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Quality and Outcomes

Cardiac Transplantation in African Americans: A Single-Center Experience

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NBSTRACT

Background: In view of limited data on the subject of graft and patient survival differences between African American (AA) and non-AA heart transplant recipients, we reviewed our experience.

Hypothesis: There is a higher mortality among AA recipients compared with non-AA recipients after cardiac transplantation.

Methods: The study included all AA patients who have received a heart transplant in our center since 1983. Stepwise Cox regression was used for covariates affecting the survival. The χ^2 test was employed to identify the effects of a mechanical assist device and pretransplant creatinine (Cr) on the outcomes in AA and non-AA patients. Kaplan-Meier curves were used to examine survival.

Results: The average survival among AA recipients was 5.4 years, compared with 12 years for the non-AA recipients, with 1-, 5-, and 10-year survival rates of 80%, 55%, and 25%, respectively. This was found to be statistically inferior to the survival probabilities of 92%, 78%, and 58% for the non-AA group (P < 0.005). Based on stepwise Cox regression, the variables such as ethnicity (P < 0.05), pretransplant Cr (P < 0.05), presence of a mechanical assist device (P < 0.005), and United Network for Organ Sharing (UNOS) status at transplant (P < 0.05) independently predicted the outcomes. Kaplan-Meier analysis of pretransplant Cr level and survival showed that the AA group did significantly worse for all Cr classes.

Conclusions: There is a statistically significant difference in outcomes between AA and non-AA patients after cardiac transplantation. African American patients have decreased survival over a period of time. Pretransplant Cr, ethnicity, presence of a mechanical assist device, and UNOS status at transplantation are independent predictors of outcomes.

Introduction

Following the development of an effective immunosuppressive regimen for cardiac transplant recipients, transplant surgeons recognized that graft and patient survival depended on factors other than immunosuppression as well. Former studies have identified some valid recipient-related and donor-related risk factors adversely influencing mortality and rejection rate after heart transplantation. ^{1–3} Some of the known risk factors include older donor age, ⁴ earlier date of transplantation, ischemic etiology, history of smoking in the recipient, African American (AA) ethnicity of the recipient, ^{5–8} and positive donor cytomegalovirus (CMV) serology. ⁹

Factors that influence graft survival in AA recipients may be immune mediated and non-immune mediated.

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Additional Supporting Information may be found in the online version of this article.

Non-immune-mediated mechanisms such as conventional atherosclerotic risk factors may determine the propensity to develop advanced graft atherosclerosis. Demographic factors such as advanced age, smoking, diabetes mellitus (DM), and chronic renal insufficiency may induce earlier atherosclerosis via nonimmune mechanisms. Similarly, other nonimmune mechanisms may also have a major role, resulting in poorer outcomes. These factors could be related to socioeconomic status, access to health care, and noncompliance with immunosuppressive medications. 10 A recent multicenter study looking at 364 pediatric heart transplant recipients at 6 centers showed that AA patients have a genetic background that may predispose to a proinflammatory or a lower immune-regulatory environment, as measured by the presence of single-nucleotide polymorphisms.11

In view of limited data on the subject of graft and patient survival differences between AA and non-AA recipients, we reviewed our experience of cardiac transplantation in our AA recipients.

Methods

We conducted a human subjects institutional review board-approved retrospective chart-review study at a single institution. We have performed >800 heart transplants between 1979 and 2009 in our center. Due to loss of some of the earlier medical records, we included all cases dating from 1983. From among all recipients, 37 adults and children were of AA ethnicity.

The data collected include various pretransplant and posttransplant characteristics. In addition, we analyzed posttransplant complications, dividing them into the following categories: rejections, infections, neoplasms, and adverse drug effects. The rejection episodes predominantly manifested as exercise intolerance, heart failure (HF), and consequently hemodynamic compromise or atrial flutter/fibrillation. Diagnosis was made by history, examination, or echocardiogram with or without positive biopsy results. Chronic rejections also manifested as advanced graft atherosclerosis or coronary artery vasculopathy and their attendant ischemic complications, such as myocardial infarction or arrhythmias. Cellular rejection was based on the International Society for Heart and Lung Transplantation (ISHLT) grade 2R or more. Antibody-mediated rejection was defined clinically as allograft dysfunction on echocardiography or hemodynamic compromise on rightheart catheterizations, without evidence of cellular rejection on endomyocardial biopsy or with biopsy evidence of C4d deposition in the capillaries.

Data were collected and evaluated using SPSS software (IBM, Armonk, NY). We used stepwise Cox regression for covariates affecting the survival, such as AA or non-AA ethnicity, pretransplant creatinine (Cr), and presence or absence of mechanical assist device therapy. The χ^2 test was employed to identify the effects of a device and pretransplant Cr on the outcomes in AA or non-AA patients. Kaplan-Meier curves were used to examine survival.

Results

Among the 37 AA heart transplant patients, 28 (75.6%) were males and 9 (24.4%) were females. African American

patients were relatively younger, with mean age at the time of transplant of 41 years (48.4 years in non-AA recipients, $P\!=\!0.003$). Baseline characteristics showing the differences between AA and non-AA recipients are shown in Table 1.

The most common etiology of the pretransplant HF in this group was nonischemic cardiomyopathy, seen in 33 (89%) patients. Most of those (82%) were diagnosed as idiopathic dilated cardiomyopathies. Table 2 provides a detailed breakdown of the etiology of HF among AA recipients. In comparison, the predominant etiology of HF among non-AA patients was ischemic in nature and the difference was highly significant (P = 0.0001). African Americans were relatively sicker at the time of transplant, and 26 of the 37 patients were in UNOS status I (74.3%), compared with 55.5% (n = 350) in non-AA group (P = 0.02). Glomerular filtration rate (GFR) was calculated based on 24-hour urine collection or the Modification of Diet in Renal Disease (MDRD) formula, and the average value was 61. No significant difference was noted with regard to pretransplant serum Cr, body mass index (BMI), ischemic time, and presence of support devices.

Results of routine preoperative studies in AA recipients were evaluated. As expected, the mean right atrial pressures and wedge pressures were elevated (11.42 and 23.48 mm Hg, respectively). The mean pulmonary vascular resistance was

Table 2. Etiology of Heart Failure in African American Patients

Nonischemic Cardiomyopathy, $n = 33$	Ischemic Cardiomyopathy, $n = 4$
Idiopathic dilated cardiomyopathy, 27	
Congenital heart disease, 2	
Viral cardiomyopathy, 1	
Valvular heart disease, 1	
Muscular dystrophy, 1	
Peripartum cardiomyopathy, 1	

Table 1. Baseline Characteristics

Characteristic	African American	Non-African American	P Value
Male, n (%)	28 (75.6)	582 (79.1)	0.558
Female, n (%)	9 (24.4)	154 (20.9)	0.356
Age, y, mean (range)	41 (34–48)	48.4 (47–50)	0.003
Serum Cr, mg/dL, mean (range)	1.28 (1.09–1.47)	1.18 (1.15–1.21	0.158
Mean GFR, mL/min/1.73 m²	61	64.7	0.143
Mean BMI, kg/m²	26.2	24.9	0.180
Ischemic etiology, n (%)	4 (11)	337 (45.8)	0.0001
Mean ischemic time, min	181	179	0.841
Presence of mechanical assist device, n (%)	7 (19.4)	133 (18.1)	0.488
UNOS status I (Ia and Ib), n (%)	26 (74.3)	350 (55.5)	0.020
Abbreviations: BMI, body mass index; Cr, creatinine; GFR, glomerular filtration rate; UNOS, United Network for Organ Sharing.			

Table 3. Pretransplant Characteristics of African American Transplant

Laboratory Study	Mean Value
RAP, mm Hg	11.42
PAP, mm Hg	34.61
PCWP, mm Hg	23.48
Cardiac output, L/min	4.58
TPG, mm Hg	10.46
PVR, Wood units	2.77
LVEF (MUGA), %	18.3
RVEF, %	22.52
LVEF (echo), %	14.5
LVEDD, mm	70
WBC/mm³	7.9×10^3
Hct, %	36.3
Na, mEq/L	135.5
Cr, mg/dL	1.18
GFR, mL/min/1.73 m ²	61

Abbreviations: Cr, creatinine; echo, echocardiography; GFR, glomerular filtration rate; Hct, hematocrit; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MUGA, multigated acquisition scan; Na, sodium; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVEF, right ventricular ejection fraction; TPG, transpulmonary gradient; WBC, white blood cell count.

2.77 Wood units, which is within the recommended range for cardiac transplant. Further information on pretransplant hemodynamic parameters, as well as some laboratory findings in AA transplant recipients, is provided in Table 3.

In the posttransplant phase, 28 patients (75%) were diagnosed with cellular or humoral rejections and some patients had ≥1 episode of rejection, thus accounting for a total of 39 clinical rejection episodes. Coronary vasculopathy was noted in 8 patients. Table 4 lists the various posttransplant complications, including rejections, HF episodes, and infections. Out of the 39 clinical rejection episodes, the majority (n = 23, 59%) were encountered in the first year posttransplant. The remaining 16 rejections occurred after the first year of transplant. Table 5 summarizes the number of rejection episodes and the time to rejection among our AA transplant recipients.

The average survival among our study population was 5.4 years, compared with 12 years for the non-AA population, with 1-, 5-, and 10-year survival rates of 80%, 55%, and 25%, respectively. This was found by χ^2 analysis to be statistically inferior to the 1-, 5-, and 10-year survival probabilities of 92%, 78%, and 58% for the non-AA group (P = 0.002; Figure 1).

Among the 37 AA transplant recipients, 16 (43%) were alive at the time of initial manuscript preparation and 21 had died. The cause of death was identified in 14 of the 21 patients based on clinical findings and/or autopsy. The remaining

Table 4. Types of Complications in African Americans After Heart

Complication	No. of Episodes No.	o. of Patients
Rejection without HF		
Cellular	18	12
Humoral	6	4
Rejection with HF		
Biopsy proven	4	2
Biopsy negative/clinically suspected	11	10
HF, negative biopsy, not treated	3	3
AGAS	8	8
Infections		
Sepsis/bacterial	6	6
CMV	7	7
Herpes	2	2
Coccidiomycosis	2	2
Influenza	2	2
Aspergillus	1	1
Nocardia	2	2
Drug adverse effects		
Renal failure	2	2
Pancytopenia	1	1
Miscellaneous		
Seizures	2	2
Stroke	3	2
Heart block	3	2
Arrhythmia	1	1
Tamponade	2	2
Abbreviations: AGAS, advanced cytomegalovirus; HF, heart failure.	graft atheroscler	rosis; CMV,

7 patients died of unknown causes. The known causes of death were HF (6), sudden cardiac death (1), a complication of a coronary artery bypass grafting procedure (1), septic shock (2), pulmonary embolism (1), fat embolism (1), spinal surgery complication (1), and intracranial hemorrhage (1).

In addition to the pretransplant laboratory values, we evaluated posttransplant laboratory values, such as the 1-year cardiac catheterization for the AA recipients. The test results for all of the 29 survivors at 1 year have been compared with those of long-term survivors (we defined long-term survivors as patients surviving 5 years after transplant, 12 in number). Hemodynamic parameters at 1 year after transplant are shown in Table 6.

Risk factors for survival were also studied, including AA/non-AA ethnicity, UNOS class at time of transplant,

Table 5. Posttransplant Rejections and Time to Rejection Among African Americans

Time From Transplant to Rejection Episode	No. of Rejection Episodes
<1 week	3
1 week to 1 month	8
1 month to 1 year	12
>1 year	16

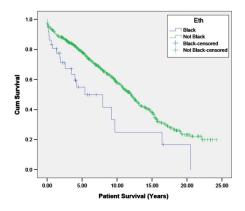


Figure 1. The survival of African Americans after cardiac transplantation is worse compared with non–African Americans (P < 0.05). Abbreviations: Cum, cumulative.

Table 6. Data at 1-Year Posttransplant in African Americans

Parameter	Overall	Long-term Survivors
RAP, mm Hg	7.59	8.25
PCWP, mm Hg	12.3	14.4
LVEF, %	59.5	62.66
Cardiac output, L/min	5.67	6.79

Abbreviations: LVEF, left ventricular ejection fraction; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure.

ischemic time, pretransplant Cr, BMI, and presence or absence of mechanical support devices. Using the stepwise Cox regression of graft survival, the variables such as ethnicity ($P \le 0.05$), pretransplant Cr ($P \le 0.05$), presence or absence of a device $(P \le 0.005)$, and UNOS status at transplant ($P \le 0.05$) independently predicted outcomes. Kaplan-Meier analysis of pretransplant Cr level and survival showed that the AA group did significantly worse for all Cr classes ($<1.4 \,\mathrm{mg/dL}$ and $>1.4 \,\mathrm{mg/dL}$, with P values of <0.01). Similarly, the survival among AA patients was significantly worse compared with non-AA patients within individual UNOS class and whether a mechanical support device was present or absent in the pretransplant phase (see Kaplan-Meier curves later). We also analyzed the sex difference and survival in AA/non-AA patients, freedom from death by infection and rejection, and none of the results were found to be statistically significant.

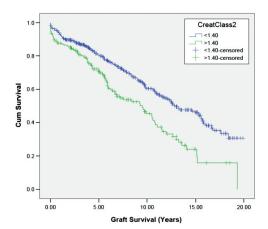


Figure 2. Overall survival was worse when pretransplant Cr was >1.4 mg/dL, as opposed to <1.4 mg/dL (*P* was significant at <0.05). Abbreviations: Cr, creatinine; Cum, cumulative.

Discussion

In this retrospective study, we looked at various pretransplant and posttransplant characteristics of our AA heart transplant recipients. The most common etiology of HF in our patient population was nonischemic cardiomyopathy, with a majority having a diagnosis of idiopathic cardiomyopathy. Average age at the time of transplant was lower in our study. Park et al previously reported that AA patients, compared with non-AA patients, were transplanted at a significantly younger age and the majority had idiopathic dilated cardiomyopathy. Another study by Pamboukian et al showed similar results. African Americans have higher rates of uncontrolled, long-standing hypertension, 12,13 likely accounting for the observed higher rate of nonischemic cardiomyopathy.

Among our patients, 8 (22%) received a mechanical assist device prior to transplant. The result of the analysis shows that the presence or absence of a pretransplant mechanical assist device independently predicts the outcome ($P \le 0.005$). This is consistent with prior studies that demonstrated high mortality following cardiac transplant in patients who required mechanical support prior to transplant.^{7,14}

We have documented a higher incidence of rejection episodes in our AA population. The most common cause of death was HF. It is highly likely that the higher rates of graft failure in this group resulted in poor outcomes. Liu et al showed that AA recipients were more likely to die of graft failures than white patients. 15 Although the evidence is far from conclusive, several studies have suggested that infections could trigger rejection in different transplant settings. Cainelli and Vento examined the evidence linking CMV, adenovirus, parvovirus, and herpes simplex virus infections to vasculopathy leading to cardiac allograft rejection. ¹⁶ Two studies have associated CMV infection with an increased frequency of acute allograft rejection in heart transplant patients. 17,18 Our patient population had CMV infection as the most common posttransplant infection. This may have played a role in higher rejection rates observed among our patient group, as compared with some other studies that have shown a lower incidence of rejection rates in the AA population.8 African Americans were much sicker at the time of transplant, with 74.3% patients in UNOS status I. Singh et al also reported similar findings in their study, in which AA and Hispanic patients were more likely to be listed with higher urgency (UNOS status I) compared with white patients (P < 0.001). ¹⁹ Despite this difference, we noted that survival among AA patients was significantly worse compared with non-AA patients within individual UNOS class.

We noted an overall posttransplant survival for AA recipients of 5.4 years, with 1-year, 5-year, and 10-year survival rates of 80%, 55%, and 25%, respectively. Our numbers are not significantly different from other reports, especially when the relatively small number of patients is considered. Park et al recorded 70%, 58%, 51%, 38%, and 32% for AA recipients after 1, 3, 5, 7, and 9 years, respectively. 6 Kanter et al concluded that the donor-recipient race mismatch predicted poorer graft survival (5-year graft survival 48.9% vs 72.3%, P = 0.0032). Our patients were relatively sick when transplanted; 64.86% were in New York Heart Association class IV, and 78% required inotropic support prior to transplant. This is probably another major reason why our AA patients did not fare well. We feel that higher incidence of CMV infection, more rejection episodes resulting in graft failure, and HF are other likely explanations.

Acute kidney injury (AKI) requiring dialysis posttransplant can increase mortality that frequently exceeds 50%. Boyle et al studied the factors that predispose to AKI in their study done on 756 cardiac transplant recipients.²¹ History of DM, prior cardiac surgery, and a high baseline Cr value due to chronic kidney disease have all been noted to be independent risk factors for development of AKI, thereby causing high posttransplant mortality. Pretransplant Cr was an independent predictor of outcome in our study as well. Kaplan-Meier analysis of pretransplant Cr level and graft survival showed that the AA group did significantly worse for all Cr classes in our study.

In our study, UNOS status at transplant was found to be an independent predictor of outcome, with a P value of <0.05. Champagnac et al and Dubois et al have shown 10% to 20% higher mortality rates at 1 year. 22,23 However, a more recent study by Baron et al did not find statistically significant differences in survival rates among various UNOS status groups.²⁴ Differences in study populations and endpoints may explain this discrepancy.

The influence of race on survival after cardiac transplantation is an area of considerable debate. Survival differences have been noted between AA recipients and white recipients in the past. Recently, posttransplant survival in white, AA, and Hispanic recipients was studied by Singh et al in an analysis of data from the United States from 1987 to 2008.²⁵ They compared the outcomes in 5 successive eras. African American recipients were noted to be at an increased risk of early death or retransplant in adjusted analysis. Early posttransplant (first 6 months after transplant) survival was noted to have improved equally in all 3 groups; however, longer-term survival improved only in whites, not among the Hispanic and AA recipients.

Similar findings have been noted with poor outcomes in AA patients with regard to a number of disease processes such as cancer²⁶ and solid-organ transplantation.²⁷ In a study done to compare the outcomes of AA and white recipients transplanted for end-stage solid-organ disease, Moore et al demonstrated that there was a significant difference in graft survival between AA and white recipients, with AA recipients having worse 5-year graft survival.²⁷ They concluded that a higher prevalence of DM, hypertension, hepatitis C virus and anti-HCV antibodies; higher acute and chronic rejection rates; and noncompliance among AA recipients might be the reasons for the observed difference. However, the study failed to show similar differences in liver or heart transplant recipients. Nair et al, in a review of the UNOS database, reported that AA recipients had poorer survival than whites after orthotopic liver transplantation.²⁸

There are contradicting results in various studies conducted with a handful of single-center experiences showing no significant effect of race on patient survival after cardiac transplantation.^{27,29} Cohen et al pointed out that the race of the donor was not found to be a risk factor influencing recipient mortality.²⁹ Interestingly in their study, donor-recipient race mismatch was not a factor that influenced recipient survival. However, there are a few single-institutional studies^{5,6} and some multi-institutional Cardiac Transplant Research Database studies that show a significant effect of recipient race on mortality.^{7,8}

Felkel et al reviewed 137 patients retrospectively for steroid-free immunosuppression.⁵ From their study, remarkably improved survival was shown in white patients who could be successfully weaned from steroids. African American recipients appeared to have generally decreased long-term survival compared with white recipients. Park et al published similar results. The group claimed that disproportionate human leukocyte antigen (HLA) matching may contribute to the disparity in patient survival following cardiac transplantation. They showed that the AA recipients, as compared with whites, received more poorly matched organs, which, upon matching for class I antigens, resulted in modest improvements in survival.

In a multi-institutional event-driven analysis that included 33 North American heart transplantation institutions, Higgins et al pointed out that the younger recipients, AA patients, recipients with ≥ 4 HLA mismatch, and those who were on a long-term (>6 months) left ventricular assist device were at a higher risk of developing rejection-related death. They postulated that these subgroups of patients received a survival benefit with cytolytic induction therapy. Lubitz et al reviewed demographic, clinical, and pharmacological data from 220 consecutive adult heart transplant recipients who survived beyond 3 months.⁸ African American race and pretransplant DM were associated with excess mortality. Variables associated with lower mortality included steroid withdrawal, statin therapy, and angiotensin receptor blocker therapy after transplantation. In their study, AA recipients who received steroids had a higher risk of mortality, but this hazard disappeared if steroids were successfully discontinued. Girnita et al suggested that AA patients have a genetic background that may predispose to a proinflammatory or a lower regulatory environment as measured by the presence of singlenucleotide polymorphisms. 11 These authors also suggested that AA patients might have a genetic predisposition to an unfavorable transplant environment, which can also affect the pharmacokinetics of immunosuppressive drug therapy.

Ethnicity was an independent predictor of outcome in our study ($P \leq 0.05$). Kaplan-Meier survival curves comparing AA and non-AA patients demonstrated a significant decrease in survival (P < 0.05) among AA patients as compared with the non-AA patients. Kaplan-Meier analysis of pretransplant Cr level and graft survival showed that the AA group did significantly worse for all Cr classes in our study. Multifactorial etiologies may have been operative, as shown by several reports above.

Study Limitations

Our study was conducted in a single center in Arizona. Less than 5% of transplant recipients in our center were of AA ethnicity. This definitely has resulted in a small sample size compared with some of the studies quoted previously, in which AA patients constituted 10% to 22% of recipients. Geographic distribution and referral base may have resulted in such a discrepancy. Despite such a limited sample size, the findings are striking and have echoed some of the results of bigger studies, and hence are valid.

Multiple modifiable and nonmodifiable factors may be operative, but improvement of posttransplant outcomes in minorities is definitely desirable. Early identification and referral of AA HF patients, possible earlier listing for transplant, careful matching of donors, and more frequent and vigilant posttransplant care with early recognition and treatment of rejection episodes and prevention and treatment of CMV infection may help to improve outcomes in this relatively unfavorable population.

Conclusion

We have demonstrated that there is a statistically significant difference in outcomes between AA and non-AA patients after cardiac transplantation. African American patients have decreased survival over time. Pretransplant Cr, ethnicity, presence of a mechanical assist device, and UNOS status at transplant are the independent predictors of outcomes.

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