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Improved Survival in Pediatric Heart Transplant Recipients: Have White, Black and Hispanic Children Benefited Equally?

T. P. Singh^{a,b}, C. S. Almond^{a,b}, and K. Gauvreau^{a,c}

^aDepartment of Cardiology, Children's Hospital Boston, Boston, MA

^bDepartment of Pediatrics, Harvard Medical School, Boston, MA

^cDepartment of Biostatistics, Harvard School of Public Health, Boston, MA

Abstract

We assessed whether the improvement in post-transplant survival in pediatric heart transplant (HT) recipients during the last 2 decades has benefited the major racial groups in the US equally. We analyzed all children <18 years of age who underwent their first HT in the US during 1987–2008. We compared trends in graft loss (death or re-transplant) in white, black and Hispanic children in 5 successive cohorts (1987–1992, 1993–1996, 1997–2000, 2001–2004, 2005–2008). The primary endpoint was early graft loss within 6 months post-transplant. Longer-term survival was assessed in recipients who survived the first 6 months. The improvement in early post-transplant survival was similar (hazard ratio [HR] for successive eras 0.80, 95% confidence interval [CI] 0.7, 0.9, $P=0.24$ for black-era interaction, $P=0.22$ for Hispanic-era interaction) in adjusted analysis. Longer-term survival was worse in black children (HR 2.2, CI 1.9, 2.5) and did not improve in any group with time (HR 1.0 for successive eras, CI 0.9, 1.1, $P=0.57$; $P=0.19$ for black-era interaction, $P=0.21$ for Hispanic-era interaction). Thus, the improvement in early post-HT survival during the last 2 decades has benefited white, black and Hispanic children equally. Disparities in longer-term survival have not narrowed with time; the survival remains worse in black recipients.

INTRODUCTION

Racial disparities in health outcomes may widen or narrow with advances in medical care.(1, 2) Improvement in outcomes due to technological advances may at first benefit the more affluent and the more educated racial groups disproportionately and result in widening of disparities.(2–5) Disparities may narrow however if improved outcomes result from a wider application of newly accepted technologies (5), quality improvement measures (3) or interventions specifically designed to reduce racial and ethnic disparities.(4)

Address for Correspondence: Tajinder P. Singh, MD, MSc, Department of Cardiology, Children's Hospital Boston, 300 Longwood Ave, Boston, MA 02115, Tel: 617-355-0558; FAX: 617-734-9930, TP.Singh@cardio.chboston.org.

Disclosure

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Racial differences in post-transplant outcomes are well known in pediatric heart transplant recipients. Several studies have reported that black children are at higher risk of graft rejection and have shorter allograft life compared to white or non-black children.(6–9) These differences exist even as the overall post-transplant survival has continued to improve during the last 2 decades.(10, 11) It remains unknown however whether the improved post-transplant survival, often referred to as the “era effect”, is due to better outcomes in all racial groups, narrowing of racial differences in outcomes with time or some combination of these two mechanisms.

We hypothesized that children of major racial/ethnic groups in the United States (US) have benefited equally from improvement in post-transplant survival during the last 2 decades. Because the era effect is primarily attributed to improved “early” post-transplant survival (10–12), the primary objective of this study was to compare era effect for post-transplant survival during the first 6 months after heart transplant in white, black and Hispanic children. We also assessed race-era interaction for longer-term survival (conditional upon surviving the first 6 months post-transplant) as a secondary outcome because racial differences in outcomes may not appear until later in post-transplant course (8, 9) and thus any intervention directed at reducing these differences in outcomes would likely benefit longer-term survival the most.

MATERIALS AND METHODS

Study Population

All children < 18 years of age who underwent their primary heart transplant in the US between January 1, 1987 and March 31, 2008 were identified in the Organ Procurement and Transplantation Network (OPTN) database. The OPTN database includes data on all transplant recipients in the US as submitted by the members of the network. The Health Resources and Services Administration, U.S. Department of Health and Human Services, provides oversight to the activities of the OPTN contractor, the United Network of Organ Sharing.

We excluded children who received a heart re-transplantation or multi-visceral transplantation. All children were followed from the time of heart transplant until death, re-transplant or the day of last observation on February 25th, 2009.

Study Design and Definitions

We compared baseline characteristics and trends in graft loss (death or re-transplant) in white, black and Hispanic children in 5 successive heart transplant cohorts (those transplanted during years 1987–1992, 1993–1996, 1997–2000, 2001–2004, and 2005–2008) in the OPTN database. All clinical and demographic variables were defined at the time of transplant unless stated otherwise. The primary end-point was time to early graft loss, defined as a composite of death (all-cause mortality) and re-transplant within the first 6 months post-transplant. A secondary outcome was time to graft loss conditional upon surviving the first 6 months and assessed with time 0 as 6-months post-transplant (conditional survival). To assess whether racial differences in outcomes could be attributed

to differences in their immune suppression, we assessed trends in use of newer maintenance immune suppression medications, tacrolimus and mycophenolate mofetil, at the time of hospital discharge and at 1-year post-transplant in the three racial groups. We also assessed racial trends in graft rejection during the first year post-transplant.

Patient race/ethnicity (a mandatory variable) were reported to the OPTN database by the transplanting center as one of the following: white, black, Hispanic/Latino, Asian, American Indian/Alaska Native, Native Hawaiian/Pacific Islander, Multiracial, and Other. Due to the small sample size of transplant recipients from minorities other than blacks and Hispanics (5% of all recipients), these patients were not analyzed in this study.

To define the level of hemodynamic support as a risk factor, a child was defined to be on extra-corporeal membrane oxygenation (ECMO) if supported on ECMO, on ventilator if supported by a ventilator but not on ECMO, and on inotropes, if supported by inotropes but not a ventilator or ECMO. To assess renal function at the time of transplant, we estimated creatinine clearance using serum creatinine and the Schwartz formula.(13)

Statistical Analysis

Summary statistics are presented as median (25th, 75th percentile) or number (percent). Baseline characteristics in white, black and Hispanic children were compared using the chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. The three groups were evaluated for trends in the distribution of listing diagnoses in successive eras. Un-adjusted survival rates were computed using the Kaplan-Meier method. A multivariable Cox proportional hazards model for early (6 months) post-transplant survival was developed using forward selection; variables significant at the 0.10 level based on a likelihood ratio test were retained in the model. A similar method was used for analyzing longer-term survival starting at 6 months post-transplant, limiting analysis to recipients who survived the first 6 months post-transplant (conditional survival). For both early and longer-term survival, terms for race-era interaction were added to the main-effects models to assess whether there were racial differences in improvement in post-transplant survival over time. Continuous variables were fitted in both models with a restricted cubic spline to allow for the most flexible relationship between the variable and the outcome. Because of a shorter period of follow-up in more recent recipients, we performed a sensitivity analysis in which we modeled longer-term, conditional survival in 6-month survivors while censoring their follow-up at 4-years post-transplant to compare survival during equivalent period of follow-up in all eras. The data were analyzed using statistical software SAS version 9.1 (SAS Institute Inc, Cary, NC) and STATA version 10.0 (StataCorp LP, College Station, TX).

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

RESULTS

Study Population

During the study period, 4983 children < 18 years of age underwent their first heart transplant in the US. Of these, 3204 were white, 887 were black and 642 were Hispanic. These 4733 children formed the analytic cohort for this study. The OPTN database reported race and ethnicity as two separate variables. For all white, black and Hispanic children in the study, race and ethnicity variables were reported to be identical.

The baseline demographic and clinical characteristics of the racial groups are summarized in Table 1. White children were more likely to be supported by ECMO or ventilator at the time of heart transplant ($P < 0.001$ for distribution of invasive support). Black children were more likely to be older, have cardiomyopathy and be supported by a ventricular assist device compared to white and Hispanic children ($P < 0.001$ for all). White children comprised a lower proportion, and black and Hispanic children a higher proportion, of transplant recipients in successive eras (Figure 1A, $P < 0.001$ for distribution). The proportion of transplant recipients with congenital heart disease decreased with time (Figure 1B, $P < 0.001$ for trend in whites, 0.11 in blacks and 0.002 in Hispanics). Notably, white children were more likely to be supported by ECMO or ventilator at the time of transplant in all eras (Figure 1C, $P < 0.001$).

None of the patients had any missing data for the variables age, gender, race/ethnicity, diagnosis, hemodynamic support, dialysis and the date of transplant. For children with missing data on any other variable, we created the corresponding indicator variable “variable not reported” to allow these subjects to contribute their other risk factors in the multivariable model.

Early (6-month) Post-transplant Survival

Overall, graft loss occurred in 2005 (42.4%) transplant recipients (1664 deaths, 341 re-transplants). Re-transplantation contributed a smaller proportion to the composite end point of death or re-transplantation in black (14%) compared to white (18%) and Hispanic (20%) recipients.

Early graft loss occurred in 720 (15.2%) transplant recipients (676 deaths, 44-retransplants). Freedom from early graft loss improved from 77.3 % for patients who underwent heart transplant during 1987–1992 to 89.7 % for those who underwent transplant during 2005–2008. Figure 2 illustrates Kaplan-Meier survival curves, unadjusted for baseline risk factors, in white, black, and Hispanic children during the five study eras truncated at 6 months after transplant. Unadjusted early transplant survival (freedom from early graft loss) improved in successive eras in white children but less consistently in black and Hispanic children. Six-month survival was essentially identical in the three groups in the most recent era (2005–2008) (Figure 2D).

In multivariable analysis (Table 2), the era of transplant was a significant predictor of early graft loss. Adjusted for baseline clinical risk factors, children who received a heart transplant during 2005–2008 were 50% less likely to die or receive a re-transplant within 6 months

compared to those who underwent their heart transplant during 1987–1992 (hazard ratio [HR] 0.5, 95% confidence interval [CI] 0.4, 0.7; $P<0.001$). Other risk factors for death or re-transplant within 6 months were younger age, female gender, congenital heart disease, prior sternotomy, ventilator or ECMO support at the time of transplant, longer ischemic time, renal dysfunction, higher serum bilirubin, and donor age <1 year. Hispanic children had a survival advantage in adjusted analysis and were 30% less likely to die compared to white children.

When race-era interaction terms were added to the main-effects multivariable model in Table 2, they were not significant statistically. Similar, statistically non-significant results were obtained when race-era interaction terms were added to the multivariable model after the variable “era” was changed to an ordinal variable with 1987–1992 as the referent era (HR for era 0.8, 95% CI 0.7, 0.9, $P<0.001$, $P=0.24$ for black-era interaction, $P=0.22$ for Hispanic-era interaction). Thus, there was no significant difference among racial groups in improvement in early post-transplant survival over time.

Longer-Term (Conditional) Survival

Annual attrition (death or re-transplant) in 6-month survivors was 3.5% in white, 4.0% in Hispanic and 6.1% in black children. Adjusted for baseline risk factors (recipient and donor age, race, gender, diagnosis, renal function, $\text{PRA}>10\%$), there was no improvement in longer-term survival in successive eras (Table 3). The risk of death or re-transplant in black children was more than twice that of white children (HR 2.2, 95% CI 1.9, 2.5, $P<0.001$) in adjusted analysis. Addition of race-era interaction terms to the multivariable model in Table 3 demonstrated no statistically significant race-era interaction. Furthermore, there was no significant race-era interaction when the variable “era” in the model was treated as an ordinal variable with 1987–92 era as the referent period (HR for era 1.0, 95% CI 0.9, 1.1, 0.57, $P=0.19$ for black-era interaction, $P=0.21$ for Hispanic-era interaction). Finally, when post-transplant follow-up was censored at 4 years for recipients in all eras, these findings remained unchanged and there was no era effect in any racial group (HR for era 0.96, 95% CI 0.88, 1.05, $P=0.88$ for black-era interaction, $P=0.23$ for Hispanic-era interaction).

Racial Trends in Immune Suppression and First-year Rejection

The percentage of children on tacrolimus and those on mycophenolate immune suppression at hospital discharge increased in successive eras in all racial groups. The percentage of white, black and Hispanic children on mycophenolate at the time of hospital discharge were similar in all eras, however a higher proportion of black children appeared to be on tacrolimus during the recent eras. (Figure 3, Panels A–B). The percentage of children on these drugs at 1-year post-transplant also increased progressively and were similar among the three racial groups during the 3 recent eras when such data were available (data not shown). First-year rejection data were missing in $>80\%$ of children during the first 2 eras. The percentage of children who were reported to have a rejection episode during the first post-transplant year decreased between the 3rd and the 5th era in white (62%, 38% and 28% during 1997–2000, 2001–2004 and 2005–2008, respectively), black (67%, 43% and 33%, respectively) and Hispanic (45%, 41% and 28%, respectively) children. Of 1729 children with rejection data, those with a rejection episode during the first post-transplant year

(n=729) were at higher risk of graft loss on longer-term follow-up compared to children who were rejection-free during the first year in adjusted analysis (HR=1.8, CI 1.4, 2.2, P<0.001). There was no era effect for longer-term survival in children stratified by first-year rejection, overall or in any racial group.

DISCUSSION

There are three main findings of this study. First, there has been a significant demographic shift in the racial distribution of children undergoing heart transplantation with a progressive increase in proportion of black and Hispanic transplant recipients in successive eras. Second, the risk-adjusted, early post-transplant survival has improved similarly in white, black and Hispanic children during the last 2 decades. Third, among children who survived the first 6 months after their heart transplant, the risk of longer-term graft loss has not improved in any racial group during this period.

This is the first study to assess racial trends in post-transplant survival during the last 2 decades in pediatric heart transplantation. Mahle et al previously described worse post-transplant survival in black children after heart transplant in the US but did not assess racial trends in outcomes over time.(9) More recently, Singh et al demonstrated that the risk-adjusted era effect in pediatric heart transplant recipients was entirely due to improvement in survival during the first 6 months post-transplant but could not assess the effect of race because the registry analyzed lacked this variable.(12) In the present study, we report that the major racial groups have enjoyed a similar degree of improvement in survival during the first 6 months post-transplant, however, because long-term outcomes have remained stagnant, black children remain at a two-fold higher risk of longer-term graft loss compared to white and Hispanic children. This translates to a median graft life in black children that is less than 50% compared to other groups.(9) Several studies suggest that the worse post-transplant survival in black children may be due to a higher risk of rejection (6–8) which may be mediated by both genetic and socioeconomic factors.(14–16) To the extent that our findings serve to identify specific periods where racial gaps still exist, it may be possible to design targeted strategies to eliminate these gaps and ultimately improve survival in pediatric heart transplantation. Although racial disparities may decrease with broad quality improvement initiatives, interventions targeted at high-risk groups that “pull up” their survival curves may also improve *overall* post-transplant survival. This approach is similar to that proposed for targeting high-risk groups for preventing cardiovascular disease in addition to the preventive measures applicable to the entire population.(17)

The major risk factors for early post-transplant graft loss include the complexity of cardiac diagnosis, the severity of heart failure and the presence and severity of end-organ dysfunction at the time of transplant. The improvement in early post-transplant survival in pediatric heart transplantation may be attributed to advances in selection of heart transplant candidates, in the care of children awaiting heart transplantation, in donor management, in intra-operative techniques and in post-operative care of transplant recipients.(18–20) These advances share a common theme - they are all applicable during the intensive and mostly in-hospital patient care close to transplant surgery. A similar improvement in early post-transplant survival among racial groups suggests that these advances have been widely

implemented among transplant centers and that the early post-transplant care is standardized and does not vary by race. This improvement in hospital outcomes is sustained by a close outpatient follow-up during the first 6 months post-transplant which is protocol-driven in most centers and minimizes any racial differences in outcomes. It is less clear why longer-term outcomes have not improved in any racial group even though the follow-up care of survivors of heart transplantation has also evolved with the availability of newer immune suppression drugs (21), functional assays to monitor immune suppression (22, 23) and antigen assays to monitor for viral activity.(24) This finding may be secondary to persistent issues with adolescent non-adherence and due to transplant centers' willingness to accept higher risk candidates in the more recent eras (such as those with multiple risk factors) whose risk cannot be entirely captured in these risk-adjusted models. As a result, the observed decrease in first-year rejection rates in recent eras has not yet translated into improved long-term survival.

The increased risk of longer-term graft loss in black children is well known (9) and has been mostly attributed to biologic (genetic and immunologic) differences among racial groups. For example, black children have a higher prevalence of genotypes associated with reduced immune suppression exposure and efficacy compared to white and Hispanic children as well as genotypes associated with a pro-inflammatory state.(14) Lower socioeconomic position, known to be more prevalent in black children, may also contribute to worse outcomes.(25). Finally, because adolescent recipients are more likely to be noncompliant with immune suppression (26) and black recipients in our study were, on average, older than white or Hispanic recipients, a residual confounding with age in the observed association of black race with worse outcomes cannot be excluded. Our analysis shows that a modestly higher proportion of black children had a rejection episode during the first year post-transplant in all eras compared to other racial groups. A similar association of graft loss with black race has also been described in renal transplantation and has been attributed to a combination of genetic, immunologic and socioeconomic factors.(27–29) Given that newer immune suppression agents (such as mycophenolate mofetil and tacrolimus) reduce rejection rates and may improve long-term graft survival in heart transplant recipients (30–32), our finding that a similar percentage of racial groups received maintenance mycophenolate and tacrolimus in all eras makes it unlikely that the longer-term survival in black children has been worse due to a disparity in use of newer immune suppression medications. Reduction and elimination of disparities in health care and health outcomes is a national priority in the US.(33) Although single-center studies have reported improved outcomes in black transplant recipients, the results have been attributed to quality improvement initiatives or newer immune suppression protocols rather than to efforts to reduce disparities.(34, 35) It is hoped that intervention studies currently in progress in various medical disciplines will improve our understanding of the effectiveness of various measures in reducing racial disparities.(36) The magnitude of increased risk of graft loss in black children suggests that interventions that significantly lower this risk will result in clinically important overall improvement in post-transplant survival.

We were somewhat surprised to find that in all eras, white children had more severe heart failure at the time of transplant and were thus more likely to be supported on a ventilator or ECMO compared to black or Hispanic children. Given that previous research has not

observed a difference in heart failure severity among racial groups at the time of listing but has found 50 to 60% higher wait-list mortality in black and Hispanic children (37), this finding raises the possibility that the observed differences may reflect variability in threshold for removing children from the waiting list in response to clinical deterioration. This possibility is supported by our finding that Hispanic children had lower early post-transplant mortality suggesting that they were lower-risk patients at transplant. Clinical decision to remove a candidate from the waiting list as heart failure worsens is complex and requires consideration of illness severity, presence of end organ dysfunction and patient/parental preferences.(33, 37, 38) Further research is clearly needed to better understand this finding.

This study has limitations. Being a retrospective study, the absence of variables in the OPTN database that would allow mechanistic insights into our findings, particularly those related to longer-term graft loss in transplant recipients, was an important limitation of these data. For example, data on frequency and severity of rejection episodes, compliance with clinical follow-up and with immune suppression, socioeconomic variables and post-transplant medical insurance would have provided significant insights into these findings. Second, the duration of longer-term follow-up was different in patients in successive eras. Whether the more recent cohorts will develop a survival advantage on longer follow-up is not known. Finally, the variables race and ethnicity were recorded as reported by the individual centers with a potential of misclassification bias for some patients. However, this misclassification is likely to be non-differential and not likely to affect study results because of the relatively large sample size.

In conclusion, the improvement in early post-transplant survival during the last 2 decades has benefited white, black and Hispanic pediatric heart transplant recipients equally. Longer-term survival has not improved in any racial group. Targeted efforts in high-risk transplant recipients may improve long-term and overall survival in pediatric heart transplantation.

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Figure 1A

Figure 1B

Figure 1C

Figure 1.

Demographic trends in pediatric heart transplant recipients during the 5 eras. Black and Hispanic children comprised a higher proportion of transplant recipients with time (1A), the proportion of patients with congenital heart disease declined with time (1B) and, for all eras, white children were more likely to be supported by ECMO or ventilator at the time of transplant (1C).

Figure 2A

Figure 2B

Figure 2C **Figure 2D** **Figure 2.**

Early post-transplant survival in white (A), black (B) and Hispanic (C) children during the five eras. Fig 2D demonstrates unadjusted post-transplant survival in transplant recipients during 2005–2008 in the three groups.

Figure 3A **Figure 3B**

Figure 3.
Racial trends in use of tacrolimus (A) and mycophenolate mofetil (B) as maintenance immune suppression at hospital discharge

Table 1

Baseline Characteristics of Heart Transplant Patients, by Racial Group

	White (n=3204)	Black (n=887)	Hispanic (n=642)	Total (n=4733)	P Value
Age at Transplant, yr	3 (0 to 12)	8 (1 to 14)	2 (0 to 10)	3 (0 to 12)	<0.001
Gender Female	1332 (42)	409 (46)	281 (44)	2022 (43)	0.05
Donor Age, yr (n=4726)	4 (0 to 13)	8 (1 to 17)	4 (0 to 11)	4 (0 to 14)	<0.001
Diagnosis					<0.001
Cardiomyopathy	1162 (36)	447 (50)	276 (43)	1885 (40)	
Congenital	1722 (54)	301 (34)	301 (47)	2324 (49)	
Other	320 (10)	139 (16)	65 (10)	524 (11)	
VAD at Transplant	170 (5)	81 (9)	28 (4)	279 (6)	<0.001
Type of Support					<0.001
ECMO	193 (6)	36 (4)	22 (3)	251 (5)	
Ventilator	543 (17)	123 (14)	93 (14)	759 (16)	
Inotropes	808 (25)	286 (32)	189 (29)	1283 (27)	
None of above	1660 (52)	442 (50)	338 (53)	2440 (52)	
PGE Support at Transplant	258 (8)	34 (4)	58 (9)	350 (7)	<0.001
Ischemic Time, hr (n=4483)	3.5 (2.8 to 4.3)	3.3 (2.5 to 4.0)	3.7 (2.8 to 4.5)	3.5 (2.7 to 4.3)	<0.001
PRA > 10% (n=2898)	266 (13)	69 (14)	53 (14)	388 (13)	0.88
Dialysis After Listing	50 (2)	10 (1)	6 (1)	66 (1)	0.35
Creatinine Clearance (n=3389)					0.02
< 40	218 (10)	44 (7)	53 (11)	315 (9)	
40	2004 (90)	626 (93)	444 (89)	3074 (91)	
Creatinine at Transplant (n=3440)	0.5 (0.4 to 0.8)	0.6 (0.4 to 0.8)	0.5 (0.4 to 0.7)	0.5 (0.4 to 0.8)	<0.001
Creatinine Clearance (n=3389)	102 (65 to 138)	107 (77 to 140)	99 (66 to 140)	103 (68 to 138)	0.02
Bilirubin at Transplant (n=3029)	0.8 (0.5 to 1.6)	0.8 (0.5 to 1.5)	0.8 (0.4 to 1.5)	0.8 (0.5 to 1.5)	0.31
Prior Sternotomy (n=1175)	341 (45)	74 (36)	81 (38)	496 (42)	0.02
Medicaid Insurance	646 (20)	428 (48)	328 (51)	1402 (30)	<0.001

Values are summarized as number (percent) or median (inter-quartile range). Yr (year) VAD (Ventricular Assist Device), ECMO (Extra-corporeal Membrane Oxygenation), PG (Prostaglandin), PRA (Panel Reactive Antibodies)

Table 2

Multivariable Model for Early Graft Loss (Within 6-Months Post-transplant)

	Hazard Ratio	95% CI	P Value
Age at Transplant	**	**	0.09
Gender Female	1.2	(1.0, 1.4)	0.02
Donor Age < 1 yr	1.4	(1.1, 1.7)	0.003
Diagnosis (vs. CM)			
Congenital	1.8	(1.5, 2.3)	<0.001
Other	1.5	(1.1, 1.9)	0.007
Type of Support (vs. none)			
ECMO	3.4	(2.6, 4.4)	<0.001
Ventilator	1.8	(1.5, 2.2)	<0.001
Inotropes	1.1	(0.9, 1.3)	0.57
Ischemic Time	**	**	0.01
Dialysis After Listing	2.1	(1.4, 3.1)	<0.001
Creatinine Clearance (vs. 40)			
<40	1.8	(1.4, 2.3)	<0.001
Not reported	1.5	(1.1, 2.0)	0.006
Bilirubin at Transplant	**	**	0.05
Prior Sternotomy			
Yes	1.7	(1.1, 2.4)	0.009
Not reported	1.5	(1.1, 2.2)	0.03
Era (vs. 1987–1992)			
1993–1996	1.0	(0.8, 1.3)	0.98
1997–2000	0.7	(0.5, 1.0)	0.03
2001–2004	0.6	(0.4, 0.9)	0.007
2005–2008	0.5	(0.4, 0.7)	<0.001
Race (vs. White)			
Black	1.1	(0.9, 1.3)	0.38
Hispanic	0.7	(0.5, 0.9)	0.005

The model consists of race and era variables (main effects) without interaction terms and all variables from Table 1 significant at 0.10.

** No hazard ratios are associated with these continuous variables because restricted cubic splines were used to model them.

Yr (year), CM (Cardiomyopathy), ECMO (Extra-corporeal Membrane Oxygenation)

Table 3

Multivariable Model for Longer-term Graft Loss *

	Hazard Ratio	95% CI	P Value
Age at Transplant	**	**	<0.001
Gender Female	1.3	(1.2, 1.5)	<0.001
Donor Age	**	**	0.003
Diagnosis (vs. CM)			
Congenital	1.1	(1.0, 1.3)	0.08
Other	1.2	(1.0, 1.5)	0.02
Creatinine Clearance (vs. 40)			
<40	1.5	(1.1, 1.9)	0.01
Not reported	1.2	(1.0, 1.4)	0.05
PGE Support at Transplant	0.6	(0.4, 0.8)	<0.001
PRA (vs. 10%)			
>10%	1.3	(1.1, 1.6)	0.003
Missing	0.9	(0.8, 1.1)	0.32
Era (vs. 1987–1992)			
1993–1996	1.0	(0.9, 1.2)	0.63
1997–2000	1.0	(0.8, 1.2)	0.76
2001–2004	1.1	(0.9, 1.4)	0.31
2005–2008	1.0	(0.7, 1.4)	0.80
Race (vs. White)			
Black	2.2	(1.9, 2.5)	<0.001
Hispanic	1.1	(0.9, 1.4)	0.17

The model consists of race and era variables (main effects) without interaction terms and all variables from Table 1 significant at 0.10.

* Conditional upon surviving 6 months post-transplant.

** No hazard ratios are associated with these continuous variables because restricted cubic splines were used to model them.

Yr (year), ECMO (Extra-corporeal Membrane Oxygenation), PG (Prostaglandin), PRA (Panel Reactive Antibodies)