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Heart Transplantation Survival Outcomes of HIV Positive and Negative Recipients

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Abstract

Background—In the era of antiretroviral therapy, HIV-positive patients have reduced mortality from HIV infection and increased morbidity from end stage heart failure. The number of HIV-positive heart transplantation recipients remains scant. Long-term survival has not been rigorously studied. We compared survival outcomes of heart transplantation in HIV-positive recipients to HIV-negative recipients.

Methods—Clinical data from all adult heart transplantations were extracted from the UNOS Dataset. The impact of recipient HIV status was analyzed with Cox proportional hazards modeling, 1:3 propensity score matching and Kaplan-Meier survival analysis.

Results—Seventy-five HIV-positive recipients and 29,848 HIV-negative recipients were identified. Race distributions differed between the recipient groups, with Blacks comprising a larger proportion of the HIV-positive recipient group (46.7% versus 20.9%, $p < 0.001$). The mean year of transplant was significantly later in the HIV-positive recipient group. The rate of acute rejection in the HIV-positive group was higher than the HIV-negative group (38.7% versus 17.7%, $p < 0.001$), as was rate of antirejection treatment administration such as IVIG or plasmapheresis (26.7% versus 10.4%, $p < 0.001$). There was no difference in 30-day, 1-year, and 5-year survival of HIV-positive recipients versus HIV-negative recipients. Recipient HIV infection was not a significant covariate in predicting survival in a Cox proportional hazards model.

Summary—Short- and moderate-term survival following heart transplantation is similar in HIV-positive and HIV-negative recipients, although data are very limited. This suggests that

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Disclosures

None declared.

HIV-positive recipients should not be excluded from transplant candidacy solely based upon HIV serostatus.

Introduction

Due to the major therapeutic revolution of combination antiretroviral therapy (ART), the lethality of human immunodeficiency virus (HIV) has significantly reduced.^{1,2} The gap in life expectancy in the United States between people with and without HIV has narrowed from 44 years in 1997 to 12 years in 2011.³ Five, 10, and 15 year survival after seroconversion are now 99%, 93%, and 89% respectively.⁴ As a result, cardiovascular disease and heart failure have become increasingly prevalent. The reason for a rise in heart failure among HIV patients is multifactorial, including direct myocardial effects of the virus itself⁵; high prevalence of contributory comorbidities such as hypertension, dyslipidemia and heavy alcohol consumption⁶; antiretroviral therapy⁷ and immune response.⁸ It is estimated that approximately 2,300 HIV positive patients are living with advanced heart failure.⁹

Cardiac transplantation in HIV-positive recipients has been extremely limited, with the first US case report published in 2003¹⁰ and a few subsequent case series.^{9, 11} Modest case series have reported survival outcomes comparable to the general cardiac transplantation population.⁹ Despite this, HIV infection is considered a relative contraindication to transplantation at most centers.¹² With the passage of the HIV Organ Policy Equity Act in 2013 legalizing the study of organ donation between HIV-positive donors and recipients, increased attention has been given to this topic within the transplantation field. Given the changing landscape, the purpose of this study was to compare survival outcomes of cardiac transplantation in HIV-positive recipients with HIV negative recipients.

Methods

Patient population and data collection

The United Network for Organ Sharing (UNOS) provided Standard Transplant Analysis and Research files containing de-identified donor and recipient data from October 1987 to March 2019. The database contains prospectively collected donor and recipient data for all organ transplants performed in the United States. The UNOS database was reviewed for all first-time heart transplant recipients between January 2005 and June 2019 and their donors. Multi-organ transplants, age under 18, and patients with missing survival data were excluded.

Patients were identified as HIV-positive if they were noted to have HIV positive serology at the time of transplant. This study was deemed exempt by Duke University's Institutional Review Board.

Outcomes and statistics

Descriptive analysis of baseline donor and recipient characteristics were performed, stratified by recipient HIV status. Donor/recipient sex mismatch was defined as a female donor with male recipient. Baseline donor and recipient demographic data were described as percent (count) for categorical variables and median (interquartile range) for continuous

variables. Unadjusted comparisons between cohorts were performed using the Wilcoxon rank sum test for continuous variables and the Pearson chi-squared test or Fisher's exact test for categorical variables. The primary outcome was overall survival. Secondary outcomes of interest included length of hospital stay, acute rejection prior to discharge, and the occurrence of the following in the first 5 years following transplant: coronary artery disease diagnosis, end-stage renal disease requiring dialysis during follow-up, and hospitalizations during follow-up.

Unadjusted survival was estimated with the Kaplan-Meier method, and compared with the log-rank test. The adjusted association between HIV status and post-transplant survival was assessed using multivariable Cox proportional hazards modeling. Covariates were selected *a priori* based upon clinical experience, prior literature, and variable availability within the dataset and in addition to recipient HIV status included recipient age, sex, race/ethnicity, heart failure etiology, history of prior cardiac surgery, diabetes, pre-transplant mechanical circulatory support usage, donor/recipient sex mismatch, donor age, graft ischemic time, transplant era, and annualized heart transplant center volume. Linearity of continuous variables with the hazard of the outcome was confirmed using restricted cubic splines with 4 pre-specified knots based upon each variable's distribution. Where linearity was violated, continuous variables were modeled using piecewise linear splines for ease of interpretation. At least a 10:1 ratio of events to degrees of freedom was maintained to prevent overfitting.

To further account for imbalances in baseline demographic characteristics between the two cohorts, a propensity score matching sensitivity analysis was undertaken by matching each HIV positive recipients to 3 HIV negative recipients using several covariates, which were selected according to similar studies and clinical expertise. Using HIV status as the exposure, an optimal 1:3 propensity score matching algorithm was performed without replacement using a nearest neighbor algorithm, where the closest match for each patient is chosen one at a time without trying to minimize a global distance measure, with a standard caliper width of 0.1 of the standard deviation of the propensity score (R packages: "matchit", "optmatch", R Foundation for Statistical Computing, Vienna, Austria). Variables included in the regression model were donor age, race, cause of death, diabetes, cocaine use, alcohol use, and cigarette use as well as recipient age, sex, race, medical condition, diabetes, IV antibiotic requirement, VAD use, inotropes, heart failure etiology, transplant year, and ischemic time.

Two-sided p-values <0.01 were considered statistically significant. Multivariable modeling was performed as complete case analyses. All statistical analyses were performed using R version 3.5.1.

Results

A total of 75-HIV positive recipients and a corresponding 29,848 HIV-negative recipients met inclusion criteria. There were no HIV-positive donors. Baseline demographic and clinical characteristics of donors and recipients are represented in Tables 1, 2, and Supplemental Table 1, respectively. There were no significant differences among the donors. The median length of follow-up time was 1.99 years (IQR, 0.56–4.75) in the HIV-positive

recipients and 3.78 years (IQR, 1.05–7.04) in the HIV-negative recipients ($p=0.001$). Among the recipients, there was a significant difference in the distribution of race, with more HIV-positive recipients being Black compared to HIV-negative recipients (46.7% versus 20.9%, overall $p<0.001$). The mean year of transplant was significantly later in the HIV-positive recipient group [2016, interquartile range (IQR) 2014–2018 compared to the HIV-negative recipient group (2013, IQR 2009–2016). There were no other significant differences in demographic data, preoperative clinical acuity, preoperative mechanical support, distance from donor hospital to transplant center, or induction immunosuppression.

Table 3 displays the unadjusted transplant outcomes by HIV status. HIV-positive recipients had significantly longer lengths of hospital stay compared to their HIV-negative peers (18 days, IQR 12–31; 15 days, IQR 11–23 respectively). The rate of acute rejection during initial hospitalization in the HIV-positive recipient group (38.7%) was higher than the HIV-negative recipient group (17.7%, $p<0.001$), as was rate of antirejection treatment administration such as IVIG or plasmapheresis (26.7% versus 10.4%, $p<0.001$). There were no differences in coronary artery disease at follow up, renal failure, postoperative rehospitalization for rejection or infection.

A Cox proportional hazards model was created (Table 4) to adjust for potential independent predictors of survival and confounders. HIV infection was not associated with an increased risk of mortality. Other identified independent predictors of worse survival included higher donor age, higher recipient age, Black recipients, non-ischemic dilated cardiomyopathy etiology, recipient diabetes, recipient ECMO support prior to transplant, recipient prior cardiac surgery, graft ischemic time, transplant era 2005–2009, and lower transplant annualized volume.

Thirty-day, 1-year, and 5-year survival of the HIV-positive recipient cohort was 96.0%, 88.1%, and 80.2%, respectively; survival in the HIV-negative recipient cohort survival was 96.1%, 90.1%, and 78.2%, respectively. Kaplan-Meier survival analysis (Figure 1) demonstrated no difference in survival between the HIV-positive and HIV-negative recipient groups.

One:three propensity score matching was undertaken to compare HIV-positive recipients with matched HIV-negative controls to assess risk of mortality between the two groups (Supplemental Tables 2, 3, and 4). For the selected group of HIV-negative matched controls, rate of ICU status prior to transplant was higher (45.8%) compared to the HIV-positive recipient group (25.3%) and year of transplant was later (2019, IQR 2008–2019) compared to the HIV-positive recipient group (2016, IQR 2014–2018).

Comment

Heart failure in patients with HIV has become more common.¹³ In the ART era, the more distinctive HIV-related severe dilated cardiomyopathy has become less common, mirroring decreases in other forms of severe organ function uniquely characteristic of HIV. However, heart failure that is more typical in pathophysiology has become more common overall.¹³ In the pre-ART era, 10% of patients with HIV died of cardiac disease, while the incidence in

the ART era is closer to 25%. In the ART era, diastolic dysfunction predominates, occurring in 43–50% of cases compared to systolic dysfunction in only 8%.^{12,14–16}

In this retrospective analysis of the Thoracic UNOS database, we analyzed survival outcomes of HIV-positive heart transplant recipients compared with all HIV-negative recipients as well as with a 1:3 propensity matched control group. The 1- and 5-year survival rates were comparable; no significant difference in survival between the groups was appreciated and HIV status was found to not be an independent predictor of mortality risk. Compared to the general heart transplantation population as reported in from the ISHLT Registry, the HIV-positive recipient population had a younger median age, higher proportion of Black patients, and a higher proportion of non-ischemic dilated cardiomyopathy etiology.

Our findings suggest that HIV infection in an otherwise healthy transplant recipient would not significantly impact survival. These findings are supported by previously published case series of HIV-positive heart transplant recipients.⁹ In a case series of 18 HIV-positive heart recipients, Uriel et al reported a slightly lower pre-transplant VAD rate (38%) with survival comparable to the general heart transplant recipient population (1-, 2-, and 5-year survival 100%, 100%, and 63% respectively). A prior case series of 7 recipients showed similar survival results.¹¹

We report a higher rate of initial acute rejection in the HIV-positive recipient group, which has not been well described elsewhere in the heart transplantation literature. These findings are similar to that described in the kidney transplant literature, in which the HIV-infected cohort of kidney recipients had a higher-than-expected rate of rejection by a factor of 2 to 3.¹⁷ This may in part be explained by a high rate of alternative dosing regimens noted in these patients. Other potentially significant factors could include the use of antiretrovirals that affect cytochrome P-450–3A metabolizing enzymes¹⁸; transmission of leukocyte antigen molecules of the host to another host, thus inducing allosensitization¹⁹; increased responsiveness of T cells in HIV infection and nonspecific enhancement of alloimmunity²⁰; and the role of memory alloreactive T cells.^{21,22} In our study there was no difference in rate of hospitalization for subsequent rejection episodes, suggesting that the long-term clinical impact of the acute rejection may be modest. Our UNOS data lacks sufficient granularity to indicate the immunologic status of recipients that could support or refute these theories. Close study of post-transplant immunologic function in this population in the future is warranted.

Despite an increase in the number of HIV infected patients comprising the overall heart failure population, HIV infection is still considered a relative contraindication to transplant at most centers.¹² A survey of US and Canadian transplant centers conducted by Uriel et al in 2014 found that 57% reported HIV infection to be an absolute contraindication to listing; rationales included 1) perception of HIV-positive patients as high risk recipients to be avoided given scarce organ supply; 2) concern for immunosuppression-triggered progression of HIV to AIDS, and 3) drug interactions which could worsen outcomes. Fifty-nine percent of transplant centers reported that high risk donors should be avoided given organ scarcity. Given that we were able to 1:3 match HIV negative recipients with a risk profile similar to those who were HIV-positive, and that survival outcomes were comparable

to the general heart transplantation population, one could argue that organ donation in high risk recipients is already readily occurring with acceptable results. With respect to the concern that immunosuppression required for heart transplantation could trigger progression to AIDS: although our data do not contain this level of detail on post-transplant AIDS or concomitant opportunistic infections, in the kidney transplant experience, HIV remained stable post-transplantation with few HIV-associated complications.¹⁷ Lastly, concerning potential drug interactions potentially worsening clinical outcomes: this theory remains valid given the elevated rejection rates seen in the kidney population, which may in part reflect the impact of certain antiretrovirals on cytochrome P-450 metabolism.

There are several limitations to our study. We do not know how many HIV-positive patients were screened prior to arriving at the final group of candidates that ultimately received transplantation; presumably, the HIV-positive recipient cohort is a highly selected subgroup of the HIV positive population overall. Given the nature of how UNOS data are reported, we were unable to obtain any information about the HIV-positive patients that were deemed inappropriate for transplant listing. Each center may also have a unique screening process which is not described in this study. As alluded to prior, we were unable to examine outcomes based on typical markers of HIV disease severity, namely CD4 count, viral load via RT-PCR, degree of immunosuppression, rejection grade, specific rejection therapy received, and allograft dysfunction.

Furthermore the quality of the outcomes data is highly dependent upon the quality of the input data from each reporting center. Given the average year of transplant was later in the HIV-positive recipient group, clinical outcomes such as renal failure and coronary artery disease may be favorably biased toward that group because the reporting time was shorter. Additionally, the quantification of risk that is required to perform propensity score matching may not accurately reflect the complexity of all of the clinically relevant covariates that each transplant recipient represents, thus running the risk of oversimplification. Though the propensity score matching did not result in perfect matching, it is unlikely that this would have significantly impacted the results, given that the Cox proportional hazards model results supported the same conclusions.

Finally, the outcomes from this study are based on subjects transplanted under prior heart transplant allocation guidelines, and there was insufficient data to fully re-categorize all studied recipients into the current allocation scheme. Early studies have demonstrated an increased use of temporary mechanical circulatory support in the current allocation era.²³ Due to the sample size of this study, we cannot exclude the possibility of an interaction between use of temporary mechanical support and HIV status in post-transplant outcomes. Temporary mechanical support use was factored into our propensity match and multivariable analysis, and as expected, was a risk factor for mortality, while HIV status did not impact outcomes after heart transplantation.

Conclusion

As HIV survivorship continues to improve, there will be an increasing population of HIV-positive patients with heart failure, and some that progress to end stage heart failure. More

research is required to understand the post-transplant outcomes in HIV-positive recipients, and to more closely examine how rejection occurs as it does in renal transplant recipients. Infectious and neoplastic processes need to be examined closely as longer-term survival data are gathered. These results suggest that heart transplantation in HIV-positive recipients confers a higher rate of initial acute rejection, but the same survival as seen in similar patients that are HIV-negative. Preliminary analyses indicate that this is an underrepresented population. We conclude that HIV infection should not, in isolation, be considered an absolute contraindication to transplant.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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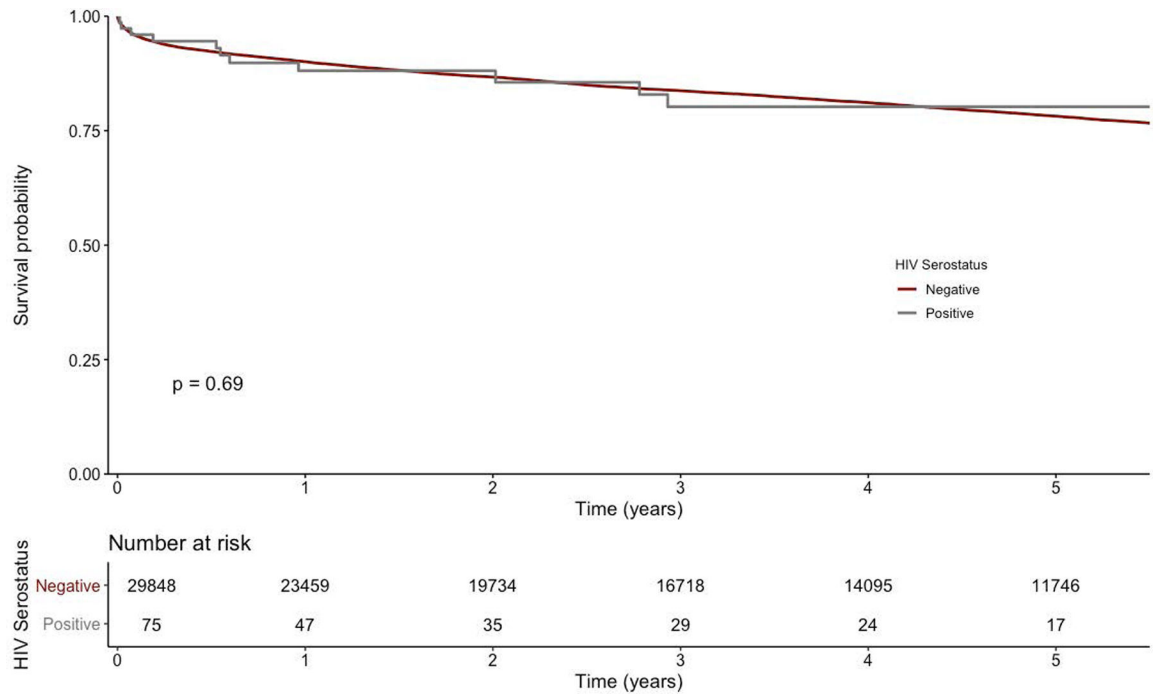


Figure.1. Kaplan-Meier curve for orthotopic heart transplant patients stratified by recipient HIV status. P value represents the two-sided log-rank test. Numbers at risk are provided at the bottom of the graph.

Table 1.

Donor Characteristics. Demographic and Clinical Characteristics of Heart Donors, Stratified by HIV Status of Recipient, January 2005 – June 2019

Variable	HIV - recipient (n=29,848)	HIV + recipient (n=75)	p-value
Male gender	21,183 (71.0%)	55 (73.3%)	0.747
Donor age (median years, IQR)	30 (22–40)	33 (23–38)	0.481
Donor BMI (median kg/m ² , IQR)	26.3 (23.2–30.2)	25.2 (23.0–29.8)	0.308
Donor ethnicity			0.111
White	19,171 (64.2%)	44 (58.7%)	
Black	4,741 (15.9%)	12 (16.0%)	
Hispanic	4,997 (16.7%)	19 (25.3%)	
Other	939 (3.1%)	-	
Donor history			
Cigarette use	4,023 (13.5%)	10 (13.3%)	1.000
Cocaine use	5,468 (18.3%)	21 (28.0%)	0.044
Alcohol abuse	4,775 (16.0%)	10 (13.3%)	0.638
Diabetes	1,008 (3.4%)	3 (4.0%)	1.000
LVEF	60 (55–65)	60 (59–65)	0.514
Inotrope use at procurement	13590 (45.5%)	24 (32.0%)	0.025
Donor cause of death			0.012
Anoxia	7,602 (25.5%)	28 (37.3%)	
Cerebrovascular/stroke	5,787 (19.4%)	10 (13.3%)	
Head trauma	15,633 (52.4%)	35 (46.7%)	
CNS tumor	180 (0.6%)	2 (2.7%)	
Other	645 (2.2%)	-	
ABO blood type			0.147
A	10,732 (36.0%)	28 (37.3%)	
B	3,301 (11.1%)	11 (14.7%)	
AB	646 (2.2%)	4 (5.3%)	
O	15,169 (50.8%)	32 (42.7%)	
IQR, interquartile range; LVEF, left ventricular ejection fraction; CNS, central nervous system			

Table 2.

Recipient Characteristics. Demographic and Clinical Characteristics of Orthotopic Heart Transplant Recipients, Stratified by HIV Status of Recipient, January 2005 – June 2019

Variable	HIV - recipient (n=29,848)	HIV + recipient (n=75)	p-value
Male sex	22,114 (74.1%)	60 (80.0%)	0.301
Sex mismatch	4,165 (14.0%)	13 (17.3%)	0.499
Age (median years, IQR)	56 (46–63)	50 (38–61)	0.004
BMI (median kg/m ² , IQR)	27.0 (23.7–30.6)	27.3 (24.4–30.0)	0.788
Ethnicity			<0.001
White	19,817 (66.4%)	31 (41.3%)	
Black	6,237 (20.9%)	35 (46.7%)	
Hispanic	2,456 (8.2%)	7 (9.3%)	
Other	1,338 (4.5%)	2 (2.7%)	
Recipient history			
Diabetes	8,277 (27.7%)	15 (20.0%)	0.172
Malignancy	2,339 (7.8%)	4 (5.3%)	0.555
Cerebrovascular disease	1,629 (5.5%)	3 (4.0%)	0.764
Heart failure etiology			0.003
Ischemic	9,505 (31.8%)	14 (18.7%)	
Non-ischemic dilated	14,512 (48.6%)	51 (68.0%)	
Other	5,831 (19.5%)	10 (13.3%)	
Recipient creatinine (median mg/dL, IQR)	1.2 (1.0–1.5)	1.2 (1.0–1.5)	0.739
Recipient bilirubin (median mg/dL, IQR)	0.7 (0.5–1.2)	0.6 (0.4–1.1)	0.088
Pre-transplant status			0.262
Intensive care unit	9,159 (30.7%)	19 (25.3%)	
Hospitalized (non-ICU)	4,823 (16.2%)	17 (22.7%)	
Not hospitalized	15,863 (53.2%)	39 (52.0%)	
Medical therapy			
IV antibiotics in two weeks before transplant	3,087 (10.3%)	9 (12.0%)	0.779
IV inotropes prior to transplant	11,470 (38.4%)	20 (26.7%)	0.049
Ventilator support prior to transplant	440 (1.5%)	4 (5.3%)	0.022
Durable LVAD support prior to transplant	10,425 (34.9%)	29 (38.7%)	0.577
Temporary MCS prior to transplant	3,692 (12.4%)	17 (22.7%)	0.011
IABP	2,985 (10.0%)	12 (16.0%)	0.125
ECMO	421 (1.4%)	2 (2.7%)	0.667
Temporary VAD	520 (1.7%)	4 (5.3%)	0.054
ABO blood type			0.591
A	12,071 (40.4%)	29 (38.7%)	
B	4,445 (14.9%)	15 (20.0%)	

Variable	HIV - recipient (n=29,848)	HIV + recipient (n=75)	p-value
AB	1,659 (5.6%)	5 (6.7%)	
O	11,673 (39.1%)	26 (34.7%)	
Days on waitlist (median days, IQR)	90 (26–258)	87 (33–227)	0.683
Waitlist status at transplant			-
Old 1A	16,414 (55.0%)	42 (56.0%)	
Old 1B	9,418 (31.6%)	16 (21.3%)	
Old 2	2,029 (6.8%)	3 (4.0%)	
New 1	168 (0.6%)	1 (1.3%)	
New 2	887 (3.0%)	7 (9.3%)	
New 3	504 (1.7%)	1 (1.3%)	
New 4	352 (1.2%)	3 (4.0%)	
New 5	8 (0.0%)	-	
New 6	68 (0.2%)	2 (2.7%)	
Graft ischemic time (median hours, IQR)	3.2 (2.4–3.8)	3.4 (2.7–3.9)	0.224
Distance from donor hospital to transplant center (median miles, IQR)	91 (13–287)	164 (18–404)	0.053
Antibody-based induction immunosuppression	15,177 (50.8%)	33 (44.0%)	0.285
Year of transplant (median, IQR)	2013 (2009–2016)	2016 (2014–2018)	<0.001
Length of follow up (median years, IQR)	3.78 (1.05–7.04)	1.99 (0.56–4.75)	0.001
IQR, interquartile range; BMI, body mass index; ICU, intensive care unit; IV, intravenous; LVAD, left ventricular assist device; MCS, mechanical circulatory support; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; VAD, ventricular assist device			

Table 3.

Selected Short-Term Unadjusted Clinical Outcomes of Orthotopic Heart Transplant Recipients January 2005 – June 2019, Stratified by Recipient HIV Status

Variable	HIV - recipient (n=29,848)	HIV + recipient (n=75)	p-value
Length of hospital stay (days, median [IQR])	15 (11–23)	18 (12–31)	0.006
Acute rejection episode prior to discharge	5,286 (17.7%)	29 (38.7%)	<0.001
Treated with antirejection medication	3,091 (10.4%)	20 (26.7%)	<0.001
Coronary artery disease at follow up	6,824 (22.9%)	10 (13.3%)	0.068
End stage renal disease requiring dialysis	1,874 (6.3%)	4 (5.3%)	0.921
Hospitalized during follow-up	16,077 (53.9%)	35 (46.7%)	0.257
For rejection	3,617 (12.1%)	6 (8.0%)	0.360
For infection	7,534 (25.2%)	10 (13.3%)	0.025
IQR, interquartile range			

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Table 4.

Cox Proportional Hazards Model Results of Post Transplant Survival, January 2005 – June 2019

Predictor	Hazard Ratio	95% Confidence Interval		p-value
		Lower	Upper	
HIV positive recipient	0.94	0.53	1.65	0.820
Donor age (per 5 years)	1.06	1.05	1.07	<0.001
Recipient age				
<45 (per 5 years)	0.91	0.89	0.93	<0.001
>45 (per 5 years)	1.20	1.16	1.24	<0.001
Recipient male sex	0.96	0.91	1.02	0.181
Recipient ethnicity (reference: White)				
Black	1.32	1.24	1.40	<0.001
Hispanic	1.00	0.91	1.10	0.995
Other	0.96	0.85	1.09	0.550
Donor/recipient sex mismatch	1.05	0.98	1.13	0.147
Recipient heart failure etiology (reference: ischemic)				
Non-ischemic dilated	0.79	0.75	0.84	<0.001
Other	0.98	0.89	1.02	0.13
Recipient diabetes	1.27	1.20	1.33	<0.001
Recipient durable LVAD support	1.07	1.01	1.14	0.016
Recipient ECMO support	1.95	1.61	2.37	<0.001
Recipient temporary VAD support	1.21	1.00	1.45	0.048
Recipient IABP support	1.06	0.98	1.16	0.161
Recipient prior cardiac surgery	1.13	1.07	1.19	<0.001
Graft ischemic time (per hour)	1.08	1.06	1.11	<0.001
Transplant era (reference: 2005–2009)				
2010–2014	0.85	0.78	0.88	<0.001
2015–2019	0.82	0.77	0.89	<0.001
Transplant center annualized volume				
<20 (per 5 transplants)	0.93	0.90	0.96	<0.001
>20 (per 5 transplants)	1.07	1.04	1.11	<0.001

LVAD, left ventricular assist device; ECMO, extracorporeal membrane oxygenation; VAD, ventricular assist device; IABP, intra-aortic balloon pump