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Tacrolimus Trough Concentration Variability and Disparities in African American Kidney Transplantation

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Abstract

Background—Low tacrolimus concentrations have been associated with higher risk of acute rejection, particularly within African-American (AA) kidney transplant recipients; little is known about inpatient tacrolimus variability impact on racial disparities.

Methods—Ten year, single-center, longitudinal cohort study of kidney recipients. Inpatient tacrolimus variability was assessed using the coefficient of variation (CV) measured between 1 month posttransplant and the clinical event, with a comparable period assessed in those without

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DJT: hypothesis, study design, data acquisition, data analysis, manuscript writing

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MAPS: hypothesis, manuscript editing and resubmission editing

FAT: hypothesis, study design, manuscript editing

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DISCLOSURES

The authors declare no conflicts of interest.

events. Pediatrics, nontacrolimus/mycophenolate regimens and nonrenal transplants were excluded. Multivariable Cox regression models were used to analyze data.

Results—1411 recipients were included (54.4% AA) with 39 521 concentrations utilized to assess inpatient tacrolimus CV. Overall, inpatient tacrolimus CV was higher in AAs vs non-AAs ($39.9 \pm 19.8\%$ vs. $34.8 \pm 15.8\%$ $p < 0.001$). Tacrolimus variability was a significant risk factor for deleterious clinical outcomes. A 10% increase in tacrolimus CV augmented the risk of acute rejection by 20% (aHR 1.20, 1.13–1.28; $p < 0.001$) and the risk of graft loss by 30% (aHR 1.30, 1.23–1.37; $p < 0.001$), with significant effect modification by race for acute rejection, but not graft loss. High tacrolimus variability (CV $> 40\%$) was a significant explanatory variable for disparities in AAs; the crude relative risk of acute rejection in AAs was reduced by 46% when including tacrolimus variability in modeling and reduced by 40% for graft loss.

Conclusions—These data demonstrate that inpatient tacrolimus variability is strongly associated with acute rejection in AAs and graft loss in all patients. Tacrolimus variability is a significant explanatory variable for disparities in AA recipients.

INTRODUCTION

In contemporary kidney transplantation, tacrolimus is considered the cornerstone of maintenance immunosuppression therapy.¹ There is robust evidence to demonstrate that tacrolimus-based regimens reduce the risk of acute rejection and graft loss, particularly in high immunologic risk recipients.^{2–5} Recent U.S. data demonstrates that nearly 95% of all kidney transplants performed in 2015 were discharged on tacrolimus.⁶ Yet, this agent has significant limitations, most notably its side effect and pharmacokinetic profiles. Tacrolimus is associated with deleterious adverse drug reactions, including neurotoxicity, metabolic sequelae and nephrotoxicity, while also demonstrating substantial inter- and inpatient variability with regards to dosing, clearance and 12-hour trough concentrations.⁷ Tacrolimus is metabolized primarily via the cytochrome P450 3A4/5 isoenzyme system (CYP 3A4/5) and because of this is prone to drug-drug interactions and variation due to genetic polymorphisms.^{7, 8} There are a number of studies demonstrating that high inpatient tacrolimus variability is associated with increased risk of acute rejection, graft dysfunction and graft loss.^{9–16}

African-Americans (AAs) represent a high-risk group of kidney recipients, as historic and recent data clearly demonstrate higher rates of acute rejection and graft loss following transplant.^{17–20} There have been numerous studies elucidating the explanatory factors associated with this disparity, including biologic differences (immunologic risk and gene polymorphisms) and socioeconomic disadvantages.^{21–26} AAs are substantially more likely to express the CYP 3A5 *1 polymorphism, which is linked to increased tacrolimus clearance and variability.^{8, 27–29} We recently conducted an analysis demonstrating that early posttransplant mean 12-hour tacrolimus trough concentrations are significantly lower in AA kidney transplant recipients, as compared to non-AAs, and this was associated with higher rates of acute rejection.³⁰ Yet, there is paucity in the data examining the impact of tacrolimus trough variability on racial disparities in transplantation. Thus, the primary aim of this study was to determine if inpatient tacrolimus trough variability significantly differs

by race; with the secondary objective of assessing the impact tacrolimus trough variability has on racial disparities in kidney transplantation.

MATERIALS AND METHODS

Study design and patients

This was an IRB-approved single-center retrospective cohort study of adult kidney transplant recipients utilizing detailed baseline and follow up data acquired through interrogation of the electronic health record (EHR) linked to center specific data (Standard Transplant Analysis Files [STAR]) supplied by the United Network of Organ Sharing (UNOS). Patients were included if they received a kidney transplant between July 1, 2005 and July 31, 2015. This starting date was chosen because our center began using tacrolimus as first line therapy in July 2005. We ended the study in July 2015 to allow for at least 1 year of posttransplant data to accrue, as the study follow up period ended on August 31, 2016. Pediatrics (<18 years of age), those receiving nonrenal transplants, those not receiving de novo tacrolimus/mycophenolate based regimens and those without sufficient tacrolimus concentrations to assess variability were excluded from the study (See Supplemental Figure 1 for the Consort diagram).

Study definitions

The primary exposure variable of interest was inpatient tacrolimus variability, which was defined as the patient-specific mean coefficient of variation ($\%CV = [\sigma/\mu]*100$) assessed during specific follow up periods based on the outcome of interest. First, all tacrolimus concentrations were electronically captured from the EHR (n=69 652); this included levels drawn at the transplant center, those drawn at outside laboratories that automatically populate our EHR and levels that were manually entered our EHR system by data coordinators. All whole blood tacrolimus 12-hour trough concentrations were measured using liquid chromatography–mass spectrometry (LC-MS). Concentrations that were below detectable limits were included and classified as 0 ng/mL, while those above 30 ng/mL or those drawn after 11:00 AM were excluded as these are were not likely to be true 12-hour trough concentrations. The exposure period to assess tacrolimus variability depended on the outcome. All patients received mycophenolate and prednisone adjunct immunosuppression and all patients were on immediate release (IR) tacrolimus. Mycophenolate doses were started at 1000 mg PO BID and prednisone was 20 mg PO daily at discharge, tapered to 5mg PO daily by 6 weeks posttransplant. For acute rejection, in those that had an event, all levels that occurred between month 1 posttransplant to the day prior to the rejection were included. Concentrations measured after the event were excluded. In those without rejection, concentrations measured between posttransplant month 1 and up to 387 days posttransplant, which was the mean time to rejection, were included. In this regard, we minimized the potential of the nonrejection group from having a longer exposure period for tacrolimus variability and limited follow up bias by exposure group. For the outcome of graft loss, a similar methodology was used. We excluded concentrations in the first month posttransplant, as variability during this period may reflect perioperative issues unrelated to patient behaviors/factors; however, for completeness, we did conduct sensitivity analyses which included this period. After assessment of the distribution of %CV across the study

population and the %CV-risk response curve, a cut point of >40% was set to define high tacrolimus variability. We also conducted 4 exposure sensitivity analyses, by varying the tacrolimus variability time periods (posttransplant day 0 to clinical event, posttransplant 1 month to 1 year or clinical event, 3 months posttransplant to 1 year or clinical event and 3 months posttransplant to clinical event). We also conducted sensitivity analyses by assessing outcomes based on CVs between 20 and 60%.

Race was the secondary variable of interest, defined as self-reported AA or non-AA. Our center has very few Asians and Hispanics; thus, the clear majority of non-AA recipients were Caucasian. Additional variables assessed for this analysis included recipient demographics (age, sex, weight, comorbidities, previous transplant, time on dialysis), donor information (age, sex, race, type), transplant characteristics (PRA, HLA mismatches, cold ischemic time), immunosuppression (induction and maintenance therapy) and the number of tacrolimus concentrations in each patient assessed for the tacrolimus CV estimate.

Outcomes

Acute rejection and graft loss were the outcomes of interest, assessed using time to event methodology. Acute rejection was defined as biopsy proven and treated, based on Banff criteria (severity 1A).³⁰ The date of rejection was set as the date of biopsy. Secondary rejection assessments included late acute rejection (after 1 year posttransplant), severe rejection (Banff classification of 2A, 2B, 3 or AMR) and antibody-mediated rejection ([AMR]).³⁰ Graft loss was defined as return to chronic dialysis or retransplantation, based on EHR data supplemented with UNOS STAR files. For the purposes of this study, death was not considered as graft loss, but was accounted for using a competing risk model.

Statistical Analysis

Summary descriptive statistics were utilized based on the data type; means $\pm$ standard deviation (SD) for continuous normally distributed data, medians with interquartile ranges (IQR) for ordinal and abnormally distributed continuous data and percentages for categorical data. Two-sided univariate comparisons were conducted using the independent t test, Mann Whitney U test or Chi square test as appropriate, based on data type and distribution. Prior to modeling, all variables were assessed for distribution of data and multicollinearity. Cox regression was utilized for time to event analyses, with a Fine and Gray competing risk model used to estimate the cumulative incidence function for the outcome of graft loss.³¹ A marginal model was used to provide robust adjusted estimates after accounting for clustering by duplicate patients (retransplants). Sequential modeling was conducted, comparing hazard ratios (HR) and adjusted hazard ratios (aHR) in AAs between nested models to assess the influence of covariates on racial disparities. Multivariable logistic regression was used to determine which baseline factors were predictive of high tacrolimus variability (CV >40%). Multiple sensitivity analyses were also conducted, by varying the tacrolimus exposure period, definitions of high variability and rejection definition to assess for the robustness of estimates. SAS version 9.4 (SAS Institute, Cary, NC) was utilized for all analyses.

RESULTS

A total of 1891 kidney transplants occurred during the study period; of these, 93 (4.9%) were excluded for age <18 years, 208 (11.0%) were excluded for receiving nonrenal transplants, 79 (4.2%) were excluded for not receiving tacrolimus and mycophenolate-based immunosuppression and 100 (5.3%) were excluded for insufficient data to assess tacrolimus variability, leaving 1411 (74.6%) in the final study cohort. There were 643 (45.6%) non-AAs and 768 (54.4%) AAs in the analysis (see Supplemental Figure 1 for the Consort diagram). Median follow-up time was 4.6 years (IQR 2.4, 7.1) for the entire cohort, which did not significantly differ by race (non-AA 4.7 years [IQR 2.6, 7.2] vs. AA 4.5 years [IQR 2.3, 6.9]; $p=0.180$). Table 1 displays the baseline characteristics of the study cohort, stratified by race. There were substantial differences between the groups with regards to age, weight, ESRD diagnoses, time on dialysis, previous transplantation, donor characteristics (age, sex, race, living donor) immunologic risks (HLA mismatches, PRA, cold ischemic time, DGF) and induction therapy. In general, the AA cohort was at higher risk for deleterious outcomes based on baseline characteristics.

A total of 39 521 tacrolimus trough concentrations were utilized in the clinical pharmacokinetic analysis to assess variability associated with graft loss and 23 658 trough concentrations were used to assess variability associated with acute rejection (1 month posttransplant to event). There were significant differences in tacrolimus trough concentrations and tacrolimus variability by race. The mean tacrolimus trough concentration was 8.5 ± 1.3 ng/mL in non-AAs vs. 8.1 ± 1.3 ng/mL in AAs ($p<0.001$), with the CV being 39.9 ± 19.8 % in AAs and vs. 34.8 ± 15.8 % in non-AAs ($p<0.001$). Overall, tacrolimus variability was a significant risk factor for deleterious clinical outcomes. A 10% increase in the CV of tacrolimus concentrations increased the adjusted risk of acute rejection by 20% (aHR 1.20, 1.13–1.28; $p<0.001$); a 10% increase in tacrolimus CV also increased the adjusted risk of graft loss by 30% (aHR 1.30, 1.23–1.37; $p<0.001$). Supplemental Figures 2 and 3 display the fully adjusted estimated acute rejection free survival and estimated cumulative incidence of graft loss, comparing those with tacrolimus CV 40% vs. >40%, respectively.

Figure 1 displays the tacrolimus variability (%CV) between AAs and non-AAs for the outcomes of acute rejection and graft loss. The %CV was significantly higher in AAs with acute rejection, as compared to AAs that did not develop rejection (42 ± 24 % vs. 33 ± 17 %; $p<0.001$); which was not apparent in non-AAs (32 ± 15 % vs. 31 ± 15 %; $p=0.501$). However, both AAs (50 ± 25 % vs. 36 ± 16 %; $p<0.001$) and non-AAs (41 ± 18 % vs. 33 ± 15 %; $p<0.001$) with graft loss had significantly higher tacrolimus variability. There were several baseline factors that were predictive of high tacrolimus variability, as displayed in Table 2; this included AAs, which had 44% higher odds of having high tacrolimus variability (aOR 1.44, 95% CI 1.12–1.86; $p=0.004$). Other baseline risk factors associated with high tacrolimus variability included hypertension, diabetes, years on dialysis, AA donor, deceased donor, and donor age. Supplemental Table 1 displays the sensitivity analysis by varying tacrolimus exposure time periods and assessing graft loss, acute rejection and clinical outcomes, with late rejection, severe rejection and AMR as supplemental outcomes. The results were consistent with the primary analysis, as AAs had significant differences in tacrolimus CV for

acute rejection (overall, late and severe, but not AMR) and graft loss, while both AAs and non-AAs demonstrated differences for graft loss across all tacrolimus variability exposure time periods.

High tacrolimus variability (CV >40%) was a significant explanatory variable for posttransplant outcome disparities in AAs, as depicted in Figure 2. In sequential modeling, the relative risk of acute rejection in AAs (HR 1.68, $p<0.001$; Figure 2A) was reduced by 46% by solely including tacrolimus variability (aHR 1.37, $p=0.067$; Figure 2B). In the fully adjusted model, which included baseline characteristics as well as tacrolimus variability, the relative risk of acute rejection in AAs was 72% lower (aHR 1.19, $p=0.417$; Figure 2C), as compared to the crude risk in AAs. For graft loss, the influence of high tacrolimus variability on racial disparities was equally pronounced. The crude risk of graft loss was 42% higher in AAs, as compared to non-AAs (HR 1.42, $p=0.015$; Figure 2D). Adding tacrolimus variability into the model attenuated the relative risk by 40% (aHR 1.25, $p=0.138$; Figure 2E). Fully adjusting the model by including baseline characteristics led to similar risks in AAs, as compared to non-AAs (aHR 0.95, $p=0.770$; Figure 2F). Iterative modeling demonstrated that tacrolimus variability was a strong explanatory variable for racial disparities, which was robust across varied entry into the models. The addition of tacrolimus CV reduced the relative risk of AA race on graft loss by 19 to 40% and the relative risk of AA race on acute rejection by 13 to 46%, depending on entry into the modeling. Table 3 displays granular results of sequential modeling, demonstrating that for acute rejection disparities, significant explanatory variables beyond tacrolimus CV included demographics and immunologic risks. For graft loss, significant explanatory variables for racial disparities beyond tacrolimus CV included demographics and comorbidities. Supplemental Table 2 displays the sensitivity analysis for sequential modeling; regardless of the tacrolimus CV exposure period definition, it is consistently a significant explanatory variable for racial disparities for both acute rejection and graft loss; tacrolimus CV reduces the relative impact of AA race on acute rejection by 22 to 31% and by 12 to 43% for graft loss. The 1 exception is when tacrolimus CV was confined between 1 month and 1 year posttransplant, as this did not impact the influence of race on graft loss (HR 1.42 vs. aHR 1.42). These sensitivity analyses demonstrate that tacrolimus CV definitions that included concentrations after 1 year posttransplant tended to attenuate racial disparities to a larger degree.

DISCUSSION

The results of this study demonstrate that high tacrolimus trough concentration variability is significantly associated with increased risk of graft loss in both AAs and non-AAs; with high tacrolimus trough variability being associated with acute rejection, late rejection and severe rejection only in AAs. Further, these findings demonstrate that tacrolimus trough concentration variability has a significant impact on racial disparities, attenuating the relative risk of acute rejection in AAs up to 46% and the relative risk of graft loss in AAs up to 40%. This is the first study we are aware of that comprehensively assessed the impact of tacrolimus trough variability on racial disparities in kidney transplantation.

There are several recent studies demonstrating that increased tacrolimus trough variability is a significant risk factor for deleterious posttransplant outcomes. Sapir-Pichhadze et al, conducted a study in 356 renal transplant recipients, demonstrating that a 1 unit change in tacrolimus trough standard deviation increased the risk of a composite of acute rejection, glomerulopathy or graft loss by 27% (aHR 1.27, 1.03–1.56). This study did several sensitivity analyses and assessed the time-varying impact of tacrolimus to provide robust estimates. However, the authors did not report the number of patients of African descent and did not assess the influence of race on this association.¹² O'Regan et al, published a study in 2016 conducted in 394 kidney transplant recipients, demonstrating that for each change in tacrolimus %CV quartile, the adjusted risk of graft loss increased 36% (aHR 1.36, 1.05–1.78). However, similar to the Sapir-Pichhadze analysis, race was not reported or assessed in this study.¹⁰ Another study, also published in 2016, which included 220 renal transplant recipients, demonstrated that patients with high tacrolimus variability (top tertile of %CV) had more than twice the odds of developing moderate to severe graft fibrosis and tubular atrophy at 2 years posttransplant (OR 2.47, 1.09–5.60). Like the studies described above, race was not reported or accounted for in analyses.¹⁵ Finally, Whelan et al, recently demonstrated that high tacrolimus inpatient variability significantly increased the risk of acute rejection, reduced estimated glomerular filtration rates (GFRs) and increased graft loss in 366 renal transplant recipients receiving a low-exposure tacrolimus regimen. However, only 18 patients were nonwhite.¹⁶ Based on the country of origin these studies were conducted, there were likely few if any patients of African descent in these analyses. There are several other studies also demonstrating that high tacrolimus variability, measured either by standard deviation or %CV, increases the risk of acute rejection and poor graft outcomes.^{9, 11, 13} However, none of these studies assessed the impact of tacrolimus variability on racial disparities. Thus, the results of our investigation are confirmatory with regards to the impact of tacrolimus variability on posttransplant outcomes in the overall population and are novel with regards to its impact on disparities for AAs.

There are several potential reasons why tacrolimus trough concentration variability is significantly higher in AAs, as compared to non-AAs. Two likely explanations for this are related to known differences in the prevalence of CYP 3A5 gene polymorphisms and medication adherence across AA and non-AA populations. Up to 85% of AAs express the CYP 3A5 *1 functional allele, resulting in substantially enhanced metabolic capacity for numerous drugs, including tacrolimus; non-AAs express this allele at a much lower rate (~25%).^{8, 27} The impact of CYP 3A5 on tacrolimus variability is not fully elucidated, with both positive and negative associations in the literature.^{11, 33–35} However, given the limitations of these studies, including small sample-size and limited information on race, the true impact of CYP 3A5 polymorphisms of tacrolimus trough variability has yet to be determined.¹³ It is important to note that we did not assess the correlation between CYP 3A5 genotype, tacrolimus variability and outcomes in this study; thus, future studies assessing genotype and its impact on tacrolimus variability and clinical outcomes, particularly within AA recipients, are needed. There is recent evidence that the use of computer generated algorithms, with or without the use of CYP 3A5 genotyping, can improve early tacrolimus dosing accuracy and potentially, reduce variability and improve outcomes.^{36, 37} With regards to medication adherence, we and others have demonstrated that AA kidney transplant

recipients are at increased risk of medication nonadherence posttransplant and this is likely to be a strong correlate with tacrolimus variability.^{12, 13, 22, 38, 39}

The finding that high tacrolimus trough variability is an important mediator for racial disparities is intriguing, and may be related to the known higher immunologic risk profile in AA transplant recipients. Studies demonstrate AAs possess differences related to T cell subtypes, immune reactivity to antigens, polymorphisms in HLA and cytokine production that clearly increase immunogenicity.²⁶ As AAs are considered high immunologic risk, they are likely more susceptible to deleterious outcomes associated with immunosuppression modifications and variability; thus potentially explaining this phenomena of high tacrolimus variability as a mediator of disparate outcomes in AAs.^{32, 40–45}

The implications of these findings suggest that reducing tacrolimus trough concentration variability may help mitigate racial disparities in posttransplant outcomes. There are several methods to realistically achieve this. Prospective genotyping for CYP 3A5 prior to transplant may inform clinicians and improve the accuracy of early tacrolimus dosing, leading to reduced variability.^{8, 37} Unfortunately, 2 randomized controlled trials (RCTs) failed to demonstrate improvements in outcomes with CYP 3A5 genotype-guided dosing of tacrolimus. However, there were a number of limitations to these studies; most importantly the low frequency of the *1 functional allele due to low numbers of patients of African descent in these trials (both conducted in Europe).^{46–48} Thus, a prospective study assessing genotype-directed tacrolimus dosing in an AA kidney transplant population is still warranted. Another potential method to reduce tacrolimus variability in AAs is to improve medication adherence. We and others have demonstrated that the use of mobile health technology may significantly improve medication adherence and outcomes in transplantation.^{49–51} There are ongoing prospective RCTs to further assess this intervention as a promising mechanism to improve graft survival and potentially reduce racial disparities. Finally, the introduction of once daily extended release formulations of tacrolimus has provided intriguing data demonstrating reduced tacrolimus trough variability, particularly within AA recipients.^{52, 53} Clearly, these interventions require further scrutiny through RCTs. It is likely that a multimodal patient-centered approach to this issue will be needed to truly impact disparities, as 1 intervention is unlikely to be effective in all patients.²¹

There are several limitations to this study worthy of discussion. The most important limitation of this study is that we did not capture, assess or account for the impact of adjunct maintenance immunosuppression on outcomes, including mycophenolate doses, prednisone doses and conversions to other agents (sirolimus, everolimus, belatacept). As these factors likely impact outcomes and may differ by race, there is potential for unmeasured confounding in this regard. Another limitation is that we defined our tacrolimus variability exposure period starting at 1-month posttransplant; whereas previous studies utilized levels drawn after several months posttransplant to assess for variability. This is likely the reason our study has relatively high variability in relation to previous analyses.^{9, 10, 12} We did conduct several sensitivity analyses and found that tacrolimus variability was a robust risk factor for deleterious outcomes and explanatory variable for racial disparities. We also were not able to assess tacrolimus dose or manufacturer in this analysis, due to the nature of the electronic data extraction; however, all patients were on BID IR tacrolimus. Another

limitation related to the retrospective nature of the data is the inability to assess for true 12-hour trough values. We attempted to mitigate this issue by excluding levels that were clearly not true troughs based on results and time of lab draw. Another limitation was that tacrolimus concentrations obtained during hospitalization were also included in this analysis and we used a 10-year cohort and the study time period was long in relation to other studies.^{13–16} While this increased the sample-size, follow-up time and power of the analysis, it also meant that clinical care changed during the study period. This includes measurement of risk factors, including PRA, and donor marginality. Thus, our study results may be somewhat prone to residual or unmeasured confounding. We assessed for this through conducting sensitivity analyses, using a multitude of iterative sequential models and determined that our estimates were robust across these models. We also assessed for correlation by transplant vintage using a marginal Cox model and found the estimates to be of similar magnitude.

In conclusion, these results demonstrate that tacrolimus trough concentration variability is a significant mediator of racial disparities in AA kidney transplant recipients and future studies should focus on developing and implementing interventions designed to reduce this high variability seen in AAs, with hopes of improving disparate outcomes in this high-risk patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

AA	African-American
aHR	Adjusted Hazard ratio
AMR	Antibody-mediated rejection
aOR	Adjusted odds ratio
CV	Coefficient of variation
CYP	Cytochrome P450
DGF	Delayed graft function
EHR	Electronic health record

ESRD	End stage renal disease
GFR	Glomerular filtration rate
HLA	Human leukocyte antigen
HR	Hazard ratio
IL2-RA	Interleukin-2 receptor antibody
IQR	Interquartile range
IR	Immediate release
LC-MS	Liquid chromatography–mass spectrometry
μ	mean
OR	Odds ratio
PRA	Panel reactive antibody
σ	standard deviation
STAR	Standard transplant analysis files
UNOS	United network of organ sharing;

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Figure 1. Boxplots of tacrolimus variability (%CV), stratified by race and outcome (top: acute rejection; bottom: graft loss).

Figure 2.

Estimated rejection-free survival (2A, 2B and 2C) and cumulative incidence of graft loss (2D, 2E and 2F) compared between non-AAs and AAs in iterative models. Models 2A and 2D are unadjusted (crude risk), models 2B and 2E are adjusted for tacrolimus variability (CV >40%) and models 2C and 2F are fully adjusted.

*Adjusted for tacrolimus variability (CV >40%) and number of tacrolimus concentrations

^Adjusted for tacrolimus variability, number of tacrolimus concentrations, age, sex, weight, ESRD diagnosis, diabetes, time on dialysis, previous transplant, current PRA, HLA

mismatches, cold ischemic time, living donor, donor sex, donor race, induction therapy and delayed graft function

Table 1

Baseline recipient demographics, donor information, transplant characteristics and outcomes stratified and compared by race.

Characteristic	NonAfrican American (n=643)	African American (n=768)	p value
Mean Age (years±SD)	53.0±14.0	50.7±13.2	0.002
Female Sex	37.6%	40.9%	0.214
Mean Weight (kg±SD)	83.4±19.7	86.3±18.6	0.005
Primary diagnosis for ESRD			
Hypertension	20.7%	39.1%	<0.001
Diabetes	19.8%	29.7%	<0.001
Glomerular Disease	18.8%	13.0%	0.003
History of diabetes	27.1%	38.7%	<0.001
Dialysis prior to transplant	71.7%	92.2%	<0.001
Mean Time on Dialysis (years±SD)	1.9±2.0	3.8±2.9	<0.001
Previous Kidney Transplant	9.6%	5.1%	<0.001
Donor Mean Age (years±SD)	38.7±15.0	35.7±15.8	<0.001
Donor Female Sex	46.5%	39.3%	0.007
Donor African-American	14.9%	34.8%	<0.001
Living Donor	25.5%	7.2%	<0.001
Median HLA Mismatches (IQR)	4 (3, 5)	5 (4, 5)	<0.001
Median current PRA (% , IQR)	0 (0, 28)	0 (0, 37)	0.011
Current PRA >20%	28.7%	34.8%	0.017
Mean cold ischemic time (hrs±SD)	17.3±12.0	18.6±9.4	0.029
Induction Therapy			
IL-2 RA Induction	62.3%	56.7%	0.035
Cytolytic Induction	37.4%	42.0%	0.082
Delayed Graft Function	8.9%	17.1%	<0.001
Overall Acute Rejection	10.0%	15.8%	0.001
Late Acute Rejection	3.1%	5.7%	0.002
Severe Acute Rejection	3.1%	6.3%	0.006
Antibody-Mediated Rejection	0.5%	0.9%	0.321
Estimated Graft Loss			0.015

Characteristic	NonAfrican American (n=643)	African American (n=768)	p value
1 Year	2.4%	3.6%	
3 Year	5.9%	8.6%	
5 Year	10.8%	15.4%	

Table 2

Factors associated with increased tacrolimus trough variability.

Characteristic	Tacrolimus CV 40% (n=878)	Tacrolimus CV >40% (n=533)	p value
African American	49.8%	62.1%	<0.001
Hypertension	28.8%	33.8%	0.050
Diabetes	31.4%	37.8%	0.047
Dialysis prior to transplant	81.6%	85.0%	0.096
Mean Time on Dialysis (years±SD)	2.6±2.5	3.2±3.0	0.001
Donor African-American	23.5 %	29.5%	0.013
Living Donor	17.3 %	12.6%	0.017
Donor Age (years±SD)	36.3±15.5	38.2±15.4	0.026
Overall Acute Rejection	8.5%	16.2%	<0.001
Late Acute Rejection	2.8%	10.2%	<0.001
Severe Acute Rejection	2.9%	4.3%	0.212
Antibody-Mediated Rejection	0.4%	1.1%	0.120
Estimated Incidence of Graft Loss			
1 Year	1.6%	5.5%	<0.001
3 Year	3.9%	13.0%	
5 Year	7.1%	23.0%	

Multivariable sequential models demonstrating the impact domains of variables have on racial disparities.

Table 3

Variable Domains	Acute Rejection			Graft Loss		
	HR	95% CI	p value	HR	95% CI	p value
AA Unadjusted Risk	1.68	1.25–2.26	<0.001	1.42	1.07–1.88	0.015
+Tacrolimus CV >40%	1.37	0.98–1.92	0.067	1.25	0.93–1.67	0.138
+Age, Gender, Weight	1.25	1.89–1.76	0.191	1.18	0.89–1.57	0.261
+Diagnosis, Diabetes, Dialysis Time	1.20	0.82–1.76	0.348	1.05	0.74–1.47	0.798
+Retransplant, HLA Mismatches, PRA, Cold Time	1.19	0.78–1.80	0.423	0.94	0.66–1.35	0.739
+Donor Type, Sex, Race	1.19	0.78–1.81	0.424	0.95	0.65–1.37	0.773
+Induction and DGF	1.19	0.78–1.82	0.417	0.95	0.65–1.38	0.770