

The Impact of Race on Survival After Heart Transplantation: An Analysis of More Than 20,000 Patients

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Background. Evidence exists for race-linked discrepancies in survival after orthotopic heart transplantation (OHT). The United Network for Organ Sharing database provides an opportunity to examine the effect of race on outcomes in a large cohort of adult OHT patients.

Methods. We retrospectively reviewed the United Network for Organ Sharing data for 20,185 adult patients receiving primary OHT (1997 through 2007). Patients were divided into groups of specific race and also stratified by donor and recipient race-matching. The impact of race on mortality was examined using multivariable Cox proportional hazard regression analysis incorporating 23 variables and interaction terms between donor and recipient race. Mortality (30 days, 90 days, 1 year, 2 years, and 5 years) and rejection in the first year were examined. Cumulative post-OHT survival was modeled using the Kaplan-Meier method.

Results. Of 20,185 patients, 12,381 (61%) were race matched (75% of whites, $n = 11,456$; 17% of African

Americans, $n = 514$; 30% of Hispanics, $n = 391$; 5% of Asians, $n = 19$). Five thousand six hundred fourteen patients (28%) died during the study. African American recipients have an 11.4% absolute decrease in 10-year survival compared with whites. After risk adjustment, African American recipients have a 46% increase in the risk of cumulative mortality (hazard ratio, 1.46; 95% confidence interval, 1.24 to 1.72; $p < 0.001$). Decreased survival in African American recipients was not improved with race-matched OHT, nor was there a survival advantage with race-matching in any racial subgroup. Decreased survival in African American recipients persisted after censoring deaths in the first year.

Conclusions. Our study represents the largest modern cohort evaluating race in adult OHT. African American recipients have significantly worse survival after OHT. Race-matching did not confer improved survival.

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Race is an admittedly imperfect and somewhat ill-defined criterion used to group people, encompassing social, economic, and biologic differences. Nevertheless, evidence exists of race-linked differences in the incidence, pathophysiology, and treatment of many cardiovascular diseases. Research has focused on race-linked biologic differences as well as socioeconomic factors impacting access to care [1–3].

Transplantation provides a unique opportunity to study biologic differences associated with race, given the introduction of donor antigens into the recipient. The effect of donor and recipient race on outcomes has been studied in abdominal and thoracic solid-organ transplantation [4–9]. Although results vary, many studies indicate decreased survival in patients with race-mismatched transplants or recipients of specific races.

Although the impact of donor and recipient race has been explored in pediatric orthotopic heart transplantation (OHT) [10–12], only single-center studies have examined race in adults [6–8, 13]. These studies disagree on whether recipient race or race matching is the more important factor impacting outcomes. This study evaluates the impact of donor and recipient race on mortality after OHT using data from the multiinstitutional prospectively collected United Network for Organ Sharing (UNOS) open transplantation cohort. We hypothesize that donor–recipient race matching does not have a significant impact on outcomes and that the mechanisms underlying race-linked outcome differences are likely to be complex.

Material and Methods

Data Source

We used Standard Transplant Analysis and Research files with follow-up data provided by UNOS. Patient identifiers were excluded. Our institutional review board determined formal review was unnecessary. The dataset

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comprises a prospective open cohort of US OHT patients from 1987 to 2007 with follow-up through May 2008.

Study Design

We retrospectively examined adults (>17 years) receiving primary OHT from 1997 to 2007. The cohort was divided by recipient race and, further, by donor–recipient race matching. Patients were combined to form overall race-matched and race-unmatched groups. Specific race groups (white, African American [AA], and Hispanic) were examined; Asian, Pacific Islander, American Indian, and multiracial were combined (“other”) owing to small sample size.

Variables Examined and Outcome Measures

The dataset contains more than 400 preoperative, intraoperative, and postoperative variables. Variables examined included primary diagnosis, demographics (age, sex, race, education, and insurance), pre-OHT mechanical ventilation or intensive care unit admission, comorbidities (diabetes mellitus, percent ideal body weight [% IBW], creatinine levels, and hypertension), and transplant variables (ischemic time, human leukocyte antigen [HLA] mismatch, transplant year, and wait-list time). Additionally, indicators of pre-OHT acuity (inotropic drug and intraaortic balloon pump use) and hemodynamic measurements (mean pulmonary arterial pressure, pulmonary vascular resistance, and cardiac index) were examined. Donor variables, including age, race, sex, cytomegalovirus status, diabetes, and cigarette use, were examined.

The primary end point was all-cause cumulative mortality. Rejection episodes in the first year and 30-day, 90-day, 1-year, 2-year, and 5-year mortality rates were also examined.

Statistical Analysis

Baseline characteristics among races were examined using one-way analysis of variance (continuous variables) and the χ^2 test (categorical variables). For significant associations, post hoc pairwise comparisons were performed using the Tukey-Kramer method (continuous variables) or univariate logistic regression (categorical variables).

Cumulative survival was estimated using the Kaplan-Meier method, focused on time intervals with adequate follow-up. Censoring occurred for the primary end point (mortality), losses to follow-up, and those reaching the end of follow-up.

Multivariable analysis was performed using logistic and Cox proportional hazards regressions to examine the impact of race on rejection and mortality, respectively. To determine the interaction between donor and recipient race, specific terms testing effect modification between each donor and recipient race pair were incorporated. Variables were chosen based on biologic plausibility, postulated associations, and significance on univariate exploratory analysis ($p \leq 0.2$). Covariates were incorporated in a forward and backward stepwise fashion using the likelihood ratio test for significance. The final model incorporated recipient covariates: race, age older than 60 years, recipient–

donor sex-mismatch, college education, insurance, transplant year, % IBW, creatinine, diabetes history, hypertension, pre-OHT cardiac index, pre-OHT inotropic drug use, pre-OHT intraaortic balloon pump use, pre-OHT mechanical ventilation, idiopathic cardiomyopathy diagnosis, ischemic cardiomyopathy diagnosis, and pre-OHT hospitalization; donor covariates: race, age, ischemic time, diabetes history, cytomegalovirus mismatch, and HLA mismatch (0 or 1 antigen matches); and donor–recipient race interaction terms.

For all analyses, a probability value of less than 0.05 (two-tailed) was significant. Means are presented with standard deviations; hazard ratios and odds ratios (OR) are presented with 95% confidence intervals (CI). Statistics were performed using STATA software (v9.2SE, StataCorp LP, College Station, TX).

Results

Cohort Statistics

From 1997 to 2007, 23,996 OHT patients were followed by UNOS. After exclusion of previous transplants ($n = 839$), children ($n = 2,933$), and patients with inadequate data ($n = 39$), the final study population was 20,185. The mean age of the cohort was 52 ± 12 years with 23.6% women ($n = 4,768$).

Recipient race distribution was 76.2% white ($n = 15,373$), 14.6% AA ($n = 2,940$), 6.4% Hispanic ($n = 1,289$), 2.0% Asian ($n = 394$), 0.3% American Indian or Alaskan Native ($n = 69$), 0.2% Hawaiian or Pacific Islander ($n = 43$), and 0.4% multiracial ($n = 77$). Donor race distribution was 72.0% white ($n = 14,524$), 12.1% AA ($n = 2,441$), 13.5% Hispanic ($n = 2,720$), 1.3% Asian ($n = 265$), 0.4% American Indian or Alaskan Native ($n = 89$), 0.2% Hawaiian or Pacific Islander ($n = 37$), and 0.5% multiracial ($n = 109$; Fig 1). Five thousand six hundred fourteen patients died during the study (7.0 deaths/100 person-years). Mean follow-up was 47 ± 38 months.

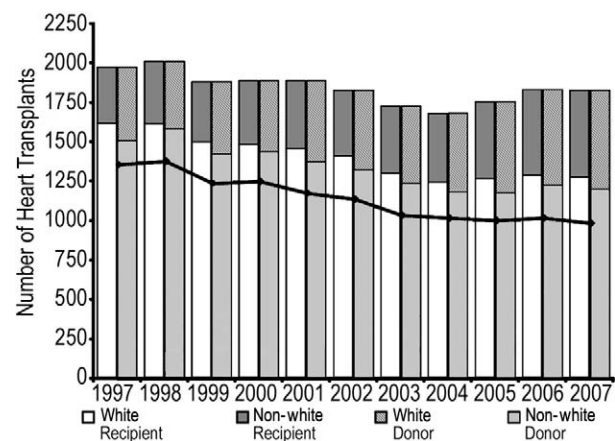


Fig 1. Orthotopic heart transplantations performed by year (1997 through 2007), stratified by donor and recipient race (white versus nonwhite). Line shows number of race-matched orthotopic heart transplantation performed yearly (United Network for Organ Sharing data, May 2008).

Overall, 12,381 (61%) recipients received race-matched hearts. Stratified by recipient race, 11,456 (74.5%) whites, 514 (17.5%) AAs, 391 (30.3%) Hispanics, 19 (4.8%) Asians, 1 (1.4%) American Indian or Alaskan Native, and no Pacific Islanders or Hawaiians received race-matched organs. The annual percentage of race-matched transplants varied from 53% to 68%, with a downward trend with time. Throughout the study period, the number of adult OHTs stayed constant, ranging from 1,671 to 2,001 OHT per year (Fig 1).

Baseline Characteristics

There were significant differences among recipients of different races (Table 1). Nonwhite recipients were younger, more likely to be female, and less likely to be race or sex matched to their donors when compared with white recipients. Whites were more likely to have private insurance or self-pay, whereas nonwhites had a higher percentage of Medicaid and “other” insurance. However, the majority of all patients were self-paid or possessed private insurance. Hispanic, AA, and other race recipients were less likely to have a college education.

Significant differences in transplant diagnosis, comorbidities, and pre-OHT support were found among recipients of different races (Table 1). Ischemic cardiomyopathy was more common in white recipients, whereas idiopathic cardiomyopathy was more common in nonwhites. Hispanic recipients were more likely to have diabetes, whereas AAs more frequently had hypertension. Statistically significant differences existed in variables such as cardiac index, creatinine, % IBW, pulmonary arterial pressure, and pulmonary vascular resistance. Whites were less likely to be supported by inotropic drugs and hospitalized, but had longer wait-list times compared with AAs and Hispanics. However, absolute differences in these markers of clinical acuity and hemodynamic variables were small and unlikely to be clinically significant.

Donors in the white group were slightly older and more likely to use cigarettes. Nonwhites had a higher proportion of recipients who were cytomegalovirus mismatched and HLA mismatched (0 or 1 antigen matches) to their donors. As the majority of OHT donors and recipients were white (>70%), whites were more likely to be race matched to their donors, whereas AA, Hispanic, and other race recipients were more likely to be race mismatched.

Survival

Examining survival by recipient race demonstrated AA recipients had worse 10-year survival compared with other recipients (Fig 2). African American recipient 10-year survival was 45.8%, 11.4% lower than whites and 10.8% lower than Hispanics. When deaths in the year after OHT were censored, the lower survival for AA recipients persisted (Fig 3). There was no significant difference when stratifying survival by donor race (Fig 4).

Patients receiving race-matched hearts appeared to have 4.4% higher cumulative 10-year survival than those receiving unmatched hearts (Fig 5). However, when examining survival within each race, no individual race demonstrated improvement in survival with race match-

ing (Table 2). This suggests that the increased survival in the race-matched groups is likely owing to the skewed stratification of race matching, with the unmatched group having a significantly higher proportion of AA recipients. Significantly poorer survival of AA recipients in the unmatched group leads to the spurious conclusion that race matching has a beneficial effect.

Univariate Analysis

Without risk adjustment, recipient AA race appeared to have a significant impact on the hazard of death (Table 3). Donor race did not affect the risk of death. Other markers of recipient acuity, socioeconomics, education, transplant diagnoses, and donor factors that impacted the hazard of death were incorporated into the multivariable models.

Multivariable Analyses

After risk adjustment, AA recipient race continued to increase the risk of death (Table 3). African American recipients had a 46% increase in risk-adjusted cumulative mortality compared with white recipients (hazard ratio, 1.46; 95% CI, 1.24 to 1.72; $p < 0.001$). Donor race did not impact mortality risk. Interaction terms examining the modification effect of specific combinations of donor and recipient races did not demonstrate any reduction in the risk of death with race-matched transplants. Of note, the risk-adjusted model demonstrated an increased risk of death for Hispanic recipients (hazard ratio, 1.42; 95% CI, 1.13 to 1.77; $p = 0.002$). The only significant interaction term was that between Hispanic recipients and AA donors, which appeared to decrease the risk of death (hazard ratio, 0.34; 95% CI, 0.12 to 0.93; $p = 0.04$). Additional covariates significantly affecting mortality on multivariable analysis included % IBW, age older than 60 years, Medicaid insurance, Medicare insurance ($p = 0.056$), recipient diabetes, recipient hypertension, pre-OHT inotropic drugs, pre-OHT mechanical ventilation, pre-OHT hospitalization, donor age, sex-mismatch, and ischemic time.

When the multivariable model was applied using logistic regression for covariates impacting the odds of a rejection episode in the year after OHT, donor race, recipient race, and all interaction terms were not significant. However, HLA mismatch (OR, 1.24; 95% CI, 1.10 to 1.41; $p = 0.001$) and Medicaid (OR, 1.30; 95% CI, 1.05 to 1.62; $p = 0.02$) or “other” insurance (OR, 1.51; 95% CI, 1.15 to 1.98; $p = 0.003$) increased the odds of rejection. A college education (OR, 0.88; 95% CI, 0.78 to 0.997; $p = 0.04$) decreased the odds of rejection. Other covariates impacting rejection were recipient age older than 60 years, creatinine, % IBW, and transplant year.

Comment

In this study, we present multiinstitutional UNOS data from 11 years of US OHT to examine race-related outcomes. African American recipient race was associated with an absolute reduction in 10-year survival of 11.4% compared with whites. This difference was not explained by deaths in the year after OHT, and became more pronounced with time. After risk adjustment, AA recipient race increased the risk of cumulative mortality by

Table 1. Baseline Characteristics Stratified by Recipient Race

All Patients (N = 20,185)	White (N = 15,373)	African American (N = 2,940)	Hispanic (N = 1,289)	Other (N = 583) ^a	p Value ^b
Recipient demographics					
Age (y)	53.4 ± 11.2	46.9 ± 12.7 ^c	49.0 ± 13.0 ^c	48.3 ± 13.0 ^c	<0.001
Age ≥ 60 y	5,132/15,373 (33.4%)	479/2,940 (16.3%) ^c	277/1,289 (21.5%) ^c	114/583 (19.6%) ^c	<0.001
Male	12,122/15,373 (78.9%)	1911/2,940 (65.0%) ^c	951/1,289 (73.8%) ^c	433/583 (74.3%) ^c	<0.001
Sex matched	11,070/15,373 (72.0%)	1987/2,940 (67.6%) ^c	871/1,289 (67.6%) ^c	373/583 (64.0%) ^c	<0.001
Race matched	11,456/15,373 (74.5%)	514/2,940 (17.5%) ^c	391/1,289 (30.3%) ^c	—	<0.001
Recipient insurance					
Private insurance/self-pay	9,986/15,373 (65.0%)	1,460/2,940 (49.7%) ^c	571/1,289 (44.3%) ^c	358/583 (61.4%)	<0.001
Medicare	3,533/15,373 (23.0%)	716/2,940 (24.4%)	306/1,289 (23.7%)	96/583 (16.5%) ^c	0.001
Medicaid	1,142/15,373 (7.4%)	604/2,940 (20.5%) ^c	287/1,289 (22.3%) ^c	78/583 (13.4%) ^c	<0.001
Other	630/15,373 (4.1%)	145/2,940 (4.9%) ^c	121/1,289 (9.4%) ^c	48/583 (8.2%) ^c	<0.001
Recipient education level					
College or graduate	5,804/11,345 (51.2%)	901/2,221 (40.6%) ^c	304/912 (33.3%) ^c	254/397 (64.0%) ^c	<0.001
Precollege	5,541/11,345 (48.8%)	1,320/2,221 (59.4%) ^c	608/912 (66.7%) ^c	143/397 (36.0%) ^c	<0.001
Primary diagnosis					
Ischemic cardiomyopathy	8,247/15,373 (53.7%)	683/2,940 (23.2%) ^c	501/1,289 (38.9%) ^c	229/583 (39.3%) ^c	<0.001
Idiopathic cardiomyopathy	4,480/15,373 (29.1%)	1,637/2,940 (55.7%) ^c	519/1,289 (40.3%) ^c	227/583 (38.9%) ^c	<0.001
Hypertrophic cardiomyopathy	267/15,373 (1.7%)	21/2,940 (0.7%) ^c	20/1,289 (1.6%)	14/583 (2.4%)	<0.001
Congenital heart disease	395/15,373 (2.6%)	36/2,940 (1.2%) ^c	32/1,289 (2.5%)	15/583 (2.6%)	<0.001
Recipient hemodynamics and comorbidities					
Diabetes	3,153/15,028 (21.0%)	600/2,873 (20.9%)	322/1,256 (25.6%) ^c	124/563 (22.0%)	0.001
Hypertension	5,364/13,919 (38.5%)	1,146/2,570 (44.6%) ^c	411/1,120 (36.7%)	178/508 (35.0%)	<0.001
Creatinine (mg/dL)	1.4 ± 1.0	1.5 ± 1.1 ^c	1.3 ± 1.0	1.3 ± 0.8	<0.001
% IBW	126.2 ± 22	126.6 ± 27	125.3 ± 23	117.4 ± 23 ^c	<0.001
Pre-OHT cardiac index (L/min)	2.4 ± 0.8	2.2 ± 0.8 ^c	2.3 ± 0.8	2.4 ± 0.8	<0.001
Pre-OHT mean PAP (mm Hg)	28.6 ± 10.3	31.0 ± 10.2 ^c	29.8 ± 11.1 ^c	29.2 ± 10.5	<0.001
Pre-OHT PVR (dyne · s/cm ⁵)	2.3 ± 1.9	2.8 ± 2.1 ^c	2.7 ± 2.2 ^c	2.7 ± 2.0 ^c	<0.001
Pre-OHT inotropic drugs	7,255/15,373 (47.2%)	1,535/2,940 (52.2%) ^c	654/1,289 (50.7%) ^c	288/583 (49.4%)	<0.001
Pre-OHT IABP	820/15,373 (5.3%)	141/2,940 (4.8%)	66/1,289 (5.1%)	38/583 (6.5%)	0.3
Pre-OHT ventilation	425/15,373 (2.8%)	56/2,940 (1.9%) ^c	46/1,289 (3.6%)	17/583 (2.9%)	0.01
Pre-OHT ICU care	5,499/15,359 (35.8%)	1,091/2,936 (37.2%)	473/1,287 (36.8%)	225/581 (38.7%)	0.3
Pre-OHT hospitalization	8,248/15,359 (53.7%)	1,733/2,936 (59.0%) ^c	734/1,287 (57.0%) ^c	329/581 (56.6%)	<0.001
Days on wait list	230 ± 365	197 ± 349 ^c	182 ± 332 ^c	154 ± 286 ^c	<0.001
Donor variables					
White donor	11,456/15,373 (74.5%)	1,985/2,940 (67.5%) ^c	742/1,289 (57.6%) ^c	341/583 (58.5%) ^c	<0.001
African American donor	1,755/15,373 (11.4%)	514/2,940 (17.5%) ^c	104/1,289 (8.1%) ^c	68/583 (11.7%)	<0.001
Hispanic donor	1,804/15,373 (11.7%)	386/2,940 (13.1%) ^c	391/1,289 (30.3%) ^c	139/583 (23.8%) ^c	<0.001
Other race donor	358/15,373 (2.3%)	55/2,940 (1.9%)	52/1,289 (4.0%) ^c	35/583 (6.0%) ^c	<0.001
Donor diabetes	310/15,294 (2.0%)	59/2,928 (2.0%)	25/1,285 (2.0%)	8/571 (1.4%)	0.8
Donor age	31.6 ± 12.7	31.3 ± 12.5 ^c	30.4 ± 12.3 ^c	29.7 ± 12.6	0.001
Cigarette use	4,715/15,217 (31.0%)	869/2,909 (29.9%) ^c	343/1,267 (27.1%) ^c	152/577 (26.3%)	0.003
HLA mismatch	7,057/12,826 (55.0%)	1,591/2,434 (65.4%) ^c	662/1,133 (58.4%) ^c	302/476 (63.5%) ^c	<0.001
CMV mismatch	5,339/15,373 (34.7%)	723/2,940 (24.6%) ^c	332/1,289 (25.8%) ^c	117/583 (20.1%) ^c	<0.001
Ischemic time (h)	3.1 ± 1.0	3.1 ± 1.0	3.1 ± 1.1	3.2 ± 1.1	0.3

^a "Other" race includes Asian, Pacific Islander, American Indian, and multiracial recipients. ^b p value based on results of either one-way analysis of variance (continuous variables) or χ^2 test (categorical variables). ^c Post-hoc pairwise comparison $p < 0.05$ (reference = white recipient) by Tukey-Kramer method (for continuous variables) or univariate logistic regression (for categorical variables).

CMV = cytomegalovirus; HLA = human leukocyte antigen; IABP = intraaortic balloon pump; IBW = ideal body weight; ICU = intensive care unit; OHT = orthotopic heart transplantation; PAP = pulmonary arterial pressure; PVR = pulmonary vascular resistance.

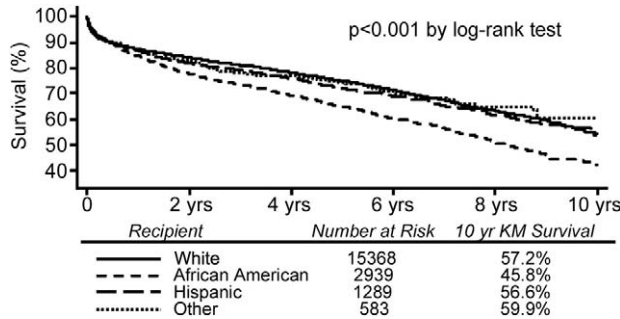


Fig 2. Kaplan-Meier (KM) survival estimates after orthotopic heart transplantation stratified by recipient race (United Network for Organ Sharing data, May 2008).

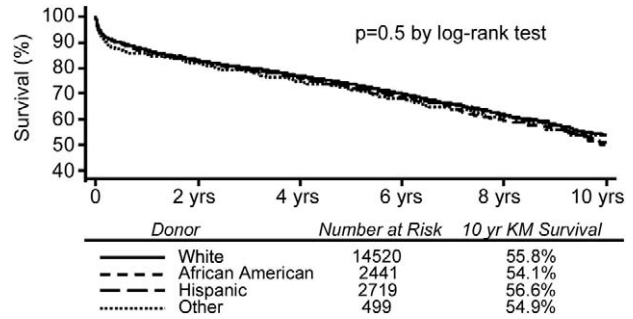


Fig 4. Kaplan-Meier (KM) survival estimates after orthotopic heart transplantation stratified by donor race (United Network for Organ Sharing data, May 2008).

46% when compared with whites. Although donor-recipient race matching appeared to increase survival on initial Kaplan-Meier survival estimates, further analysis demonstrated this to be the result of disproportionate numbers of AA recipients in the unmatched group.

Examination of mortality data by race also indicated that the initially observed race-matching effect was attributable to a skewed stratification. No survival differences were observed within individual races with race matching, nor did donor race have a significant effect on survival. Univariate and multivariable Cox proportional hazards analyses also indicated significantly worse outcomes in AA recipients, but no beneficial effect of race matching. Given the analyses performed, it is clear that race matching does not improve survival after OHT.

Accordingly, poor survival in AA recipients cannot be attributed to a race-mismatch effect. Although survival of AA recipients was lower than that of other race recipients at 1 year and longer, there was no improvement when AAs received AA hearts (Table 2).

The increased risk of death for Hispanic recipients predicted using our multivariable model is likely not clinically significant. Unlike the survival differences in AA recipients, for Hispanic recipients there is no agreement between the multivariable analysis and Kaplan-Meier survival estimates, short-term mortality data, or univariate analysis. Also, the sample size for Hispanic

recipients is smaller than that for AA and white recipients and more likely to be a spurious finding using this complex statistical methodology.

The decreased survival in AA recipients is striking, and elucidating the reasons has important implications for resolving this disparity. However, this endeavor is quite complex. Race is somewhat ill defined and confounded by many socioeconomic factors, in addition to any underlying biologic differences. Nevertheless, insight can be gained from our multivariable analyses on survival and rejection. It should be noted that this survival difference becomes more pronounced with time. Consequently, variables that increase the odds of rejection in the first year likely contribute, but are unlikely to be the entire explanation. Compared with whites, both Hispanic and AA recipients share differences in baseline characteristics, such as insurance type, sex-matching, education, transplant diagnosis, and donor factors. Yet, Hispanics do not manifest the poorer survival of AAs after OHT.

Two biologic factors that are more prevalent in AA recipients compared with other races are HLA mismatch and the prevalence of hypertension. Preoperative hypertension persists after OHT and increases the stress on the transplanted heart. With hypertension more than 6% more prevalent in AA recipients, and notably more difficult to control in AAs [1], this could be a long-term contributor to poorer outcomes. Human leukocyte antigen mismatch is a putative contributor to poor survival in

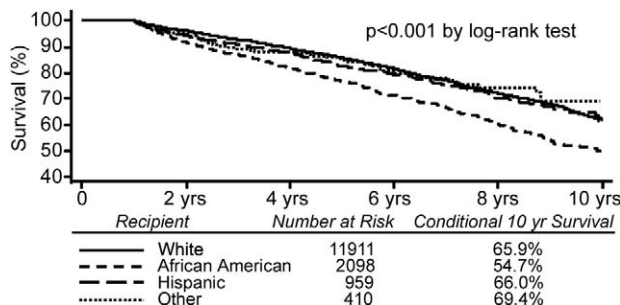


Fig 3. Conditional Kaplan-Meier survival estimates after orthotopic heart transplantation stratified by recipient race, censoring for deaths in the first year (United Network for Organ Sharing data, May 2008).

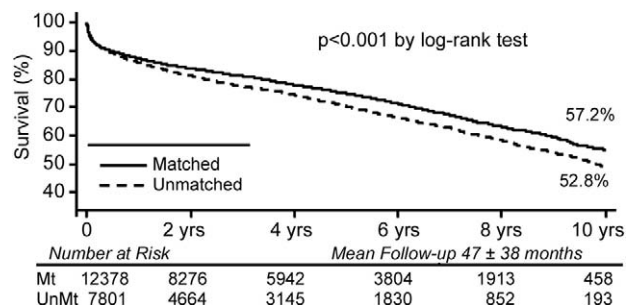


Fig 5. Kaplan-Meier survival estimates after orthotopic heart transplantation stratified by donor-recipient race matching (United Network for Organ Sharing data, May 2008). (Mt = matched; UnMt = unmatched.)

Table 2. Effect of Race-Matching on Unadjusted Kaplan-Meier Estimates of Survival Overall and Stratified by Race^a

Group	Survival Time				
	30 Days	90 Days	1 Year	2 Years	5 Years
Overall (n = 20,185)					
Matched (n = 12,381)	94.4% (94.0–94.8)	91.6% (91.1–92.1)	87.6% (87.0–88.1)	84.0% (83.3–84.7)	75.1% (74.1–75.9)
Unmatched (n = 7,804)	94.6% (94.1–95.1)	91.7% (91.0–92.3)	86.1% (85.3–86.9)	81.4% (80.4–82.3)	70.5% (69.3–71.7)
p value ^b	0.5	0.9	0.008	<0.001	<0.001
White (n = 15,373)					
Matched (n = 11,456)	94.3% (93.9–94.8)	91.6% (91.1–92.1)	87.6% (87.0–88.2)	84.2% (83.5–84.9)	75.4% (74.5–76.3)
Unmatched (n = 3,917)	94.2% (93.4–94.9)	91.2% (90.2–92.0)	86.8% (85.7–87.9)	83.7% (82.5–84.9)	73.8% (72.1–75.3)
p value ^b	0.7	0.4	0.2	0.4	0.1
African American (n = 2,940)					
Matched (n = 514)	94.9% (92.5–96.5)	92.6% (89.9–94.6)	85.1% (81.6–88.0)	80.0% (76.0–83.4)	67.7% (62.6–72.3)
Unmatched (n = 2,426)	95.1% (94.1–95.9)	92.1% (90.9–93.1)	84.6% (83.1–86.0)	77.2% (75.4–79.0)	64.2% (61.8–66.5)
p value ^b	0.8	0.7	0.8	0.3	0.3
Hispanic (n = 1,289)					
Matched (n = 391)	95.0% (92.3–96.8)	91.9% (88.6–94.3)	89.0% (85.3–91.8)	84.7% (80.4–88.1)	75.0% (69.1–80.0)
Unmatched (n = 898)	94.6% (92.9–95.9)	92.1% (90.1–93.8)	85.9% (83.4–88.1)	80.9% (78.0–83.4)	70.4% (66.7–73.9)
p value ^b	0.8	0.9	0.2	0.2	0.1

^a Values are hazard ratios with 95% confidence intervals in parentheses.

^b p value according to Mantel-Cox log rank test.

AA recipients [7, 13]. In this study, HLA mismatch did not independently impact survival after risk adjustment, although it did increase the odds of rejection, potentially leading to decreased graft longevity. Additionally, AAs had an increased likelihood of donor–recipient sex-mismatch, which was found in this and another study to increase the risk of death independent of race [14].

Our analysis implicates discrepancies in socioeconomic factors as contributing to poorer outcomes in AAs. Medicaid and “other” type insurance were more prevalent in AA recipients, both of which increased the odds of rejection (30% and 51%, respectively), although Medicaid insurance conveyed a 39% increase in the hazard of death after OHT as compared with private insurance. Additionally, the lower percentage of AA recipients with a college education increases the odds of rejection. Such differences in education and socioeconomic status impact outcomes in an independent manner, contributing to poor outcomes in AA recipients.

Previous Work

The effect of race on outcomes after OHT has been most thoroughly explored in the pediatric OHT literature. A review of the pediatric UNOS database by Mahle and associates [10] reported graft survival in AAs to be less than 50% that of other recipients. This effect persisted after risk adjustment for socioeconomic factors and race mismatch (which was noted not to affect survival) [10]. An institutional review of 169 pediatric OHTs by Kanter and colleagues [11] reported decreased survival in AAs, but concluded that race mismatch rather than AA recipient race was driving this effect.

Studies addressing race in adult OHT are limited to single centers; large reviews have not addressed race as a covariate affecting mortality [15]. Park and colleagues [7, 13]

identified poorer outcomes in AA recipients, suggesting HLA mismatching could be contributing. Mehra and colleagues [6] suggested specific immunosuppressive regimens could mitigate poorer AA recipient survival, hence arguing for race-linked biologic differences contributing to poor outcomes. Conversely, Pamboukian and colleagues [8] reported no race-linked survival difference in 103 OHT recipients, attributing this to care at their comprehensive transplant center. Clearly, there is uncertainty regarding the forces driving poorer survival in AA OHT recipients.

This study, which provides an overview of modern US OHT, demonstrates that AA recipients have decreased survival compared with other race recipients. Donor race does not impact survival. Donor–recipient race matching did not improve survival for any race recipient. This study, among others in solid-organ transplantation, identifies poorer outcomes in AA recipients. Given that race is a complex and ill-defined entity, confounded by socioeconomic factors, it is surprising that such a strong survival trend was present. Our analysis suggests that socioeconomic and educational factors, as well as HLA matching, contribute to race-linked outcome discrepancies. However, given that recipient race remained significant after risk adjustment for these factors, it is possible that unidentified race-linked biologic factors also contribute.

The underlying mechanisms driving these outcomes merit further investigation. It is likely that socioeconomic and educational factors impacting outcomes are surrogates for access to care, issues of compliance, and the ways in which patients engage the health-care system. A patient’s insurance status plays a crucial role in this interaction and was shown to impact both rejection and survival. This study serves to highlight the disparity in outcomes of AA OHT recipients. Based on our analysis, the relationship between race and outcomes in OHT is

Table 3. Univariate and Multivariable Predictors of Mortality After Orthotopic Heart Transplantation

Predictor	Univariate Analysis		Multivariable Analysis	
	HR (95% CI)	p Value ^a	HR (95% CI)	p Value ^b
Recipient race				
White	Reference	Reference		
African American	1.42 (1.32–1.52)	<0.001	1.46 (1.24–1.72)	<0.001
Hispanic	1.08 (0.96–1.21)	0.2	1.42 (1.13–1.77)	0.002
Other	1.01 (0.85–1.20)	0.9	0.86 (0.57–1.30)	0.5
Donor race				
White	Reference	Reference		
African American	1.05 (0.97–1.14)	0.2	1.07 (0.90–1.27)	0.5
Hispanic	1.03 (0.95–1.12)	0.5	0.94 (0.79–1.12)	0.8
Other	1.07 (0.91–1.27)	0.4	1.06 (0.71–1.57)	0.8
Race interaction terms				
White-inclusive terms		Reference		
Recipient race–donor race				
AA–AA			1.04 (0.74–1.48)	0.8
AA–H			1.13 (0.74–1.71)	0.6
AA–O			0.53 (0.16–1.79)	0.3
H–H			0.65 (0.41–1.05)	0.08
H–AA			0.34 (0.12–0.93)	0.04
H–O			0.95 (0.35–2.56)	0.9
O–AA			1.16 (0.44–3.17)	0.8
O–H			1.67 (0.78–3.60)	0.2
O–O			2.18 (0.76–6.22)	0.1
Additional variables				
Sex mismatch	1.14 (1.08–1.21)	<0.001	1.14 (1.02–1.27)	0.02
% IBW	1.003 (1.001–1.004)	<0.001	1.003 (1.001–1.005)	0.005
Age > 60 y	1.18 (1.12–1.25)	<0.001	1.23 (1.11–1.37)	<0.001
Private insurance/self-pay		Reference		
Medicaid	1.40 (1.29–1.53)	<0.001	1.39 (1.18–1.63)	<0.001
Medicare	1.28 (1.21–1.37)	<0.001	1.12 (1.00–1.25)	0.056
Other pay	1.23 (1.09–1.39)	0.001	1.17 (0.95–1.44)	0.1
College graduate	0.87 (0.82–0.93)	<0.001	0.98 (0.89–1.07)	0.6
Recipient creatinine (mg/dL)	1.04 (1.03–1.06)	<0.001	1.02 (0.998–1.04)	0.08
Recipient diabetes	1.26 (1.18–1.34)	0.002	1.28 (1.14–1.43)	<0.001
Recipient HTN	1.16 (1.09–1.22)	<0.001	1.13 (1.03–1.25)	0.01
Transplant year	0.99 (0.98–1.00)	0.3	0.99 (0.97–1.01)	0.4
Ischemic cardiomyopathy	1.09 (1.03–1.15)	0.001	0.93 (0.80–1.09)	0.4
Idiopathic cardiomyopathy	0.89 (0.84–0.95)	<0.001	0.89 (0.76–1.04)	0.1
Hypertrophic cardiomyopathy	0.76 (0.59–0.98)	0.03		
Congenital heart disease	1.35 (1.15–1.59)	<0.001		
Cardiac index (L/min)	0.97 (0.93–1.00)	0.08	1.04 (0.98–1.11)	0.2
Mean PAP (mm Hg)	1.005 (1.003–1.008)	<0.001		
PVR (dyne · s/cm ⁵)	1.02 (1.01–1.04)	0.002		
Inotropic drugs at OHT	1.07 (1.01–1.13)	0.01	0.88 (0.79–0.98)	0.025
IABP at OHT	1.30 (1.17–1.46)	<0.001	1.11 (0.90–1.36)	0.3
Mechanical ventilation at OHT	2.35 (2.08–2.67)	<0.001	1.92 (1.44–2.56)	<0.001
ICU care at OHT	1.20 (1.14–1.26)	<0.001		
Hospitalized at OHT	1.23 (1.16–1.30)	<0.001	1.20 (1.07–1.35)	0.002
HLA mismatch (0 or 1 antigen matched)	1.11 (1.05–1.18)	<0.001	1.08 (0.98–1.18)	0.1
Age of donor (y)	1.01 (1.01–1.02)	<0.001	1.01 (1.01–1.02)	<0.001
Donor diabetes	1.19 (0.99–1.43)	0.06	1.18 (0.87–1.59)	0.3
Donor cigarette use	1.17 (1.11–1.24)	<0.001		

Continued

Table 3. Continued

Predictor	Univariate Analysis		Multivariable Analysis	
	HR (95% CI)	p Value ^a	HR (95% CI)	p Value ^b
CMV mismatch	1.06 (1.00–1.12)	0.04	1.04 (0.94–1.15)	0.4
Ischemic time (h)	1.09 (1.06–1.11)	<0.001	1.06 (1.02–1.11)	0.006

^a p value from univariate Cox proportional hazards regression. ^b p value from multivariable Cox proportional hazards regression model.

AA = African American; CI = confidence interval; CMV = cytomegalovirus; H = Hispanic; HLA = human leukocyte antigen; HR = hazard ratio; HTN = hypertension; IABP = intraaortic balloon pump; IBW = ideal body weight; ICU = intensive care unit; O = other race; OHT = orthotopic heart transplantation; PAP = pulmonary arterial pressure; PVR = pulmonary vascular resistance.

complex, with biologic and socioeconomic or educational factors independently impacting survival.

Limitations

Our study is limited by its retrospective approach. The UNOS dataset likely does not include all important confounders, such as detailed economic data germane to the question at hand. Large data sets rely on accurate coding. We cannot confirm that coding errors do not exist, but we assume that they are generally random and unlikely to create bias. Our study was not designed to delineate the underlying mechanisms by which race affects survival. The data set does not provide comprehensive information from which to draw appropriate conclusions regarding the “why” behind mortality.

Conclusions

We have presented a large modern cohort of OHT patients to study race-related differences in outcomes. African American recipients have significantly decreased survival after OHT. This effect cannot be attributed to race mismatch and persists when censoring for deaths in the first postoperative year. Also, no improvement in survival was observed with race-matched transplants regardless of race. Further studies are necessary to delineate the underlying mechanisms accounting for decreased survival in AA recipients.

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DISCUSSION

DR ROBERT S.D. HIGGINS (Chicago, IL): I would like to congratulate you and your colleagues for an excellent presentation and manuscript evaluating the impact of donor-recipient

race matching in heart transplantation. I also want to thank you for the opportunity to review your manuscript in advance. As you have pointed out, congestive heart failure affects millions of

patients in the United States and is responsible for extraordinary morbidity and mortality. While transplantation provides state of the art treatment for this lethal condition, the impact of race and in particular race matching between donors and recipients has not been fully explored. Your evaluation of the impact of race matching between donors and recipients using the Organ Procurement and Transplantation Network data from UNOS (United Network for Organ Sharing) between 1997 and 2007 provides critically important information in the retrospective series of over 20,000 adult patients receiving orthotopic heart transplants.

While demonstrating that African American recipients have an 11.4% absolute decrease in 10-year survival compared to Caucasians, your analysis confirms that survival was not affected by matching the race of the donor with the race of the recipient as might be expected from a theoretical or biologic perspective. Your results are consistent with those of our group and the analysis of the overall results of heart transplantation as a treatment for advanced heart failure in African Americans in the United States. Recipient race appears to be a more powerful determinant of outcome (survival) than donor matching or other early factors influencing outcomes before 1 year.

I have two specific questions which might help us understand your results further. In particular, I would ask how do you interpret the impact of sociologic variables such as college education, lower socioeconomic status, or insurance on biologic processes and the impact of pretransplant diagnoses such as hypertension and idiopathic dilated cardiomyopathy on allograft rejection and survival in African Americans?

What are the biologic and sociologic factors that you think have the greatest contribution to the overall poor outcome of African Americans after heart transplantation, since this is the axis at which we can direct our efforts to address and reduce this disparity in outcomes?

Thank you again for the opportunity to review your manuscript and I look forward to your answers.

DR ALLEN: Thank you, Dr Higgins, for those kind words and for your questions. Regarding your first question, I think that socioeconomic and educational variables impacting these biological processes and outcomes are really a surrogate for access to care, issues of compliance, and the ways in which patients interact with the health-care system. Certainly, a patient's insurance plays a crucial role in their interaction with the health-care system. And we have made similar observations in lung transplantation to those that we are making now in heart transplantation.

I believe that studies such as this one really highlight patients who are at greater risk for poor outcomes related to processes of

care and compliance issues. The identification of this problem and its possible etiologies allows us as transplant providers to construct better systems with which these high-risk patients can be targeted to avoid poorer outcomes in the future. College education's impact on rejection in the first year is a good example. I think that it is intuitive that a patient with a college education will more easily maneuver the complexities of immunosuppressive medications and identify when they should seek assistance from their health-care provider. A potential solution for patients who are not college educated is a process of care which initiates more intensive education for these patients on how to manage their medications and which symptoms should bring them to the hospital. The most important question now is how to overcome the propensity for poorer outcomes in certain patients.

Secondly, what are the biologic factors? I would say certainly conventional HLA (human leukocyte antigen) mismatch has been studied and thought to contribute to poor outcomes. Though it didn't impact mortality in our study, it did increase the rate of rejection.

Another possibility is race-linked differences in responses to immunosuppressive medications. This has certainly been investigated in the past with interesting results. Additionally, one must consider the differences in the prevalence of cardiovascular disease and risk factors in African Americans as contributing to their poorer post-heart transplant survival. For example, differences in the prevalence and effective treatment of essential hypertension could certainly contribute to poorer outcomes after heart transplantation. These factors are not impacted by replacing a patient's heart, but affect the longevity of the graft.

DR CONSTANTINE MAVROUDIS (Cleveland, OH): Did you study the effect of diabetes on racial differences? When I noted the survival curves, they appeared to be parallel, and I was questioning if most of the mortality occurred early because due to diabetes rather than issues relating race.

DR ALLEN: Initially, the Kaplan-Meier curves of overall race-matched versus unmatched patients did appear to be parallel after the first few years. However, when we examined survival specifically by recipient race, the poorer survival of African American recipients was striking. These differences were not affected by censoring deaths in the first year—implying that these differences are actually mediated by longer term factors, and in fact, the difference in survival continued to increase with time. Moreover, diabetes was a covariate in our multivariable analysis which did independently predict mortality. Still, African American recipient race continued to increase the risk of mortality after risk adjustment.