Influence of Race on Kidney Transplantation in the Department of Defense Healthcare System

James D. Oliver, III a, b  Robert T. Neff d  David B. Leeser a, e  S.J. Swanson g  
C.M. Yuan a  Edward M. Falta a  Eric Elster a, c  Bruce Reinmuth b  Erin M. Bohen d  
Rahul M. Jindal a, f  Kevin C. Abbott a, d

a Organ Transplantation, Walter Reed Army Medical Center, b Walter Reed Army Institute of Research, c Department of Surgery, National Naval Medical Center, d Nephrology SVC, Department of Medicine, Walter Reed Army Medical Center, Washington, D.C., e Division of Transplant Surgery, Department of Surgery, Weill Cornell Medical College, New York, N.Y., f Brookdale University Medical Center, Brooklyn, N.Y., and g Christiana Care, Newark, Del., USA

Key Words
Kidney transplantation, influence of race · Department of Defense healthcare system · Transplant outcomes, race

Abstract

Background: We report the influence of race on transplant outcomes in the Department of Defense (DOD) system. Methods: Retrospective cohort analysis of all kidney transplants performed at WRAMC from 1996 to 2005. Kaplan-Meier analysis was used to assess for differences in graft survival, and Cox regression was used to calculate adjusted hazard ratios for graft loss. For our analyses, we used the cutoff of 6 years (year 2000) when we introduced thymoglobulin induction; maintenance immunosuppression consisted of mycophenolate mofetil and tacrolimus, and rapid steroid taper (completed withdrawal at 6 weeks) was used for all patients. Results: There were 220 transplants (91 Blacks, 107 Caucasians and 22 Asians). Because the curve for graft survival for Blacks over time violated the proportional hazards assumption (at 6 years post-transplant), analysis was segregated into two segments. Through 6 years of follow-up, graft survival was 77% for Blacks and 81% for non-Blacks (p = 0.74 by log rank). Through 9 potential years of follow-up, graft survival for Blacks was 56% and 78% for Whites (p = 0.005). In Cox regression analysis, Black race, compared with non-Black race, was not significantly associated with graft loss at 6 years, but was significantly associated with graft loss occurring after 6 years. Conclusions: In the DOD health system, no significant differences were seen in graft survival among recipients of different races at 6 years. Black recipients who received a kidney transplant before the year 2000 showed decreased graft survival compared to non-Blacks. This was consistent with change in immunosuppressive regimen in our institution with the introduction of thymoglobulin induction and maintenance therapy with tacrolimus, mycophenolate mofetil and withdrawal of prednisone at 6 weeks.

Introduction

The US Renal Data System (USRDS) has reported that more than 20 million Americans have kidney diseases, most common causes are diabetes and hypertension.
Blacks are nearly four times more likely than Caucasians to develop kidney failure requiring dialysis or renal transplant [1]. Among new patients with kidney failure caused by high blood pressure, >50% are Blacks. Kidney transplant recipients of African descent have been found to have poor allograft survival in most studies [2]. The reason for this is multifactorial. Black patients have longer waiting times, poorer access to dialysis, greater number of pre-transplant transfusions, poor matching for HLA antigens, insurance coverage and poorer adherence [3]. Other investigators have found that differential metabolism of immunosuppressive agents may account for these differences [4].

The hypothesis that universal coverage for immunosuppressive medications will improve long-term outcomes in patients of African descent is not borne out in all publications. In the UK, where there is lifelong universal health coverage for medications, the outcome for Black patients was inferior to that for Indo-Asian and Caucasian transplant recipients. Rudge et al. [5] used the UK national database between 1998 and 2003 and found that there was inferior 3-year transplant survival for Black versus Caucasian and Asian patients (p = 0.03). They found that median waiting time to transplantation was significantly more for Black and Indo-Asian patients, while the degree of HLA matching achieved for Black and Asian patients was also inferior versus Caucasian patients. Interestingly, although Indo-Asian patients also had longer waiting times and poorer HLA match, outcomes were similar to Caucasian patients. Doodeniya et al. [6] compared the outcomes in Indo-Asians and Caucasian patients at the Hammersmith Hospital, London, and in the UK National Transplant Database, and found that co-morbid conditions in the two groups were similar, except for a significantly higher incidence of diabetes in the Indo-Asian groups. After transplant, the incidence of delayed graft function, rejection episodes, graft and patient survival were similar. Therefore, it seems that the Black patients fare poorly versus both Indo-Asian and Caucasian patients despite universal health coverage in the UK.

In France, which also has universal health coverage, Black recipients do as well as Caucasians [7]. The authors postulated that if significant physiologic differences between Blacks and Whites existed, they should be evident worldwide, not limited to a single country such as the USA. The authors concluded that lack of coverage must be the major variable placing Blacks at risk, attributing the lack of differences seen between races in the European system to the model of universal, government-sponsored insurance that covers not only immunosuppressive medications but also other agents. However, the effect of genetic and physiological factors was not discussed as the Black patients in France were of Caribbean and Sub-Saharan Africa descent, which is different from the ancestry of Black patients in the USA and elsewhere.

In the USA, there is no universal healthcare system; however, there is a managed care system for veterans and active duty personnel and their dependents. In the Veterans Administration system, it has been shown that despite free availability of post-transplant medications, disparity in graft survival among races, in particular for Blacks, was still present [8]. The Department of Defense (DOD) transplant system provides a unique prospective in terms of healthcare. It may be of interest to see whether racial differences in kidney transplant outcomes persist in such a system. We, therefore, report outcomes after kidney transplantation by race in the DOD health system.

Methods

After review of the research protocol by WRAMC Department of Clinical Investigation Research Review Service, this study received an IRB Exemption Certification. A retrospective review of data from chart and computer records was performed on all patients transplanted at WRAMC between 1996 through 31 December 2005, followed for a minimum of 3 months unless death or graft loss was documented earlier. After collection of all necessary data, identifiers were removed, and analysis was performed. Data on donor and characteristics were abstracted by the transplant service data coordinator. A major change to the regimen was introduced in 2000, when thymoglobulin induction, mycophenolate mofetil (MMF) and tacrolimus maintenance therapy, with rapid corticosteroid taper to withdrawal at 6 weeks, was used for all Black recipients, and most of all recipients, in the absence of major contraindications.

Unadjusted differences in characteristics between Black recipients and recipients of other races utilized χ² analysis for categorical variables and Student’s t test for continuous variables (Mann-Whitney U test used for variables non-normally distributed). Kaplan-Meier analysis was used to depict unadjusted graft survival curves for various patient characteristics, especially recipient race. Cox regression analysis was used to calculate adjusted hazard ratios for graft loss. Covariates in analysis included donor and recipient age, donor and recipient race, recipient body mass index, donor type (deceased donor, living related, living unrelated), cold ischemic time, peak panel reactive antibody %, induction and maintenance immunosuppression, donor and recipient CMV status. Interactions (two-way only) between covariates and recipient race were explored.

Missing values were explored for random occurrence and multiple interpolations (per SPSS Missing Values 7.0) were used to construct datasets for analysis.
Results

From 1 January 1996 to December 2005, 238 patients received kidney transplants at WRAMC. Of these, 9 (3.8%) did not have a reliable follow-up and patients who were within 3 months of transplantation were excluded, leaving 220 patients for analysis. Characteristics of the study population, stratified by recipient race (Black vs. all others) are shown in Table 1. Figure 1a, b shows unadjusted Kaplan-Meier plots of kidney allograft survival, including death with function, stratified by race during the study period. Asian recipients had the highest graft survival, followed by Whites, and Blacks had the lowest graft survival. Because the curve for graft survival for Blacks over time violated the proportional hazards assumption (at 6 years post-transplant), analysis was segregated into two segments. Through 6 years of follow-up, graft survival was 77% for Blacks and 81% for non-Blacks (p = 0.74 by log rank). Through 9 potential years of follow-up, graft survival for Blacks was 56% and 78% for Whites (p = 0.005). This was consistent with the observation that a period effect in the year 2000 (the change of regimen to 100% thymoglobulin induction and MMF maintenance for all Black patients), in a setting of equal access to care, including medications, was associated with attenuation of the disparity in graft outcomes for Blacks versus Whites. Most patients received tacrolimus with rapid steroid taper (complete withdrawal at 6 weeks). Pre- or post-transplant diabetes was not associated with graft failure or patient survival.

Table 2 shows the variables in the final model including donor and recipient age, race, recipient gender, donor type, recipient body mass index, donor CMV+ kidney into CMV− recipient, maintenance and induction immunosuppression, HLA mismatch, preemptive transplant, peak PRA >20%, and cold ischemic time. In Cox regression analysis, Black race, compared with non-Black race, was not significantly associated with graft loss at 6 years, but was significantly associated with graft loss occurring after 6 years.

Discussion

The disparity of transplant outcomes by recipient race in the USA, particularly for the Black race, has proved remarkably persistent since initial reports were first published [9]. These disparities exist in multiple healthcare settings, including clinical trials where medications are essentially provided without charge [10]. The fact that...
Blacks have higher rates of graft failure than Caucasians is all the more remarkable considering that these patients have significantly better survival on dialysis than Caucasians, as reported consistently in the USRDS [1]. It is known that Blacks in the USA face many disadvantages before and after kidney transplantation – longer waiting times for transplant, higher degrees of sensitization, HLA mismatch, and other factors that portend inferior outcomes [11–13]. Nevertheless, even after careful adjustment for these factors, Black recipient race was an enduring risk factor for premature graft failure in the USA. Potential explanations may consist of unmeasured confounders, such as genetic polymorphisms, or systematic differences in management or access to care based primarily on socioeconomic status, for which race is often a surrogate [14].

The effect of race on kidney transplant outcomes has been actively investigated in Canada which has a universal health system. Tonelli et al. [15] studied over 21,000 adults of East Asian and Indo-Asian versus Caucasian patients who initiated dialysis from 1990 to 2000. Asian patients were less likely to receive a kidney transplant versus Caucasians; however, the adjusted death-censored
graft loss in transplant recipients was not significantly different between the ethnic groups, and the adjusted risk of death after transplantation was significantly lower in Indo-Asian than in Caucasian patients. Similar results have been shown in the Asian kidney transplant recipients in the USA. Using the UCLA Registry, Koyama and Cecka [14] showed that graft survival for cyclosporine-treated first cadaver kidney transplants was superior in Asian recipients compared to other races. This trend was again seen by Katznelson et al. [16], who found that 5-year survival rates for Asian recipients was superior to that of Hispanics, Caucasians and African-Americans. The authors surmised that this may be due to the lower incidence of sensitization, lower incidence of acute rejection and chronic rejection and primary renal disease such as IgA nephropathy and chronic glomerulonephritis which have better outcomes after kidney transplantation.

Aboriginal patients universally tend to do poorly. Tonelli et al. [17] from Canada investigated differences in survival of Caucasians versus Aborignals after commencement of dialysis. In a large study comprising of 4,333 adults of which 15.8% were Aborignals, age-adjusted death rate was significantly higher in Aborignals;
these patients were also less likely to receive a kidney transplant; however, survival was similar when adjusted for co-morbidity. Socioeconomic status did not adversely affect survival. In another study from Canada, it was found that the lower rate of transplantation in Aboriginals was not adversely affected by the distance between their residence and the nearest transplant center [18]. In the case of Australian Aboriginals, who have a significantly lower chance of getting a kidney transplant versus White Australians, graft survival is poorer in both deceased and living kidney donors and was associated with longer waiting times, poorer HLA match, higher rates of vascular rejection. Higher death rate among Australian Aboriginals was due to sepsis and increased exposure to steroids [19, 20].

Studies have been carried out to investigate the effect of socioeconomic variables resulting in graft loss in Blacks. Butkus et al. [21] found that among Blacks, immunological graft loss was associated with lower income, non-adherence and lower level of education; however, non-immunological graft loss was distributed equally across racial and income levels. They suggested that post-transplant adherence was the most significant factor. In a study of USRDS database, recipients with a higher level of education and private insurance were found to have an advantage in graft and recipient outcomes independent of racial differences [22]. In a more recent study of the USRDS database with at least 36 months’ follow up, Chisholm et al. [23] found that of the 53,997 patients, 6% were non-adherent; non-adherence risk increased with time post-transplant and decreased with age. Patients who were male and non-White were more likely to be non-adherent. They suggested that targeting these groups will increase graft survival.

Adherence with medications after organ transplantation is a major healthcare issue with implications for chronic rejection and graft loss. Patients who lose their grafts due to non-adherence may be denied a second transplant, an area of considerable controversy and debate. Furthermore, healthcare financing is assuming a central role in our society. Patients who lose their transplants due to non-adherence will result in a significant drain on finances as these patients are placed back on dialysis, a modality of treatment more expensive than a functioning transplant. In a recent systematic review of published literature on non-adherence in adult renal transplant patients from 1980 to 2001 [24], the odds of graft failure were reported to increase sevenfold in non-adherent patients; a median of 22% recipients were non-adherent while a median of 36% patients graft losses were attributed to non-adherence. Jindal et al. [25] performed a meta-analysis of literature on non-adherence after kidney transplantation to define commonalities that may help the clinician identify patients for early intervention. They found that patients who were at a higher risk of non-adherence after kidney transplants were younger, female, unmarried, and non-Caucasians. Patients who were recipients of living donor transplants and had been transplanted for a longer time with a history of a previous transplant were also at risk of non-adherence. The authors also found that patients displaying emotional problems, such as anxiety, hostility, depression, distress, lack of coping, and avoidant behaviors, were also at risk for non-adherence after kidney transplantation. It has been shown in a number of studies that non-Caucasians tend to be more non-adherent; a case may be made for targeted psychosocial intervention in this population.

In our study, Black recipients, compared to recipients of other races (Caucasian, Asian) were significantly more likely to be male, receive non-Caucasian donor kidneys, had higher levels of HLA-mismatch, lower rates of preemptive transplant, and higher use of MMF. Despite these negative factors, our analyses showed that within the first 6 years after transplant, Black patients in the DOD system do as well as Caucasians and Asians. Similar results have been seen in small single-center studies; Smith and Butterly [26] from Duke University showed that graft survival by race for living donor recipients improved over the years, which they attributed to improved immunosuppressive therapy. Foster et al. [27] from the University of Maryland also showed that a focused approach towards Blacks comprising of formal education promoting living donation resulted in comparable patient and graft survival rates. Eckhoff et al. [28] from the University of Alabama at Birmingham showed that in a large group of Black recipients, there was an improvement of graft and patient survival at 1 year, which they attributed to improved immunosuppressive therapy, however the time on dialysis, diabetes and access to medical care contributed to the disparity between the two groups after 3 years. There is certainly a ‘center’ effect whereby studies from centers with large Black transplant recipients do as well as Caucasians; this is achieved by implementing innovative educational or therapeutic programs [26–28].

A variety of strategies to reduce racial imbalance both in access to care and post-transplant management have been proposed. Strategies to improve adherence focused towards the minority populations may also help in improving graft and patient survival after kidney transplantation.
transplantation [29]. A culturally sensitive education program using minority health educator and discussion of race-specific outcomes was also suggested as a way to improve outcomes in Black recipients [30]. A novel approach would be to reduce the waiting time for Black patients as longer hemodialysis was associated with increased T-cell alloreactivity [31] by changing the kidney allocation policy by removing HLA-B matching as a priority could potentially reduce the racial imbalance [32]. Gao et al. [33] recently analyzed a retrospective cohort of DOD patients with CKD stage 3 and 4 for compliance with a variety of KDOQI recommended targets and found that compliance for Black patients was similar to Caucasians. It follows, as a corollary, that some of patients of this cohort who went to receive a kidney transplant within the DOD healthcare system obtained favorable outcomes. This study is important as it has shown that removing disparity before listing for transplantation may be critical for improved outcomes after kidney transplant [34].

Limitation in our study was the retrospective nature of our analyses and lack of control group where no induction therapy was used or where another form of induction such as anti-IL-2 receptor blockade was used. Thus, no true comparison between use of induction thymoglobulin, or maintenance medications, is appropriate from this study. However, the major strength of our study is the consistent and close follow-up in the DOD system and uniform immunosuppression with universal lifelong healthcare. Also, our global electronic medical records and direct ascertainment of medication prescriptions, laboratory results and appointments allows us unique surveillance of patients late after transplantation, regardless of their location (since patients will travel long distances to fill their medications or obtain other DOD care). In contrast to Medicare coverage for immunosuppressive medications, DOD coverage is not limited to 3 years and covers all prescribed medications, not just immunosuppressive medications. Furthermore, DOD patients are eligible for care for all medical and psychological conditions, not just those that are ‘service connected’, as in the Veterans Administration system.

To conclude, in the DOD health system, no significant differences were seen in graft survival among recipients of different races using a regimen comprising of thymoglobulin induction, with MMF and tacrolimus maintenance and withdrawal of steroids at 6 weeks. More studies need to be carried out to understand the racial differences that exist in recipients of African ancestry, in both universal and insurance healthcare systems. Universal healthcare systems may not be the panacea to improve graft outcomes in recipients of African ancestry, as it has been shown that in the UK, Black patients do not fare as well as Caucasians. On the other hand, some centers in the USA with a large Black population can still obtain results that are equivalent to that achieved with the DOD patients. There is an undefined element which needs to be explored, which may ultimately lead to improvement of graft survival in patients of African ancestry. This may perhaps consist of a multi-pronged approach with increased education, shorter waiting times [35], emphasis on living kidney transplants, tailored immunosuppression and improved adherence to medications [36, 37]. However, a detailed scientific study dissecting the genetic, physiological, immunological and socioeconomic reasons for this disparity among races is lacking.

*Disclosure Statement*

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy or Army, Department of Defense, or the US Government.

References


*On request of the corresponding author, the Disclosure Statement has been included (October 28, 2008).*
Race and Kidney Transplantation


Chisholm MA, Kwong WJ, Spivey CA: Associations of characteristics of renal transplant recipients with clinicians’ perceptions of adherence to immunosuppressant therapy. Transplantation 2007;84:1145–1150.


Race and Kidney Transplantation