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Effect of Donor Ethnicity on Kidney Survival in Different Recipient Pairs— An Analysis of the OPTN/UNOS Database

C.O. Callender, W.S. Cherikh, P Traverso, A. Hernandez, T. Oyetunji, and D. Chang

Abstract

Background—Previous multivariate analysis during 4/1/94-12/31/00 from the Organ Procurement Transplant Network/United Network for Organ Sharing (OPTN/UNOS) database has shown that kidneys from Black donors were associated with lower graft survival. We compared graft and patient survival of different kidney donor-to-recipient ethnic combinations to see if this result still holds on a recent cohort of US kidney transplants.

Methods—72,495 recipients of deceased and living donor kidney alone transplants from 2001-2005 were included. A multivariate Cox regression method was used to analyze the effect of donor-recipient ethnicity on graft and patient survival within 5 years of transplant, and to adjust for the effect of other donor, recipient and transplant characteristics. Results are presented as hazard ratios (HR) with the 95% confidence limit (CL) and p-values.

Results—Adjusted HR's of donor-recipient patient survival: White to White (1), White to Black (1.22, $p=.001$). Graft survival HRS: Black to Black (1.40, $p<0.001$), Black to White (1.35, $p<0.001$), Black to Hispanic (0.87, $p=0.18$), Black to Asian (0.69, $p=0.05$).

Summary—Black donor Kidneys are associated with significantly lower graft survival when transplanted into Whites and Blacks and are only associated with lower patient survival when these kidneys are transplanted into White transplant recipients. The graft and patient survival rates for Asian and Latino/Hispanic recipients however were not affected by donor ethnicity. This analysis underscores the need for research to better understand the reasons for these disparities and how to improve the post transplant graft survival rates of Blacks.

Introduction

Our previous multivariate analysis of the Organ Procurement Transplant Network/United Network for Organ Sharing(OPTN/UNOS) database 4/1/94 – 12/31/00 revealed that black organ donorship (kidneys, liver, hearts) was associated with lower graft survival especially when transplanted into Black and White transplant recipients. However, these lower outcomes were overcome when Black donor organs were transplanted into Asians and Latino/Hispanic recipients. That study did not analyze patient survival rates except in cardiac transplant recipients, where cardiac mortality was analyzed. The present study was conducted to see if these outcomes were the same in a more recent cohort of American kidney transplants. In this study we have compared kidney graft and patient survival of a variety of donor to recipient ethnic combinations. Black to Black, Black to White, Black to Asian, Black to Latino/Hispanic,

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and Black to Others, combinations were analyzed with similar combinations of White, Latino, and other donor recipient combinations (24 in all). While the Black donor graft survival rates were similar to our previous study, only Black to White patient survival rates were altered significantly (Hazard Ratio of 1.22). All other donor recipient combinations were associated with hazard ratios that were less than one.

Materials and Methods

72,495 recipients of deceased and living donor kidney alone transplants performed from 2001-2005 on the OPTN/UNOS database were included in our analysis. In order to analyze the effect of donor recipient ethnicity on graft and patient survival within five (5) years of transplant and to adjust for the effect of other donor, recipient and transplant characteristics, a multivariate Cox Regression Method was used. Results are presented as Hazard Ratios (HR) with the 95% Confidence Limit (CL) and P-values. The White to White combination was used as the reference group and this combination was given a score of one (1) for patient and graft survival rates.

Results

Table 1 below shows the adjusted HR of graft loss and death within five years of transplantation for the selected donor to recipient ethnicity combinations. An HR of greater than one indicates reduced survival and an HR of less than one indicates better survival as compared to the reference group (White to White). Also included in these tables is the number (N) of patients in each group.

Overall Graft Loss

Table 2 below shows adjusted odds ratios of graft loss stratified by recipient within 5 years of kidney transplantation. Both Black and White recipients have statistically significantly lower graft survival than other ethnic groups. White and Black recipients tend to have a greater incidence of graft loss than recipients of other ethnicities regardless of donor ethnicity (increased Odds Ratios for both Whites and Blacks).

Both Black and White recipients have decreased graft survival with kidneys transplanted from Black donors (CI 1.400[1.316, -1.488] and 1.351[1.218, -1.499] respectively), whereas Hispanics and Asians show no increased graft loss with kidneys from black donors (0.870 [0.710, -1.067] and 0.693[0.483, -0.995] respectively). Donor ethnicity does not statistically significantly affect recipient patient survival in other groupings. Black and White recipients show similar trends of graft loss depending on the ethnicity of the kidney donor. Hispanic and Asian recipient graft survival is independent of donor ethnicity.

Table 3 below shows adjusted odds ratios of graft loss stratified by donor within 5 years of kidney transplantation.

Data depicted on this table confirms that, regardless of donor ethnicity, White and Black recipients have a higher incidence of 5 year graft loss when compared to other ethnic groups. (Odds ratio for White and Black recipients is always higher than Hispanic and Asian recipients in all donor groups). Kidneys from White and Black donors show a statistically higher incidence of graft loss in both Black and White recipient populations compared with other ethnicities.

Kidneys from Black donors do less well than those from White/Hispanic/Asian donors only among White and Black recipients (Black to White-1.351[1.218, -1.499]; Black to Black-1.400 [1.316, -1.488]; Black to Hispanic-0.870[0.710, -1.067]; Black to Asian-0.693[0.483, -0.995]).

Interestingly enough, there is no statistical difference in graft survival of Black donor kidneys between Black and White recipients. White and Black recipients show equally decreased graft survival with Black donor kidneys.

Kidneys from White donors also show decreased graft survival for White recipients (1.0 [95% CI] compared to Hispanics or Asian donor kidneys (0.764[0.700, -0.834] and 0.703[0.610, -0.810] respectively). White donor kidneys have a statistically lower graft survival in both White and Black recipients (1.0 [95%CI] and 1.146[1.084, -1.212] respectively) compared to Hispanic/Asian recipients (0.764[0.700, -0.834] and 0.703[0.610, -0.810] respectively). White donor kidneys also show a higher incidence of graft loss in Black recipients when compared with other recipients.

Overall patient survival

Table 4 below shows adjusted odds ratios of patient survival stratified by recipient within 5 years of kidney transplantation.

Our data clearly shows that there is no statistical difference by donor ethnicity in Black/Hispanic/Asian recipients. The White recipient group is the only ethnic group in which donor ethnicity affects survival and is affected by kidneys from Black donors (1.220[1.061, -1.402]).

Stratified by Donor

Table 5 below shows adjusted odds ratios of patient survival stratified by donor within 5 years of kidney transplantation.

This data confirms that the only elevated risk of death (using White donor to White recipient as baseline) occurs when Black donor kidneys are transplanted into White patients.

Interestingly however, White recipients (when compared with survival of all other ethnic groups) have a higher patient mortality when receiving transplants from White donors than any other recipient ethnicity (White to Black: 0.860[0.794, -0.930]; White to Hispanic: 0.682 [0.606, -0.768]; White to Asian: 0.699[0.581, -0.842]). Further scrutiny shows that patient mortality in only the White recipient population is increased by Black *as well as* White donor kidneys. Black/Hispanic/Asian recipient 5 year survival is not affected by donor ethnicity.

Discussion

It is important to consider the results of this analysis and our prior reports in the context that transplantation of all organs have been associated with ever improving short and long term patient and graft survival rates(2) (1 and 5 years). It is important, therefore, to recognize that after kidney transplantation patient survival rates for all ethnic groups are similar (1 year-95% and 5 years-80%). Five year graft survival rates for Blacks (African Americans) however(3) demonstrate a significant disparity especially at the five year time period. It is at this time period that graft survival rates are not as good as other ethnic groups with a disparity of as much as 13-19%; 60.9% for Blacks (African Americans) and 79.4%, 75.9%, 73.8% respectively for Asian, Latino/Hispanic, and White kidney transplant recipients. This disparity has persisted since Opelz(4) first pointed this out more than thirty years ago (1977). The reason for this disparity remains an enigma. While transplant success as measured by graft survival rates at five years are lower for Blacks (A.A.) than for all other ethnic groups. It is essential to underscore the fact that graft survival rates are good but that they are not as good for A.A. as they are in other ethnic groups. We have used the term poor in our previous manuscript(1) while it would have been more appropriate to use the term less good because the graft survival rates are not poor for any ethnic group. This analysis of the OPTN/UNOS database from 2001-2005 was carried out to see if the lower graft survival rates for kidneys from Blacks

persisted when transplanted into Blacks and Whites and if this suboptimal outcome continues to be overcome by transplanting African American organs into Latino/Hispanics and Asians. Our analysis of this most recent data base confirms the earlier findings, but also identifies a patient survival disparity with a hazard ratio of 1.22 that exists only for White recipients of Black kidneys. Interestingly all other ethnic groups have patient survival hazard ratios of less than one when they have received kidneys from Blacks. An in depth analysis of the confidence limits of the donors and recipients in tables 2-5 leads us to the following conclusions:

1. Both Black and White recipients have statistically significant lower graft survival than other ethnic groups. White and Black recipient tend to have a greater incidence of graft loss than recipients of other groupings regardless of donor ethnicity.
2. Hispanic and Asian graft survival is superior to Whites and Blacks and is independent of donor ethnicity.
3. The ethnicity of the donor affects patient survival only in White patients when kidneys from Black donors are given to White transplant recipients and is associated with lower graft survival rates with a Hazard Ratio of 1.22 (the p-value=0.005).

The use of the UNOS OPTN data registry is beneficial because it gives us the power of numbers which allow us to perform data analysis that single transplant centers would be unable to accomplish. In this registry study the largest N was 37,241 and the smallest N was 106 with five of the ten N's being over one thousand. On the other hand, registry studies are flawed in that often there is the absence of specific helpful information easily available like, the socioeconomic status; the zip code information; the type of immunosuppressives used; the education levels; the BMI's; the timing of mid level interval changes; e.g. 2, 3 and 4 year or the actual reason for the loss of the graft or the patient. The absence of these information elements limits the utilization of these rich data bases and require additional in depth analysis and prospective randomized studies to overcome these limitations.

Another limitation of registry analysis is the artificial nature of the groupings. The groupings in this study are the ethnic groups selected. All of these ethnic groups are made up of distinct and diverse subpopulations that are unique. Are these artificial groupings significant? Are they appropriate and do these groupings allow us to get meaningful and veracious answers regarding the diversities of the Homo Sapien Species? Is there true homogeneity of any of these groups? Studies that overcome these limitations require much forethought, because the deeper we dig the smaller the N's become and the smaller the N's the less powerful become our statistical significance.

Our analysis has unmasked the inherent problems associated with using the White population as the point of reference. This was done because the N was so large 37,241 and it therefore was attractive for comparisons to other groups. After analyzing our data, there appeared to be a division of the groupings into Whites and Blacks as the two groups associated with the poorest outcomes and with the Asians and Latino/Hispanics with the best outcomes. This led us to question the wisdom of the selection of the White population as the reference group. As pointed out earlier in this discussion, Asians are associated with the best transplant outcomes with Latino/Hispanic next followed by Caucasians and then the African American population with the least good outcomes. We now believe we need to reanalyze these data with the Asians as the point of reference for donor and recipient patient and graft survival outcome analysis. While the N's are much smaller, we believe this will help us to better understand the significance of our data which identify Whites and Blacks as the groups with the least good outcomes and the Asians as the group with the best outcomes.

One of the most surprising data items that we observed while not statistically significant was that while African Americans have graft survival rates and hazard ratios that are greater than

one, for all donor groupings, the donor which was associated with the hazard ratio that was closest to one was that of White donors (N=8,555) to African American recipients with a hazard ratio of 1.15. This would make Whites the best donors for kidneys for African Americans and African Americans the poorest donors (N=6,550) for other African Americans with a hazard ratio of 1.40.

It is important to point out that we have reviewed all 24 donor to recipient pairs – Blacks, Whites, Latino/Hispanic, Asians and others, and have presented the ten that had the largest N's and the most interpretable results. While as Homo Sapiens we are 99.7% the same, genetic diversity remains one of the reasons for our survival and is one of our greatest strengths. This makes attractive a look at the impact, genomics, proteomics microarray analysis and metabolomics may have in understanding the whys and wherefores of our mystifying results. It is my belief that the key to answering these questions may well come from further microarray analysis and a better understanding of the metabolomics of normal Asian and Black kidneys.

Two recent genomic analysis have now identified an increased commonality of multiple single-nucleotide polymorphisms(5,6) (allele frequencies ranging from 0.2- 0.6) in the gene encoding non-muscle myosin heavy chain type II isoform A (*MYH9*) which accounted for a 2-4 times greater risk of non diabetic End Stage Renal Disease (ESRD) among African Americans (A.A.) when compared to European Americans (E.A.). These data suggest that possession of the *MYH9* gene in the chromosome twenty-two region is a major effect risk gene which is associated with focal segmental glomerulosclerosis and hypertensive ESRD among African Americans. This association may be the initial step in helping us understand one of the many ESRD disparities that result in a higher incidence of ESRD among A.A. This association may also contribute to an understanding of the lower graft survival rates after kidney transplantation and why kidneys of A.A. survive for shorter periods of time after transplants into A.A. and E.A.

The results of transplantation in the African American population raise many more questions than the answers we have hypothesized. The meager theories we conjure are just the tip of the iceberg of data that remain submerged. In order to unravel these mysteries surrounding the health disparity evident in the disparity between Whites, Asians, Latinos, and African Americans, we must heed the call for research that these questions demand.

The complexity of the matter is hinted at by the “be blessed” and “INGAM” models of Campbell(7) and Madhere(8) and will require an in depth look at the psychoneuroimmunologic and genomic models to sufficiently answer the many questions we unravel as we delve into this iceberg. As we seek to understand why this particular health disparity so evident in transplantation exists, we must leave no discipline out as the answer will help all Homo Sapiens.

As a consequence of our findings, we are now aware of the following:

1. Black and White recipients have statistically significantly lower graft survival than Latino/Hispanic and Asian kidney transplant recipients regardless of donor ethnicity.
2. Hispanic and Asian better graft survival rates are independent of donor ethnicity.
3. Donor ethnicity affects patient survival only in White patients when kidneys from Black donors are given to White transplant recipients.
4. Further in-depth analysis of the registry is necessary to identify subpopulations of as many ethnic groups as possible.
5. An attempt to maximize the use of all available demographics and psychoneuroimmunologic data elements in the registry is necessary to allow us to

identify how we can move from retrospective to prospective analysis of these populations to better understand and answer the many questions raised by this study.

6. The need to reanalyze this data base with Asians as the reference group rather than Whites as was used in this analysis.
7. The need to recognize the multidisciplinary and complex nature of the manner in which the psychoneuroimmunologic and genomic factors merge together to cause this transplant ethnic disparity.
8. The need to understand the importance of unveiling the mysteries of the enigma (A.A. transplant disparity) in order to understand the Homosapien health enigma.
9. The final pathway in answering these questions may well lie in our using the dissecting tools of genomics, proteomics, microarray analysis, and metabolomics in the study of normal Asian and A.A. kidneys.

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Table 1
Effect of Donor Ethnicity on Kidney Survival in Different Recipient Ethnicity – An Analysis of OPTN/UNOS Database

Donor to Recipient Ethnicity	Graft Loss		Death	
	HR [95% CL]	P-value	HR [95% CL]	P-value
White to White (N=37,241)	1.00	-	1.00	-
Black to White (N=1,673)	1.35 [1.22, 1.50]	< 0.001	1.22 [1.06, 1.40]	0.005
Black to Black (N=6,550)	1.40 [1.32, 1.49]	< 0.001	0.97 [0.88, 1.06]	0.47
Black to Hispanic (N=466)	0.87 [0.71, 1.07]	0.18	0.69 [0.51, 0.98]	0.01
Black to Asian (N=217)	0.69 [0.48, 0.99]	0.05	0.59 [0.35, 0.98]	0.04
Black to Other (N=106)	1.38 [0.93, 2.04]	0.11	0.90 [0.47, 1.74]	0.77
White to Black (N=8,555)	1.15 [1.08, 1.21]	<0.001	0.86 [0.79, 0.93]	<0.001
Hispanic to Black (N=1,311)	1.20 [1.07, 1.34]	0.002	0.92 [0.77, 1.09]	0.32
Asian to Black (N=202)	1.26 [0.97, 1.64]	0.08	1.01 [0.69, 1.48]	0.97
Other to Black (N=178)	1.17 [0.85, 1.61]	0.34	1.15 [0.76, 1.75]	0.52

Table 2
Five (5) Year Graft Survival stratified by Recipient Confidence Limits

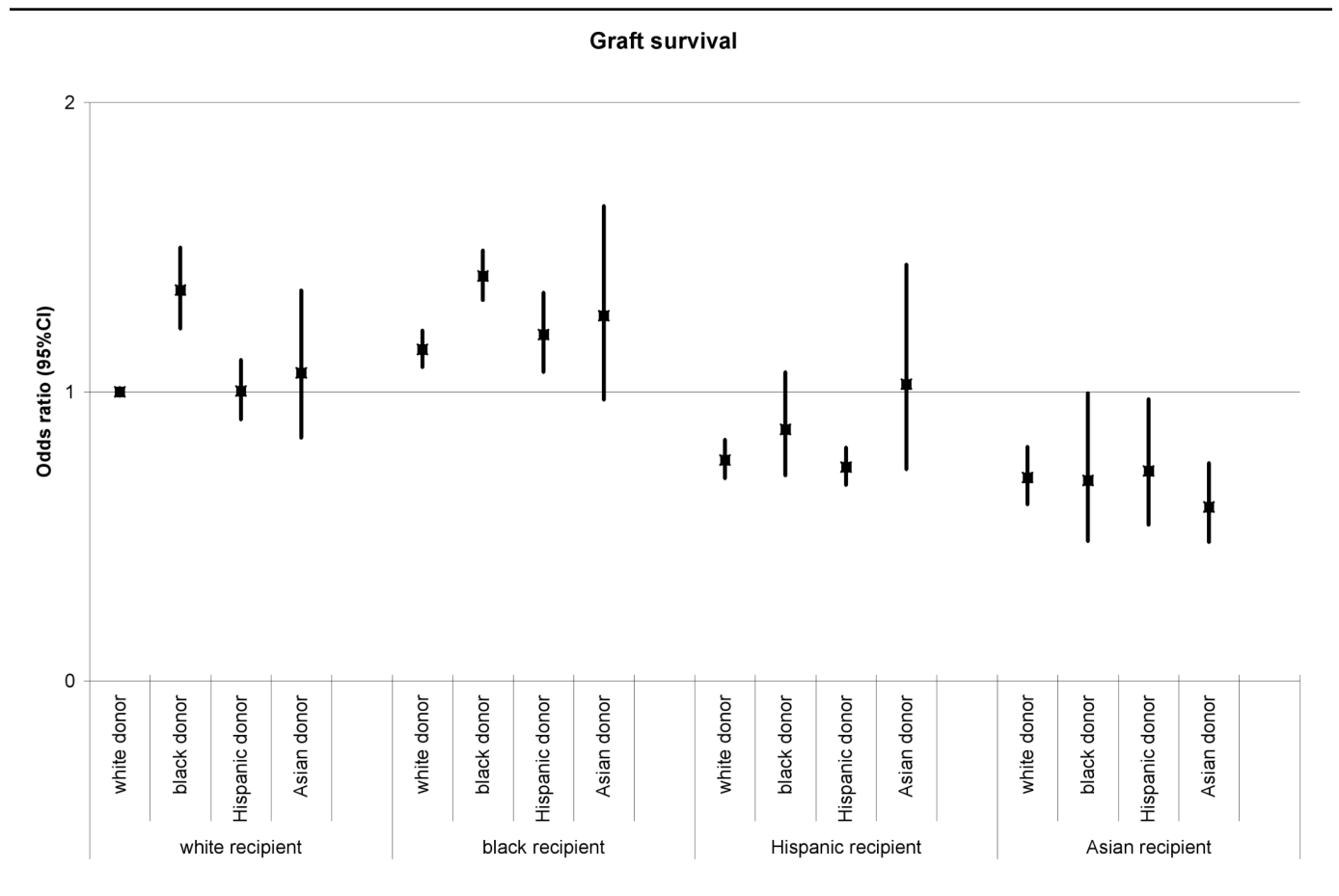


Table 3
Five (5) Year Graft Survival stratified by Donor Confidence Limits

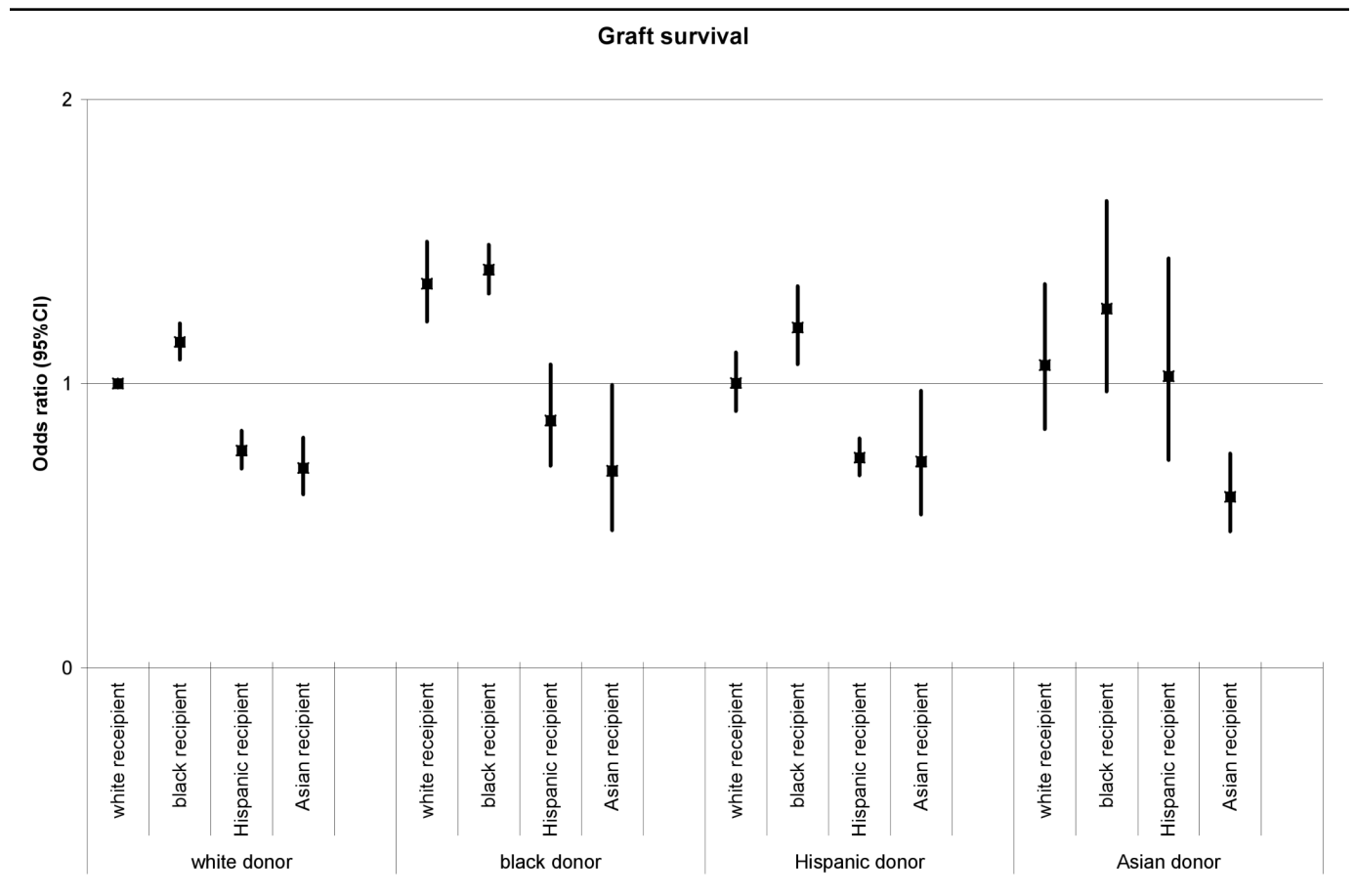


Table 4
Five (5) Year Patient Survival stratified by Recipient Confidence Limits

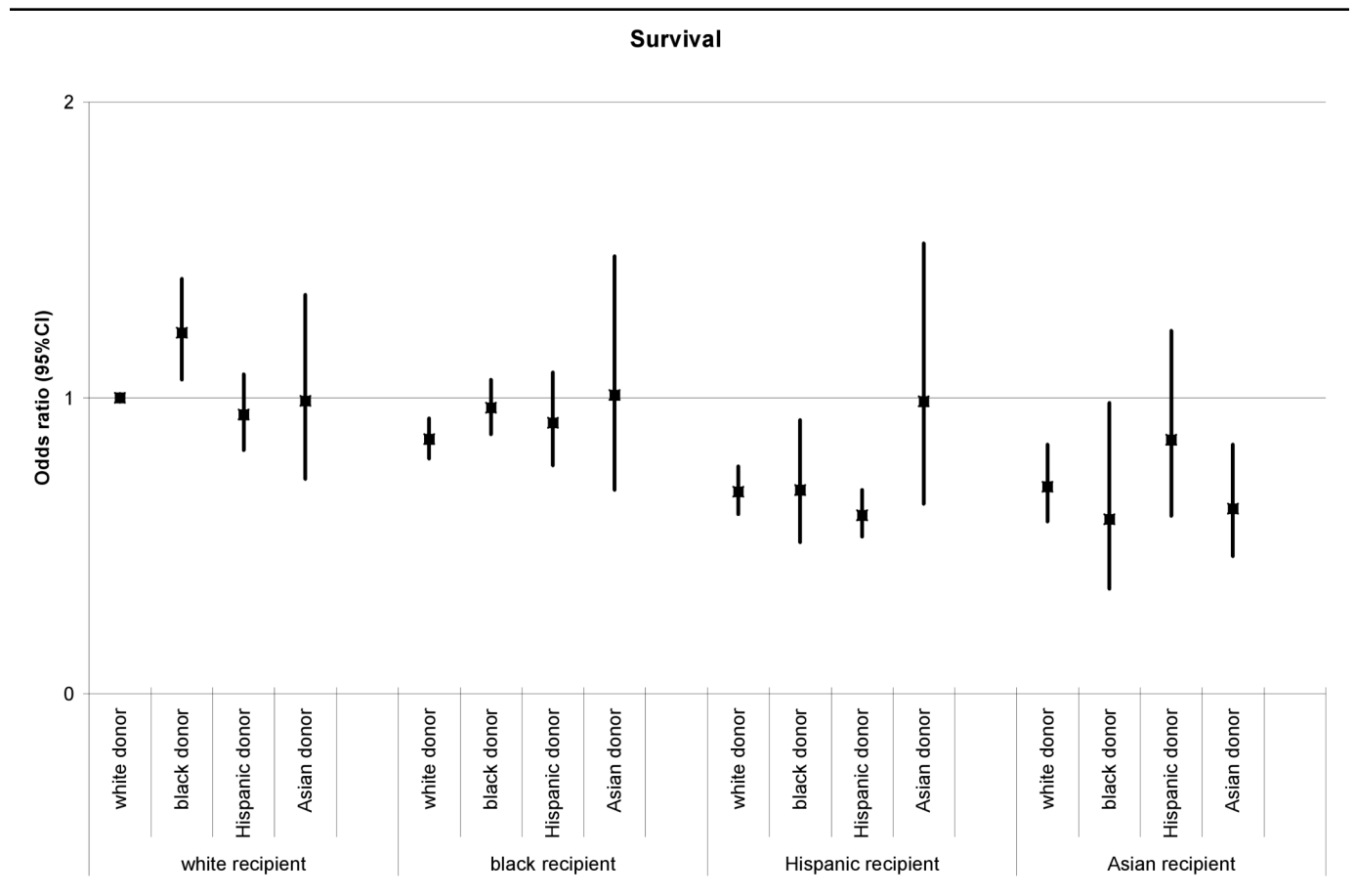


Table 5
Five (5) Year Patient Survival stratified by Donor Confidence Limits

