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Outcomes in patients undergoing cardiac retransplantation: A propensity matched cohort analysis of the UNOS Registry

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BACKGROUND: Cardiac retransplantation accounts for approximately 3% of cardiac transplantation and is considered a risk factor for increased mortality. However, factors inherent to retransplantation including previous sternotomy, sensitization, and renal dysfunction may account for the increased mortality. We assessed whether retransplantation was associated with all-cause mortality after adjusting for such patient risk factors.

METHODS: We conducted a retrospective cohort study of adult and pediatric patients enrolled in the United Network for Organ Sharing database. We identified patients undergoing cardiac retransplantation based on transplant listing diagnosis and history of previous transplant. We used propensity-score matching to identify a matched cohort undergoing initial heart transplantation.

RESULTS: In total, 62,112 heart transplant recipients were identified, with a mean age 46.6 ± 19.1 years. Of these, 2,202 (3.4%) underwent late cardiac retransplantation (>1 year after initial transplant and not for acute rejection). Compared with a matched group of patients undergoing initial heart transplantation, patients undergoing late retransplantation had comparable rates of all-cause mortality at 1 year (13.6% vs 13.8%, $p = 0.733$). In addition, overall mortality was not significantly different after matching (unadjusted hazard ratio [HR] 1.08, $p = 0.084$). In contrast, patients undergoing retransplantation within 1 year of initial transplant or for acute rejection remained at increased risk of mortality post-transplant after similar matching (unadjusted HR 1.79, $p < 0.001$).

CONCLUSIONS: After matching for comorbidities, late retransplantation in the adult population was not associated with an increase in all-cause mortality. Our findings highlight the importance of assessing indication acuity and comorbid conditions when considering retransplant candidacy.

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Survival following cardiac transplantation has improved dramatically over the last 50 years; as a result, many patients are now surviving until they develop late complications of cardiac transplantation such as cardiac allograft vasculopathy (CAV), or late graft failure.[1] In select patients with advanced CAV and graft failure, retransplantation may represent the only option to improve survival and quality of life.[2,3] The number of patients who are candidates for cardiac retransplantation is rising, and they currently comprise 3.0% of adult cardiac transplant

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recipients.[3–5] Given the potential increase in retransplantation, it is necessary to clearly define post-transplant outcomes.

There have been several studies that have described outcomes after cardiac retransplantation. In a single-center study by Goerler et al,[6] retransplantation ($n = 41$) was found to be associated with worse 1-year survival (83% vs 53%, $p < 0.01$), but their study included patients with both acute and chronic graft failure. Studies from Columbia and Stanford University showed similarly poor 1-year survival.[7,8] An analysis of 106 patients in the multi-institutional Cardiac Transplant Research Database demonstrated worse 1-year survival in patients transplanted for acute rejection, but not in patients undergoing retransplantation for CAV.[9]

An analysis of cardiac retransplant recipients using the International Society for Heart and Lung Transplantation (ISHLT) database described poor outcomes after retransplant in patients with both acute and chronic graft failure.[10] Post-transplant survival remained inferior in the subset of patients with chronic graft failure, without correction for comorbidities or sensitization status.[10] In another analysis based on the ISHLT database, retransplantation was associated with a 50% increased risk of mortality at 1 year,[4] after correcting for recipient and donor demographics as well as previous cardiac surgery. A separate analysis of the ISHLT database yielded similar findings after correcting for allosensitization, defined as panel reactive antibody (PRA) >20%.[11] Neither analysis accounted for acute indications for retransplantation in their final adjusted analyses.

There are several hypotheses for the inferior survival seen after retransplantation. All patients undergoing cardiac retransplantation had undergone previous cardiac surgery, which is also associated with decreased 1-year post-transplant survival.[12,13] In addition, patients undergoing retransplantation have been exposed to a previous allograft and could be more sensitized, which increases the risk of CAV and post-transplant mortality.[14] Patients undergoing retransplantation are also more likely to be on dialysis before transplant, which is independently associated with increased 1-year mortality post-transplant.[11] Lastly, patients undergoing retransplantation have longer cumulative exposure to immunosuppression, which may increase risk of post-transplant infections or malignancies.[5,15]

As summarized, studies addressing cardiac retransplantation outcomes did not account for all potential confounders. To address some of these limitations, we used propensity-score matching to assess whether retransplantation for a chronic indication is independently associated with worse post-transplant outcomes after correcting for important patient characteristics.

Methods

Study design and population

This was a retrospective cohort study of adult and pediatric patients enrolled in the United Network for Organ Sharing (UNOS) database between January 1996 and November 2017. Patient inclusion and exclusions are outlined in Supplementary Figure S1 (available online at www.jhltonline.org/). Patients who did not have follow-up status recorded in the database and those in whom a listing diagnosis was not recorded were excluded. Patients undergoing combined heart-lung transplantation were also excluded. Patients who underwent cardiac retransplantation were identified based on the primary diagnosis for transplantation or a record of previous transplantation. The following codes were used to identify patients undergoing cardiac retransplantation (1100, 1101, 1102, 1103, 1104, 1105, 1106, 1199) with full details in Supplementary Table S1 (available online). Patients with more than 1 transplant record in the UNOS database during the study period have different baseline characteristics and therefore were treated as separate patients, post-transplant. Timing of retransplantation was categorized as early if occurring ≤1 year from previous transplant or late if >1 year. A period of 1 year was chosen based on previous definitions,[15,16] with CAV becoming the main indication for retransplantation after that time.[11] In addition, patients with acute or hyperacute rejection were identifed using diagnosis codes 1100 and 1101. Patients undergoing retransplantation for acute rejection were considered separately based on existing evidence for worse post-transplant outcomes in this group.[9] Patients undergoing cardiac retransplantation for acute indications, or before 1 year, were considered as a separate cohort (early/acute).

PRA and calculated PRA were combined as a single variable given inconsistent recording of PRAs in the UNOS database. Calculated PRA was preferentially included if both were available. The higher of class I or class II PRA was used if stratified values were available similar to other reports using the UNOS database.[17,18] Patients without documented sensitization status were excluded ($n = 6{,}525$). Patients with either a history of previous cardiac surgery or previous heart transplant were considered to have had a previous sternotomy.

Outcomes

Our primary outcome was post-transplant all-cause mortality. Our secondary outcomes included 1-year patient survival and survival free of all-cause mortality or retransplantation. Retransplantation reflects second retransplant in the late retransplantation group.

Statistical analysis

Baseline characteristics of patients undergoing cardiac retransplantation were compared with patients undergoing initial cardiac transplant. Continuous variables were summarized as mean (standard deviation) if normally distributed and compared using a Student's *t*-test. Continuous variables which were not normally distributed were summarized as median (interquartile range [IQR]) and compared using a Wilcoxon's rank sum test. Categorical variables are summarized as number (proportion) and compared using a chi-square test. In the primary analysis, 1:1 nearest-neighbor propensity-score matching was performed using factors included in the Scientific Registry of Transplant Recipients (SRTR) 1-year patient survival model as of January 2017 to match retransplant patients with patients undergoing initial transplant (Model 1: propensity matching).[19] Recipient variables included: age, sex, race, education, diabetes, left ventricular assist device (LVAD), total artificial heart, previous cardiac surgery, dialysis before transplant, transfusions since transplant listing, ventilator before transplant, pulmonary artery systolic pressure (PASP), pulmonary capillary wedge pressure, cardiac output, body mass index, serum creatinine, total bilirubin, and total ischemic time. Donor variables included: age, sex, race, cause of death, diabetes, history of malignancy, cocaine use, other drug use, public health service high-risk donor, body mass index, donor-to-recipient weight ratio, donor-to-recipient height

ratio, Epstein-Barr virus serostatus, blood urea nitrogen, and donor anti-hypertensive medications. Sensitization status was included given its hypothesized importance in the outcomes of patients undergoing cardiac retransplantation. Time periods were based on groups previously used in the ISHLT registry and included in the matching variables (1996−2001; 2002−2008; 2009−2017).[1]

A secondary analysis was performed (Model 2: parsimonious propensity matching), with propensity-score matching using only characteristics with hypothesized clinical importance (age, sex, PRA, previous sternotomy, and pre-transplant dialysis). In addition, a multivariable Cox proportional hazards analysis (Model 3: multivariable analysis) was performed in the entire cohort using variables included in propensity matching (Model 1).

In order to fully evaluate the mechanisms underlying post-transplant outcomes, additional sensitivity analyses were performed using the primary analysis (Model 1) without matching for sternotomy, and separately without matching for PRA (including patients without sensitization status). Lastly, the primary analysis was performed separately in pediatric (age < 18 years) and adult (age ≥ 18 years) patients as well as stratified by time period.

Baseline demographics of the matched populations were compared. Matched and unmatched 1-year events rates were reported and Kaplan-Meier survival curves were used to visualize the impact of cardiac retransplantation on post-transplant outcomes. Univariable Cox proportional hazards modeling was used to assess the association between cardiac retransplantation and post-transplant survival as well as with the rate of death or retransplantation.

The proportional hazards assumption was assessed using Schoenfeld residuals and was found to be valid in the primary analyses. Collinearity was assessed with a covariance matrix, and no significant collinearity identified. All statistical tests were 2-sided, and a p value < 0.05 was considered significant. All analyses were performed using Stata/IC version 13.1 (StataCorp, College Station, TX).

Results

In total, 62,112 patients were identified in the UNOS heart transplant database, of which 2,202 (3.5%) underwent late cardiac retransplantation at a median of 9.4 years (IQR 5.7−14.0 years) after initial transplant. An additional 349 (0.6%) patients underwent early/acute retransplant at a median of 154 days (IQR 4−322 days). Time to retransplantation for both groups are outlined in Figure 1. Median follow-up was 5.0 years (IQR 1.7−9.6 years), with slightly shorter follow-up in patients undergoing late retransplantation compared with initial heart transplantation (median 4.9 vs 5.0 years, $p = 0.015$).

Patient demographics are outlined in Table 1. Patients undergoing late cardiac retransplantation were younger, with mean age 36.9 vs 47.3 years ($p < 0.001$), were less likely to receive an LVAD before transplant (4.3% vs 22.5%, $p < 0.001$), and were more likely to require dialysis before transplantation (9.3% vs 3.1%, $p < 0.001$). In the non-propensity matched analysis, patients undergoing late cardiac retransplantation were more likely to die within 1 year (13.8% vs 10.9%, $p < 0.001$). Early/acute retransplantation was associated with the highest rate of death within 1 year (35.0% vs 13.8%, $p < 0.001$). Kaplan-Meier survival curves for patients undergoing intial transplant, late retransplantation, or early/acute retransplantation (acute rejection, hyperacute rejection or within 1 year of initial transplant) are shown in Figure 2. Patients undergoing early/acute retransplantation (unadjusted hazard ratio [HR] 1.95, 95% confidence interval [CI] 1.69−2.26, $p < 0.001$) or late retransplantation (unadjusted HR 1.22, 95% CI 1.14−1.30,

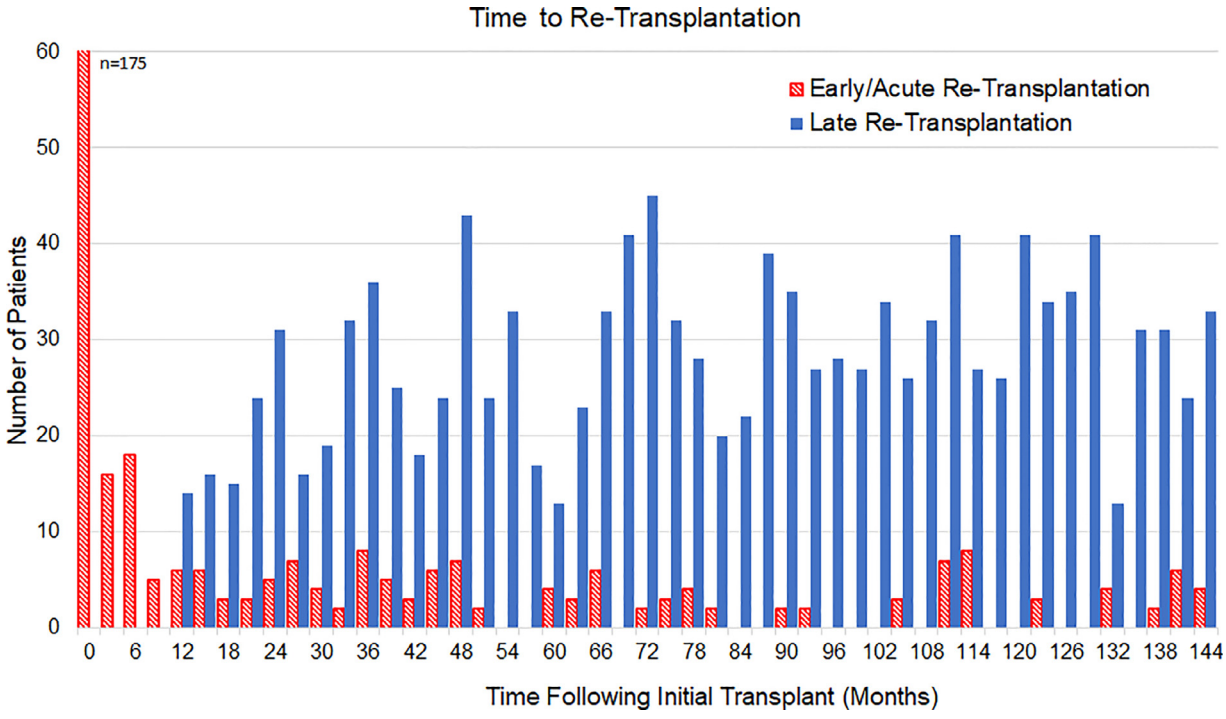

Figure 1 Distribution of time to retransplantation in patients classified as late (blue) and early/acute (red) retransplantation. Early/acute retransplantation includes patients retransplanted within 1 year and those retransplanted for acute or hyperacute rejection. An additional 657 patients underwent late retransplantation more than 12 years after their initial transplant.

Table 1 Baseline Population Characteristics

Characteristics	All patients ($n = 62,112$)	Late retransplant ($n = 2,202$)	Early retransplant ($n = 349$)	Initial transplant ($n = 59,553$)	p Value late vs early	p Value late vs initial
Recipient						
Age (years)	46.6 ± 19.1	36.9 ± 19.3	39.6 ± 20.0	47.3 ± 18.7	0.015	<0.001
Male	46,438 (72.2%)	1,332 (60.5%)	213 (61.0%)	4,4893 (72.7%)	0.860	<0.001
Body mass index	25.9 (22.3–29.8)	23.8 (18.9–28.2)	24.6 (20.4–28.9)	26.0 (22.5–29.8)	0.243	<0.001
Diabetes	13,471 (21.0%)	333 (15.1%)	51 (14.6%)	14,382 (20.9%)	0.872	<0.001
PRA (%)	0 (0–8)	4 (0–52)	0 (0–20)	0 (0–7)	<0.001	<0.001
Sensitized (PRA ≥ 10%)	15,485 (24.1%)	1,004 (45.6%)	114 (32.7%)	14,367 (23.3%)	<0.001	<0.001
Prior sternotomy	20,976 (32.6%)	2,202 (100.0%)	349 (100.0%)	18,425 (29.8%)	1.000	<0.001
Pre-transplant dialysis	2,186 (3.4%)	204 (9.3%)	71 (20.3%)	1,911 (3.1%)	<0.001	<0.001
LVAD	13,540 (21.8%)	94 (4.3%)	56 (15.7%)	13,390 (22.5%)	<0.001	<0.001
TAH	35 (0.3%)	1 (0.3%)	0 (0.0%)	34 (0.3%)	1.000	1.000
Ventilator since listing	338 (0.5%)	8 (0.4%)	7 (2.0%)	323 (0.5%)	0.002	0.365
Transfused since listing	14,725 (22.9%)	462 (21.0%)	181 (51.9%)	14,082 (22.8%)	<0.001	0.046
PASP	42 (32–49)	35 (27–42)	41 (33–45)	42 (32–50)	<0.001	<0.001
PCWP	19 (13–24)	19 (13–20)	19 (18–22)	19 (13–24)	<0.001	<0.001
Cardiac output	4.4 (3.6–5.0)	4.4 (3.5–4.8)	4.4 (3.5–4.6)	4.4 (3.6–5.1)	0.606	0.012
Donor						
Age (years)	26 (19–39)	24 (17–37)	24 (17–36)	26 (19–39)	0.802	<0.001
Male	43,962 (68.4%)	1,342 (60.9%)	242 (69.3%)	42,378 (68.6%)	0.003	<0.001
Diabetes	1,463 (2.3%)	42 (1.9%)	2 (0.6%)	1,419 (2.3%)	0.078	0.246
Cocaine use	6,772 (10.5%)	178 (8.1%)	26 (7.5%)	6,568 (10.6%)	0.751	<0.001
Other drug use	13,856 (21.5%)	335 (15.2%)	66 (18.9%)	13,455 (21.8%)	0.082	<0.001

LVAD, left ventricular assist device; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; PRA, panel reactive antibody; TAH, total artificial heart.

PRA ≥ 10% was considered sensitized. Categorical variables expressed as number (proportion). Continuous variables expressed as mean (standard deviation) If normally distributed and as median (interquartile range) if not normally distributed.

$p < 0.001$) had worse survival in unadjusted analyses when compared with initial heart transplant recipients.

Model 1. Propensity matching

The characteristics of the matched groups are shown in Table 2. The populations were not perfectly matched for sensitization (45.6% in retransplant vs 41.6% in matched patients, $p = 0.007$). Patients undergoing retransplantation had lower PASP (median 35 vs 42 mm Hg, $p < 0.001$), with a similar proportion of patients with PASP ≥ 60 mm Hg (2.4% vs 2.8%, $p = 0.507$). In the propensity matched cohort, late retransplantation was not associated with increased 1-year mortality (13.8% vs 14.5%, $p = 0.517$). During overall follow-up 914 (41.5%) late retransplantation patients died and 884 (40.2%) initial transplant patients died. In addition, 65 (3.0%) late retransplantation patients and 60 (2.7%) initial transplant patients underwent retransplantation (second retransplant in the late retransplantation group). Kaplan-Meier survival curves for all-cause mortality are shown in Figure 3, and curves for all-cause mortality or retransplantation in Figure 4. Late retransplantation was not associated with a significant increase in all-cause mortality (unadjusted HR 1.08, 95% CI 0.98–1.18, $p = 0.084$) or the combined outcome of death or retransplantation (unadjusted HR 1.07, 95% CI 0.98–1.18, $p = 0.114$).

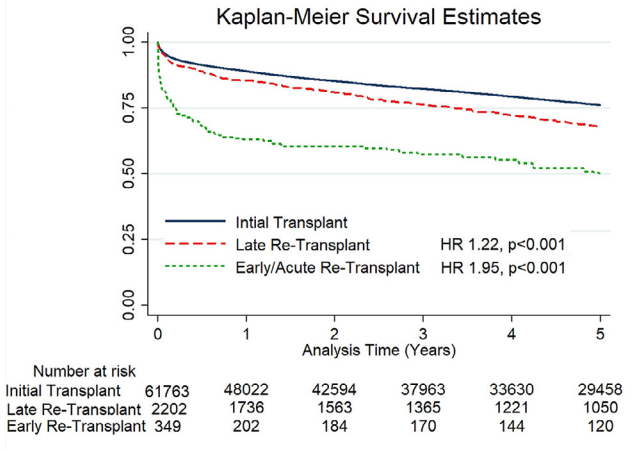

Figure 2 Kaplan-Meier survival curves for all-cause mortality or retransplantation before propensity-score matching. Early/acute retransplantation includes patients retransplanted within 1 year and those retransplanted for acute or hyperacute rejection. HR, hazard ratio.

Propensity matching was performed in patients undergoing retransplantation within 1 year ($n = 214$) or for acute rejection ($n = 135$). One-year mortality remained higher in early/acute retransplant recipients compared with the matched cohort (35.0% vs 21.6%, $p < 0.001$). During overall follow-up, 199 (55.7%) early/acute retransplant patients died and 174 (48.7%) initial transplant patients died, with 15 (4.2%) early/acute retransplant patients and 12 (3.4%) initial transplant patients undergoing retransplantation.

Table 2 Population Characteristics of Matched Populations

Characteristics	All patients ($n = 4,404$)	Retransplant ($n = 2,202$)	Initial transplant ($n = 2,202$)	p Value
Recipient characteristics				
Age (years)	37.0 ± 20.7	36.9 ± 19.3	37.0 ± 22.0	0.798
Male	2,650 (60.2)	1,332 (60.5%)	1,341 (61.0)	0.759
Body mass index	24.0 (19.2–28.4)	23.8 (18.9–28.2)	24.3 (19.6–28.3)	0.061
Diabetes	629 (14.3)	333 (15.1%)	339 (15.4%)	0.834
PRA	3 (0–51)	4 (0–52)	2 (0–50)	0.023
Sensitized (PRA ≥ 10%)	1,919 (43.6%)	1,004 (45.6%)	915 (41.6%)	0.007
Prior sternotomy	4,404 (100.0)	2,202 (100.0%)	2,202 (100.0%)	1.000
Pre-transplant dialysis	402 (9.1%)	204 (9.3%)	198 (9.0%)	0.753
LVAD	207 (4.7%)	94 (4.3%)	113 (5.1%)	0.200
TAH	51 (1.2%)	24 (1.1%)	27 (1.2%)	0.779
Ventilator	10 (0.2%)	8 (0.4%)	2 (0.1%)	0.109
Transfused since listing	903 (20.5%)	462 (21.0%)	441 (20.0%)	0.455
PASP	38 (29–42)	35 (27–42)	42 (32–44)	<0.001
PASP ≥ 60	114 (2.6%)	53 (2.4%)	61 (2.8%)	0.507
PCWP	19 (14–20)	19 (13–20)	19 (14–20)	0.073
Cardiac output	4.4 (3.5–4.7)	4.4 (3.5–4.8)	4.4 (3.5–4.6)	0.270
Donor characteristics				
Age (years)	24 (17–38)	24 (17–37)	25 (17–39)	0.983
Male	2,685 (61.0%)	1,342 (60.9%)	1,343 (61.0%)	1.000
Diabetes	98 (2.2%)	42 (1.9%)	56 (2.5%)	0.185
Cocaine use	356 (8.1%)	178 (8.1%)	178 (8.1%)	1.000
Other drug use	654 (14.9%)	335 (15.2%)	319 (14.5%)	0.525
Transplant year				
1996–2001	1,102 (25.0%)	546 (24.8%)	556 (25.3%)	0.752
2002–2008	1,374 (31.2%)	651 (29.6%)	723 (32.8%)	0.021
2009–2017	1,928 (43.8%)	1,005 (45.6%)	923 (41.9%)	0.013

LVAD, left ventricular assist device; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; PRA, panel reactive antibody; TAH, total artificial heart.

Continuous variables expressed as mean (standard deviation) if normally distributed and as median (interquartile range) if not normally distributed. Categorical variables expressed as number (proportion).

Kaplan-Meier survival curves for all-cause mortality and for all-cause mortality or retransplantation in the matched population are shown in Figure 5. Early/acute retransplantation was associated with higher risk of all-cause mortality (unadjusted HR 1.79, 95% CI 1.43–2.23, $p < 0.001$) and higher rates of death or retransplantation (unadjusted HR 1.72, 95% CI 1.39–2.14, $p < 0.001$).

Sensitivity analyses with propensity matching

Propensity matching (Model 1) was repeated without matching for sternotomy. In this analysis, late retransplantation was associated with an increased risk of all-cause mortality (unadjusted HR 1.19, 95% CI 1.08–1.31, $p < 0.001$) and an increased risk of all-cause mortality or retransplantation (unadjusted HR 1.19, 95% CI 1.08–1.30, $p < 0.001$). Propensity matching (Model 1) was also repeated without matching for PRA, including those patients without documented sensitization status. In this analysis, late retransplantation was not associated with an increased risk of all-cause mortality (unadjusted HR 1.07, 95% CI 0.97–1.17, $p = 0.164$) or an increased risk of all-cause mortality or retransplantation (unadjusted HR 1.08, 95% CI 0.98–1.18, $p = 0.107$).

Propensity matching (Model 1) was performed with an analysis in pediatric (age < 18 years) and adult patients (age ≥ 18 years), results shown in Supplementary Figure S2 (available online). Pediatric patients undergoing late retransplantation were at higher risk for all-cause mortality (unadjusted HR 1.43, 95% CI 1.18–1.74, $p < 0.001$). Adult patients undergoing late retransplantation were not at higher risk for all-cause mortality (unadjusted HR 0.99, 95% CI 0.89–1.10, $p = 0.806$). Lastly, propensity matching (Model 1) was stratified by time period. In patients undergoing late retransplantation between 1996 and 2001, there was an increased risk of all-cause mortality (unadjusted HR 1.24, 95% CI 1.07–1.45). However, in later cohorts there was no increase risk of all-cause mortality associated with late retransplantation (2002–2008: unadjusted HR 0.93, 95% CI 0.80–1.09, $p = 0.377$; 2009–2017: unadjusted HR 1.08, 95% CI 0.90–1.30, $p = 0.415$).

Model 2. Parsimonious propensity matching

A sensitivity analysis was performed with propensity-score matching only for age, sex, PRA, previous sternotomy, and pre-transplant dialysis. One-year mortality was

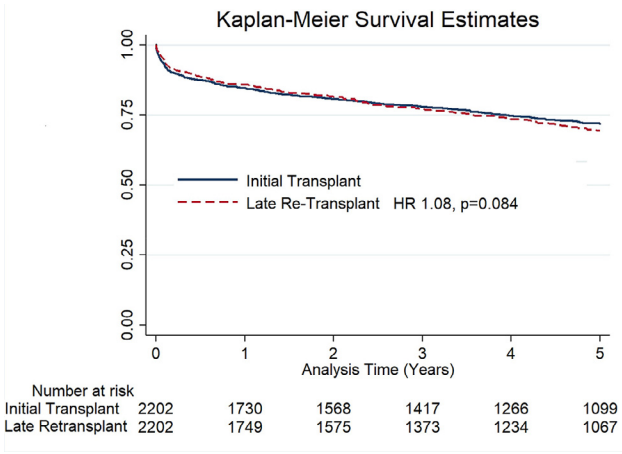

Figure 3 Kaplan-Meier survival curves for all-cause mortality after propensity-score matching (Model 1). HR, hazard ratio.

not significantly different in late retransplant recipients compared with matched controls (13.8% vs 14.3%, $p = 0.430$). Kaplan-Meier survival curves for these groups are shown in Supplementary Figures S3 and S4 (available online). Similarly, late retransplantation was not associated with an increased risk of death (unadjusted HR 1.06, 95% CI 0.97−1.17, $p = 0.189$) or an increased risk of death or retransplantation (unadjusted HR 1.07, 95% CI 0.98−1.16, $p = 0.160$).

Model 3. Multivariable analysis

Results of the multivariable Cox proportional hazards analysis performed in the complete population are shown in Supplementary Table S2 (available online). In this analysis, late retransplantation was associated with an increased risk of death (adjusted HR 1.11, 95% CI 1.03−1.20, $p = 0.005$) and increased risk of death or retransplantation (adjusted HR 1.11, 95% CI 1.03−1.19, $p = 0.005$). However, there were significant interactions between late retransplantation and pre-transplant ventilation, Epstein-Barr virus serostatus, donor age, donor diabetes, donor cause of death, and

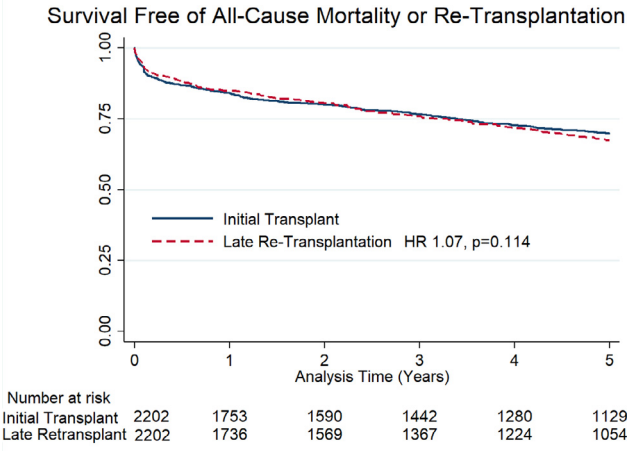

Figure 4 Kaplan-Meier survival curves for all-cause mortality or retransplantation after propensity-score matching (Model 1). HR, hazard ratio.

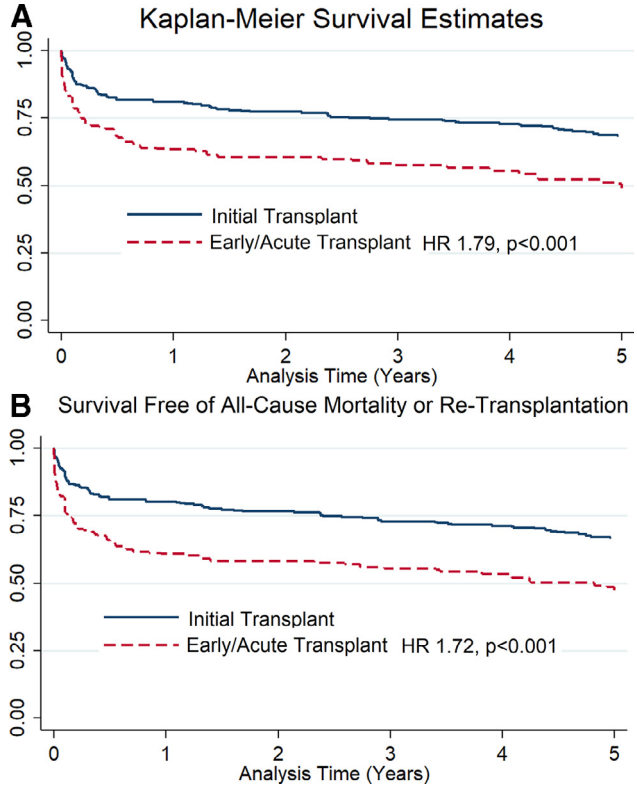

Figure 5 Kaplan-Meier survival curves for all-cause mortality (A) and all-cause mortality or retransplantation (B) after propensity matching (Model 1). Early/acute retransplantation includes patients retransplanted within 1 year and those retransplanted for acute or hyperacute rejection. HR, hazard ratio.

donor cocaine use. When interaction terms were included in the model, late retransplantation was not associated with increased all-cause mortality (adjusted HR 1.03, 95% CI 0.93−1.14, $p = 0.562$) or an increase in the combined outcome of all-cause mortality or retransplantation (adjusted HR 1.05, 95% CI 0.96−1.16, $p = 0.295$). In comparison, early/acute retransplantation was associated with increased all-cause mortality (adjusted HR 1.58, 95% CI 1.36−1.83, $p < 0.001$) and increased rates of all-cause mortality or retransplantation (adjusted HR 1.56, 95% CI 1.35−1.80, $p < 0.001$).

Discussion

In this analysis of the UNOS heart transplant database, late retransplantation was not associated with an increased risk of all-cause mortality in the adult population after adjusting for donor and recipient characteristics previously identified as independently associated with mortality by the SRTR. In contrast, retransplantation within 1 year or for acute rejection was associated with increased all-cause mortality. These results suggest that the nuances of timing and acuity of retransplantation are important drivers of post-transplant survival.

We found no increase in all-cause mortality in a cohort of patients undergoing late retransplantation after adjusting for important comorbidities. In a systematic review of retransplantation outcomes by Rizvi et al,[20] retransplantation was associated with significantly lower 1-year mortality.

However, 35.2% of patients underwent retransplantation within 30 days of initial transplant. In a smaller cohort, Saito et al[16] found that patients retransplanted more than 1 year after initial implant had similar post-transplant survival as patients undergoing initial transplantation. In contrast, early retransplantation or for acute rejection was associated with 60% increase in risk of all-cause mortality in our study. The exclusion of patients undergoing retransplantation for early or acute reasons is likely the major reason for differences in our results compared with similar previous studies.[1,6–8,11] In addition, we accounted for donor and recipient characteristics included in the SRTR 1-year patient survival equation, as well as sensitization status, which has not been performed in many previous studies.

Several factors can contribute to the increase in mortality demonstrated in patients undergoing retransplantation. Previous sternotomy, sensitization status, and renal dysfunction are factors potentially contributing excess risk in patients undergoing cardiac retransplantation.[4,11] All patients undergoing cardiac retransplantation have had a previous sternotomy, which increases the risk of mortality following transplant.[12,13] Inclusion of sternotomy as a matching variable resulted in comparison with initial transplant patients with previous sternotomy, who are also at inherently higher risk. Notably, in the sensitivity analysis that did not include sternotomy, late retransplantation was associated with an increased risk of all-cause mortality. These results suggest that previous sternotomy is one the most important variables influencing outcomes following late retransplantation. Patients undergoing retransplantation are more likely to be sensitized,[11] which increases the risk of rejection and decreases graft survival following transplanation.[21,22] Patients undergoing renal retransplantation have an increased risk of cellular rejection (without evidence of antibody-mediated rejection) suggesting a mechanism outside of antibody formation.[23] Finally, longer exposure to calcineurin inhibitors predisposes to renal dysfunction and potentially dialysis.[24] Pre-transplant creatinine has a strong impact on post-transplant survival,[25] which may be partially mitigated by performing combined heart-kidney transplantation.[26] In the analysis accounting only for these factors (parsimonious propensity matching), late retransplantation was not associated with increased all-cause mortality, suggesting that these factors are important.

Many risk scores currently include retransplantation as an predictor of poor patient outcomes.[19] The SRTR 1-year graft survival prediction tool uses retransplantation in addition to other recipient and donor factors to predict 1-year mortality.[19] However, the equation does not include sensitization status, which is independently associated with post-transplant outcomes.[21,22] We found that late retransplantation is not independently associated with post-transplant mortality and needs to be considered in the context of other patient factors, including sensitization. Notably, in pediatric patients late retransplantation was associated with increased all-cause mortality. This discrepancy may be related to increased risk of late rejection in this group,[27] or there may be different influencing post-transplant pediatric outcomes that were not accounted for in our analysis. However, our results were similar in the sensitivity analyses of adult patients as well as the most recent time periods. Therefore, our results support the current practice of considering retransplantation in adult patients with chronic graft failure because of CAV without other significant comorbidities.

Our study has a few important limitations. We combined several measures of PRA as a single variable representing sensitization. While this has been used in previous analyses,[17,18] the direct clinical applicability is unclear. The subset of patients who undergo retransplantation represent a selected group of patients. We identified a small proportion of retransplant patients requiring bridging LVAD therapy, which may be an important predictor of outcomes in these patients.[11] Although the propensity matching model was well balanced overall, some residual differences were present that may have impacted our findings. Additonally, unmeasured factors, such as frailty, may also be important covariates but are not included in our analyses. Therefore, we cannot exclude small differences in post-transplant outcomes. Finally, although we found that post-transplant mortality was similar after adjusting for important comorbidities, we did not assess all clinically important outcomes or quality of life. In addition, there are cost and ethical concerns regarding cardiac retransplantation, which we have not considered but have been more fully addressed by other authors.[6,28,29]

Conclusions

After matching for important donor and recipient characteristics, late retransplantation was not associated with increased all-cause mortality or need for retransplantation in the adult population. In contrast, retransplantation within 1 year or for acute rejection was associated with increased all-cause mortality. Our results highlight the importance of assessing indication acuity and comorbid conditions when assessing retransplant candidacy.

Disclosure statement

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Supplementary data

Supplementary data associated with this article can be found in the online version at www.jhltonline.org/.

Supplementary materials

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