that have not been described previously.