

## ORIGINAL ARTICLE

# The impact of time-varying clinical surrogates on disparities in African-American kidney transplant recipients – a retrospective longitudinal cohort study

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## SUMMARY

An improved understanding of the impact of clinical surrogates on disparities in African-American (AA) kidney transplantation (KTX) is needed. We conducted a 10-year retrospective longitudinal cohort study of electronically abstracted clinical data assessing the impact of surrogates on disparities in KTX. Clinical surrogates were assessed by posttransplant year (1, 2, 3 or 4) and defined as acute rejection (Banff  $\geq 1A$ ), mean SBP  $>140$  mmHg, tacrolimus variability (CV)  $>40\%$ , mean glucose  $>160$  mg/dl and mean hemoglobin  $<10$  g/dl. We utilized landmark methodology to minimize immortal time bias and logistic and survival regression to assess outcomes; 1610 KTX were assessed (54.2% AAs), with 1000, 468, 368 and 303 included in the year 1, 2, 3 and 4 complete case analyses, respectively. AAs had significantly higher odds of developing a clinical surrogate, which increased in posttransplant years three and four [OR year 1 1.99 (1.38–2.88), year 2 1.77 (1.20–2.62), year 3 2.35 (1.49–3.71), year 4 2.85 (1.72–4.70)]. Adjusting for the five clinical surrogates in survival models explained a significant portion of the higher risks of graft loss in AAs in post-transplant years three and four. Results suggest focusing efforts on improving late clinical surrogate management within AAs may help mitigate racial disparities in KTX.

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## Key words

African-Americans, clinical outcomes, graft survival, kidney transplantation

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## Introduction

Although recent data demonstrates some improvements in racial disparities, within contemporary kidney transplantation, African-Americans (AAs) continue to experience a substantially higher rate of graft loss. Two recent studies of national US data estimate that AAs have between 30% and 37% higher risk of graft loss at

5-years posttransplant [1,2]. This disparity has been well-documented for over 40 years and the risk of graft loss in AAs starts early and continue throughout the posttransplant period [3,4]. Studies have demonstrated a number of important explanatory factors likely driving this disparity, including substantial barriers to access for evaluation, wait-listing and transplant [5], heightened immunologic risks [6], pharmacogenomic and dynamic

differences in immunosuppression [7] and reduced control of posttransplant comorbidities, particularly cardiovascular risk factors [8–10]. As this body of literature has grown in abundance, it is now clear that because the etiologies of racial disparities in transplant are complex, interventions to mitigate this disparity must be multidimensional if significant advances are to be expected.

Formative research demonstrates that improving a number of potentially mutable clinical surrogates, including acute rejection and control of comorbid conditions may reduce racial disparities [11,12]. However, research is still needed that seeks to accurately define the predominant modifiable post-transplant factors driving disparities for AAs in contemporary kidney transplantation. Further, as these disparities occur during a long posttransplant timeframe, a better understanding of the optimal timing of intervention delivery is needed [4]. Thus, the objective of this study was to utilize a large retrospective cohort of kidney transplant recipients with detailed clinical follow-up obtained through electronic medical record abstraction to identify the major modifiable clinical surrogates explaining racial disparities, while also assessing if the impact of these surrogates vary based on posttransplant year.

## Patients and methods

### Study design

This was a 10-year, single-center, retrospective, longitudinal cohort study with the primary aim of determining the impact of time-varying clinical surrogates on disparities in AAs for graft loss in adult kidney transplant recipients. The study timeframe was from January 2007 to December 2016 with clinical follow-up through December 2017. We utilized landmark analysis to define distinct exposure and outcome periods and minimize immortal time bias, as follows: For the posttransplant year 1 assessment, all patients had to have at least 1 year of follow-up without graft loss or death. For the years 2 through 4 assessments, all patients had to have at least 2, 3 and 4 years of follow-up without graft loss or death, respectively [13]. Clinical surrogates were defined based on previous research and clinical judgment and defined as acute rejection, glucose control, blood pressure control, anemia, leukopenia, neutropenia, electrolyte aberrations [magnesium (Mg) and potassium (K)] and nonrejection AKI events (defined as an acute risk in creatinine >50% not associated with acute rejection) [11,14]. All baseline and follow-up data were

abstracted from the electronic health records (EHRs) from both inpatient and outcome visits, as well as data from outside hospitals, using a previously described and validated process [15]. This study was reviewed and improved by the local Institutional Review Board (IRB) and has been conducted in accordance with the ethical standards detailed within the 2000 Declaration of Helsinki and the 2008 Declaration of Istanbul.

### Patients and immunosuppression

We considered kidney transplants occurring within the aforementioned timeframe for inclusion in the study. Pediatrics (<18 years at time of transplant), recipients of nonrenal transplants (pancreas, liver, heart or lung) and those not receiving tacrolimus-based immunosuppression were excluded. To prevent immortal time bias, patients with lack of follow-up, graft loss or death within year 1, 2, 3 and 4 were excluded from the year 1, 2, 3 and 4 analyses, respectively. To appropriately compare nested models, we excluded those with any missing clinical surrogate data in the complete case analyses. Race was defined by self-report and classified as AA (non-Hispanic Black) and non-AA (Caucasian, Hispanic, Asian, Other) and there was no missing data concerning race. Greater than 90% of the non-AA cohort was comprised of Caucasians.

During the entire study timeframe, our immunosuppressant protocol consisted of induction therapy with either an IL-2 receptor antagonist or rabbit anti-thymocyte globulin, depending on immunologic risk (PRA, re-transplant, cold ischemic time, delayed graft function). Maintenance immunosuppression consisted of tacrolimus (immediate-release), mycophenolate mofetil and prednisone. Goal 12-h trough levels of tacrolimus were between 8 and 12 ng/ml in the first year posttransplant, followed by 6–10 ng/ml thereafter. Mycophenolate mofetil was dosed at 1 g PO BID and prednisone was tapered to 5 mg PO daily by posttransplant day 45.

### Clinical surrogates

Of the nine clinical surrogates assessed for this study, preliminary analyses revealed five were associated with graft loss or appreciably influenced racial disparities; these included acute rejection, systolic blood pressure (SBP), glucose, tacrolimus variability and hemoglobin levels. The other four clinical surrogates assessed, including leukopenia/neutropenia, Mg abnormalities, K abnormalities and nonrejection AKI events were not associated with graft loss and did not influence racial

disparities. We defined acute rejection as biopsy-proven with a Banff grade of  $\geq 1A$  or higher. SBP control was defined as a mean of  $>140$  mmHg, glucose control was defined as a mean of  $>160$  mg/dl, high tacrolimus variability was defined as a mean coefficient of variation (CV)  $>40\%$  and anemia was defined as a mean hemoglobin of  $<10$  g/dl. We chose these cut points after analyses demonstrated them to have the strongest association with graft loss, while also being clinically relevant. Other cut points that were considered for this analysis included: mean SBP  $>130$ ,  $>150$ ,  $>160$ ,  $>170$  and  $>180$  mmHg, mean glucose  $>140$ ,  $>180$  and  $>200$  mg/dl and mean hemoglobin  $<11$  and  $<12$  g/dl. We abstracted data for these assessments electronically from the EHR, which included a total of 1238 kidney biopsies, 208 250 SBPs, 146 000 glucose levels, 63 353 tacrolimus levels and 79 588 hemoglobin levels [14]. We excluded all SBPs, glucose levels, tacrolimus levels and hemoglobin levels within 7 days posttransplant or those measured outside the four exposure periods (years 1, 2, 3 and 4 post-transplant). Both inpatient and outpatient data were included in mean calculations, as well as external labs drawn at outside facilities. We computed inpatient means for each patient within each exposure period (year 1, 2, 3 or 4) and each patient had to have at least two measurements within the given exposure period for an estimate to be computed.

## Outcomes

The primary outcome for this analysis was time to graft loss, defined as return to chronic dialysis or retransplantation. We accounted for death as a competing risk as detailed in the statistical analysis section. As a sensitivity analysis and because graft function likely influences SBP, glucose and hemoglobin control, time to reduced graft function was also assessed as an outcome. This was defined as time to eGFR (using 4-variable MDRD)  $<45$ ,  $<30$  and  $<15$  ml/min/m<sup>2</sup> in three separate modeling iterations. A patient had to have at least two low eGFRs were considered a low eGFR event, with the date of the second eGFR utilized in modeling.

## Statistical analysis

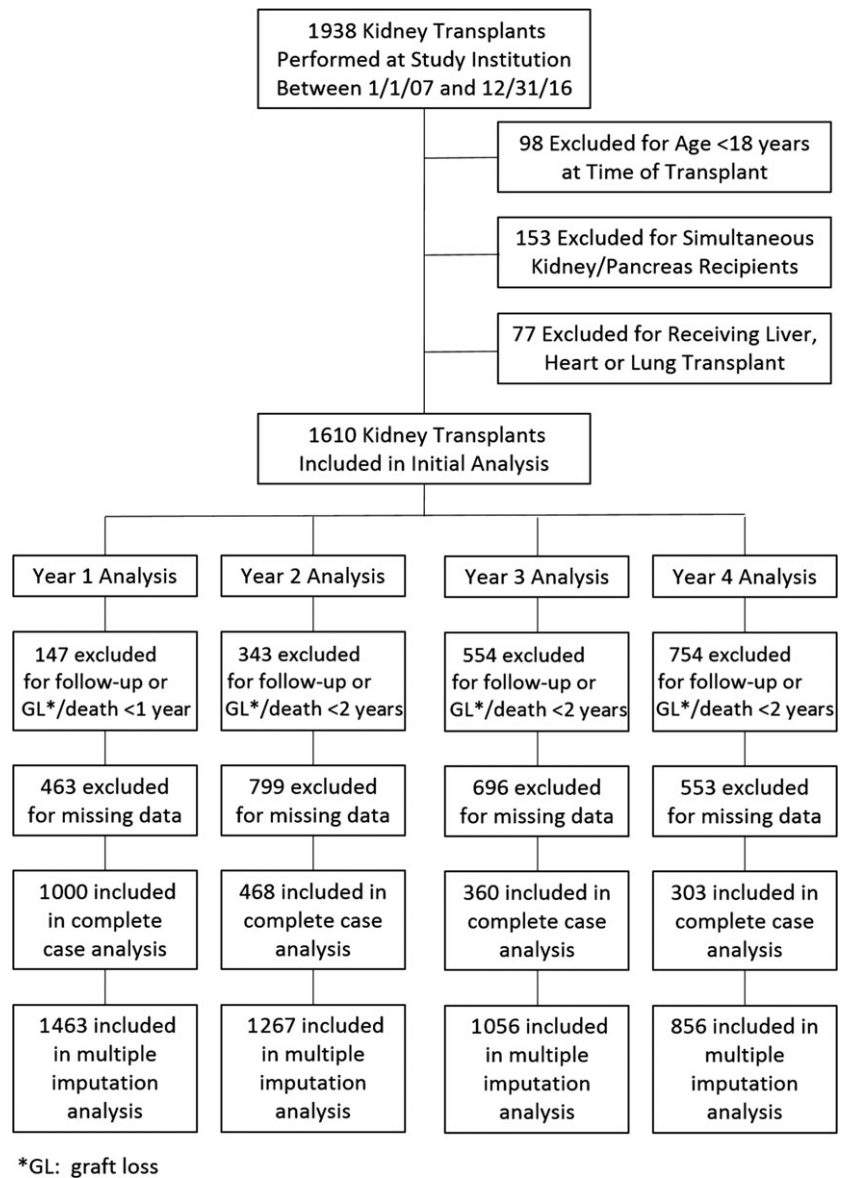
Baseline descriptive statistics utilized proportions to display results for categories, means  $\pm$  standard deviations (SD) for continuous variables and medians with interquartile ranges (IQR) for ordinal or nonnormally distributed data. We made univariate comparisons using the chi square test, Student's *t*-test or Mann Whitney *U*

test, as appropriate. Crude odds-ratios (OR) with 95% confidence intervals (95% CI) were utilized to compare clinical surrogates between non-AAAs and AAAs, stratified by posttransplant year. We utilized iterative, nested, multivariable competing risk models to assess the impact of time-varying clinical surrogates on racial disparities for graft loss (and low eGFR for the sensitivity analyses) for each of the four posttransplant exposure years. Death was accounted for as a competing risk event using Fine and Gray methodology, with results reported as subdistribution hazard ratios (SDHRs) [16]. Prior to modeling, assumptions of proportionality of the hazards and multicollinearity were assessed. To evaluate the impact of missing data, estimates from the complete case analysis were compared to results using imputed data. Multiple imputation (MI) was conducted for the four exposure cohorts using the fully conditional specification (FCS) methodology, with 20 MI datasets created for each of the four landmark cohorts [17]. A two-sided *P*-Value  $<0.05$  was considered significant. SAS 9.4 (SAS Institute, Cary, NC, USA) was utilized for all statistical analyses.

## Results

A total of 1938 kidney transplants were performed at the study institution between January 1, 2007 and December 31, 2016. Of these, 98 were excluded for age  $<18$  years, 153 were excluded for pancreas transplant and 77 were excluded for nonrenal transplants, leaving 1610 in the final study cohort. In the year 1 analysis, there were 147 excluded for graft loss, death or lack of follow-up within a year of transplant and 463 excluded for missing data, leaving 1000 transplants in the complete case analysis. For the year 2 through 4 analyses, exclusions for graft loss, death or lack of follow-up were 343, 554 and 754, and missing data were 799, 696 and 553, respectively; leaving 468, 360 and 303 in the complete case analyses for years 2, 3 and 4, respectively. The multiple imputation datasets included 1463, 1267, 1056 and 856 in the year 1, 2, 3 and 4 analyses, respectively (see Fig. 1 for the Consort flow diagram).

For the overall cohort, the mean age was roughly 52 years, with 54% being AA and 40% being female. Nearly all patients had a history of hypertension ( $>90\%$ ), with 35% having diabetes and 18% having CAD. Living donors comprised 16% of the study population, with a mean KDPI of  $48 \pm 27\%$ . At baseline, AAAs were significantly younger, had higher BMIs and were more likely to have a history of hypertension, diabetes and stroke; on average, AAAs also spent a



**Figure 1** Consort flow diagram displaying how the final cohort was created, as well as each yearly cohort within the four landmark analyses. Final cohort sizes within each posttransplant year for both the complete case and multiple imputation analyses are included as well.

significantly longer time on dialysis prior to transplant, had more HLA mismatches and were more likely to be sensitized. In terms of donor characteristics, AA were significantly less likely to receive a living donor, but more likely to receive an AA donor organ (see Table 1 for baseline characteristics of the cohort, also stratified and compared by race).

Table 2 displays the clinical surrogate event rates compared between non-AAs and AAs and stratified between the four posttransplant year assessments. During the first year post-transplant, AA were significantly more likely to have reduced BP and glucose control and had twice the odds of having at least one clinical surrogate [OR 1.99 (1.38–2.88)]. In year 2, AAs had poorer control of BP and 77% higher odds of at least one

clinical surrogate event [OR 1.77 (1.20–2.62)]. In year 3, AAs had reduced control of BP and glucose and 2.4 times the odds of at least one clinical surrogate [OR 2.35 (1.49–3.71)]; while in year 4, AAs had reduced BP control, more acute rejections, increased tacrolimus variability and nearly three times the odds of at least one clinical surrogate event [OR 2.85 (1.72–4.70)].

The influence of the yearly clinical surrogate assessment on disparities in AAs for graft loss are represented in Table 3 and Fig. 2. Within the first year surrogate cohort, AAs had 56% higher crude risk of graft loss [SDHR 1.56 (1.09–2.23), first model in Table 3 and the top left side of Fig. 2]. Adjusting for the five clinical event surrogates (rejection, high glucose, high SBP, high tacrolimus CV and low hemoglobin) did not

**Table 1.** Baseline characteristics compared between non-AA and AA recipients.

Variable	Overall cohort (N = 1610)	Non-AA (N = 736)	AA (N = 874)	P-value Non-AA vs AA
Age (mean ± SD)	51.7 ± 13.9	52.8 ± 14.3	50.8 ± 13.4	0.004*
AA	54.3%	NA	NA	NA
Female	39.7%	37.1%	41.9%	0.051†
BMI (mean ± SD)	28.5 ± 6.4	27.8 ± 6.3	29.1 ± 6.4	<0.001*
History of hypertension	94.6%	92.1%	96.7%	<0.001†
History of diabetes	35.4%	30.4%	39.6%	<0.001†
History of CAD	17.6%	17.8%	17.4%	0.831†
History of stroke	6.3%	4.2%	8.1%	0.001†
Previous transplant	8.9%	11.4%	6.9%	0.001†
Years on dialysis (mean ± SD)	2.9 ± 2.8	1.8 ± 2.0	3.9 ± 3.0	<0.001*
HLA mismatches, median (IQR)	4 (3.5)	4 (3.5)	5 (4.5)	<0.001‡
Current cPRA, median (IQR)	0 (0.11)	0 (0.0)	0 (0.25)	<0.001‡
Cold ischemic time (mean ± SD)	16.4 ± 9.6	14.8 ± 10.5	17.8 ± 8.5	<0.001*
Living donor	16.8%	26.9%	6.4%	<0.001†
Donor age (mean ± SD)	37.0 ± 15.7	38.4 ± 15.4	35.8 ± 15.9	0.001*
Donor AA	26.7%	16.1%	35.6%	<0.001†
Donor female	14.6%	46.3%	37.6%	0.001†
KDPI (mean ± SD)	48.4 ± 26.9	47.8 ± 27.2	48.7 ± 26.8	0.518*
Cytolytic induction	40.5%	37.9%	42.7%	0.050

\*Student's *t*-test.

†Chi square test.

‡Mann Whitney *U* test.

appreciably change this risk [aSDHR 1.54 (1.107–2.22), second model in Table 3 and top right side of Fig. 2]. In the second year cohort, AAs had 78% higher crude risk of graft loss [SDHR 1.78 (0.92–3.44), third model in Table 3 and left side second down in Fig. 2]. Accounting for the five aforementioned clinical surrogates reduced this risk to 56% [aSDHR 1.56 (0.79–3.07), fourth model in Table 3 and right side second down in Fig. 2]. For the third posttransplant year, the unadjusted risk of graft loss in AAs was 50% higher than non-AAs [SDHR 1.50 (0.66–3.40), fifth model in Table 3 and left side third down in Fig. 2]. Accounting for clinical surrogates, the risk in AAs was reduced to 8% [aSDHR 1.08 (0.46–2.53), six model in Table 3 and right side third down in Fig. 2]. Finally, in the fourth year post-transplant, AAs had 2.5 times the risk of graft loss [SDHR 2.52 (1.04–6.11), seventh model in Table 3 and bottom left in Fig. 2]; after adjusting for clinical surrogates occurring in the fourth posttransplant year, this was reduced to 80% higher risk of graft loss [aSDHR 1.80 (0.73–4.46), eight model in Table 3 and bottom right in Fig. 2].

The sensitivity analyses are displayed in Table S1 (outcomes for time to low eGFRs) and Tables S2 and S3 (missing data rates and imputed data results versus

the complete case data results, respectively). Estimates from the primary analyses were mainly consistent with the sensitivity analyses; qualitatively, the impact of rejection, SBP, glucoses, tacrolimus CV and anemia on disparities in AAs for the outcome of low eGFR were more pronounced during years 3 and 4 vs. years 2 and 3. Missing data was common in years 3 and 4, particularly tacrolimus variability assessments (Table S2). However, missing data did not appear to appreciably bias the complete case estimates, as the results were consistent in that the impact of clinical surrogates on risk of graft loss within AAs was qualitatively more pronounced during years 3 and 4 (Table S3).

## Discussion

Post-transplant, AAs continue to experience a disproportionately higher rate of graft loss; a disparity that is driven by a complex array of factors [1,2]. Because of this, interventions aimed at significantly reducing post-transplant disparities must be multifaceted if they are likely to be successful. The results of this analysis provide clinically relevant and novel information to demonstrate that focusing on reducing late posttransplant acute rejection and improving late blood pressure



**Table 2.** Clinical surrogates compared between non-AA and AA recipients occurring during the first 4 years posttransplant for each of the four respective landmark analyses.

Posttransplant clinical surrogates	Non-AA (%)	AA (%)	Odds-ratio (95% CI)	P-value*
Year one	<i>n</i> = 413	<i>n</i> = 587		
Acute rejection	5.8	5.6	0.97 (0.56–1.66)	0.899
Mean glucose >160 mg/dl	20.3	26.1	1.38 (1.02–1.87)	0.036
Mean SBP >140 mmHg	47.2	60.7	1.72 (1.34–2.22)	<0.001
Mean tacrolimus CV >40%	54.0	56.2	1.09 (0.85–1.41)	0.486
Mean hemoglobin <10 g/dl	22.5	27.1	1.28 (1.95–1.72)	0.101
Any of the above five outcomes	82.1	90.1	1.99 (1.38–2.88)	<0.001
Year two	<i>n</i> = 171	<i>n</i> = 297		
Acute rejection	1.2	4.0	3.56 (0.79–16.1)	0.079
Mean glucose >160 mg/dl	18.7	22.2	1.24 (0.77–1.99)	0.369
Mean SBP >140 mmHg	33.9	46.8	1.71 (1.16–2.53)	0.007
Mean tacrolimus CV >40%	21.6	29.0	1.48 (0.95–2.30)	0.083
Mean hemoglobin <10 g/dl	6.4	7.1	1.11 (0.52–2.35)	0.792
Any of the above five outcomes	57.3	68.1	1.77 (1.20–2.62)	0.004
Year three	<i>n</i> = 132	<i>n</i> = 228		
Acute rejection	1.5	2.2	1.46 (0.28–7.62)	0.654
Mean glucose >160 mg/dl	17.4	26.3	1.69 (0.99–2.90)	0.054
Mean SBP >140 mmHg	37.1	52.6	1.88 (1.21–2.92)	0.005
Mean tacrolimus CV >40%	21.2	26.8	1.35 (0.81–2.26)	0.240
Mean hemoglobin <10 g/dl	4.6	5.7	1.27 (0.47–3.42)	0.636
Any of the above five outcomes	56.1	75.0	2.35 (1.49–3.71)	<0.001
Year four	<i>n</i> = 114	<i>n</i> = 189		
Acute rejection	0.0	2.7	NA†	0.080
Mean glucose >160 mg/dl	18.4	25.9	1.55 (0.87–2.75)	0.133
Mean SBP >140 mmHg	36.0	52.9	2.00 (1.24–3.22)	0.004
Mean tacrolimus CV >40%	17.5	26.5	1.69 (0.95–3.02)	0.080
Mean hemoglobin <10 g/dl	5.3	9.0	1.78 (0.68–4.65)	0.235
Any of the above five outcomes	54.4	77.3	2.85 (1.72–4.70)	<0.001

\*All statistical comparisons were made using the chi-square test.

†There were no acute rejection events in the non-AA group during year 4 so an odds-ratio between non-AAs and AAs could not be computed.

control, glycemic control, anemia and targeting tacrolimus variability may have a meaningful impact on graft loss disparities in AA kidney transplant recipients. Further, this analysis provides details that identify objective goals for these clinical surrogates with estimates allowing for the design and testing of interventions that can be feasibly assessed in prospective clinical trials.

The impact of acute rejection on graft outcomes and racial disparities is well-established [11,18,19]. Over the past few decades, the absolute differences in acute rejection rates between AAs and non-AAs has converged [1,2]. The results presented here provides further insights into the timing of these event disparities. In contemporary kidney transplants, rejections occurring within the first year posttransplant appear to be similar between AAs and non-AAs, while rejections occurring later after transplant, although far less common, occur

at a higher rate in AAs, as compared to non-AAs. Late rejection may be a consequence of nonadherence to immunosuppression regimens, which occurs more frequent in AA recipients [10,20,21]. Interventions aimed at improving late medication nonadherence may reduce late rejections, potentially leading to less disparities for graft loss in AAs.

Optimizing blood pressure and glucose control has been well studied and demonstrated to improve outcomes, including mortality, cardiovascular events and renal disease within the general population [22,23]. Racial disparities in obtaining control of these cardiovascular risk factors within non-transplant are also documented [24,25]. Studies within the kidney transplant population are limited, but our research group has demonstrated a significant impact of cardiovascular risk factor control on racial disparities within a large

**Table 3.** Unadjusted and adjusted Fine-Gray models assessing risk of graft loss in AAs during the first 4 years post-transplant\*

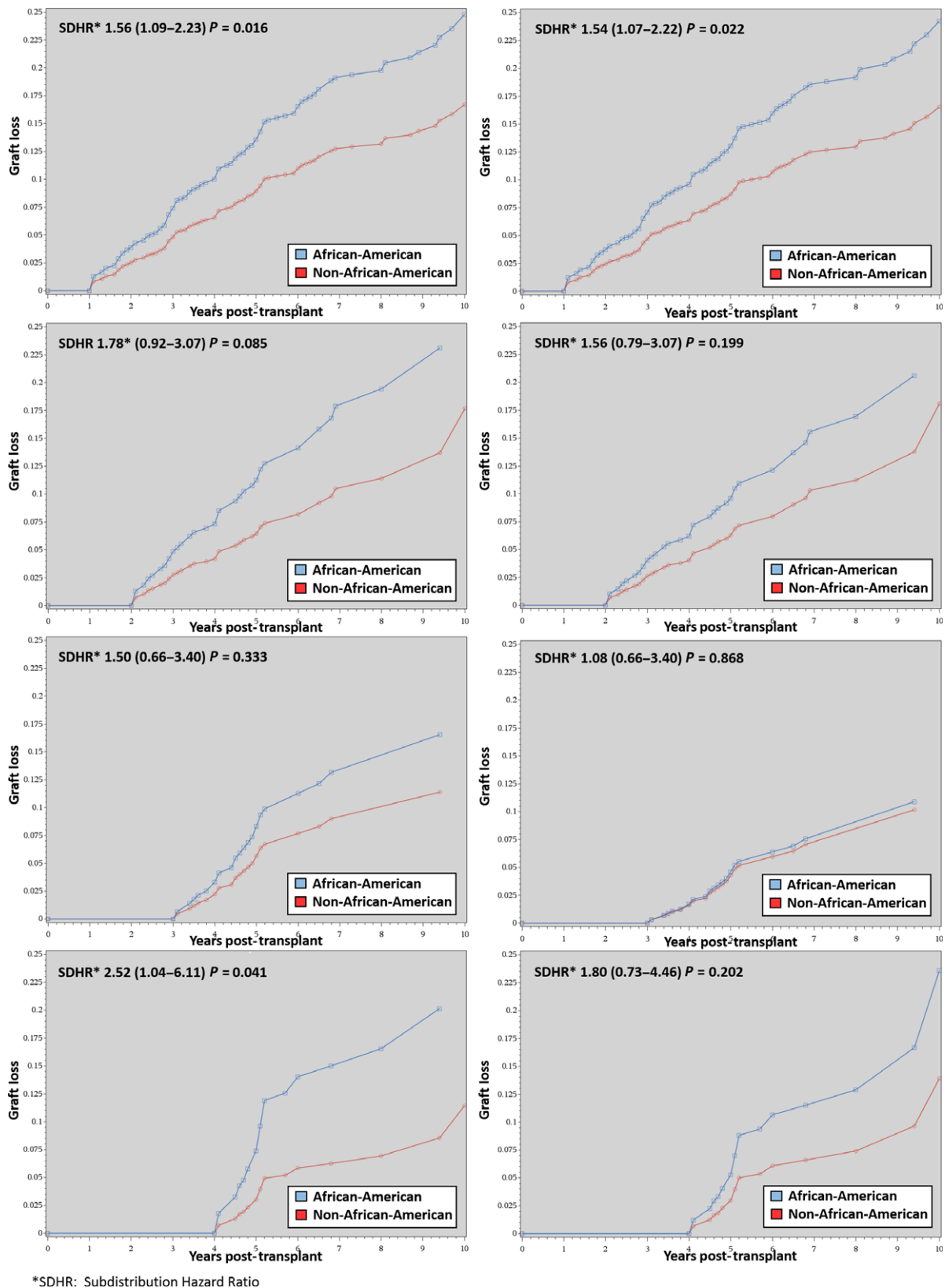
Variable	Unadjusted Year 1 SDHR (95% CI)	Adjusted Year 1 SDHR (95% CI)	Unadjusted Year 2 SDHR (95% CI)	Adjusted Year 2 SDHR (95% CI)	Unadjusted Year 3 SDHR (95% CI)	Adjusted Year 3 SDHR (95% CI)	Unadjusted Year 4 SDHR (95% CI)	Adjusted Year 4 SDHR (95% CI)
African-American	1.56 (1.09–2.23)	1.54 (1.07–2.22)	1.78 (0.92–3.44)	1.56 (0.79–3.07)	1.50 (0.66–3.40)	1.08 (0.46–2.53)	2.52 (1.04–6.11)	1.80 (0.73–4.46)
Acute rejection	–	2.32 (1.30–4.12)	–	54.39 (1.48–13.1)	–	6.78 (1.45–31.7)	–	8.84 (2.01–38.9)
Mean glucose >160 mg/dl	–	1.04 (0.69–1.56)	–	1.18 (0.61–2.30)	–	3.25 (1.50–7.06)	–	1.87 (0.91–3.83)
Mean SBP >140 mmHg	–	0.95 (0.67–1.36)	–	1.07 (0.59–1.94)	–	1.56 (0.69–3.50)	–	1.88 (0.93–3.78)
Mean tacrolimus CV >40%	–	1.28 (0.90–1.82)	–	1.72 (0.89–3.32)	–	4.13 (1.99–8.57)	–	1.74 (0.80–3.78)
Mean hemoglobin <10 g/dl	–	1.23 (0.84–1.81)	–	1.99 (0.79–5.04)	–	3.27 (1.06–10.0)	–	1.42 (0.40–5.04)

\*All statistical assessments for determining the significance of parameter estimates were made using the chi-square test statistic in both unadjusted and fully adjusted models.

population of Veteran kidney transplant recipients [10]. The results from the analysis presented here validate these findings in the non-Veteran population, while also defining optimal goals for SBP (<140 mmHg) and glucose control (<160 mg/dl). Further, our results demonstrate that there is a wider disparity in late control of these cardiovascular risk factors in AAs and these are significant factors for differences in graft loss. Focusing efforts to improve late control may have an impact on racial disparities for graft loss [26].

A number of studies demonstrate that tacrolimus variability is a known risk factor for acute rejection and graft loss, inferred to be a direct result of reduced medication adherence [27–29]. We have recently demonstrated that tacrolimus variability is higher in AAs and has a strong association with acute rejection and graft loss [30]. Within the results presented here, tacrolimus variability was highest in the overall cohort early after transplant and then subsequently decreased in later years. However, high tacrolimus variability was more common in AAs in later years (Table 2) and multivariable modeling suggests its impact on graft loss was also more influential in later years (Table 3). The time-varying impact of high tacrolimus variability potentially has important implications, as it may be a proxy for late immunosuppression nonadherence [21]. Further, iterative modeling demonstrated tacrolimus variability in later posttransplant years was an important explanatory variable for graft loss disparities in AA recipients. Thus, reducing racial disparities for graft loss through mitigating the impact of high tacrolimus variability in the later years after transplant may be a promising avenue for future interventional trials. It is important to note that dosing regimen and goal level ranges change overtime, and this may influence tacrolimus variability in later years. As we could not assess dosing changes of tacrolimus with this study, further analyses are required to assess the time-varying impact of tacrolimus variability, while controlling for goal trough level ranges and dosing changes.

Anemia is also a well-known risk factor for posttransplant graft loss [31–33]. In the renal disease populations, anemia has a higher prevalence and severity in AAs, which is likely a reflection of lower hemoglobin levels in nonrenal disease AAs, the effects of alpha-thalassemia genomic deletions and a higher incidence of iron deficiency. Further, AAs tend to be more refractory to vitamin D and erythropoietin supplementation [34,35]. There is limited data assessing racial differences in anemia incidence and severity in the posttransplant population. In a multicenter retrospective study, Yorgin



**Figure 2** Competing risk models displaying the cumulative estimated incidence for graft loss, compared between non-AAs and AA for the four landmark analyses (posttransplant year 1, 2, 3 and 4). The figures on the left are the crude unadjusted risk and the figures on the right are adjusted for clinical surrogates that were measured during the exposure period for each of the four landmark analyses, respectively.



*et al.* [36] demonstrated anemia rates at 1-year post-transplant were similar in non-AAs and AAs; yet at 5 years, AAs had lower hematocrit z-scores, indicative of higher rates and severity of late posttransplant anemia. In our analysis, AAs had 11–28% higher odds of low hemoglobin within the first 2 years after transplant, which increased to 78% higher odds by posttransplant year four. Further research is warranted to determine if the disparities in the incidence and severity of post-transplant anemia can be mitigated through interventions aimed at correcting known underlying differences within the AA population, such as vitamin and iron deficiencies and erythropoietin resistance.

Based on this and previous research, assessing and addressing late clinical surrogates in order to provide optimal care appears to be an important factor in racial disparities for graft survival [15,20,26]. In our experience within transplant centers systems of care and care models, much focus is put on close follow-up of transplant patients within the first year or two after transplant. A significant portion of kidney transplant recipients then transition care back to the community, with the primary system of care coordinated provided by primary care or nephrology. The Transplant Center usually only follows patients peripherally at this point, with annual “check-up” visits. The research presented here suggests different care models may be warranted, if the transplant community expects to improve long-term graft outcomes, particularly within AA recipients. Perhaps through enhanced long-term care coordination, remote monitoring, telehealth interventions and the use of innovative technology, improvements in long-term clinical surrogate goal obtainment can occur. This may be a difficult task and one that is not currently supported within the financial and regulatory framework of transplantation, which clearly focuses on short-term outcomes as the primary measure of high-value care; but one that appears to be needed to significantly improve racial disparities in transplantation [37,38]. This is further exemplified by the fact that there was a significant amount of missing data in the later years after transplant; an indication that care has transitioned, either in part or fully, to the outside community. The multiple imputation analysis suggests that this level of missing data did not appreciably bias our estimates of the impact of late clinical surrogates on racial disparity outcomes. However, the models using the imputed dataset did have the lowest adjusted risk for AA recipients, suggesting improved management of late clinical surrogates may appreciably impact disparities.

There are a number of important limitations to this study. First, this was a single-center analysis. As such, the findings may not be fully applicable to all transplant centers. The sociodemographic composition of the kidney transplant population within our transplant center is highly representative of the Southeastern US and substantially differs as compared to the Northeastern, Western US and international populations. Thus, these results and their implications cannot be applied to all transplant centers without further validation across different geographic regions. Second, due to its retrospective design, this study may be prone to confounding and bias. The use of detailed follow-up clinical data within the EHR likely mitigated some of this concern; yet missing data, particularly in the later years posttransplant was significant (likely due to limited follow-up within the transplant center). Also, data from both inpatient and outpatient healthcare encounters was included, which may impact inpatient means and estimates. In later posttransplant years, patients are often managed by outside providers, which also can influence low rates of lab assessments and estimates during these years. We conducted a number of sensitivity analyses, including MI, to ensure our estimates were unlikely to be biased [17]. These results demonstrated consistent estimates to the complete case analyses. Third, this study cohort was created using a 10-year timeframe to allow for adequate power and follow-up to assess graft survival disparities. Because of this, changes in the clinical care of transplants may influence the applicability of these results to current or future kidney transplant recipients. There were major advances that occurred during this timeframe, including the screening and reporting of donor-specific HLA antibodies, cross-match assessment, cPRA and kidney allocation policies. Further, donor and recipient characteristics have evolved as well. In recent times, we are utilizing marginal donors, while recipients tend to be older with more comorbidities. However, the prevention, identification and treatment of acute rejection, hypertension, diabetes and anemia did not substantially change during this period. Finally, it should be noted that these results provide the identification of potentially modifiable clinical surrogates that offer the promise of reducing racial disparities. We also were not able to assess clinic appointment adherence and medication refill adherence, both of which are likely to impact control of these clinical surrogates and graft outcomes. Therefore, these findings of associations should not be misconstrued as causal or that interventions to reduce these clinical surrogates will definitively reduce disparities in AAs. Prospective interventional trials are needed to adequately determine the impact of

modifying clinical surrogates on graft loss disparities within AA recipients.

Taken in their entirety, these results provide preliminary evidence that late clinical surrogates, including acute rejections and reduced control of SBPs, glucoses, increased tacrolimus variability and anemia, may have a significant impact in graft loss disparities for AA kidney recipients. Given the limitations of this retrospective exploratory analysis, further research is clearly required in order to determine if interventions aimed at mitigating these clinical surrogates can appreciably improve racial disparities in kidney transplantation.

### Authorship

DJT: designed study, acquired data, analyzed data, wrote paper, edited resubmission. ZS: designed study, acquired data, analyzed data, edited paper, edited resubmission. NAP: designed study, analyzed data, edited paper, edited resubmission. JNF: designed study, analyzed data, edited paper, edited resubmission. TM: designed study, analyzed data, edited paper, edited resubmission. PM: designed study, analyzed data, edited paper, edited resubmission. DD: designed study, analyzed data, edited paper, edited resubmission.

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### Conflict of interest

The authors have no conflicts of interest to disclose as it relates to the content of this manuscript.

### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Assessment of early and late phase data on disparities in AAs for the outcomes of time to eGFR less than 45, 30 and 15 ml/min/m<sup>2</sup>.

**Table S2.** Rates of missing data stratified by year and race.

**Table S3.** Sensitivity analyses demonstrating the results of the complete case analysis compared to the multiple imputation analysis.

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