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Racial differences in renal replacement therapy initiation among children with a non-glomerular cause of chronic kidney disease

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Abstract

Purpose—African American (AA) adults with chronic kidney disease (CKD) have a faster progression to end stage renal disease (ESRD) and are less likely to receive a kidney transplant. It is unclear whether AA children experience renal replacement therapy (RRT) for ESRD sooner than non-AA children after accounting for socioeconomic status (SES).

Methods—Among children with non-glomerular CKD in the Chronic Kidney Disease in Children (CKiD) study, we investigated time to RRT (i.e., first dialysis or transplant) after CKD onset using parametric survival models and accounted for SES differences by inverse probability weights (IPWs).

Results—Of 110 AA and 493 non-AA children (median age= 10 years), AA children had shorter time to first RRT: median time was 3.2 years earlier than non-AA children (95%CI: −6.1, −0.3). When accounting for SES, this difference was diminished and non-significant (−1.6 years; 95%CI: −4.6, +1.5) and its directionality was consistent with faster GFR decline among AA children (−6.2% vs. −4.4% per year, p= 0.098). When RRT was deconstructed into dialysis or transplant, the time to dialysis was 37.5% shorter for AA children and 53.7% longer for transplant. These inferences were confirmed by the frequency and timing of transplant after initiating dialysis.

Conclusions—Racial differences in time to RRT were almost fully accounted for by SES and the remaining difference was congruent with a faster GFR decline among AA children. Access to

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transplant occurred later, yet times to dialysis were shorter among AA children even when accounting for SES which may be due to a lack of organ availability.

Keywords

pediatric nephrology; chronic kidney disease; health disparities; renal replacement therapy; inverse probability weights

INTRODUCTION

African-Americans (AAs) with chronic kidney disease (CKD) have a higher rate of CKD progression and incidence of end stage renal disease (ESRD) [1] than non-AAs. Additionally, AA adults are less likely to have renal transplantation than non-AA adults with ESRD [2], although recent work suggests these differences are attenuating over time [3]. Racial and socioeconomic status (SES) differences in CKD severity observed in adults [4–6] are also reported in pediatric populations [7,8].

Several potential causes for racial differences in CKD progression exist. One recently identified cause among adults and children is the high risk *APOL1* genotype [9–12], which is prevalent in about 13% of the AA population [10] and is associated with focal segmental glomerulosclerosis [12] and increased incidence of ESRD. Other research has shown that low SES, lack of social support, perceptions of poor treatment by medical professionals and a lack of knowledge of renal disease and treatment contribute to worse outcomes among AA adults, and a lower likelihood of kidney transplant referral [13–15]. Racial differences in transplant access have also been observed in pediatric populations and this difference is largely, but not entirely due to SES [16,17]. In the present analysis, we further investigate the association of AA race with the initiation of dialysis and kidney transplantation in a large, epidemiologic cohort of children with CKD who were free of *APOL1*, a genetic risk factor for accelerated CKD progression. Since kidney transplantation is the preferred method of treatment for children with late stage CKD [18,19], we sought to explore and characterize any racial differences in time to first renal replacement therapy (RRT) and the initiation of different RRT modalities (dialysis or transplant) to help define targets for improved clinical management.

Since AA race is strongly related to glomerular disease due to the *APOL1* genotype [12,20], and glomerular disease is related to different disease trajectories than non-glomerular causes [21], we restricted to children with a non-glomerular cause of CKD (comprising most of the pediatric CKD population [22–24]) in the Chronic Kidney Disease in Children (CKiD) study and considered free of the high risk *APOL1* genotype. A primary challenge in characterizing racial differences is accounting for the confounding effects of SES [25–27]. To address this, inverse probability of exposure weights [28,29] were used as a marginal structural model approach to account for SES as a confounder of the relationship between race and progression to first RRT. Our specific aims were to a) characterize disease progression (time to RRT and changes in GFR) by race (AA vs. non-AA) using the clinically meaningful time scale of years since CKD onset; b) use inverse probability weights to account for SES as a

confounder of the race and CKD progression relationship; and c) compare deconstructed RRT events (i.e., first occurrence of dialysis and transplant) by race accounting for SES.

MATERIALS AND METHODS

Study participants and design

The CKiD study is a prospective observational cohort study initiated in 2003 to investigate the natural history of CKD, with participants recruited at 54 pediatric nephrology centers in the US and Canada. Children were eligible for enrollment in CKiD based on age (1–16 years) and estimated glomerular filtration rate (eGFR) (30–90 mL/min/1.73m^2). The primary diagnosis of CKD was determined at baseline for each participant and adjudicated as either non-glomerular or glomerular. Non-glomerular diagnoses included the following conditions: aplastic/hypoplastic/dysplastic kidneys, cystinosis, medullary cystic disease/juvenile nephronophthisis, and obstructive uropathy, among others; full descriptions of the CKD diagnoses have been reported [30,31]. The study protocol was approved by the Institutional Review Boards of each participating center and informed consent and assent were obtained from all participants according to local requirements.

African American race and *APOL1* genotype

The primary exposure of interest was parental or self-reported African American race based on selection of “white, black/African American, American Indian/Alaska Native, Asian, Native Hawaiian/Pacific Islander, or other”. AA participants were characterized by the presence of any “black/African American” response.

Of 115 AA children with non-glomerular CKD, 84 had consented to genetic testing and were genotyped for *APOL1* risk alleles. Only 6% (5/84) were identified as having *APOL1* high risk alleles and we excluded these children from our analytic sample since *APOL1* status potentially confounds the race and ESRD relationship. Since 94% of AA children with non-glomerular disease and genetic testing were free of high risk *APOL1*, we assumed the remaining 31 who were not tested were also free of this risk profile.

Outcomes

The scale for time to first RRT was years since CKD onset, as determined by congenital origin of disease or the estimated time origin of pathology based on participant or clinical report. Time since CKD onset was anchored at 2 years (i.e., entry to analysis began at 2 years after CKD onset), since there were few children enrolled in CKiD at early stages of their disease. Annual estimated GFR measurements were calculated from serum creatinine, cystatin c and blood urea nitrogen from equations developed in the CKiD study [32].

Adjustment for socioeconomic status

Inverse probability weighting methods [28,29] were used to account for confounding due to socioeconomic status. Logistic regression was used to generate propensity scores with AA race as the outcome and variables related to the construct of socioeconomic status at the time of study entry. Variables included household income (categorized with cutoff values at $30 000 and $75 000 which were chosen to have approximately a third of the study population in

each category), abnormal birth history (a single variable defined as birthweight less than 2500 grams or less than 36 weeks gestational age or birth weight for gestational age less than 10th percentile), receiving food assistance in the past year, family receiving any form of public insurance, maternal education less than college, and not having a private doctor visit in the past year). Male sex was also included as a covariate in this propensity score model since there were proportionally more boys in the AA group. The inverse of these propensity for exposure scores (p for AA participants and $1-p$ for non-AA participants) were scaled (stabilized) to the marginal proportion for each group [33]. To check for balance of propensity scores and confounding covariates, the distributions of propensity scores and univariate weighted differences were compared. The analysis of the adjusted association of AA race and outcome reduces to a simpler analysis by weighting each individual to his/her inverse probability weight.

Analysis of time to renal replacement therapy and longitudinal changes in GFR

Incorporating left truncation due to children being enrolled at different lengths of time since 2 years past CKD onset, non-parametric estimates of survival functions were derived for RRT, as a composite event, and then for dialysis and transplant as competing events. Parametric accelerated failure time models using the Weibull distribution stratified by race were fit for RRT as the event, allowing each race group to modify both the location (β; determinant of median time of survival) and scale (σ; determinant of interquartile ratio) parameters [34]. The pth percentile of a Weibull distribution ($WE(\beta, \sigma)$) is $\exp(\beta) \times [-\ln(1-p)]^{\sigma}$. We used the ratio of percentiles (AA to non-AA) as the measure of association which is constant in the particular case of equal scale parameters. The models (unweighted and weighted) were evaluated based on the goodness of fit to the non-parametric survival curves.

Changes in GFR over time were characterized by a linear mixed effects model (unweighted and weighted) with random intercepts and slopes. The dependent variable was GFR (in the log scale) and the independent variables were years from study entry, an indicator for AA race and the interaction between years and AA.

Dialysis and transplant as competing events and transplantation after dialysis

Mixtures of two Weibull distributions using maximum likelihood methods jointly described the incidence of dialysis and transplant as competing events [35]. For each competing event, parameter estimation included β and σ (describing the Weibull distributions) and π (corresponding to the proportion undergoing dialysis, with $1 - \pi$ describing the proportion undergoing transplant), and these were allowed to vary by race.

Although considering the first occurrence of dialysis and transplantation is congruent with a competing risks approach, categorizing first RRT by dialysis or transplant is a limitation since dialysis is often a preparatory therapy for future transplant. To address this, the incidence of and timing to transplant after the initiation of dialysis was described by race.

RESULTS

Of the total 891 children in CKiD, 616 (69%) had an underlying non-glomerular cause of CKD, of whom 501 were non-AA with the remaining 115 self-reported as AA. Eight non-AA children were excluded because they had an unknown date of CKD onset or had no follow-up time. Of the 115 AA children, 5 were identified as having the high risk *APOL1* genotype and were excluded since they were considered at higher genetic risk for accelerated CKD progression. A total of 603 (493 non-AA and 110 AA children) comprised the analytic sample.

Table 1 presents characteristics at study entry of the participants stratified by race. The AA children were more likely to be boys (75% vs. 64%), have had an abnormal birth history (45% vs 29%), have any form of public health insurance (64% vs. 40%), be from a low income household (61% vs. 27%), have a maternal education less than college (79% vs. 65%), have received food assistance (35% vs. 15%), and were less likely to have seen a private MD in the previous year (61% and 75%).

Among the 493 non-AA children, 104 (21%) initiated RRT: 47 (10% of 493) received dialysis first and 57 (12% of 493) received transplant first. Of the 110 AA children, 31 (28%) initiated RRT, of whom 25 (23% of 110) received dialysis and 6 (5% of 110) received kidney transplant as their initial RRT modality.

Propensity scores were developed from a logistic regression model using SES variables as predictors of the outcome of AA race (presented in Table 2). The strongest associations with AA race were being a boy (OR: 2.33), household income (OR for low income: 2.31; OR for high income: 0.37), and abnormal birth history (OR: 2.12). While the other variables were not statistically significantly associated, their inclusion was necessary to obtain balance on indicators of SES. Propensity scores (p) for each participant were generated from this model and converted to inverse probability weights (IPWs) and scaled to the marginal proportions of non-AA and AA children [33] such that the weight for the ith AA participant was equal to $(110/603)/p_i$; and for the jth non-AA participant was equal to $(493/603)/(1-p_j)$. After applying the IPWs to the dataset, Table 3 describes the univariate differences as a diagnostic evaluation for balance on key variables. Balance was achieved such that there were no significant differences for the SES variables (and gender) that were included in the model.

Figure 1A displays the unadjusted non-parametric estimates of time to RRT with Weibull models superimposed for both non-AA and AA children. The median time to RRT was 3.2 years earlier for AA children compared to non-AA children (95%CI: −6.1, −0.3). In contrast, Figure 1B shows the same plot weighted according to the IPWs that account for SES indicators. There were no differences in time to RRT between AA and non-AA children until about 16 years after disease onset, at which point more AA children experienced RRT than non-AA children. Compared to non-AA children, the median time to RRT in the weighted analysis was only 1.6 years shorter for AA children (95%CI: −4.6, +1.5). A full description of the models, including levels of statistical significance, are presented in Supplemental Table 1.

Table 4 presents the results from the longitudinal model characterizing GFR changes over time. AA children had a faster rate of GFR decline than non-AA children (−6.2% vs. −4.3%, p for difference= 0.040), and these rates persisted even when adjusting for SES factors although the difference was borderline significant (−6.2% vs. −4.4%, p for difference= 0.098).

Figures 2A and 2B present the joint estimated time to dialysis and transplant as competing first RRT events, by race, based on unadjusted and adjusted (i.e., weighted) analyses, respectively. Mixtures of Weibull distributions for each event were estimated in a unified model [34–36] and are included as dashed lines in the graphs. Only the location parameters (βs) differed by race. The differences were attenuated but remained substantial when weighted to adjust for SES. The weighted model indicated that AA children had a 37.5% (= [exp(2.71 − 3.18) − 1] × 100) shorter time to dialysis as first RRT (95%CI: −60.9%, −0.2%), and 53.7% (= [exp(3.14 − 2.71) − 1] × 100) longer time to transplant as first RRT(95%CI: −10.4%, +164.0%). A full description of the models, including levels of statistical significance, are presented in Supplemental Table 2.

Figure 3 depicts the frequency and timing of transplantation for children who initiated dialysis, by race. Among the 47 non-AA children whose first RRT was dialysis, 57% (27) received transplant at a later date (median years after dialysis= 0.41, IQR= 0.22, 1.12). In contrast, among the 25 AA children who initially received dialysis, 28% (7) received transplant afterward (median years after dialysis= 1.19, IQR= 0.57, 3.24). These results were consistent with the analysis deconstructing RRT initiation to dialysis and transplant.

DISCUSSION

Our study showed that among children with a non-glomerular cause of CKD, socioeconomic factors largely explained the unadjusted faster progression to first RRT observed in AA relative to non-AA children. Nonetheless, using a competing risks approach to dissect the type of RRT and after adjusting for SES factors, AA children were more likely to receive a kidney transplant as the first RRT at substantially longer times after CKD onset. Using decline in GFR as another measure of CKD progression, we showed that AA children of comparable SES to non-AA children did decline faster. This is congruent with a slightly earlier time to initiate RRT in adjusted analysis (1.6 years earlier) and more importantly, may in part explain why dialysis was offered as the first therapy for ESRD among AA children compared to transplant. We speculate that differential GFR trajectories by race may perhaps be due to unmeasured genetic (e.g., non-*APOL1*) or metabolic factors, but it is more likely due to unmeasured SES variables that are strongly related to this particular disease process [37].

While time to RRT and GFR decline are two metrics of disease progression, there are important distinctions between the two. Time to RRT reflects a component of biological disease processes, but is also determined largely by clinical decisions, family preparedness/consent, and availability of organs. These variables are likely strongly influenced by SES factors. Decline in GFR is a physiologic measure of disease progression which may be less associated with the measured SES variables.

A major challenge in investigating racial health differences is disentangling the effect of SES factors and race [27]. Using inverse probability of exposure weights worked well to accomplish this and provided marginal estimates of effect (i.e., the overall effect in the population had the SES factors been equally distributed by race [38]). Parametric survival methods and mixture models offered a full characterization of times to first RRT and specific modalities and fit the data well, a major strength of this analysis [34–36]. This approach extended beyond hazard ratios (a commonly used metric of risk) and provided a richer characterization of times to event [36]. In addition, the mixture approach is free of the assumptions of proportionality of cause-specific and subhazard functions which in the context of competing risks is perilous [39]. These parametric models allow for calculation of hazard ratios, and also provide the distributions of times to event and proportions experiencing each competing event (dialysis or transplantation), which offers a more complete epidemiologic description of RRT in this population. To our knowledge, this paper is the first to use the clinically and epidemiologically meaningful time scale of years since CKD onset to characterize time to treatment for ESRD, rather than study entry. Allowing for late entries capitalized on the heterogeneity of disease onset and study entry in the cohort.

There were several limitations to this analysis. First, this analysis assumed that 31 AA children who were not genotyped for *APOL1* were free of the high risk alleles. This assumption was based on the finding that 79 of 84 children (94%) tested for *APOL1* did not have the high risk genotype. The impact of misclassification was expected to be low although we cannot discount this as a missing data problem. Secondly, this study did not include RRT incidence during the first two years after CKD onset since the study had only few children recruited at those early times. Third, this analysis did not include neighborhood level SES characteristics which likely also play a role in incidence of ESRD. It should be noted though that individual SES explained nearly all of the observed racial differences in time to RRT.

The differences observed in initial therapy modality after adjusting for SES may reflect sociocultural and institutional differences not captured by SES. Furthermore, transplantation is intimately linked to organ availability from donors of similar blood types, tissue markers and genetic characteristics, all factors associated with race. This likely explains earlier dialysis among AA children in CKiD since previous work has suggested that AA children are less likely to receive living donor transplants, despite increased deceased donor transplants for all children, due to their higher priority and change in allocation policy in 2005 [40].

With numerous adult [6,13,41] and pediatric studies [16,19,40,42] describing racial differences in CKD progression and RRT, disparities in access to kidney transplantation, not explained by SES, persisted in the CKiD cohort. This suggests that factors outside of physician roles may be more effective to reduce these differences, such as public health interventions to increase donor availability, promote patient and family adherence to therapy, and encourage completion of the transplant evaluation process for activation on the transplant waiting list.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of abbreviations

AA	African-American
CKD	Chronic kidney disease
CKiD	Chronic Kidney Disease in Children Study
ESRD	End stage renal disease
GFR	Glomerular filtration rate
IPWs	Inverse probability weights
RRT	Renal replacement therapy referring to composite event of dialysis or transplant
SES	Socioeconomic status

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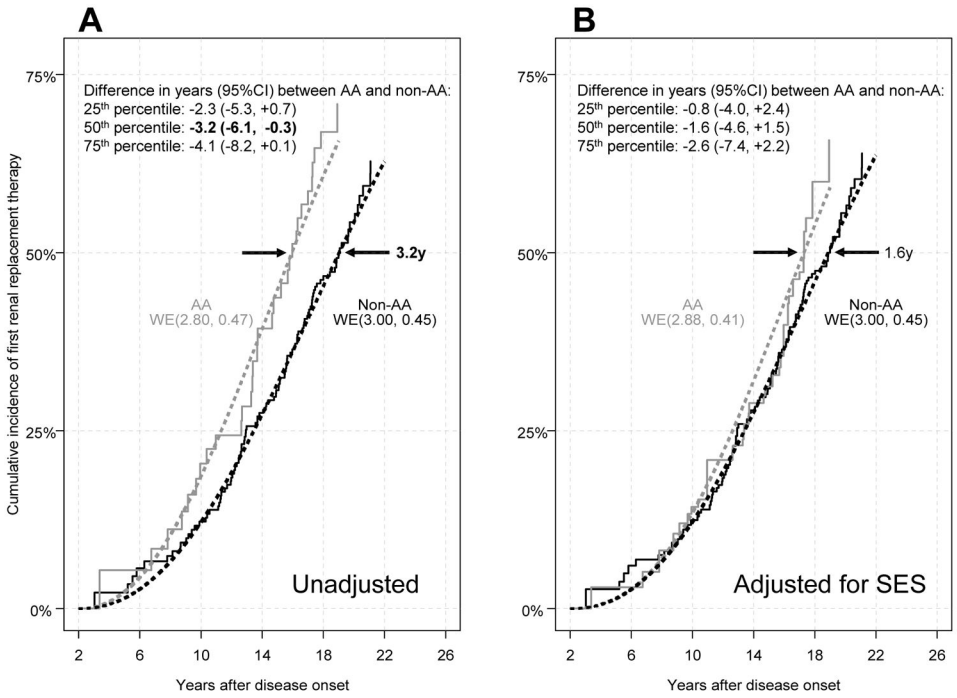

Figure 1.

Figure 1A. Unadjusted non-parametric survival step functions of incidence of first renal replacement therapy (RRT), by race. Figure 1B. Weighted by inverse probability weights non-parametric survival step functions of incidence of first RRT adjusted for socioeconomic status (SES) factors listed in Table 2. Dashed lines are based on Weibull distributions for each group with location (β) and scale (σ) and denoted as WE(β,σ).

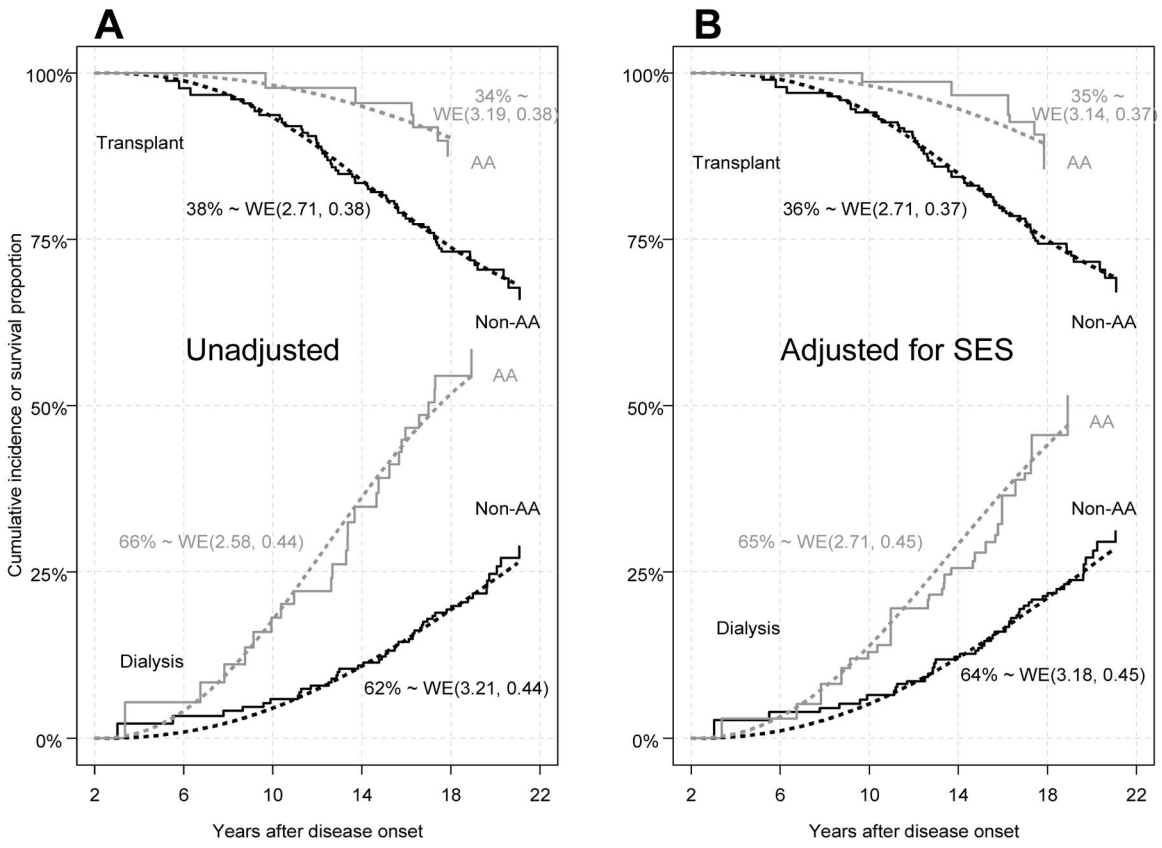

Figure 2.

Figure 2A. Unadjusted non-parametric survival step functions of incidence of first occurrence of dialysis or transplant as competing events, by race. Figure 2B. Weighted by inverse probability weights non-parametric survival step functions of incidence of first occurrence of dialysis or transplant as competing events, by race, adjusted for socioeconomic status (SES). Dashed lines are based on a mixture of Weibull distributions for each group with location (β) and scale (σ) and denoted as WE(β,σ) with corresponding estimated proportions experiencing each competing event.

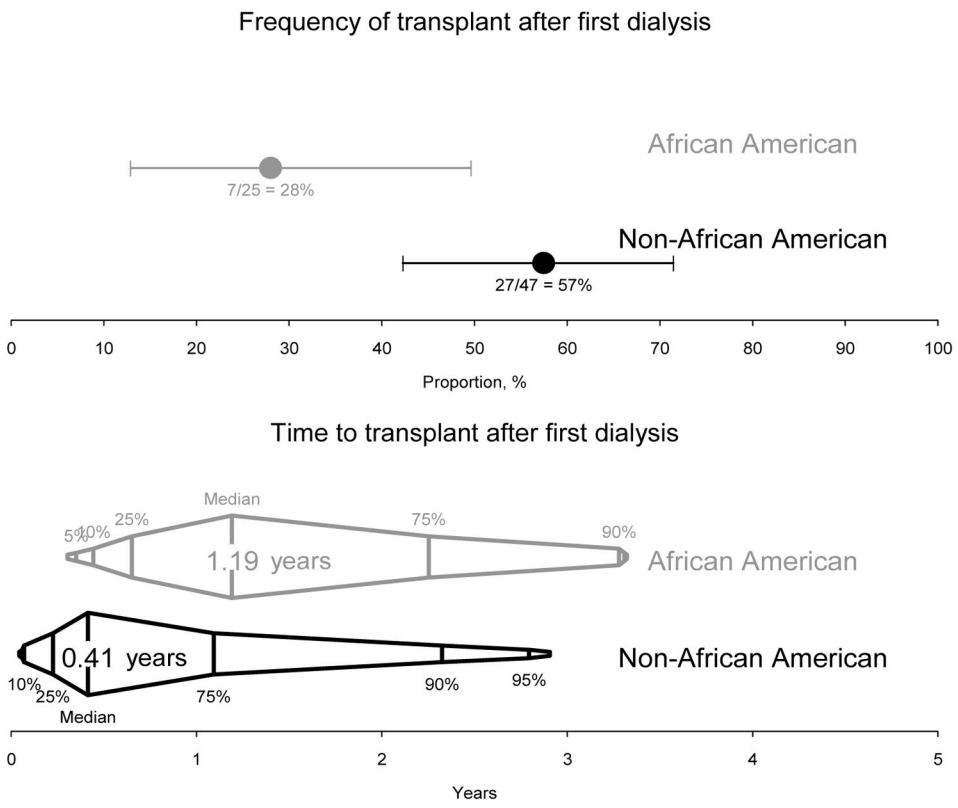

Figure 3.

Frequency and timing of kidney transplant after first dialysis, by race. Line segments around proportions receiving transplant are 95% exact confidence intervals. Percentile boxplots depict the distributions of times to transplant after first dialysis.

Table 1

Baseline descriptive statistics (Median [IQR] or % (n)) of demographic, socioeconomic and clinical characteristics by race among children with a non-glomerular cause of CKD. P-values are based on the Wilcoxon rank sum test for continuous variables and Fisher's exact test for categorical variables.

Variable	Non-African American N= 493	African American N= 110	P-value
Age at study entry	10.2 [6.6, 13.7]	9.6 [5.4, 13.2]	0.282
Male	64% (314)	75% (83)	0.020
Hispanic ethnicity	15% (73)	10% (11)	0.224
Congenital CKD	72% (353)	80% (88)	0.075
Birth weight (g)	3175 [2778, 3600]	3005 [2523, 3400]	0.010
Abnormal birth history	29% (137)	45% (45)	0.002
Socioeconomic indicators			
Any private insurance	73% (349)	46% (50)	<.001
Any public insurance	40% (193)	64% (70)	<.001
Income < $30K	27% (131)	61% (65)	<.001
Income ≥ $30K to $75K	37% (181)	30% (32)	
Income > $75K	36% (174)	9% (10)	
Maternal education less than college	65% (316)	79% (85)	0.004
Food assistance in past year	15% (73)	35% (38)	<.001
Private MD in past year	75% (368)	61% (66)	0.003
Renal characteristics at study entry			
GFR (ml/min|1.73m^2)	49 [36, 60]	56 [42, 67]	0.006
Urine protein:creatinine, mg/mg of creatinine	0.28 [0.11, 0.78]	0.32 [0.13, 0.94]	0.223
Normal proteinuria (< 0.2 mg/mg of Cr)	42% (197)	36% (38)	0.220
Elevated proteinuria (0.2 to 2 mg/mg of Cr)	51% (239)	52% (55)	
Nephrotic proteinuria (>2 mg/mg of Cr)	8% (36)	12% (13)	
Clinical characteristics at study entry			
Height percentile	24.8 [7.2, 54.8]	33.8 [9.0, 61]	0.110
Weight percentile	42.4 [15.9, 75.3]	55.1 [19.5, 83.4]	0.090
BMI percentile	62.3 [33.8, 87.2]	64.0 [33.0, 89.4]	0.432
SBP percentile	64.3 [36.8, 84.8]	67.7 [44.4, 90.5]	0.047
DBP percentile	68.4 [45.1, 87.0]	79.9 [59.1, 92.7]	<.001
Hypertension	32% (154)	41% (43)	0.113
Longitudinal data			
Total study visits	2089	455	--
Total person-years	2177.5	475.4	--
Any renal replacement therapy (RRT)	21% (104)	28% (31)	--
Dialysis as first RRT	10% (47)	23% (25)	--
Transplant as first RRT	12% (57)	5% (6)	--

Table 2

Multivariate logistic regression results from propensity score model estimating the odds of being African American race. **Bold** indicates $p < 0.05$.

Variable	Odds ratio	95% confidence interval
Male	**2.33**	**(1.40, 3.88)**
Income < $30K	**2.31**	**(1.33, 4.03)**
Income ≥ $30K to $75K	1	NA
Income > $75K	**0.37**	**(0.17, 0.80)**
Abnormal birth history	**2.12**	**(1.32, 3.42)**
Food assistance in past year	1.43	(0.81, 2.54)
Any public insurance	1.27	(0.75, 2.15)
Maternal education less than college	0.95	(0.53, 1.72)
Private MD in past year	0.71	(0.44, 1.14)

Table 3

Baseline demographic, socioeconomic and clinical characteristics based on weighted pseudopopulation from the propensity score logistic model. P-values are based on weighted t-tests for continuous variables and the Chi-square test for categorical variables.

Variable	Non-African American N= 493	African American N= 110	P-value
Age at study entry	10.0 [6.5, 13.4]	10.5 [6.7, 14.6]	0.251
Male	66% (325.3)	71% (74.4)	0.328
Hispanic ethnicity	17% (82.4)	10% (10.7)	0.090
Congenital CKD	72% (355.7)	70% (73.3)	0.630
Birth weight (g)	3147 [2693, 3572]	3090 [2807, 3487]	0.704
Abnormal birth history	32% (151.7)	30% (29.2)	0.599
Socioeconomic indicators			
Any private insurance	69% (326.7)	62% (65)	0.200
Any public insurance	45% (213.4)	48% (50.5)	0.519
Income < $30K	33% (161.4)	33% (34.3)	0.826
Income ≥ $30K to $75K	36% (174.9)	39% (39.6)	
Income > $75K	31% (150.4)	28% (28.9)	
Maternal education less than college	68% (329.5)	71% (73.5)	0.562
Food assistance in past year	19% (92)	21% (21.8)	0.629
Private MD in past year	73% (356.4)	74% (77.6)	0.744
Renal characteristics at study entry			
GFR (ml/min|1.73m^2)	49 [36, 60]	58 [43, 68]	<.001
Urine protein:creatinine, mg/mg of creatinine	0.3 [0.11, 0.78]	0.21 [0.09, 0.71]	0.134
Normal proteinuria (< 0.2 mg/mg of Cr)	41% (194.2)	48% (49.4)	0.245
Elevated proteinuria (0.2 to 2 mg/mg of Cr)	51% (241.8)	42% (42.9)	
Nephrotic proteinuria (>2 mg/mg of Cr)	8% (36)	9% (9.6)	
Clinical characteristics			
Height percentile	23.7 [6.6, 53.2]	29.9 [8.4, 56.7]	0.311
Weight percentile	41.6 [15.0, 74.7]	51.5 [20.4, 80.8]	0.100
BMI percentile	63.1 [33.7, 88.4]	62.2 [32.6, 89.7]	0.611
SBP percentile	64.7 [37.4, 84.8]	66.2 [46.6, 90.5]	0.014
DBP percentile	68.7 [45.1, 87.4]	79.9 [57.1, 91.1]	<.001
Hypertension	33% (156.1)	40% (40.7)	0.167

Table 4

GFR at study entry (ml/min|1.73m^2) and percent change per year, by race, based on mixed effects (random intercepts and slopes) regression models.

	Unadjusted		Adjusted for SES	
	Non-African American	***African American***	***Non-African American***	***African American***
GFR at study entry (95%CI)	47.9 (46.4, 49.3)	53.3 (50.0, 56.8)	47.8 (46.3, 49.2)	55.0 (50.9, 59.4)
P-value	Reference	**0.003**	Reference	**0.001**
Change per year (95% CI)	**−4.3% (−5.1%, −3.6%)**	**−6.2% (−7.8%, −4.6%)**	**−4.4% (−5.1%, −3.6%)**	**−6.2% (−8.2%, −4.1%)**
P-value	Reference	**0.040**	Reference	0.098