

Received: 2017.09.21
Accepted: 2017.11.07
Published: 2018.02.16

Transplant Center Variability in Disparities for African-American Kidney Transplant Recipients

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Source of support: Research reported in this publication was supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under Award Number K23DK099440

Background: Disparities research has traditionally focused on patient-level variables to ascertain predominant risk factors driving differences in outcomes for African-American (AA) kidney transplant recipients. Our objectives were to determine the magnitude and impact of transplant center variability for graft outcome disparities.

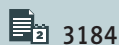
Material/Methods: This was a retrospective cohort study analyzing 25 years of U.S. national transplant registry data at both the patient and center levels using univariate descriptive statistics and multivariable modeling.

Results: A total of 257,024 recipients from 191 centers were analyzed; AAs represented 31.1% of recipients. After adjusting for baseline characteristics, AAs had 42% higher risk of graft loss (aHR 1.42, 95% CI 1.39 to 1.45; $p < 0.001$). Center variability for graft outcome disparities in AAs was significant (race*center interaction term $p < 0.05$), with the aHRs ranging from 0.5 to 4.9; 46% of centers demonstrated a non-statistically significant disparity (aHR $p > 0.05$) and 25% of centers had a large AA disparity (aHR > 1.75). In a more recent transplant time period (2000–14), overall racial disparities decreased but center-level disparities increased in variability. Center-level factors significantly associated with increasing disparity included higher acute rejection rates, fewer transplants per year, longer length of stay, lower use of calcineurin inhibitors (CNI), and lower living donor rates.

Conclusions: There is evidence of significant center-level variability in graft outcome disparities for AA kidney recipients. Further, there appears to be a number of center-level factors associated with this variability, including acute rejection rates, CNI use, number of transplants per year, and, in recent years, low living donor rates.

MeSH Keywords: African Americans • Graft Survival • Kidney Transplantation • Tertiary Care Centers

Full-text PDF: <https://www.annalsoftransplantation.com/abstract/index/idArt/907226>



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Background

Since the advent of kidney transplantation as a viable option to treat end-stage renal disease (ESRD), post-transplant outcome disparities in African-American (AA) recipients have been well documented. The first reports of potential racial disparities were in 1977, when Opelz and colleagues demonstrated a 10% increase in graft loss within AAs at 3 years post-transplant, as compared to whites. Since then, most analyses designed to study the causes of this disparity and interventions to mitigate this issue have solely focused on patient-level risk factors [1]. This research has elucidated a number of important individual factors within AA recipients that are likely to be explanatory variables or mediators of outcomes disparities; these include biologic and immunologic variations that increase the risk of acute rejection [2–5], socioeconomic status (SES) barriers [6,7], reduced access to healthcare, medication non-adherence [8], and comorbidities [9–11].

To date, there is limited data assessing transplant-center or systems-level factors related to disparities in AA recipients. Outside of transplant, there is a growing body of evidence to demonstrate that health outcomes disparities in AAs go beyond patient-level risk and are intricately related to health-systems factors. Disparate outcomes in AAs for acute myocardial infarction (AMI), end-of-life, and a variety of surgeries have all been correlated with a health system effect; such that differences in disparities vary by system or that system-level factors are mediators of disparities in AAs [12–14]. Further, there are data that demonstrate that significant healthcare segregation occurs, such that a minority of healthcare systems care for the vast majority of AAs [15,16]. Transplant-center variability in performance and outcomes with standardized benchmarking and reporting has been a hallmark of quality assessment for US programs for decades for all patients, including AA and whites [17–19]. However, to date, there have been no analyses that focus on transplant-center variability as it specifically relates to disparities in AA recipients. Given the growing body of evidence that systems-level factors influence racial disparities in US healthcare delivery, we assessed center-level/health systems variability that contributes to disparities for AA kidney transplant recipients and determined which center-level factors were associated with these racial inequalities.

Material and Methods

Study design

This was a retrospective cohort study utilizing national U.S. kidney transplant registry data acquired from the United Network of Organ Sharing (UNOS). After local IRB approval and completing a data use agreement (DUA), UNOS Standard

Transplant Analysis and Research files (STAR) were acquired. We requested and were approved to receive center-identified data, such that each recipient's transplant center and location was known and available for analysis and reporting. Patients were included in this study if they received a kidney transplant at a U.S. transplant centers between 1990 and 2014. Pediatrics (<18 years of age at the time of transplant), non-renal transplant recipients, those of a race/ethnicity other than white or AA, and those receiving a transplant from a center that performed less than 50 transplants in AAs during the study period were excluded. We excluded Asians, Hispanics, and other races/ethnicities for ease of comparison and excluded transplant centers performing less than 50 transplants in AAs to exclude small numbers when conducting center-stratified analyses. Thus, this analysis compared AA to comparisons to assess racial disparities, with whites set as the reference group and AA set as the risk group. To assess for changes in disparities and center-level variability over time, the overall cohort was compared to a restricted cohort, which included only transplants performed between 2000 and 2014. This time period was chosen as a comparison because previous studies have demonstrated reduced racial disparities in graft loss for kidney transplants occurring after 2000 [20,21].

Variables and definitions

The primary exposure variable for this study was self-identified recipient race; dichotomized as either white (reference group) or AA (risk group). The secondary exposure variable of predominant interest for this study was transplant center. This variable was treated as a categorical class-level variable in modeling. Additional variables that were included in the analysis in models included recipient sociodemographics (age, gender, body mass index [BMI], functional status [using Karnofsky estimation], primary diagnoses), donor information (donor age, donor race, donor gender, donor type [living, deceased, expanded criteria]), years on dialysis, days on the waiting list, previous kidney transplant, transplant characteristics (panel reactive antibody [PRA] levels, human leukocyte antigen [HLA] mismatches, cold ischemic time), and baseline immunosuppression (induction therapy and maintenance therapy). See Table 1 for a complete list of each of these variables (Education, employment and insurance were excluded from the models (center-specific modeling) because the level of missingness precluded a number of center-specific models from converging).

Study outcomes

The primary outcome of interest was graft loss, defined as a patient's return to chronic dialysis or retransplantation. Death was not considered as graft loss, but was accounted for as a competing risk event in analyses. Additional outcomes assessed

Table 1. Baseline characteristics for the overall and restricted cohorts.

Variable	Overall cohort	Restricted cohort
Cohort time period	1990 to 2014	2000 to 2014
Number of transplant centers	191	169
Number of patients	257,024	173,488
Median age (IQR)	49 (38, 59)	52 (41, 61)
Female gender	39.4%	39.3%
African American race	31.1%	33.0%
Median BMI (IQR)	26.5 (23, 31)	27.3 (24, 32)
Median Karnofsky functional status (IQR)	90 (80, 100)	90 (80, 100)
Completed High School	45.3%	44.5%
Primary insurance – Medicare or Medicaid	59.5%	58.8%
Working at the time of transplant	35.2%	35.2%
Primary diagnosis for ESRD		
Hypertension	21.4%	22.9%
Diabetes	22.3%	21.9%
Median days on wait list (IQR)	387 (142, 864)	443 (157, 984)
Median years on dialysis (IQR)	1.5 (0.2, 3.5)	1.6 (0.1, 3.8)
Median donor age (IQR)	40 (26, 50)	41 (28, 51)
Donor Female gender	46.8%	50.0%
Donor African American race	14.3%	15.1%
Living donor	34.4%	37.9%
Expanded criteria donor	8.9%	10.3%
Median HLA mismatches (IQR)	4 (2, 5)	4 (3, 5)
PRA >20%	7.2%	6.6%
PRA >80%	2.6%	2.6%
Median cold ischemic time (hrs ±SD)	14.3 (3, 22)	12.0 (2, 20)
Previous kidney transplant	12.9%	12.6%
Induction therapy		
IL-2 receptor antagonist	20.5%	27.1%
Cytolytic therapy	44.8%	51.7%
Immunosuppression at discharge		
Tacrolimus	57.1%	78.4%
Cyclosporine	34.8%	14.6%
Mycophenolate	64.7%	80.8%
Azathioprine	17.3%	1.2%
mTOR Inhibitor	5.5%	7.5%
Corticosteroids	78.7%	72.7%

included delayed graft function, defined as the need for dialysis within 7 days of transplant, acute rejection, defined as biopsy proven or clinically suspected and treated, and death. Social Security Master Death Files (SSMDF) were linked by UNOS and used to augment/validate transplant center-reported death.

Statistical analysis

To determine if racial disparities significantly differed by transplant center, Cox regression modeling was used. Adjustment for clustering by center was made via frailty and adjustment for competing risk due to mortality was made using the Fine and Gray methodology. Time to graft loss was measured in days from date of transplant to date of chronic dialysis or re-transplantation. Those who did not experience the primary outcome were considered censored at the end of the observation period, time of death or loss of follow up, whichever came first. In the Cox model, race was set as the primary variable of interest, adjusted for baseline covariates (listed in Table 1) with transplant center and a race*transplant center interaction terms entered into the models. This was done for both the overall and restricted cohorts. Once the race*center interaction was established as statistically significant, Cox regression models were stratified by transplant center and the resulting adjusted hazard ratios (aHRs) for AAs displayed using caterpillar plots. Variability of the center-specific aHRs for AAs were assessed using standard descriptive statistics, including frequency histograms and the coefficient of variation. These center-level variability statistics were then compared between the overall and restricted cohorts.

Next, to assess for center-level factors associated with disparities in AAs, a stepwise linear regression model was used ($p > 0.1$ was set to remove variables from model in a backward fashion) with the dependent variable being the center-level aHR for AA recipients. The independent variables were the center-level mean differences between AA and whites for baseline characteristics (recipient demographics, donor information, and immunosuppression utilization) and post-transplant outcomes other than graft loss and death (DGF, length of stay, number of transplants per year, and acute rejection rates). As length of stay is also an outcome, we did assess models with and without this variable to demonstrate consistency and robustness of estimates. This linear modeling was conducted for both the overall and restricted cohorts. Model diagnostics for the Cox model (proportional hazard assumption) as well as the linear regression model (normality, homoscedasticity) were made using residual analysis. Missingness was assessed using multiple imputation. A two-sided p -value of < 0.05 was considered statistically significant and all analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

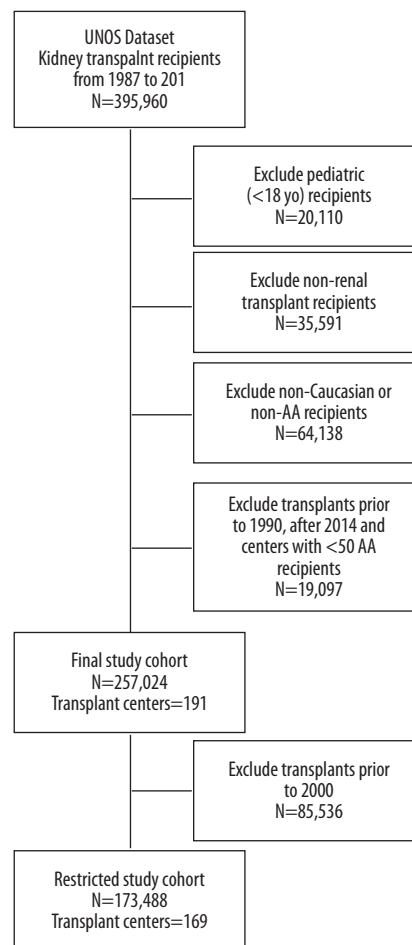


Figure 1. CONSORT diagram depicting how the overall and restricted area study cohorts were developed.

Results

Between 1987 and 2014, a total of 395 960 kidney transplants were performed at 299 transplant centers within the US. Of these, 20 110 (5.1%) were excluded for age < 18 years, 35 591 (9.0%) were excluded for receiving non-renal transplants, 64 138 (16.2%) were excluded for race/ethnicity, and 19 097 (4.8%) were excluded for being transplanted outside the study time period or for being transplanted at a center that conducted < 50 transplants in AAs; leaving a total of 257 024 transplants occurring at 191 transplant centers included in the final analysis. In the restricted 15-year cohort (2000 to 2014 time period), an additional 85 536 transplants and 22 centers were excluded, leaving 173 488 transplants from 169 transplant centers (see Figure 1 for the Consort diagram).

The baseline characteristics of the study cohort and restricted cohort are displayed in Table 1. The median age was 49

Table 2. Transplant center characteristics based on proportion of AA recipients.

Center Characteristic	Low% of AA recipients (n=143,805; 98 centers)	High% of AA recipients (n=113,219; 93 centers)
Number of transplants per year (SD)	59±44	49±43
Center location		
Midwest	40%	13%
Northeast	23%	18%
South	16%	68%
West	20%	1%
Living donors	38%	30%
Female	39%	40%
African-Americans	19%	47%
Mean recipient age (years ±SD)	49±14	48±13
Below High School education	2.7%	3.4%
Working at the time of transplant	38%	32%
Medicare as primary insurance	50%	60%
Utilized cytolytic induction	47%	42%
Utilized tacrolimus	55%	60%
Delayed graft function	16%	20%
Initial length of stay (days ±SD)	4.5±2.0	4.5±2.2
Acute rejection	23.4%	21.8%

years, which increased to 52 years in the later time period; roughly 39% were female and 31% were AA (which increased to 33% in the later time period). Years on dialysis and days on the waiting list increased in the later transplant cohort as well. The prevailing etiologies of ESRD were hypertension and diabetes, which was consistent throughout both time periods. Other notable trends including using more marginal donors (older age, expanded criteria) and more potent immunosuppression in more recent transplant years. Transplant center characteristics, stratified by the proportion of AA recipients (below and above national median), are displayed in Table 2. Centers with high proportions of AA recipients in general performed fewer transplants per year, were predominantly located in the South, had fewer living donors and a transplant population with more socioeconomic disadvantages (more public insurance use, less educated, more unemployment).

Clinical outcomes for the overall and restricted cohorts are displayed in Supplementary Table 1. Overall acute rejection occurred in 22.7% of patients, which significantly decreased in the later cohort (18.6%); 10-year estimated rates of graft and patient survival in the overall cohort were 78% and 73%,

respectively. These rates also significantly improved in the later cohort (82% and 77%, respectively).

In terms of racial disparities, overall, AAs had 42% higher risk of graft loss, as compared to whites (aHR 1.42, 95% CI 1.39 to 1.45; $p < 0.001$), which was slightly reduced in the 2000–14 restricted cohort (aHR 1.39, 95% CI 1.36 to 1.44, $p < 0.001$). There was significant variability in graft outcomes for AAs, as compared to whites, by transplant center for both the overall and restricted cohorts ($p < 0.05$ for race*center interaction term in both overall models). Figure 2 illustrates the caterpillar plots displaying the variability in AA disparities by transplant center. In the overall cohort, 57% of centers had statistically significant disparities in graft survival for AA recipients (aHR $p < 0.05$), with 25.3% having a large AA disparity (aHR > 1.75). The variability in disparities by center was substantial, with a CV of 31.8%. In the restricted cohort, fewer centers had statistically significant disparities in AAs (36%), but more centers had a large disparity (aHR > 1.75 , 26.8%). The variability in the disparities by transplant center was higher in the later cohort, with a CV of 41.1% (vs. 31.8%). The frequency histograms of the aHR in AAs by transplant center (right side of

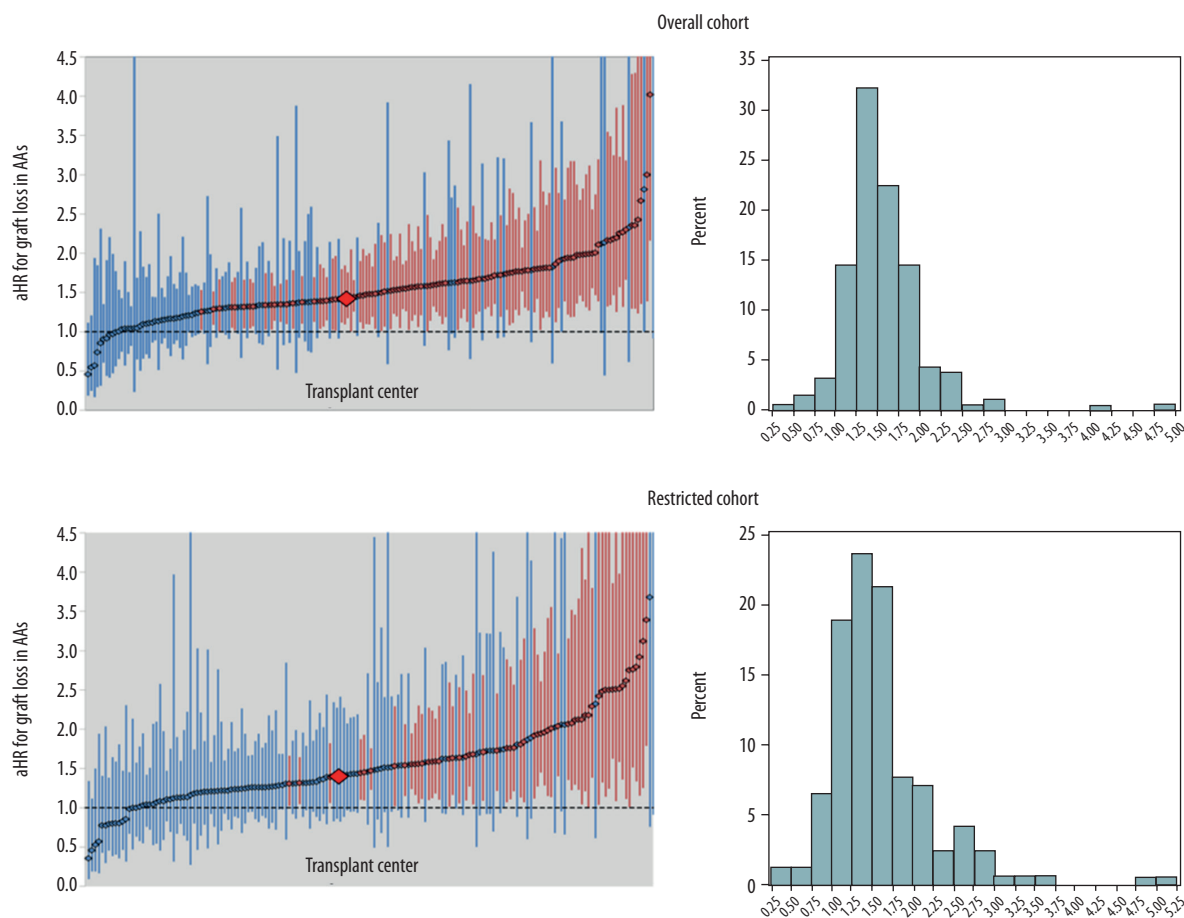


Figure 2. Characterization of racial disparities by transplant center. The caterpillar plots display the ranked transplant-centers across the horizontal axis and the center-specific adjusted hazard ratios (aHRs) in African-Americans for graft loss along the vertical axis. The red dots and lines represent statistically significant disparities while the blue dots and lines represent statistically insignificant findings. The large red diamond in the center represents the overall aHR estimate for all patients in the cohort. The histograms to the right of each caterpillar plot display the distribution of the aHRs by transplant center. The top histogram is the overall cohort and the bottom is the restricted cohort.

Figure 2) demonstrate a fairly normal distribution in the entire cohort with a slight right-skewed distribution in the later cohort; such that there were more centers in the later cohort with larger disparities in AAs.

Center-level factors associated with AA disparities for graft loss are displayed in Supplementary Table 2 (overall cohort) and Supplementary Table 3 (restricted cohort). More transplants per year, increasing donor age, and high levels of calcineurin inhibitor (CNI) use (cyclosporine and tacrolimus) were all associated with reduced center-level disparities in AAs; while a longer length of stay and higher acute rejection rate were associated with increased center-level disparities. For the restricted cohort, the trends were similar, in that more transplants per year (within AA recipients) and higher CNI use were associated with reduced disparities, while more deceased donor

transplant (vs. living donors) and higher acute rejections was associated with increasing disparities in AA recipients.

Discussion

The results of this analysis demonstrate there is substantial transplant center-level variability in graft outcome disparities for AA kidney recipients when compared to the reference group of white recipients. Further, although graft outcome disparities for AA recipients have somewhat improved in recent years, center-level variability has actually significantly increased. Finally, these results also suggest a number of factors significantly associated with either increased (e.g., acute rejection and deceased donor rate) or reduced (e.g., more transplants per year, CNI use, and donor age) disparities in AA

recipients. These findings provide the first published analysis we are aware of that specifically assesses center-level variability and factors associated with racial disparities in transplantation and provide preliminary evidence to suggest focusing on optimizing transplant program care processes, clinical protocols and policies as a potential mechanism to mitigate disparities in AA recipients.

There is research from outside of transplantation demonstrating a significant hospital effect for disparities in AAs. Barnato and colleagues conducted an analysis of administrative Medicare data and record review in those treated at 4690 US hospitals for acute myocardial infarction (AMI). The authors demonstrated significant race-hospital segregation, in that nearly all AAs with AMI were treated at a minority of hospitals (~20%). Further, there were significant racial disparities between AA and whites for AMI quality measures, which were mediated through a hospital effect; adjusted models with a fixed-effect hospital variable mitigated the magnitude of disparities. The authors concluded that hospital-level effects and differences in utilization are substantial contributors to observed AMI treatment disparities between AAs and whites [12]. Lucas and colleagues utilized national Medicare data to demonstrate that AAs had higher 30-day postoperative mortality for an array of cardiovascular and cancer surgeries. For most surgeries, individual patient-risk only mildly mitigated this risk, while hospital factors (number of transplants per year and a fixed-effect hospital variable) significantly attenuated the higher risks in AAs for nearly all surgeries. Further, AA race was associated with likelihood of urgent surgery [14]. Another study demonstrated that end-of-life ICU care varied by race, which was mitigated by hospital effect, such that when models were adjusted by a fixed or random hospital variable, the impact of race was attenuated [13]. Studies also demonstrate significant segregation by race, in that hospital-based care for AAs tends to cluster at facilities that have lower national quality performance ratings [15,16]. The results from our study provide a similar pattern, in that there is a significant between-center effect for racial disparities in transplantation; the variability in disparities by center was significant, and this variability has actually widened over time, despite a narrowing in the overall level of disparities in AAs [20,21].

It is important to note that there are numerous patient -and neighborhood-level factors that can influence graft outcomes that were not measured or accounted for within this analysis [6–8]. Although education, employment, and insurance status, all strong proxies of socioeconomic status, are within the UNOS registry, the level of missing precluded analysis of these factors within the center-level assessments. Additional factors that likely influence outcomes and may help explain racial disparities include neighborhood factors, area-level health statistics, access to affordable housing and food, and cultural

barriers. Clearly, future research is needed to better understand how these factors differ by the regions that transplant centers serve and if these differences account for the variability in racial disparities demonstrated by this analysis.

There is also research assessing physician-level factors associated with racial disparities. Sequist and colleagues conducted an analysis of 6814 patients with diabetes (33.1% AA) cared for by 90 physicians. In multivariate models, variability in diabetes outcomes was explained predominately by patient-level sociodemographics (13–38%) and within-physician effects (66–75%), with little between-physician effect. Thus, contrary to the aforementioned systems-level analyses, the authors concluded that racial disparities in diabetes outcomes were not due to AAs receiving clustered management from physicians that provide low-quality care, but rather were due to receiving lower-quality care across all physicians in general [22]. We were not able to assess physician-level effects in our analyses, because this information is not available in registry data and it is likely that care is provided by a team of providers, including multiple physicians.

The implications of our findings suggest that a potential mechanism to mitigate racial disparities in kidney transplantation, beyond focusing on patient-level risk mitigation, is to better understand how system-level factors impact outcomes. Our preliminary data suggest that minimizing acute rejection differences, reducing prolonged hospital length of stay, increasing living donation, and utilizing CNI-based regimens in AAs may help reduce outcome disparities. Immunosuppression regimens and their impact on acute rejection and graft loss disparities have been well-studied in kidney transplantation [23]. Potent regimens, which include cytolytic induction therapy and CNIs, are likely to have more sustained and dramatic impact on AAs, a group which is known to have substantial immunologic risk factors [24–27].

Beyond immunosuppression choice, center-level protocols, policies, pathways, care structure, and overall culture are also likely to have a substantial impact on racial disparities in kidney transplantation, although this is an area that is not well-studied. In 2012, Chin and colleagues published a paper describing a roadmap and best practices for organizations to use to reduce racial disparities in health care. Within the paper, the authors outline 6 steps a health care organization can use, which include recognizing disparities, committing to reducing them, implementation quality improvement, ensuring equity is an integral component of these improvement initiatives, designing and testing interventions, and sustaining improvements. Best practices at organizations include assessing the capacity of the facility to intervene, fostering a culture of equity, appointing specific staff to reduce disparities, motivating staff to be equitable, incorporating disparity interventions

into existing systems and structures of care, involving the target population in the planning of programs, and being realistic about goals and timelines [28,29]. Clearly, these are strategies that can align with a transplant center's goals and philosophy. As transplantation is a highly regulated medical discipline, it is already very well versed in quality assessment and process improvement (QAPI) [30]. Thus, if a transplant center serves minority populations with known disparities, it would be important to incorporate improving equity into its QAPI programs. There are likely some transplant centers that currently do this as part of their mission, and future research should work to identify high-performing centers as it relates to focusing interventions, QAPI, and care models with a primary aim of reducing disparities within AA recipients.

There are a number of limitations that should be noted with this analysis. First, retrospective registry data was utilized, which limited our ability to analyze center-level characteristics to those in the dataset. Thus, additional center-factors that may impact racial disparities, such as hospital quality measures, physician specialty availability, staffing ratios, and social support systems, were not available to assess. Further, there are a number of patient-level

socioeconomic factors that have been demonstrated to influence racial disparities that could not be measured or accounted for in this study, including income, prior drug abuse, marital status, caregiver support, and employment after transplant. Missing data is also an issue with registry data analyzed over long periods of time, particularly with proxies of socioeconomic status, such as insurance, employment, and education. Missingness was assessed using multiple imputation and results were robust across these analyses. Due to these limitations, more studies are warranted that can conduct comprehensive assessments of center-level mediators of racial disparities in transplantation.

Conclusions

In summary, these data provide evidence of significant center-level variability in graft outcome disparities for AA kidney recipients, with this variability increasing in recent years. There appears to be a number of center-level factors associated with this variability, including acute rejection rates, CNI use, number of transplants performed per year, and, in recent years, living donor rates.

Supplementary Tables

Supplementary Table 1. Clinical outcomes for the overall and restricted cohorts.

Outcome	Overall cohort	Restricted cohort
Delayed graft function	17.7%	16.9%
Acute rejection		
6 month	14.1%	8.7%
1 year	15.3%	9.9%
Overall	22.7%	18.6%
Graft loss		
1 year	5.9%	4.5%
3 year	10.9%	9.0%
5 year	15.4%	12.9%
10 year	22.3%	18.0%
Death		
1 year	4.3%	3.8%
3 year	9.3%	8.5%
5 year	14.7%	13.4%
10 year	26.9%	22.8%

Supplementary Table 2. Center specific factors associated with racial disparities for the overall cohort.

Center Level Difference	% Impact on AA disparity	95% confidence interval	p-Value
Number of transplants (In increments of 10 per year)	-1.7	-2.9 to -0.5	0.0076
Years on dialysis	14.2	-0.9 to 29.3	0.0675
Donor age	-4.7	-8.3 to -1.1	0.0106
BMI (kg/m ²)	-0.1	-0.2 to 0.0	0.0691
Length of stay (days)	20.4	4.5 to 36.3	0.0126
Cyclosporine use	-3.5	-5.7 to -1.4	0.0017
Tacrolimus use	-3.2	-5.4 to -1.1	0.0033
Primary diagnosis PKD	-2.7	-5.2 to -0.3	0.0321
Cold ischemic time (min)	-2.2	-4.6 to 0.2	0.0696
Acute rejection	2.2	1.0 to 3.5	0.0006

Supplementary Table 3. Center specific factors associated with racial disparities for the restricted cohort.

Center Level Difference	% Impact on AA disparity	95% confidence interval	p-Value
Number of transplants in AAs (In increments of 10 per year)	-5.3	-8.8 to -1.8	0.0037
Proportion of AA recipients	1.1	0.5 to 1.7	0.0003
Donor age	-4.9	-10.5 to 0.6	0.0845
HLA mismatches	45.9	-2.4 to 94.3	0.0645
BMI (kg/m ²)	-23.8	-40.3 to -7.3	0.0054
Cyclosporine use	-6.9	-10.4 to -3.5	0.0001
Tacrolimus use	-6.0	-9.3 to -2.7	0.0006
Deceased donor proportion	1.7	0.3 to 3.0	0.0151
Primary diagnosis PKD	-3.3	-6.4 to -0.3	0.0336
Acute rejection	2.0	0.1 to 3.8	0.0373

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