End Stage Renal Disease After Pediatric Heart Transplantation: A 25-Year National Cohort Study

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Abstract

Background—End stage renal disease (ESRD), defined as need for chronic dialysis and or kidney transplantation (KTx), is a known complication after heart transplant (HTx). However, factors associated with ESRD are not well elucidated. The objectives of this study were to determine the prevalence, risk factors, and outcomes associated with ESRD after pediatric-HTx.

Methods—Scientific Registry of Transplant Recipients data were linked, using direct identifiers, to the United States Renal Data System to identify patients (>18 years) who underwent primary HTx between 1989 and 2013. Risk factors for ESRD and death were analyzed using Cox-regression analysis.

Results—Combining the above two databases identified ~25% additional HTx patients who developed ESRD which were not captured by either database alone. During a median follow up of 11.8 years, 276/6901 (4%) patients developed ESRD. The actuarial risk of developing ESRD 10 and 20 years post-HTx were 3, and 16%. Age at HTx >1 year, African-American race, year of HTx <2000, hypertension, diabetes-mellitus, heart re-transplant, acute dialysis, graft failure, and hospitalized infection were found to be significant risk factors for ESRD development. Those who remained on chronic dialysis had higher risk of mortality compared to those who received KTx (Hazard ratio 31.4, 95% CI [20.8, 48.4], $P < 0.0001$).

Conclusions—ESRD after pediatric-HTx, is more prevalent in HTx survivors than documented by a transplant database alone. A number of factors develop at or after HTx that increase risk for developing ESRD. Use of KTx in post HTx ESRD is associated with improved survival.

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Disclosures:

The data reported here have been supplied by the Scientific Registry of Transplant Recipients (SRTR) and the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government.

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Keywords

End stage renal disease; heart transplant; kidney transplant; dialysis

INTRODUCTION

Over time, the pediatric heart transplant (HTx) recipient's survival has improved with reduced early post-transplant mortality.^{1–3} End stage renal disease (ESRD, defined as need for chronic dialysis and or kidney transplant [KTx]), is a well-recognized complication after pediatric HTx with a previously reported incidence of 3%.^{4,5} Even though ESRD is a predictor of 2 to 6-fold increased risk of mortality after HTx,^{4,5} the prevalence, risk-factors, and outcomes associated with ESRD are not well elucidated. ESRD necessitating KTx is being increasingly recognized^{4–7} and poses an increased demand on an already scarce donor pool.⁸ Early recognition of potential risk-factors is important as this may help discern strategies to slow progression to or prevent this complication in this vulnerable population.⁵

Pediatric HTx-recipients are now surviving for decades after HTx surgery.⁹ As they age, the likelihood of ESRD increases considerably over time. Unfortunately, the data collection becomes incomplete as patients transition from specialized pediatric care to adult care services.¹⁰ Due to limitations in analysis derived from single-center studies, registries have been used to better understand outcome following solid-organ transplantation.^{4–7} The Scientific Registry of Transplant Recipients (SRTR) is a mandatory reporting database of all solid-organ-transplants performed in the United States since 1987.¹¹ Similarly the United States Renal Data System (USRDS) is a national ESRD registry, that maintains clinical records on ESRD patients with Medicare as their primary insurance, since 1988.¹² Linkage of major databases has lately been adopted to overcome limitations of capture and extended follow-up in single registries, thereby increasing the power to evaluate the long-term outcomes.^{4–7,13} One potential limitation of linkage is when direct identifiers are not available, necessitating probabilistic matching using demographic covariates, an imprecise method. We hypothesized that linking the SRTR with USRDS using direct identifiers will identify HTx-recipients who had ESRD that were not recorded by SRTR. Our objective was to use these linked databases to determine the prevalence, risk-factors, and outcomes associated with ESRD in a national cohort of pediatric HTx-recipients who underwent primary-HTx, over a 25-year period.

METHODS**Patients**

The study population included patients (age ≥ 18 years) registered in the SRTR who underwent primary (first) and solitary HTx between January 1, 1989 and December 31, 2013. We chose December 2013 as the end-date for inclusion of patients to allow for lags in center reporting to SRTR and claims data for ESRD. We followed these patients through December 2, 2015, the last follow-up date available in the SRTR. Patients with multiple-organ-transplants, those who received previous KTx or developed ESRD prior to primary-

HTx were excluded. (Definitions including ESRD¹⁴ are provided in Table S1, Supplementary Appendix).

Data

In this study, we merged the SRTR database with the USRDS claims data. The SRTR collects data on all donor, wait-listed candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. Outcomes of death in the SRTR are determined through linkage to the Social Security Death Master File, OPTN death date, and death date in follow-up forms.¹¹ The USRDS maintains records of any changes in vital status or methods of renal-replacement therapy including KTx. To determine the ESRD outcomes we used the Centers for Medicare and Medicaid Services (CMS) Medical Evidence Report (Form CMS-2728) for chronic dialysis submitted to the USRDS.^{5,15–17} Additionally we reviewed the standard analysis files for heart and kidney transplant dataset to determine the ESRD outcomes reported by the SRTR. The institutional review board of the Washington University School of Medicine, the SRTR, and USRDS approved the study.

Linkage

The SRTR team constructed an analysis file that contained protected health information (PHI) on all consecutive patients (age ≥ 18 years) who underwent primary-HTx between January 1, 1989 and December 31, 2013. All patients within the analysis file were assigned a unique patient code. This analysis file containing PHI was securely linked to the ESRD database by the USRDS team. Thereafter the USRDS team assigned the same unique patient code to all the individual patients who developed ESRD after HTx, in a pre-arranged secure fashion. Final data that we received from the SRTR and USRDS did not contain any PHI. However, the unique patient code assigned by both teams allowed cross-referencing between the 2-datasets.

Statistical analysis

The primary end-point was onset of ESRD, as determined by need for initiation of chronic dialysis, and/or KTx, or waitlisted for KTx. The term “chronic dialysis” was used for primary heart transplant recipients who were listed on the USRDS and were receiving any modality of hemodialysis, or peritoneal dialysis. Within the SRTR dataset, we defined ESRD as either need for chronic dialysis or receipt of a KTx or waitlisted for KTx reported within the KTx-section of SRTR. There were no patients exclusively identified in the latter category. Data were censored at death, lost to follow-up, or December 2, 2015 which ever occurred first. Risk-factors for ESRD and death were analyzed using Cox proportional hazard-regression-analysis as fixed and time-dependent-covariates. To examine the effect of ESRD on mortality; we treated ESRD as a time varying covariate in the Cox regression analysis. Standard Kaplan–Meier analyses were used to examine risk of death among patients who remained on chronic dialysis until death or end of follow-up compared to those who received KTx. To assess the importance of missing data, a sensitivity analysis was performed. (Details regarding fixed and time-dependent risk-factors analysis and sensitivity

analysis are provided in the Supplementary Appendix). Estimated glomerular filtration rate (eGFR) was calculated according to the newer bedside Chronic Kidney Disease in Children (CKiD) study formula ($0.413 \times \text{height in cm} / \text{serum creatinine in mg/dL}$) across all ages.¹⁸ Baseline eGFR was calculated at the time of heart transplant. Statistical analysis was performed using SAS version 9.4 (Cary, NC).

RESULTS

Linkage

The final study cohort included 6901 primary-HTx recipients. In the study period, 217 (3.1%) HTx-recipients developed ESRD as reported in the SRTR. Similarly, 221 (3.2%) HTx-recipients were reported to have ESRD by the USRDS. Of those, 162 ESRD patients were identified by both datasets (Figure S1). However, 55 ESRD patients were identified in the SRTR database that were missing from the USRDS. Likewise, 59 ESRD patients identified in the USRDS were missing from the SRTR. After combining the information from both the databases, a total of 276 ESRD patients were included in the final analysis.

Demographic characteristics

Median age at primary-HTx was 3.9 years. Of these 56% were males, 19% were African-American race, and almost half the patients had a history of congenital heart disease. Over 90% patients were treated with calcineurin-inhibitor (CNI) based immunosuppression after HTx, eGFR was $<60 \text{ ml/min/1.73m}^2$ in 12% patients and 385 (5.6%) needed acute-dialysis at the time of primary-HTx. The baseline demographics of HTx-recipients who developed ESRD versus those who did not are summarized in Table 1. Baseline median eGFR at HTx was lower in ESRD group compared to those who did not develop ESRD (80 vs. 84 ml/min/ 1.73m^2 , $P=0.04$). Conversely, ventricular-assist-device (VAD) use around primary-HTx were higher in those who did not develop ESRD.

ESRD after heart transplant

During a median follow-up of 11.8 (IQR [7.7, 15.2] years, 276 (4%) patients developed ESRD. The actuarial risk of developing ESRD 5, 10 and 20 years post-HTx were 1, 3, and 16% respectively (Figure 1). Of the 276 patients that developed ESRD, KTx was performed in 144 (52%). Of those 144, 59 patients (59/275=21%) received preemptive KTx, and 85 (31%) received chronic dialysis followed by KTx. However, 132 patients (48%) remained on chronic dialysis until data were censored. Of those who remained on chronic dialysis, 75 patients were on hemodialysis, and 21 patients were on peritoneal dialysis. However, about 30% (36/132) patients had missing information on the type of dialysis.

Risk factors for ESRD

Of the various fixed recipient risk-factors, age at primary-HTx, African-American race and HTx performed in earlier study era (year <2000), were found to be significant on both univariable and multivariable Cox regression analysis [Table 2]. In our multivariable fixed-effects model, pairwise comparisons among age groups revealed that patients 10 to 18-year-age at primary-HTx had 1.76-times the hazard of developing ESRD compared to infant HTx (HR 1.76, 95% CI [1.32, 2.33], $P<0.0001$). Interestingly a third (37/112=33%) of those who

developed ESRD in 10 to 18-year-age group had a history of congenital heart disease. Multivariable Cox regression analysis was performed for time-dependent risk-factors for ESRD after adjusting for age, race, and year-of-HTx. Hypertension ($P<0.0001$), diabetes-mellitus ($P=0.0009$), heart re-transplant (HRTx, $P=0.0018$), acute-dialysis ($P<0.0001$), eGFR <60 ml/min/1.73m² ($P<0.0001$), graft failure ($P=0.0002$), and hospitalized-infection ($P=0.008$) were found to be significant (Figure 2). Patients requiring acute-dialysis had significantly higher hazard of developing ESRD compared to those who did not require this temporary modality of dialysis (HR 7.46, 95% CI [5.22, 10.44], $P<0.0001$). Additionally, hypertension and diabetes-mellitus had approximately 2-times the hazard of developing ESRD compared to those who did not develop these risk factors [Figure 2, and figure S2].

Risk factors for mortality after ESRD

Of the 276 ESRD patients, 120 (43.5%) died after a median (IQR) of 1.2 years (0.25, 3.6) after developing ESRD. When treating ESRD as a time varying covariate, risk of death was significantly higher among patients who remained on chronic dialysis until death or last follow-up compared to those who received KTx (HR 31.4, 95% CI [21.0, 48.4; $P<0.0001$]) [Figure 3]. Additionally, adjusted analysis indicated that ESRD was associated with a 2.5-times higher risk of death (HR 2.5, 95% CI 2, 3.1, $P<0.0001$) compared to HTx-recipients who did not develop ESRD. We assessed fixed and time-dependent risk-factors associated with death as shown in Supplementary appendix (Figure S3, and Table S2).

DISCUSSION

Our study is notable for four new insights on ESRD after pediatric-HTx. First, combining SRTR and USRDS databases allowed us to capture nearly 25% additional HTx patients who developed ESRD which were not captured by either database alone, providing a superior estimate of the true prevalence of this major complication. Second, ESRD generally begins 10-years post-HTx and has a much faster rise in incidence thereafter. Third, a number of risk-factors are present at the time of HTx, or develop after HTx that increase the risk for developing ESRD. These include age at primary-HTx, African-American race, HTx performed in earlier study era, hypertension, diabetes-mellitus, HRTx, acute-dialysis, graft failure, and hospitalized-infection. Finally, use of KTx in post-HTx ESRD patients are associated with improved survival.

Our work expands the work by Ruebner et al.⁵ We were able to extract a higher number of patients with ESRD after HTx by looking at each database separately (n=276) as opposed to those that were common to both (n=162). We followed these patients over an extended follow-up period of 25-years. In fact, the exponential rise in the rate of ESRD is between 10 and 20-years post-HTx. This was not shown in the previous papers due to limited follow-up.^{4,5} Additionally we looked at unique risk factors for ESRD and ESRD associated mortality, such as diagnosis at primary HTx, extracorporeal membrane oxygenator (ECMO), VAD, ventilator, use of induction therapy, donor organ ischemic time, obesity, hypertension, diabetes-mellitus, heart re-transplant, graft failure, rejection, and hospitalized-infection. These variables were evaluated at HTx (fixed variables) or followed over time until an event (ESRD or death) occurred (time-dependent variables). We believe that neither database is

able to capture ESRD fully, such that neither is a gold standard. USRDS collects information on patients who have Medicare as their primary insurance and thus may miss some children with ESRD who have other primary insurance. Additionally, there is a delay in reporting of an ESRD event with USRDS. Furthermore, the quality and depth of reporting of transplant registries drops as we get further out from HTx due to incomplete reporting by transplant centers because of various reasons including lost-to-followup.^{20,21} Thus, we felt that combining both databases would give us a more accurate picture of ESRD after HTx than either database alone.

We found that the immature kidneys in infant HTx-recipients are not at greater risk for ESRD. Like Ruebner et al we found that age 10-years at HTx was associated with 1.8 fold-increased risk of ESRD.^{5,22} The unique factors contributing to kidney injury in this age group have not been elucidated. Our analysis revealed that nearly a third of these patients had history congenital heart disease at the time of primary-HTx. Considerable evidence exists that patients with advanced heart failure have long standing central venous congestion, with systemic hypoperfusion leading to some degree of kidney dysfunction.^{23–24} This issue may be compounded in complex single ventricle patients with a failing Fontan circulation listed for HTx.^{25–26}

African-American race comprised 19% of the study cohort. Not only do they have higher risk of developing ESRD, they tend to develop this at an earlier age compared to white HTx-recipients. The increased risk of ESRD in African-American population could be attributed to genetic and immunologic differences unique to this race. Studies have shown that African-Americans need much higher doses of CNI than whites to achieve similar trough levels.²⁷ This phenomenon has been attributed to differences in the bioavailability of CNI due to the CYP3A5*1 genotype which is common in this cohort.²⁸ The presence of high-risk APOL1 gene alleles also increases the risk of chronic kidney disease in African-Americans.²⁹ However, the SRTR and USRDS databases do not collect data on APOL1 genotypes in solid-organ transplant recipients or from kidney donors.

Our analysis shows that hypertension, diabetes-mellitus, and hospitalized-infection are risk factors for developing ESRD. Targeting renoprotective strategies and timely management of these modifiable risk-factors might delay the progression to ESRD in this population. HRTx accounts for approximately 6% of total pediatric HTx.³⁰ On multivariable analysis HRTx was associated with 1.7-times the hazard of developing of ESRD. It is likely that HRTx patients have some renal insufficiency going into re-transplant surgery, likely a result of a multifactorial etiology with prolonged exposure to CNI being a potential contributor. Adult studies have shown that HRTx recipients have better survival with combined KTx than with HRTx alone.³¹ Thus combined heart-kidney transplant could be considered in these patients with allograft failure and ESRD. Future work may encompass identifying threshold eGFR that validates combined heart-kidney transplant in this high risk population before the progression to ESRD.³² Most of our patients (>90%) received CNI in the early post-HTx period, thus precluding analyses of the relative contribution of early CNI use to later ESRD.

Perhaps the most striking result of our analysis was that upon treating ESRD as a time varying covariate the risk of death was markedly higher in post-HTx ESRD who remained

on chronic dialysis only until their last follow-up or death compared to those who received KTx. Our data indicate that KTx may be a major modifiable factor improving the long-term survival of HTx-recipients with ESRD. However, the higher risk of death in the chronic dialysis group could be partly confounded as these patients may have been too sick for transplant; have qualitative and/or quantitative anti-HLA antibody levels precluding KTx; or other reasons that did not allow KTx consideration. These results are consistent with the more recent evidence of excess risk of death among liver and heart transplant recipients with ESRD who remained on chronic dialysis only as the renal-replacement therapy.^{22,33}

Limitations

Our study has several limitations. First, like all other retrospective registry analyses, only variables already captured could be studied. Second, even though we chose well captured “hard” outcomes such as ESRD, it is possible that some events were still not captured. Being a relatively rare event, even a small number of misreported or unreported patients could influence our inferences. Furthermore, USRDS collects information on patients who have Medicare as their primary insurance and thus may miss some children with ESRD who have other primary insurance (but these could still have been captured in SRTR, which may account for the USRDS discrepancy). However, by linking the SRTR with USRDS, and Social Security Death Master File, we believe that precise capture of these outcomes was possible. Third, incomplete or missing data for certain variables were noted that could lead to potential misrepresentation of important exposures. Moreover, we used the bedside CKiD formula to estimate GFR at the time of HTx.¹⁸ GFR estimates built on creatinine-based formula overestimate measured kidney function in HTx-recipients.^{34–36} This is specially noted in the setting of low muscle mass and chronic illness thereby leading to lower serum creatinine levels.³⁷ Thus we may have overestimated GFR in some of our patients with normal kidney function.³⁸ Conversely, poor heart pump function often reduces the glomerular filtration fraction, so underestimated GFR in those with chronic kidney disease is also possible. Estimated GFR assessment prior to HTx was not available in ~13% of our patients due to missing creatinine values and or height. Additionally, information on long-term post-transplant immunosuppression regimens, drug dosages, and drug levels were also not available. Therefore, the effect of eGFR change with CNI use after transplant could not be determined. It would be important to know the type renal supplemental therapy that is ideal while managing ESRD patients after HTx. However, about 30% patients on chronic dialysis had missing information on the type of dialysis. Therefore, any statistical inferences we make are likely going to be biased. Of note, some variables analyzed (e.g. new onset diabetes, hypertension) have not been collected by the SRTR in the early part of the study. Thus the estimates of the hazard associated with these variables need to be interpreted with caution. The strengths of the study include accurate direct identifier linkage of a large, nationally representative cohort of HTx-recipients with the USRDS, that allowed us to evaluate the development, progression, and risk-factors associated with a rare event like ESRD over an extended follow-up period.

Conclusion

This study has shown that ESRD after pediatric HTx is more prevalent in HTx survivors than documented by a pure organ transplant database, such as SRTR, alone. A number of

factors develop at or after HTx that may increase risk for developing ESRD. Of these hypertension, diabetes-mellitus, and hospitalized-infection are modifiable risk-factors. Additionally, use of KTx in post-HTx ESRD patients is associated with better survival. Since ESRD remains an important determinant of survival and long-term outcomes after HTx, developing a risk prediction model for development of ESRD would be an important clinical tool. Future studies may focus on identifying threshold eGFR that justifies preemptive KTx or combined heart-kidney transplant in this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CDC	Centers for Disease Control and Prevention
CKiD	Newer bedside Chronic Kidney Disease in Children study formula
CMS	Centers for Medicare and Medicaid Services
CNI	Calcineurin inhibitor
ECMO	Extracorporeal membrane oxygenator
ESRD	End stage renal disease
eGFR	estimated glomerular filtration rate
HLA	Human leucocyte antigen
HRSA	Health Resources and Services Administration
HTx	Heart transplant
HRTx	Heart re-transplant
KTx	Kidney transplant
KDOQI	National Kidney Foundation Kidney Disease Outcomes Quality Initiative
OPTN	Organ Procurement and Transplantation Network
PHI	Protected health information
SRTR	Scientific Registry of Transplant Recipients

USRDS	United States Renal Data System
VAD	Ventricular assist device
WHO	World Health Organization

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Figure 1.

The Kaplan Meier graph displays risk of end stage renal disease in pediatric heart transplant survivors in the United States transplanted between January 1, 1989, and December 31, 2013.

Note: The number at risk and years since primary heart transplant on the X axis, and confidence interval (grey). The actuarial risk of developing ESRD 5, 10, and 20 years post HTx were 1, 3, and 16% respectively.

Figure 2.

Forest plot showing results of multivariable Cox regression analysis for time-dependent risk-factors for end stage renal disease after being adjusted for age, race, and year of heart transplant.

Note: Hypertension, first center reported instance of drug treated hypertension; Diabetes, first center reported instance of diabetes-mellitus; Heart re-transplant (HRTx) performed during the study period; acute dialysis, need for acute dialysis around primary heart transplant (HTx) and or HRTx; first center reported instance of estimated glomerular filtration rate, eGFR <60 ml/min/1.73m²; first center reported instance of graft failure after primary HTx; rejection, first center reported instance of acute rejection; and infection, first reported instance of hospitalized infection post HTx.

Figure 3.

Kaplan-Meier survival analysis illustrates pattern of survival for primary heart transplant recipients with end stage renal disease that remained on chronic dialysis until death or end of follow up (solid line, population 1) versus those who received kidney transplant with or without chronic dialysis (dashed line, population 2). Hazard ratio (95% CI) calculated based on time-dependent covariate analysis. The at-risk populations 1 and 2 are indicated above the X axis.

Table 1

Baseline characteristics of heart transplant recipients who underwent primary heart transplant between 1989 to 2013 and developed end stage renal disease versus those who did not develop end stage renal disease.

Characteristics	No ESRD (N=6625)	ESRD (N=276)	P value
Age at heart transplant, years	3.9 (0.5, 12.8)	5.2 (0.4, 13.2)	0.9
African American, n (%)	1279 (19.3)	56 (20.3)	0.7
Congenital heart disease, n (%)	3252 (49.1)	141 (51.1)	0.5
Pre-heart transplant diabetes [#] , n (%)	24 (0.4)	< 10	0.2
Pre-heart transplant hypertension, n(%)	597 (11.5)	12 (7.7)	0.1
*VAD, n (%)	749 (11.3)	18 (6.5)	0.01
Ventilator, n (%)	1266 (19.1)	45 (16.3)	0.2
Acute dialysis, n (%)	363 (6.6)	22 (14)	0.0002
Heart re-transplant, n (%)	524 (7.9)	79 (28.6)	<0.0001
eGFR ml/min/1.73m ²	84 (62.8, 108.8)	80 (57, 100)	0.04

Note: Age, recipient age at time of primary heart transplant; VAD, ventricular assist device; eGFR, estimated glomerular filtration rate calculated using newer bedside Chronic Kidney Disease in Children (CKiD) study formula ($0.413 \times \text{height/serum creatinine}$). Wilcoxon nonparametric test was used for continuous variables (age at heart transplant, years and eGFR ml/min/1.73m² and the corresponding values are reported as median and IQR), and a chi-square or Fisher's exact test was used for categorical data as appropriate (reported as n [%]).

[#] Centers for Medicare Medicaid policy requires the use of < 10 when cell counts are less than 10, and non-reporting of associated percentages.

* Missing values were assumed to be = 0.

Table 2

Univariable and Multivariable Cox regression analysis for fixed risk factors for development of end stage renal disease after heart transplant.

Fixed Variable	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
*Age at primary HTx, 1 – <10 years	0.95 (0.7, 1.3)	<0.0001	0.93 (0.68, 1.26)	<0.0001
*Age at primary HTx, 10–18 years	1.76 (1.33, 2.33)		1.76 (1.32, 2.33)	
Gender: Female	0.93 (0.73, 1.18)	0.5		
Race: African American vs. Other	1.84 (1.36, 2.46)	0.0001	1.9 (1.39, 2.51)	<0.0001
Year of HTx 2000 vs. < 2000	0.62 (0.45, 0.85)	0.002	0.6 (0.44, 0.82)	0.001
Dilated cardiomyopathy	1.06 (0.83, 1.34)	0.6		
Restrictive cardiomyopathy	0.92 (0.53, 1.50)	0.8		
Hypertrophic cardiomyopathy	0.96 (0.38, 1.96)	0.9		
Congenital heart disease	0.94 (0.74, 1.2)	0.6		
Obesity (≥ 95 percentile)	1.03 (0.65, 1.55)	0.9		
Donor organ ischemic time ≥ 4 hours	1.16 (0.9, 1.49)	0.2		
Induction therapy use	0.87 (0.64, 1.21)	0.4		
VAD use	1.28 (0.76, 2)	0.3		
ECMO use	0.75 (0.32, 1.46)	0.4		
Ventilator use	0.89 (0.64, 1.21)	0.5		

Note: *Fixed covariates* were evaluated at the time of primary HTx and included age at the time of primary HTx (<1 year; 1 to < 10 years; and 10 to 18 years); gender (male, female); race (African American versus others [other includes all other races like White, Hispanic, Asian, and multiracial]); year of primary heart transplant prior to year 2000 or at after year 2000; diagnosis at the time of primary HTx (congenital heart disease, dilated cardiomyopathy, restrictive cardiomyopathy, and hypertrophic cardiomyopathy); obesity (defined according to the CDC cut-points for body mass index for age at or above 95th percentile for children ≥ 2 years, or WHO body mass index for age charts for children < 24 months of age); donor organ ischemic time ≥ 4 hours; induction therapy use; VAD, ventricular assist device use; ECMO, extracorporeal membrane oxygenator use; ventilator use.

* Reference group < 1 year at primary heart transplant (HTx).