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Influence of donor and recipient sex mismatch on heart transplant outcomes: Analysis of the International Society for Heart and Lung Transplantation Registry

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cardiac allograft vasculopathy

BACKGROUND: Prior studies have presented contradictory results after analyzing associations between donor and recipient sex on survival after heart transplantation and causes of death such as acute rejection (AR) and cardiac allograft vasculopathy (CAV). We used the International Society for Heart and Lung Transplantation (ISHLT) Registry, the largest repository of heart transplant outcomes worldwide, to comprehensively address these questions.

METHOD: We studied 60,584 adult recipients of heart transplants performed between 1990 and 2008. Outcomes of interest were overall survival, death-censored allograft survival, AR, and CAV, which were studied using regression models. To assess whether donor/recipient sex mismatch affected outcomes, the experience of male recipients with female vs male donors was compared with that of female recipients with female vs male donors through inclusion of an interaction term between donor and recipient sex.

RESULTS: Significant differences were observed between male and female recipients in overall survival and death-censored allograft survival for female vs male donors. Male recipients of female allografts had a 10% increase in adjusted mortality relative to male recipients of male allografts, whereas female recipients of female allografts had a 10% decrease in adjusted mortality relative to female recipients of male allografts ($p < 0.0001$). Findings were similar for death-censored allograft survival. Differences in the effect of donor sex on AR or CAV between male and female recipients were not significant.

CONCLUSIONS: Analysis of the ISHLT data set has demonstrated a strong association between donor/recipient sex mismatch and reduced survival after heart transplantation.

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Orthotopic heart transplantation (OHT) has evolved into the treatment of choice for patients with end-stage heart disease who continue to have symptoms despite maximal medical therapy. However, outcomes after OHT remain constrained by sub-optimal long-term survival as well as by the development of acute rejection (AR) and cardiac allograft vasculopathy (CAV). These adverse events have motivated the investigation of donor- and recipient-specific characteristics that influence outcomes after OHT.

There are many reasons to believe that the sex of donors and recipients may play an important role in outcomes after OHT. The relationship between sex hormones and immunologic processes has been extensively documented but is not well understood. Several early studies identified female donor sex as an independent predictor of recipient death after OHT.[1–4] Further investigations, however, highlighted the importance of donor/recipient sex mismatch, with demonstration of reduced short- and long-term survival in male recipients of female allografts.[5–8] More recently, an analy-

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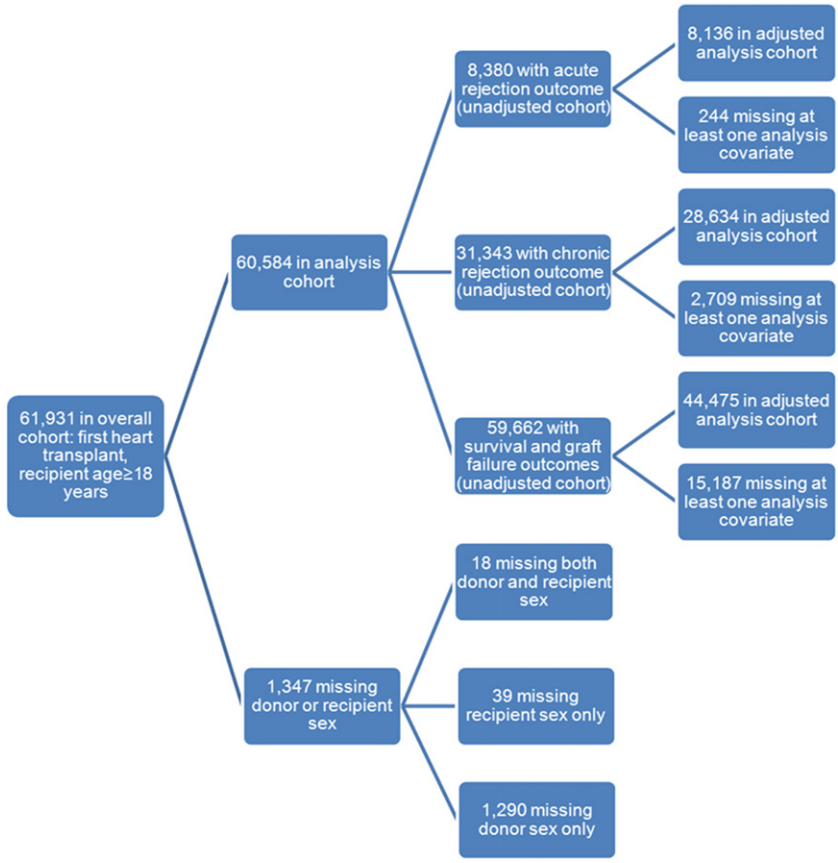

Figure 1 International Society for Heart and Lung Transplantation cohort construction and missing data.

sis of the United Network for Organ Sharing database examined the effect of donor/recipient sex matching on survival after OHT, and demonstrated that men who received male allografts had the highest cumulative 5-year survival compared with other donor/recipient sex combinations.[9]

With respect to other outcomes after OHT, several single-center studies have reported a higher incidence of AR in female allograft recipients.[10,11] Other reports have suggested that donor/recipient sex mismatch increases the number of rejection events after OHT.[7] These studies, however, are all hindered by their small sample size of 150 to 366 participants. Finally, CAV, an obliterative vascular disease of the allograft coronary arteries,[12] is the leading cause of death beyond the first year after OHT.[13,14] Although CAV may be partially immune-mediated, there is a paucity of data examining the role of sex-based differences in development of CAV. Again, single-center reports have suggested associations between donor and recipient sex mismatch and the development of CAV,[15–17] but their results are conflicting.

Given the limitations of prior work on this topic, we analyzed the International Society for Heart and Lung Transplantation (ISHLT) Registry to examine the influence of donor and recipient sex on OHT outcomes during a 20-year period. Unlike prior studies, we compare the experience of male recipients with sex-matched vs mismatched allografts with the experience of female recipients with sex-matched vs mismatched allografts through use of an interaction term between donor and recipient sex. This approach formally addresses whether donor/recipient sex mismatch is associated with the outcomes of interest.

Methods

Data source

We used registry data provided by the ISHLT, which collects data on the worldwide thoracic organ transplant experience. No patient or center identifiers were included in this analysis; therefore, institutional review board approval was not required by our center.

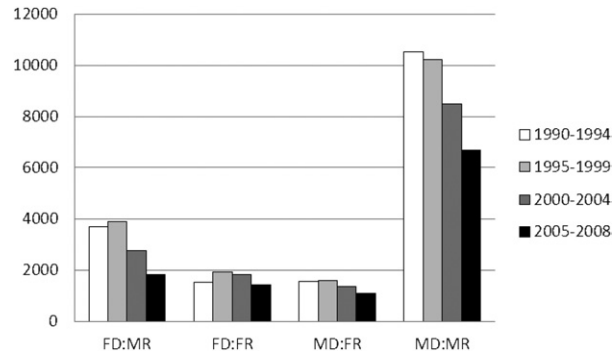

Figure 2 Distribution of heart transplants performed during the study period, stratified by donor and recipient sex and transplant era. FD, female donor; FR, female recipient; MD, male donor; MR, male recipient.

The data set consists of OHTs performed between January 1990 and December 2008, with follow-up through September 2010.

Study design

We retrospectively examined adults (aged ≥ 18 years) who received their first OHT between 1990 and 2008. Of the 61,931 subjects in the overall cohort, 1,347 were excluded due to missing data on donor or recipient sex, yielding a final cohort size of 60,584 (Figure 1).

Study variables and outcomes

The transplant data set contained 297 variables pertaining to the pre-operative, intraoperative, and post-operative period until hospital discharge after the OHT surgery. Follow-up data sets included 54 variables related to outcomes and events after OHT. We selected donor variables, recipient variables, and transplant-specific variables based on clinical relevance and results from prior studies. The end points examined were (1) time to death, (2) time to death-censored allograft failure, (3) AR (treated or not) during the first 2 years after OHT, and (4) development of CAV.

Statistical analysis

Outcome definitions. Overall survival was derived as time from OHT until death. Patients who survived their observed study period were censored at their last follow up. Death-censored allograft survival was defined as time from OHT to occurrence of allograft failure, where patients were censored at their death (if it was unrelated to allograft failure) or at the time of their last follow-up. AR was defined as acute rejection (treated or not) occurring within 2 years of OHT and was assigned to be missing if no rejection status was reported. CAV was defined as coronary artery disease ever occurring during follow-up and was assigned to be missing if CAV status was never reported during follow-up.

Table 1 Characteristics of Study Cohort, Stratified by Donor and Recipient Sex

	Female recipient		Male recipient			
Variables[a]	Female donor	Male donor	Female donor	Male donor	All	*p*-value
Total *N*	6,762 (11)	5,680 (9)	12,215 (20)	35,927 (59)	60,584	
Treatment era						<0.0001
1990–1994	1,536 (23)	1,572 (28)	3,694 (30)	10,518 (29)	17,320	
1995–1999	1,954 (29)	1,609 (28)	3,894 (32)	10,233 (29)	17,690	
2000–2004	1,848 (27)	1,386 (24)	2,788 (23)	8,487 (24)	14,509	
2005–2008	1,424 (21)	1,113 (20)	1,839 (15)	6,689 (19)	11,065	
Recipient demographics						
Age, years	49 ± 12	48 ± 13	52 ± 11	52 ± 11	51 ± 12	<0.0001
Weight, kg	64 ± 13	68 ± 14	75 ± 13	82 ± 14	77 ± 15	<0.0001
Pre-transplant status						
Hospitalized	2,028 (47)	2,422 (56)	4,110 (55)	12,781 (55)	21,341	<0.0001
On inotropes	1,676 (41)	1,874 (44)	3,116 (44)	9,664 (43)	16,330	0.0018
On life support	2,018 (50)	2,263 (55)	3,776 (56)	12,460 (58)	20,517	<0.0001
Recipient comorbidities						
Hypertension	1,075 (31)	1,092 (33)	1,976 (36)	6,854 (39)	10,997	<0.0001
Diabetes	557 (16)	543 (17)	969 (19)	3,685 (22)	5,754	<0.0001
Serum creatinine, mg/dl	1.12 ± 0.51	1.14 ± 0.49	1.35 ± 0.55	1.36 ± 0.52	1.31 ± 0.53	<0.0001
Mean PAP, mm Hg	29 ± 10	30 ± 10	30 ± 10	31 ± 11	30 ± 11	<0.0001
PVR, Woods U	2.8 ± 1.3	2.8 ± 1.3	2.6 ± 1.3	2.6 ± 1.2	2.6 ± 1.3	<0.0001
PRA, %	6.7 ± 8.5	6.6 ± 18.2	2.9 ± 11.6	2.8 ± 10.7	3.7 ± 13.1	<0.0001
Diagnosis						<0.0001
Coronary artery disease	1,617 (24)	1,356 (24)	5,949 (50)	17,427 (49)	26,349	
Cardiomyopathy	3,855 (58)	3,347 (60)	4,827 (40)	14,830 (42)	26,859	
Other	1,167 (18)	900 (16)	1,210 (10)	3,062 (9)	6,339	
Donor characteristics						
Age, years	35 ± 14	28 ± 12	37 ± 13	31 ± 12	33 ± 13	<0.0001
Weight, kg	65 ± 14	72 ± 14	71 ± 15	80 ± 14	76 ± 15	<0.0001
Cause of death						<0.0001
Anoxia	439 (7)	307 (6)	676 (6)	1,375 (4)	2,797	
Stroke	2,842 (46)	944 (18)	5,351 (47)	6,793 (21)	15,930	
Head trauma	1,920 (31)	3,080 (58)	3,058 (27)	17,926 (55)	25,984	
CNS tumor	70 (1)	48 (1)	148 (1)	257 (1)	523	
Other	911 (15)	931 (18)	2,055 (18)	6,498 (20)	10,395	
Graft ischemic time, hours	2.6 ± 1.5	2.7 ± 1.3	2.5 ± 1.5	2.6 ± 1.4	2.6 ± 1.4	<0.0001

CNS, central nervous system; PAP, pulmonary artery pressure; PRA, panel reactive antibodies; PVR, Pulmonary vascular resistance.
[a]Continuous data are shown as mean ± standard deviation and categoric data as number (%).

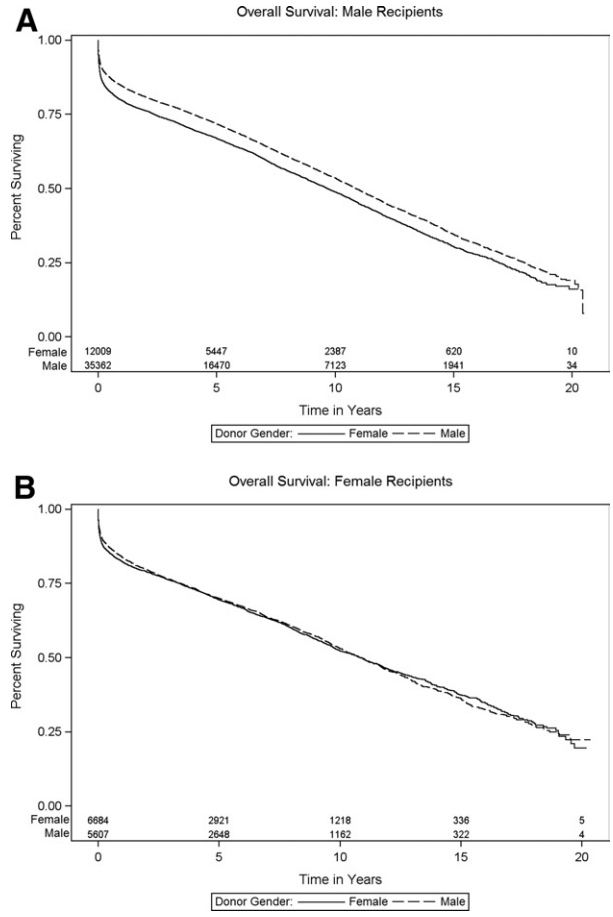

Figure 3 Kaplan-Meier estimates show overall survival for (A) male and (B) female heart transplant recipients, stratified by donor and recipient sex.

Analytic tools. Regression techniques were used to assess whether an association existed between donor/recipient sex mismatch and outcomes of interest. For time to death and time to death-censored allograft failure, Cox proportional hazards models that account for censoring were used. The former yields odds ratios (ORs) and the latter yields hazard ratios (HRs), with respective 95% confidence intervals (CI) that describe the differential risk in outcome by donor and recipient sex status. For time-to-event data, Kaplan-Meier estimates were generated to graphically depict survival curves corresponding to 4 donor/recipient sex combinations. For the binary outcomes (AR and CAV), logistic regression techniques were used. All analyses were performed with SAS 9.2 software (SAS Institute, Cary NC).

Missing data. For all analyses, a complete case analysis was performed, and patients missing at least 1 variable in the model (outcome or covariate) were excluded from the analysis. Implausible values were observed for several variables. This phenomenon most likely stems from the multinational nature of the ISHLT database resulting in the use of various measurement scales. No assumptions could be made about the measurement system used, however, for a particular value. For these variables, values that were determined to be outside a plausible range were set to missing. An exception was with pulmonary vascular resistance, where the ranges of plausible values assuming 2 common scales did not overlap and hence values on one scale (between 80 and 560 dynes-sec/cm^5) were recalibrated to the other (divided by 80 to yield Wood Units).

Potential confounders. We adjusted for recipient-, donor-, and transplant-related characteristics. These included donor and recipient age, donor cause of death, recipient diagnosis (indication for OHT), and transplant era, which was defined by year of transplant in 4 categories: 1990 to 1994, 1995 to 1999, 2000 to 2004, and 2005 to 2008. To further explore donor/recipient weight mismatch as a potential confounder, we included weight as a covariate in the models in 3 ways (1) donor and recipient weight, (2) difference between donor and recipient weight, and (3) ratio of recipient weight to donor weight. We were unable to adjust for other potentially relevant covariates (such as graft ischemic time, recipient waiting list prioritization status, and recipient comorbidities) due to the large amount of missing data for each variable.

Models. To assess whether there is an effect of donor/recipient sex mismatch on OHT outcomes, it is of interest to evaluate whether the experience of a female recipient with a female (vs male) allograft differs from that of a male recipient with a female (vs male) allograft. This is equivalent to assessing whether there is an interaction effect between the sex of the donor and recipient. Thus all models include recipient and donor sex as main effects as well as a product term of the two. Unadjusted models included only main effects and the interaction term. Adjusted models included these terms as well as the covariates listed above.

Results

Study cohort

We examined 60,584 adults (79% men) receiving their first OHT. The mean recipient age was 51 ± 12 years, and the main indications for OHT were dilated cardiomyopathy (45%) and coronary artery disease (44%). The median follow-up was 4.1 years (interquartile range, 8.2 years) and 24,531 recipients died during this follow-up period. Cate-

Table 2 Death—Unadjusted and Adjusted Cox Proportional Hazards Models

Model	Size (*n*)	Recipient	Donor	HR (95% CI)	Interaction *p*-value[a]
Unadjusted	59,662	Male	Female vs male	1.18 (1.14–1.21)	<0.001
		Female	Female vs male	1.01 (0.96–1.07)	
Adjusted	24,136	Male	Female vs male	1.10 (1.04–1.17)	<0.001
		Female	Female vs male	0.90 (0.83–0.98)	

CI, confidence interval; HR, hazard ratio.
[a]*p*-value to compare male and female recipients' experience in receiving a sex-matched vs mismatched allograft.

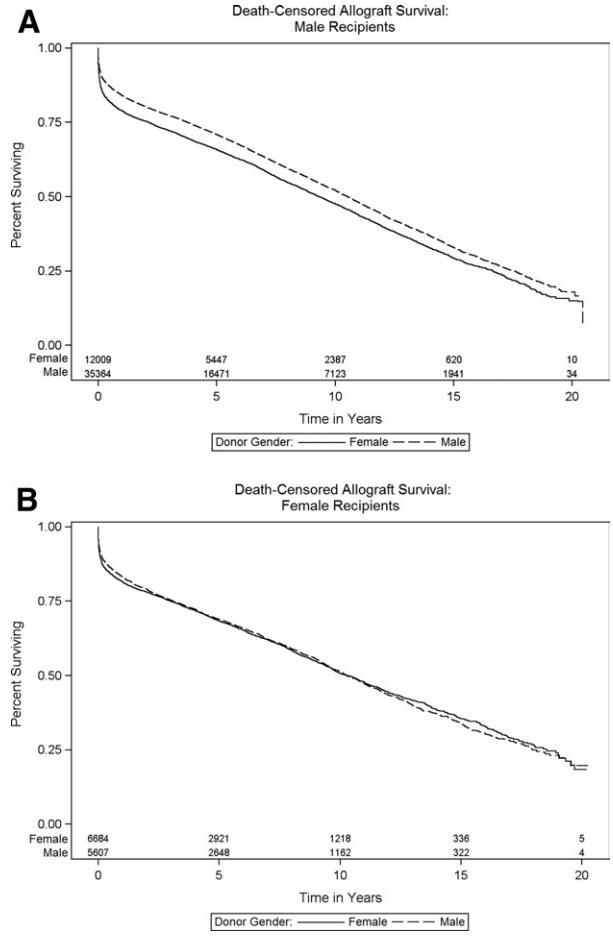

Figure 4 Kaplan-Meier estimates show of death-censored allograft survival for (A) male and (B) female heart transplant recipients, stratified by donor and recipient sex.

gorization of recipients by donor sex resulted in 4 groups: 35,927 male recipients–male donors, 12,215 male recipients–female donors, 5,680 female recipients–male donors, and 6,762 female recipients–female donors. The distribution of donor/recipient sex groups by transplant era, divided in 5-year intervals, is presented in Figure 2.

Baseline characteristics

There were significant differences between male and female recipients at baseline (Table 1). Specifically, male recipients were older and heavier. They had a higher incidence of hypertension and diabetes, higher serum creatinine, and were more likely to have coronary artery disease as the indication for OHT. Moreover, male recipients were more likely to be hospitalized and require hemodynamic support before OHT. Female recipients had higher pulmonary vascular resistance and panel reactive antibody, and a slightly longer allograft ischemic time. Donors of cardiac allografts to male recipients tended to be older and had a higher incidence of head trauma as the cause of death compared with donors of allografts to female recipients.

OHT outcomes

Our multivariate models showed significant differences between male and female recipients in overall survival and death-censored allograft survival for female vs male donors. Male recipients of female allografts had increased mortality relative to male recipients of male allografts, whereas female recipients of female allografts had reduced mortality relative to female recipients of male allografts. There were no significant differences in the effect of donor sex on AR or CAV between male and female recipients; however, these analyses were limited by the large amount of missing data on these outcomes as well as by differences between transplant centers in assessing for and reporting the presence of AR and CAV. We have presented the data for models adjusting for donor and recipient weight, among the other covariates mentioned previously. Results did not differ significantly from the models adjusting for donor/recipient weight difference and the ratio of recipient/donor weight (data not shown).

Death and death-censored allograft failure

Data on transplant recipient death and death-censored allograft failure were available for 59,662 of 60,584 (98.5%) donor/recipient pairs. The median survival was 10.6 years (interquartile range, 14.4 years). The effect of donor sex differed significantly between male and female recipients ($p < 0.001$). Specifically, among male recipients, receipt of a female relative to male allograft resulted in a 10% increase in the risk of mortality (HR, 1.10; 95% CI, 1.04–1.17). Female recipients, in contrast, experienced a 10% survival advantage after receipt of a female vs a male allograft (HR, 0.90; 95% CI, 0.83–0.98; Figure 3, Table 2).

We then examined the end point of death-censored allograft failure to focus on allograft failure events leading to

Table 3 Death-Censored Allograft Failure—Unadjusted and Adjusted Cox Proportional Hazards Models

Model	Size (*n*)	Recipient	Donor	HR (95% CI)	Interaction *p*-value[a]
Unadjusted	59,664	Male	Female vs male	1.17 (1.14–1.21)	<0.001
		Female	Female vs male	1.01 (0.96–1.07)	
Adjusted	24,136	Male	Female vs male	1.09 (1.03–1.15)	0.0003
		Female	Female vs male	0.91 (0.83–0.99)	

CI, confidence interval; HR, hazard ratio.
[a]*p*-value to compare male and female recipients' experience in receiving a sex-matched vs mismatched allograft.

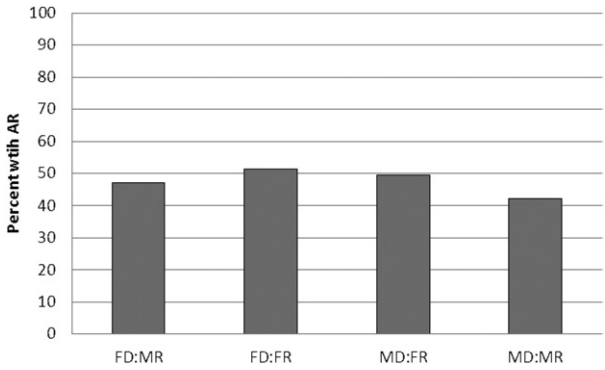

Figure 5 Incidence of acute rejection by 2 years after transplant, stratified by donor and recipient sex. FD, female donor; FR, female recipient; MD, male donor; MR, male recipient.

death or retransplant. Similar to overall survival, male and female recipients differed in their experience with respect to donor sex ($p = 0.0003$; Figure 4, Table 3). Male recipients of female allografts had a 9% increase in the risk of adjusted death-censored allograft failure relative to male recipients of male allografts (HR, 1.09; 95% CI, 1.03–1.15). Conversely, examination of female recipients revealed a slight decrease in the relative hazard of death-censored allograft failure between those receiving same vs opposite sex donor organs (HR, 0.91; 95% CI, 0.83–0.99).

AR and CAV

To further investigate possible causes for the differential survival seen between sex-matched vs mismatched allografts, we examined 2 common complications after OHT: AR and CAV. These analyses were limited by the large amount of missing data on these outcomes in the ISHLT Registry. Specifically, data on AR were available on 8,380 of 60,584 recipients (14%) and data on CAV were available for 31,343 recipients (52%). Furthermore, methods for diagnosis and voluntary reporting of these complications after OHT varied between centers. Thus, these results are suggestive but not definitive and should be interpreted with caution.

AR had a 45% incidence during the first 2 years after OHT (Figure 5). Although men who received female vs male allografts had a 22% increase in the odds of AR, and women who received female vs male allografts had no increase in the odds of AR, the effect of donor sex did not differ significantly by recipient sex ($p = 0.27$). Models that adjust for potential confounders yielded comparable descriptions of these relations (Table 4).

The overall incidence of CAV development, at any time after OHT, was 39% (Figure 6). Receipt of a female allograft was associated with a lower incidence of CAV. Specifically, men who received a female vs male allograft had a 19% lower odds of developing CAV (OR, 0.81; 95% CI, 0.74–0.88). Similarly, women who received a female vs male allograft had 18% lower odds of developing CAV (multivariate OR, 0.82; 95% CI, 0.72–0.93; Table 5), where the effect of donor sex on CAV did not differ by recipient sex ($p = 0.9$).

Discussion

We have leveraged the advantages provided by the ISHLT Registry, the largest existing data repository of OHT outcomes worldwide, to examine differences in survival after OHT based on donor and recipient sex. We then explored the survival differences identified by examining differences in AR and CAV in sex-matched vs mismatched transplants, although these analyses were limited by missing data and inconsistent data quality. In doing so, we have built upon previous studies in which these end points were studied individually.

We first examined differences in survival between our 4 donor/recipient sex strata, and demonstrated that OHT patients who receive a sex-matched allograft have improved survival compared with those with sex-mismatched allografts. This observation is especially profound for male recipients of female allografts, who consistently demonstrate the lowest short- and long-term survival. To specifically examine the relationship between sex-differences and allograft loss after OHT, we studied the end point of death-censored allograft failure, which includes allograft loss leading to death or retransplantation and excludes deaths due to causes other than allograft failure, such as infection and malignancy. As with overall survival, this analysis also showed inferior outcomes in OHT with sex-mismatched allografts, with the poorest outcomes for male recipients of female allografts.

Previous studies have demonstrated inferior survival after OHT in male recipients of female allografts. These range from single-center studies of 174[7] to 869[5] heart transplants, to multicenter registry studies including 18,000[9] to 25,000[8] OHT procedures. By using the ISHLT Registry, we were

Table 4 Acute Rejection—Unadjusted and Adjusted Logistic Regression Models

Model	Size (*n*)	Recipient	Donor	OR (95% CI)	Interaction *p*-value[a]
Unadjusted	8,380	Male	Female vs male	1.22 (1.07–1.38)	0.27
		Female	Female vs male	1.21 (1.05–1.39)	
Adjusted	7,638	Male	Female vs male	1.21 (1.05–1.39)	0.25
		Female	Female vs male	1.06 (0.87–1.28)	

CI, confidence interval; OR, odds ratio.

[a]*p*-value to compare male and female recipients' experience in receiving a sex-matched vs mismatched allograft.

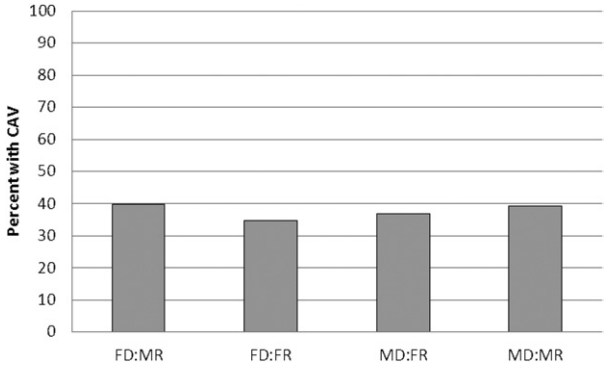

Figure 6 Prevalence of cardiac allograft vasculopathy by last follow-up visit, stratified by donor and recipient sex. FD, female donor; FR, female recipient; MD, male donor; MR, male recipient.

able to confirm these previous findings with survival data on nearly 60,000 heart allograft recipients worldwide.

Several theories have been proposed to explain the increased mortality seen after OHT with sex-mismatched allografts. By examining differences in development of AR and CAV in this large patient population, we were able to examine major complications after OHT that may have affected survival. We did not detect significant differences in AR or CAV between male and female OHT recipients, when comparing sex-matched vs mismatched transplants, suggesting that these complications did not account for the survival differences observed. However, our analyses had limitations. In the case of AR, transplant centers have varying practices with respect to endomyocardial biopsies and other routine screening techniques. Furthermore, voluntary reporting of this post-OHT complication to the Registry was low (14%). The Registry does not have a uniform definition or grading system for CAV, such that some centers may have diagnosed CAV based on angiography and others by intravascular ultrasound imaging. Furthermore, data on CAV severity was not available.

While keeping these limitations in mind, we found significantly lower odds of CAV development in recipients of female donor organs. This finding contrasts with prior single-center studies showing a higher incidence of CAV in recipients of female donor hearts.[11,16–18] The reason behind this discrepancy is unclear, but we suspect that our findings may reflect a higher prevalence of coronary atherosclerosis in male donor organs. Previous studies have shown that donor atherosclerosis is associated with the development of angiographic CAV after OHT.[19] Furthermore, "baseline" coronary angiography with intravascular ultrasound imaging at 1 month after OHT has demonstrated greater coronary artery maximal intimal thickness in male allografts.[20] Thus, recipients of female allografts may have less CAV due to less pre-existing donor disease. However, it is certainly possible that factors after OHT may result in less coronary artery endothelial injury in female allografts. Regardless, we did not detect any difference in CAV development when comparing the experiences of men and women who received a sex-matched vs mismatched allograft.

Other theories for differences in mortality between donor/recipient sex strata refer to genetic, hormonal,[21] and immunologic[22,23] factors. Sex differences in susceptibility to ischemia–reperfusion injury have also been proposed.[8] All of these theories, however, remain speculative and require further investigation. Nevertheless, this study provides further evidence for a significant survival advantage for recipients of sex-matched heart allografts. These data lend support to sex matching, when feasible, bearing in mind the complex nature of the matching process that must account for recipient acuity (waiting list status), donor and recipient blood type, and the presence of pre-formed anti-human leukocyte antigen antibodies in the transplant recipient. This survival advantage persisted after adjusting for donor/recipient weight differences and may therefore support liberalization of our current strategy for size matching.

This study is limited by its retrospective nature because we did not have control over the data quality. Reporting to the ISHLT Registry is voluntary, and there is a large amount of incomplete follow-up and missing data. This limited our ability to include potential confounders in the multivariable models, because doing so would have significantly reduced the sample size and power of our analyses. Variable definitions and inconsistencies in reporting also affected data quality. Furthermore, uniform definitions were lacking for many variables, including the study end points.

We now recognize differences between acute cellular and antibody-mediated rejection based on histologic appearance; however, AR in this data set likely encompasses both processes. In addition, as mentioned, there was no standard definition for diagnosis of CAV. This, combined with a lack of data on CAV severity, limited our ability to further explore these outcomes. We also acknowledge that center-specific differences may affect OHT outcomes—the very large and international experience represented in this database hopefully mitigates that effect.

Table 5 Cardiac Allograft Vasculopathy—Unadjusted and Adjusted Logistic Regression Models

Model	Size	Recipient	Donor	OR (95% CI)	Interaction *p*-value[a]
Unadjusted	31,343	Male	Female vs male	1.02 (0.96–1.08)	0.06
		Female	Female vs male	0.91 (0.83–1.01)	
Adjusted	20,935	Male	Female vs male	0.81 (0.74–0.88)	0.9
		Female	Female vs male	0.82 (0.72–0.93)	

CI, confidence interval; OR, odds ratio.

[a]*p*-value to compare male and female recipients' experience in receiving a sex-matched vs mismatched allograft.

In conclusion, by using the ISHLT Registry, we have demonstrated a strong association between sex-matched allografts and survival. In particular, male recipients of female allografts have reduced overall survival and death-censored graft survival, whereas female recipients of female allografts have an advantage with respect to these outcomes. These results thereby advance our knowledge of sex-related differences in heart transplantation.

Disclosure statement

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None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

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