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Chao Chen

Xuerong Wen
University of Rhode Island, xuerongwen@uri.edu

See next page for additional authors

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Outcomes in Human Immunodeficiency Virus Infected Recipients of Heart and Lung Transplants

Chen Chao[1], BS, Xuerong Wen[2], PhD, Nicholas Belviso[2], PharmD, Stephen Kogut[2*], PhD, Jerry McCauley[3]*, MD

[1]: Department of Pharmaceutical Outcomes and Policy, University of Florida, Gainesville, Florida

[2]: Health Outcomes, University of Rhode Island, Kingston, RI

[3]: Department of Nephrology, Thomas Jefferson Medical School, Philadelphia, PA

*: These authors contributed equally.

Abbreviations

HIV, Human Immunodeficiency Virus

cART, combined antiretroviral therapy

SRTR, Scientific Registry of Transplant Recipients

BMI, body mass index

HLA, human leukocyte antigen

PRA, panel reactive antibody

HBc, hepatitis B core

HCV, hepatitis C virus

EBV, Epstein-Barr virus

CMV, cytomegalovirus

ATG, anti-thymocyte globulin

IL-2, interleukin-2

DCM, dilated cardiomyopathy

CAD, coronary artery disease

DRS, disease risk score

HTR, heart transplant recipient

LTR, lung transplant recipients

IPF, idiopathic pulmonary fibrosis

COPD, chronic obstructive pulmonary disease

SD, standard deviation

IQR, interquartile range

XMATCH, histocompatibility cross match

CI, confidence interval

ISHLT, International Society for Heart Lung Transplantation

Abstract

Background

With the advent of combined antiretroviral therapy (cART), growing evidence has shown Human Immunodeficiency Virus (HIV) may no longer be an absolute contraindication for solid organ transplantation. This study compared outcomes of heart and lung transplantations between HIV positive and HIV negative recipients from a large transplant registry.

Methods

Patient survival, overall graft survival and death-censored graft survival were compared between HIV positive and HIV negative recipients. Multivariate Cox regression and Cox regression with a disease risk score (DRS) methodology were used to estimate the adjusted hazard ratios among heart transplant recipients (HTRs). Descriptive analysis was performed for HIV-positive lung transplant recipients (LTRs).

Results

In total 35 HTRs and 6 LTRs with HIV were identified. No significant difference was found in patient survival (88% vs 77%; p=0.1493), overall graft survival (85% vs 76%; p=0.2758) and death-censored graft survival (91% vs 91%; p=0.9871) between HIV positive and HIV negative HTRs in 5-year follow-up. No significant differences were found after adjusting for confounders. Among 6 HIV positive LTRs, two patients died in their first and fourth year after transplantation respectively.

Conclusions

This study supports the use of heart and lung transplant procedures in selected HIV positive patients.

(Words count: 197)

Introduction

Traditionally, transplantation eligibility hinged on a strict set of patient specific criteria. Patients infected with Human Immunodeficiency Virus (HIV) were generally excluded (1-3). The scarcity of donor organs forced practitioners to only consider patients with the best prognosis because success is dependent on a lifetime of adherence to a complex medication regimen (4). Furthermore, with continual immunosuppressant therapy as the mainstay in post-operative treatment, patients with immunocompromising conditions, such as HIV, may be more prone to adverse health outcomes (2, 5). Studies in early 1990s consistently showed shorter incubation periods for advanced disease and lower survival rates in transplant recipients infected with HIV (5-8). Additionally, some immunosuppressive therapies may inhibit the development of CD4+ T cells in patients after transplantation (9-11). However, with the introduction of combined antiretroviral therapy (cART) in 1996, survival and quality of life have improved markedly in HIV infected patients (12-14). The estimated 10-year survival rate in patients treated with cART exceeds 90%; denoting a shift in classifying HIV as an chronic infective process rather than an acute illness (15). In this new treatment era, studies supporting renal and hepatic transplantations in HIV infected patients have shown promising results (16-19). In contrast, limited instances of heart and lung transplants restricts the evidence to observational case studies (20, 21).

Even though transplantation may be the last chance of survival for patients with end-stage disease (22), many transplant centers remain reluctant to perform these procedures on patients infected with HIV (23). Despite recent reports suggesting that patients with HIV do not experience poorer health outcomes when compared to

uninfected transplant recipients (24-26), many clinicians remain steadfast in the antiquated eligibility guidelines. The case series study by Uriel et al. reported a 100% survival rate over a 5-year period without development of AIDS-defining illnesses among 7 HIV positive patients who received heart transplants (26). Similarly, Kern et al. reviewed three case studies of lung transplantations among patients with HIV infection and suggested that it might be a promising option for patients with selected end-stage lung disease (27) However, in the defense of the reluctant clinicians, these case reports are not comprehensive enough to provide conclusive evidence for supporting heart and lung transplantations in HIV infected patients. Therefore, this study aims to provide some guidance by evaluating heart and lung transplant outcomes among HIV positive and HIV negative recipients using a large transplant registry in the United States.

Methods

Data Source

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes 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), and has been described elsewhere (28). 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. This study utilized longitudinal clinical and demographic data on each patient from 2004-2016. It has been approved by the University of Rhode Island Institutional Review Board (IRB#955723-3).

Study Design

Outcomes in HIV positive transplant recipients were compared to HIV negative recipients in this retrospective cohort study. All patients who received a heart and/or lung transplant over the age of 18 were included. Any patients who received other organ transplants or who did not have a conclusive HIV serology at the time of transplantation were excluded from the study.

Patients were followed from the date of transplantation until the first occurrence of any of the following: end of the fifth transplant year, re-transplantation, death, graft failure, and loss of SRTR follow-up. The endpoints were defined as 'patient survival', 'overall graft survival', and 'death-censored graft survival'. Death with functioning graft was censored in 'death-censored graft survival' analysis, but treated as an event in 'overall graft survival'.

Statistical Analysis

Baseline cohort characteristics were summarized by calculated group means and standard deviations for continuous variables and proportional frequencies and percentages for categorical variables. Student t-tests and chi-square tests were used to quantify statistically significant differences in baseline characteristics between the HIV positive and negative groups. The Fischer's exact test was adopted, instead of Chi-square test, where any cell had an observed count less than five. The Kaplan–Meier analysis and log-rank test were used to compare the crude risk of transplantation outcomes between HIV positive and HIV negative recipients.

Multivariate Cox regression was used to adjust for confounders between HIV positive and HIV negative groups. Covariates investigated in this study included patient age, gender, race, recipient educational level, calendar year of transplantation, body mass index (BMI), receipt of induction therapy, baseline viral serology, primary cardiovascular diseases, number of human leukocyte antigen (HLA) recipient to donor mismatch, pre-transplant panel reactive antibody (PRA), histocompatibility cross match results, steroids regimen use, and ventricular assist device use. Besides HIV status, other pre-transplant viral antibody serology status were also examined, including hepatitis B core (HBc), hepatitis C virus (HCV), Epstein-Barr virus (EBV) and cytomegalovirus (CMV). The induction therapy utilized was classified as anti-thymocyte globulin (ATG), alemtuzumab, interleukin-2 (IL-2) inhibitors including basiliximab or daclizumab, other induction therapy and no induction. Primary diagnoses, defined as the reasons for receiving transplantation, were adjusted for and included dilated cardiomyopathy (DCM), coronary artery disease (CAD) and other diseases.

Transplantation in HIV infected recipients is relatively infrequent and could impact the validity of traditional multivariate regression with exposure propensity score (29-31). Disease risk score (DRS) is better suited for studies with rare exposures and was adopted as an alternative for the adjustment of confounders (30, 32). This method has been validated by previous simulated and observational studies (29, 33). To calculate DRS, each study outcome was regressed over the entire cohort on both the exposure variable and covariates (32).The score was compiled from the fitted values of the model for each study subject when setting the individual exposure variable to unexposed (32). The quintiles of the DRS were used for covariate adjustment within the

final Cox regression model to derive adjusted hazard ratios between HIV positive and negative patients with better precision (34).

All analyses were performed using SAS software, version 9.4 (SAS Institute Inc, Cary, NC). Statistical significance was based on a P value less than 0.05 and all confidence intervals used a 95% threshold.

Results

Thirty-five HIV-positive adult heart transplant recipients (HTRs) and 6 HIV-positive lung transplant recipients (LTRs) were identified using SRTR data from 2004 through 2016. The demographic and clinical characteristics of these 41 HIV-positive cases were summarized in table 1 and table 2 respectively. Statistical analyses between HIV negative and HIV positive LTRs were not conducted due to the limited number of observed occurrences. The 35 HTRs with positive HIV consisted of 25 male (71.43%) and 10 female (28.57%) patients with an average age of 49 years (SD: 12.00). In comparison, HTRs with a negative HIV serology were mostly male (74.66%) with a mean age of 53 years (SD: 12.80). Almost half of the transplantations among HIV-positive patients (51.14%) occurred in 2014-2016, while only about one-fourth of HIV-negative patients (25.95%) received transplantation in this period. HIV-positive HTRs had a significantly higher rate of chronic viral infections including hepatitis B (31.43% vs 4.51%, $p<0.001$), hepatitis C (8.56% vs 1.93%, $p=0.0491$), and cytomegalovirus (85.71% vs 59.35%, $p=0.0341$). Additionally, HIV-positive HTRs were less likely to have received anti-thymocyte globulin (ATG) as induction therapy; although, this comparison is not statistically significant (8.57% vs 19.49%, $p=0.3438$). HIV-positive HTRs had a

higher frequency of coronary arterial disease as a primary medical diagnosis when compared to patients without HIV infection (11.43% vs 4.18%, p = 0.0289). There were significantly more HIV-positive HTRs with a college level education (68.57% vs 48.93%, p=0.0461).

The median follow-up times were 2.00 years for HIV-positive HTRs and 3.00 years for HIV-negative HTRs. Among the 35 HIV-positive HTRs, two patients died at 2.78 and 2.93 years respectively and one patient did not receive a successful transplant. The remaining patients survived the whole study period with a functioning graft. Even though the results were inconclusive, HIV-positive HTRs appeared to have a better patient survival (1-year: 100% vs 89%, 3-year: 88% vs 83%, 5-year: 88% vs 77%; p=0.1493), overall graft survival (1-year: 97% vs 89%, 3-year: 85% vs 82%, 5-year: 85% vs 76%; p=0.2758), and death-censored graft survival rates (1-year: 97% vs 96%, 3-year: 91% vs 93%, 5-year: 91% vs 91%; p=0.9871) (Figure 1 a, b, and c). Adjusting for demographic and clinical characteristics using a multivariate Cox regression or DRS adjustment model did not alter the results (Figure 2).

Among the 6 HIV-positive LTRs, all patients were white with ages varying between 50 to 70 years old. Three patients had a BMI>30, one patient was female, and only one did not have a college-level education. Two patients were infected with Hepatitis B, all six patients were coinfected with cytomegalovirus and Epstein Barr virus, and none of the patients were infected with Hepatitis C. Four patients received transplants due to idiopathic pulmonary fibrosis (IPF) and one due to chronic obstructive pulmonary disease (COPD). Two patients were lost to follow-up immediately after transplantation, one patient was censored at the fourth year, and another was censored

at the fifth year. No graft failures were observed for these four patients. The remaining two patients died in 116 days and 1541 days after transplantation.

Discussions

Throughout the 12-year study period, 35 HTRs and 6 LTRs were infected with HIV; which, to our knowledge is the largest study conducted on heart and lung transplantations among HIV patients. When comparing transplantation outcomes within the total cohort (N=21,435), there was no significant difference in the rates of patient survival or graft failure. Consistent with previous reports, these findings suggest that both heart and lung transplantations may be viable options for selected HIV infected patients (20, 26, 27).

While Aguero et al. summerized previous studies showing the 1-, 2-, and 5-year survival rates for HIV-postive HTRs of 90-100%, 90-100%, and 63% (20), the survival rates in this study exhibited a more encouraging 5-year survival rate of 88%. Compared to Kern et al. study, in which all three LTRs remained alive during the study period with the longest follow-up time surpassing 4 years (27), our study observed two LTRs who died in their first and fourth year after transplantation, two who were lost to follow-up immediately after transplantation, and two who remained alive for more than four years post-transplant. HIV-positive LTRs had acceptable outcomes with wide variabillity but displayed a higher risk of poorer outcomes when compared to HIV-positive HTRs. The selection of transplant candidates should be cautious, as many factors may affect the transplant outcomes, for example, HCV positivity will put HIV patients at greater risk

than non-HIV patients after liver transplantation (16). Therefore more cases are required to examine the factors that impact health outcomes between these groups.

Overall, the knowledge of heart and lung transplantat outcomes among HIV recipients remains limited, despite the developing evidence on the safety and efficacy of kidney and liver transplants (35, 36). Similar to arguments of these kidney and liver transplant studies, this analysis suggests that HIV positivity in heart and lung transplant cadidates should not signify automatic exclusion.

HIV-infected patients are more likely to develop cardiovascular diseases including cardiomyopathy, coronary arterial disease, myocarditis, cardiomegaly, and malignancy (37-39). Similarly, HIV is assoicated with an increased risk of chronic obstrutive pulmonary disease, pulmonary fibrosis, pulmonary arterial hypertension, and lung cancer (40-42). It would be adventageous to develop a clear understanding of the outcomes and risks of heart tranplantations and lung transplantations in this patient group. Furthermore, HIV infection is no longer considered an absolute contraindication in the updated consensus guidelines developed by the International Society for Heart Lung Transplantation (ISHLT) (43, 44). However, most transplant centers still remain reluctant to perform heart or lung transplants within this population because of the concerns for infection, HIV reactivation by immunosuppressants, and drug-drug interactions (23). Even though the published literature on this topic is in its adolescent stages, this study indicates that the stigma associated with HIV on heart and lung transplant outcomes should be revisisted.

While these findings provide promising results derived from the largest known cohort of HIV positive heart and lung transplant recipeints, the conclusions remain

vulnerable to several study limitations. The most prominent of which, is the lack of HIV-positive heart and lung transplant cases observed within the registry. We suspect that as time progresses more cases will be captured. However, because this study can only make inferences about the observations included within the registry, the validity of the derived estimates remains inconclusive.

Additionally, the SRTR provides limited information about the baseline, pre-operative, and post-operative clinical depiction of each patient. For example, information regarding the viral load, CD4 count, or instances of AIDS opportunisitc infection are absent. This can introduce uncertainty when comparing outcomes across transplant recipients; who, may be suffering from varying levels of HIV severity. In contrast, HIV infected individuals who progress to the solid organ waiting-list may be healthier than the average HIV patient. In many reports, the HIV-infected patients selected exhibited undetectable viral loads, moderate CD4 counts, and a lack of AIDS-related infections. This limits the generalizatbillity of results to a healthier HIV subpopulation and introduces an unavoidable, systemic selection bias.

Along with the lack of markers depicting the clinical health of each patient, this dataset is incapable of evaluating medication adherence. The complicated home-medication regimen that the average transplant recipeint recieves can increase in complexity when the common drug-drug interactions between antiretroviral therapies and immunosuppressive therapies are introduced. If patients with superb medication adherence experienced better health oucomes than those with moderate or suboptimal adherence, this effect would never be identified.

While these limitations are not all-inclusive or completely avoidable, the results still indicate that HIV status should not trigger automatic exclusion from transplant elgibillity. Instead, clinicians should review HIV-positive transplant cindidates under updated criteria. Further research is required to develop a clearer understanding of the variables that impact health outcomes in HIV-positive heart and lung transplant recipeints as these procedures could improve prognosis by many years.

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Table 1. Demographic and clinical characteristics of US heart transplant recipients (HIV-positive vs. HIV-negative) from 2004 through 2016

Variables	HIV positive N=35	HIV negative N=21400	*p*
Year of transplant			0.0027
2004-2006	1 (2.86)	3772 (17.63)	
2007-2009	5 (14.29)	4839 (22.61)	
2010-2013	11 (31.43)	7236 (33.81)	
2014-2016	18 (51.43)	5553 (25.95)	
Pretransplant viral serology			
Hepatitis B antibody+	11 (31.43)	965 (4.51)	<0.001
Hepatitis C antibody+	3 (8.57)	413 (1.93)	0.0491
Epstein Barr virus+	27 (77.14)	16116 (75.31)	0.8100
Cytomegalovirus+	30 (85.71)	12700 (59.35)	0.0341
Induction therapy			0.3438
ATG	3 (8.57)	4147 (19.49)	
Alemtuzumab	0 (0.00)	219 (1.02)	
IL-2 inhibitors	10 (28.57)	5918 (27.65)	
Others	22 (62.86)	11092 (51.83)	
Mean age (SD)	48.69 (12.00)	52.64 (12.80)	0.0678
Age categories:			0.1953
18-45	13 (37.14)	5246 (24.51)	
46-60	14 (40.00)	9336 (43.63)	
Over 60	8 (22.86)	6818 (31.66)	
Median follow-up years (IQR)	2.00 (0.5, 4.98)	3.00 (1.00, 4.99)	0.1606
Recipient race:			<0.001
White	12 (34.29)	14549 (67.99)	
Black	20 (57.14)	4214 (19.69)	
Hispanic	2 (5.71)	1717 (8.02)	
Others	1 (2.86)	9420 (4.30)	
Recipient sex			0.6607
Male	25 (71.43)	15977 (74.66)	
Female	10 (28.57)	5423 (25.34)	
Education level			0.0461
College	24 (68.57)	10470 (48.93)	
Non-college	7 (20.00)	8479 (39.62)	
Unknown	4 (11.43)	2451 (11.45)	
Previous transplant	1 (2.86)	612 (2.86)	1.0000
Recipient BMI:			0.7779
0-20	4 (11.43)	1387 (6.48)	
20-25	10 (28.57)	6244 (29.18)	
25-30	13 (37.14)	7873 (36.79)	
Above 30	8 (22.86)	5751 (26.87)	
HLA mismatch >3	28 (80.00)	16234 (75.86)	0.2336
Steroids use	33 (94.29)	20453 (95.57)	0.6676
Ventricular assist device	15 (42.86)	6409 (29.95)	0.0958
Left ventricular assist device	6 (17.14)	3725 (17.41)	0.9672

Histocompatibility cross match			
Negative	22 (62.86)	14618 (68.31)	0.6045
Positive	1 (2.86)	816 (3.81)	
Weak positive	1 (2.86)	202(0.94)	
Unknown	11 (31.43)	5764 (26.93)	
Primary diagnoses:			0.0333
DCM	30 (85.71)	17783 (83.10)	
CAD	4 (11.43)	894 (4.18)	
Others	1 (2.86)	2723 (12.72)	

Abbreviation: HIV, Human Immunodeficiency Virus; ATG, anti-thymocyte globulin; IL-2, interleukin-2; SD, standard deviation; IQR, interquartile range; BMI, body mass index; HLA, human leukocyte antigen; DCM, dilated cardiomyopathy; CAD, coronary artery disease

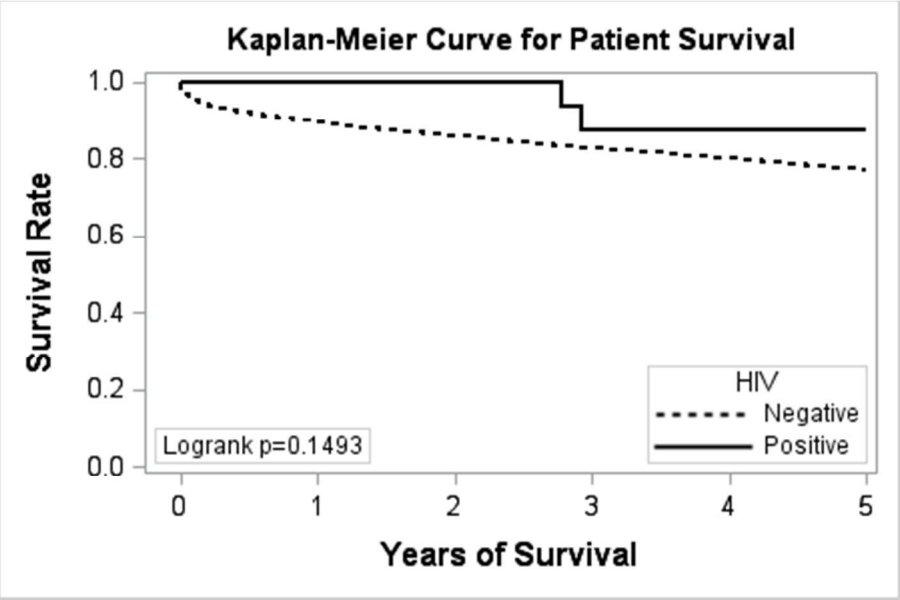
Table2. Demographic and clinical characteristics of lung transplant HIV-positive recipients from 2004 through 2016

Variables	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Year of Transplant	2004	2010	2012	2014	2016	2016
Pretransplant viral serology						
Hepatitis B antibody	+	-	+	-	-	-
Hepatitis C antibody	-	-	-	-	-	-
Epstein Barr virus	+	+	+	+	+	+
Cytomegalovirus	+	+	+	+	-	+
Induction therapy	Others	Others	Others	IL-2 inhibitors	IL-2 inhibitors	IL-2 inhibitors
Recipient age	56	63	60	70	53	57
Recipient race	White	White	White	White	White	White
Recipient sex	Male	Male	Male	Male	Female	Male
Education level	Non-college	College	College	College	College	College
Recipient BMI	Above 30	Above 30	25-30	25-30	20-25	Above 30
HLA mismatch >3	>3	>3	<=3	>3	>3	>3
Steroids use	Yes	Yes	Yes	Yes	Yes	Yes
Ventricular assist device	No	No	No	No	No	No
Left ventricular assist device	No	No	No	No	No	No
Histocompatibility cross match	Negative	Negative	Negative	Negative	Unknown	Unknown
Primary diagnoses	IPF	IPF	IPF	IPF	Others	COPD
Survival days	1826	1541	1462	116	0	0
Death	No	Yes	No	Yes	No	No
Overall graft failure	No	Yes	No	Yes	No	No

Abbreviation: HIV, Human Immunodeficiency Virus; IL-2, interleukin-2; BMI, body mass index; HLA, human leukocyte antigen; IPF, idiopathic pulmonary fibrosis; COPD, chronic obstructive pulmonary disease

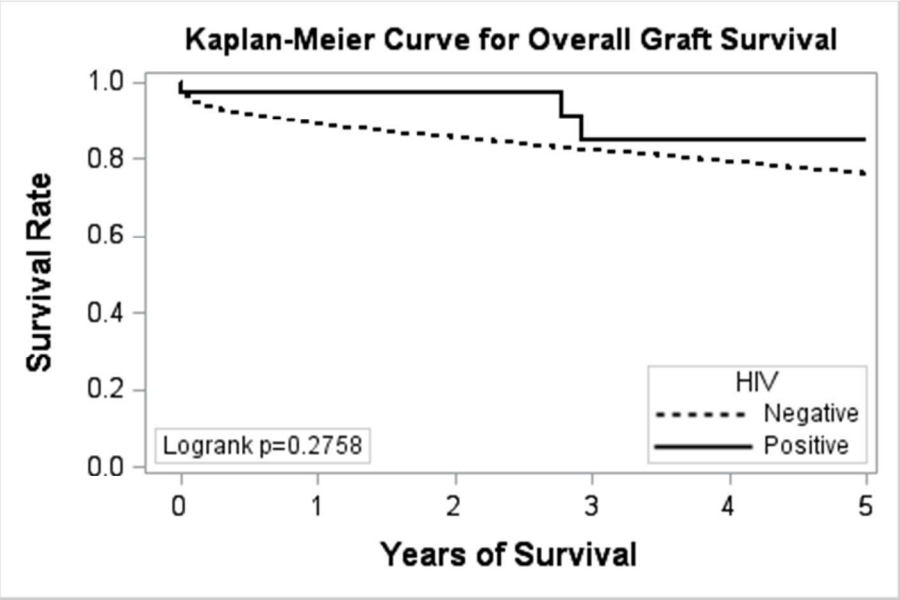
Figure 1. Kaplan-Meier curve for patient outcomes among heart and lung transplant recipients (HIV-positive vs. HIV-negative)

Figure 1.a Patient Survival (*P*=0.1493)



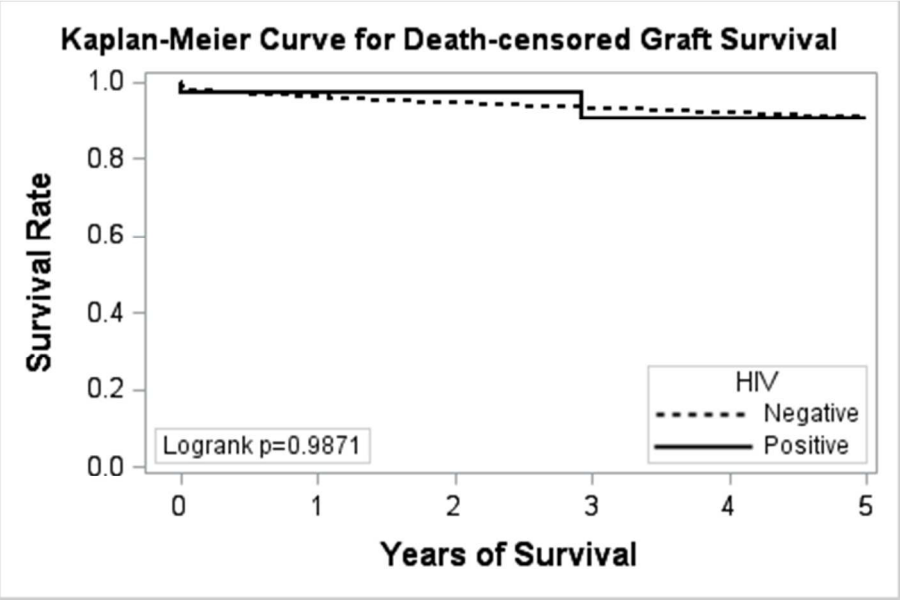
Survival Rate, %	Year 1	Year2	Year3	Year 4	Year 5
HIV	100	100	88	88	88
Non-HIV	89	86	83	80	77

Figure 1.b Overall Graft Survival (*P*= 0.2758)



Survival Rate, %	Year 1	Year2	Year3	Year 4	Year 5
HIV	97	97	85	85	85
Non-HIV	89	86	82	79	76

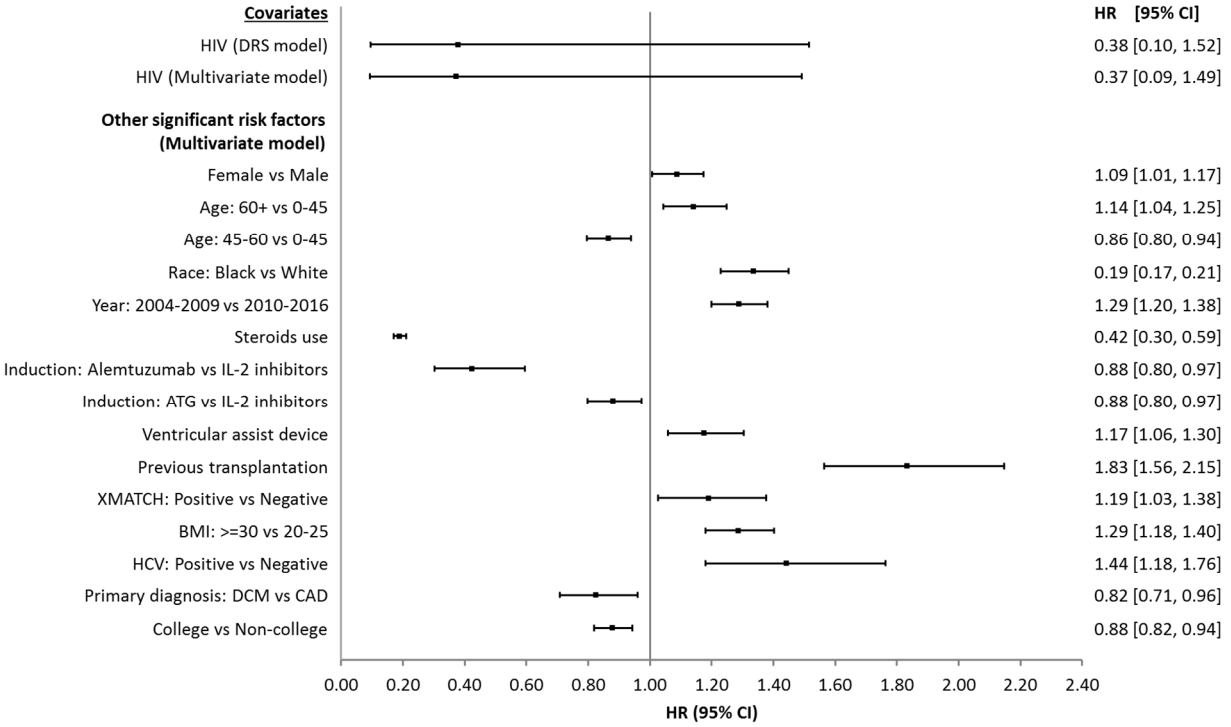
Figure 1.c Death-censored graft Survival (*P*=0.9871)



Survival Rate, %	Year 1	Year2	Year3	Year 4	Year 5
HIV	97	97	91	91	91
Non-HIV	96	95	93	92	91

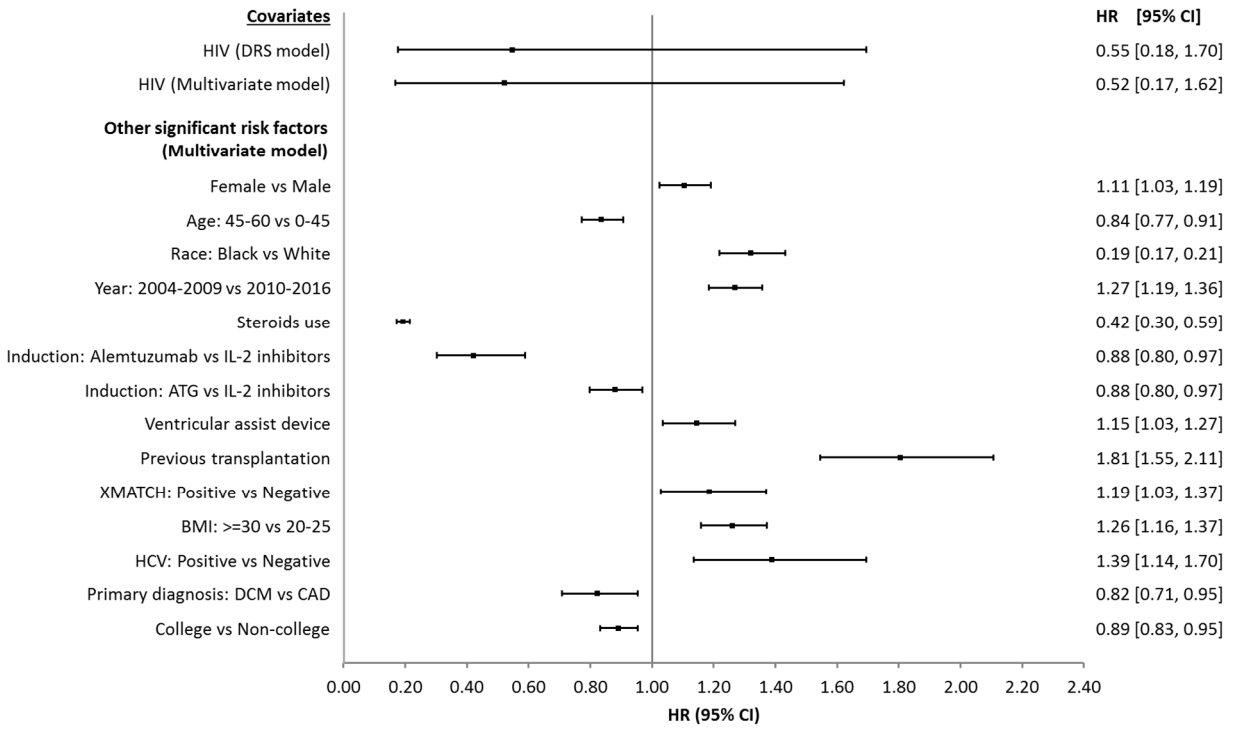
Figure 2 Forest plot of adjusted hazard ratios of HIV status and other significant risk factors for patient survival, overall graft survival and death-censored graft survival among heart transplant recipients

Figure 2a. Forest plot of adjusted hazard ratios of HIV status and other significant risk factors for patient survival among heart transplant recipients



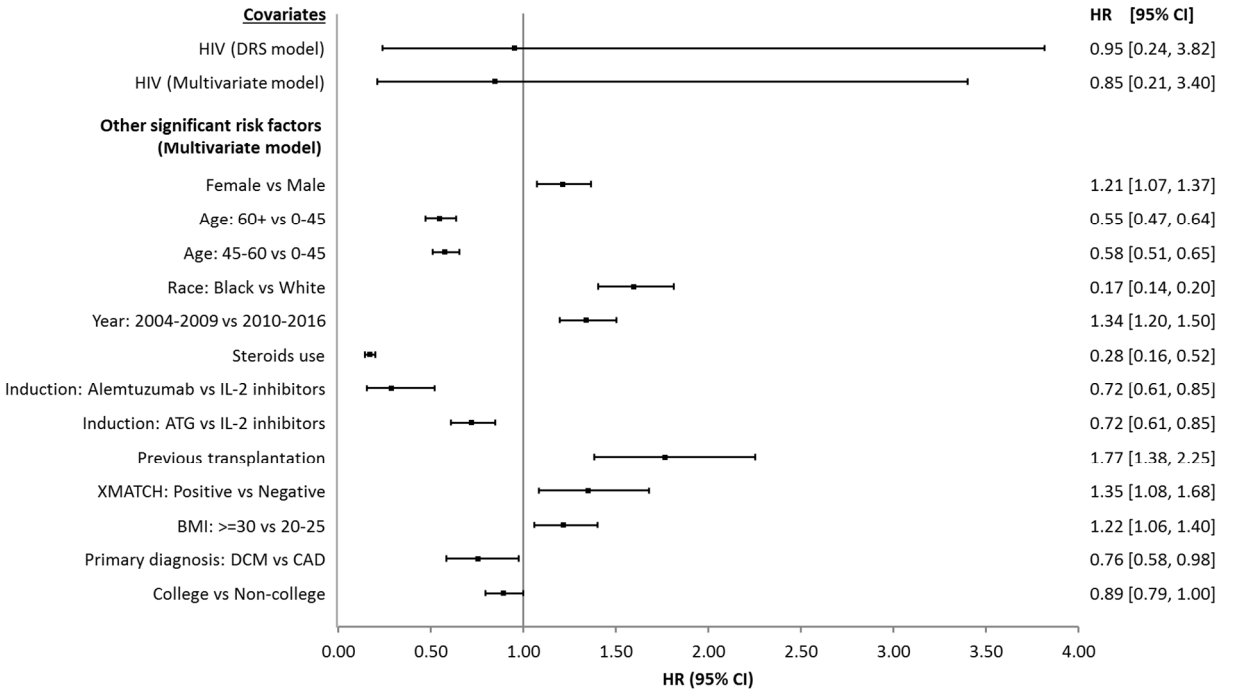
Abbreviation: HIV, Human Immunodeficiency Virus; DRS, disease risk score; XMATCH, histocompatibility cross match; CI, confidence interval; ATG, anti-thymocyte globulin; IL-2, interleukin-2; BMI, body mass index; DCM, dilated cardiomyopathy; CAD, coronary artery disease

Figure 2b. Forest plot of adjusted hazard ratios of HIV status and other significant risk factors for overall graft survival among heart transplant recipients



Abbreviation: HIV, Human Immunodeficiency Virus; DRS, disease risk score; XMATCH, histocompatibility cross match; CI, confidence interval; ATG, anti-thymocyte globulin; IL-2, interleukin-2; BMI, body mass index; DCM, dilated cardiomyopathy; CAD, coronary artery disease

Figure 2c. Forest plot of adjusted hazard ratios of HIV status and other significant risk factors for death-censored graft survival among heart transplant recipients



Abbreviation: HIV, Human Immunodeficiency Virus; DRS, disease risk score; XMATCH, histocompatibility cross match; CI, confidence interval; ATG, anti-thymocyte globulin; IL-2, interleukin-2; BMI, body mass index; DCM, dilated cardiomyopathy; CAD, coronary artery disease