Racial and Ethnic Disparities in Survival of Children with ESRD

Elaine Ku,*† Charles E. McCulloch,‡ Barbara A. Grimes,‡ and Kirsten L. Johansen*

*Division of Nephrology, Department of Medicine, †Division of Pediatric Nephrology, Department of Pediatrics, and ‡Department of Epidemiology and Biostatistics, University of California, San Francisco, California

ABSTRACT

Observational studies have reported that black and Hispanic adults receiving maintenance dialysis survive longer than non–Hispanic white counterparts. Whether there are racial disparities in survival of children with ESRD is not clear. We compared mortality risk among non–Hispanic black, Hispanic, and non–Hispanic white children who started RRT between 1995 and 2011 and were followed through 2012. We examined all-cause mortality using adjusted Cox models. Of 12,123 children included for analysis, 1600 died during the median follow-up of 7.1 years. Approximately 25% of children were non-Hispanic black, and 26% of children were of Hispanic ethnicity. Non–Hispanic black children had a 36% higher risk of death (95% confidence interval [95% CI], 1.21 to 1.52) and Hispanic children had a 34% lower risk of death (95% CI, 0.57 to 0.77) than non–Hispanic white children. Adjustment for transplant as a time-dependent covariate abolished the higher risk of death in non–Hispanic black children (hazard ratio, 0.99; 95% CI, 0.88 to 1.12) but did not attenuate the finding of a lower risk of death in Hispanic children (hazard ratio, 0.59; 95% CI, 0.51 to 0.68). In conclusion, Hispanic children had lower mortality than non–Hispanic white children. Non–Hispanic black children had higher mortality than non–Hispanic white children, which was related to differences in access to transplantation by race. Parity in access to transplantation in children and improvements in strategies to prolong graft survival could substantially reduce disparities in mortality risk of non–Hispanic black children treated with RRT.

J Am Soc Nephrol 28: 1584–1591, 2017. doi: https://doi.org/10.1681/ASN.2016060706

Although black and Hispanic patients generally experience worse health outcomes than white patients, black and Hispanic adults treated with maintenance dialysis (especially hemodialysis) have consistently been observed to have a lower risk of death compared with white adults on dialysis.[1–10] This observation persists, despite adjustment for case mix differences,[1–4,9,11–17] lower rates of transplantation,[1,8,18] higher prevalence of anemia,[17,19,20] fewer arteriovenous fistulas,[21–23] and lower dialysis doses.[16,17,19] On closer examination, the lower risk of death in black and Hispanic minorities has been noted specifically in those who are older than 50 years of age and Hispanic patients of all ages treated with dialysis, but it was not observed in younger black adults.[6,8] Whether there are differences in survival among black and Hispanic children compared with white children treated with RRT in the United States remains unclear.

Racial disparities in access to transplantation have been previously recognized among children with ESRD in the United States. Specifically, black and Hispanic children are less likely to receive deceased donor kidney transplantation, preemptive transplantation (without first receiving dialysis), and living donor transplantation.[24–27] This racial disparity in transplantation was not eliminated by implementation of programs designed to prioritize transplantation for children, such as Share 35, a policy that preferentially allocates organs from young deceased donors (<35 years old) to recipients <18 years of age.[24,26] It is possible that lower

Received June 30, 2016. Accepted October 17, 2016.

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Elaine Ku, Division of Nephrology, University of California, San Francisco, 533 Parnassus Avenue, U404, Box 0532, San Francisco, CA 94143-0532. Email: elaine.ku@ucsf.edu

access to kidney transplantation in black or Hispanic children could lead to lower overall survival given that transplantation is a much more common occurrence in children compared with adults as a result of their high priority on the transplant waitlist and confers a survival benefit over dialysis.[24,28]

A recent European registry study of children treated with RRT suggested a trend toward lower risk of death in black children, although few black children were included in the study, and the observation did not achieve statistical significance.[29] A prior study using the US Renal Data System (USRDS) suggested a higher relative risk of death in black versus white children treated with dialysis,[30] but the focus of this study was not on racial disparities and their potential explanatory factors. Because children have ready access to health care, higher priority on the transplant waitlist than most adults, and fewer comorbid conditions, which may reduce the potential for confounding, the study of racial disparities in the survival of children may be informative to our overall understanding of differences in mortality outcomes by race.[6,8]

The objectives of this study were to determine whether children who initiate RRT in the United States experience disparities in survival according to race and whether lower access to transplantation mediates any racial disparities in mortality risk. We hypothesized that the overall risk of death would be higher in non–Hispanic black and Hispanic children treated with RRT, regardless of treatment modality (dialysis or transplantation) and contrary to observations in the adult dialysis population. We also hypothesized that access to transplantation would mediate, at least in part, the higher risk of death in non–Hispanic black or Hispanic children treated with RRT.

RESULTS

Study Cohort

We identified 12,123 black, Hispanic, or non–Hispanic white children in the USRDS with available race and covariates of interest at the time of first RRT for inclusion in our study. There were significant differences in the characteristics of black, non–Hispanic white, and Hispanic children at the time of first RRT initiation (Table 1). The median age was slightly higher in non–Hispanic black children, and there was a higher prevalence of FSGS as the cause of ESRD among non–Hispanic black children. In contrast, non–Hispanic white children had a higher prevalence of congenital anomalies of the kidney and urinary tract as the cause of their ESRD, and Hispanic children had a higher prevalence of GN (excluding FSGS) as the cause of their ESRD. Medicaid use was higher in non–Hispanic black and Hispanic children. Non–Hispanic black and Hispanic children were more likely obese and receiving hemodialysis as their initial dialysis modality than non–Hispanic white children. Non–Hispanic black and Hispanic children were also less likely to receive multiple transplants during the follow-up period.

Association between Race and Mortality

Approximately 13% of the cohort (n=1600) died during 90,374 person-years of follow-up (median follow-up period =7.1 years; interquartile range, 3.5–11.0). The absolute rate of death during the follow-up period was 2.67 per 100 person-years in non–Hispanic black children, 1.57 per 100 person-years in non–Hispanic white children, and 1.21 per 100 person-years in Hispanic children. Non–Hispanic black children were more likely to die of cardiovascular causes, whereas Hispanic children were more likely to die of infectious causes (Table 1).

In multivariable analysis, the risk of death was 36% higher (95% confidence interval [95% CI], 1.21 to 1.52) in black versus non–Hispanic white children and 34% lower (95% CI, 0.57 to 0.77) in Hispanic versus non–Hispanic white children (Table 2). Adjustment for transplant as a time-dependent covariate attenuated the higher risk of death in black children (hazard ratio [HR], 0.99; 95% CI, 0.88 to 1.12) but did not substantially alter the lower risk of death in Hispanic children compared with non–Hispanic white children.

In sensitivity analysis, we examined outcomes according to the duration of follow-up time attributed to treatment with dialysis or transplantation separately. Thirty percent of the total follow-up time of non–Hispanic white children was spent on dialysis (and 70% with a functioning allograft), whereas Hispanic children spent 43% of their follow-up time on dialysis, and non–Hispanic black children spent 56% of their follow-up time on dialysis (Table 3). During the follow-up period attributed to dialysis, the risk of death was similar in non–Hispanic black children (HR, 0.96; 95% CI, 0.85 to 1.09) and 43% lower in Hispanic children (95% CI, 0.48 to 0.67) compared with that of non–Hispanic white children (Table 3). During the follow-up duration attributed to the presence of a functional allograft, the risk of death was not statistically significantly different in non–Hispanic black children (HR, 1.21, 95% CI, 0.90 to 1.61), and the risk was 34% lower in Hispanic children (95% CI, 0.48 to 0.93) compared with non–Hispanic white children.

Subgroup Analyses

We examined whether the association of race with mortality varied according to characteristics of interest, including initial RRT modality. Approximately 75% of individuals (n=9152) received at least one kidney transplant, and 1690 children received preemptive transplants, of whom only 8.4% were in non–Hispanic black children and 15.9% were in Hispanic children. Although the interaction between race and initial treatment modality (preemptive transplant, hemodialysis, or peritoneal dialysis) was not statistically significant (P>0.05), we examined the subgroup that initiated RRT with dialysis to ensure that the lower survival among non–Hispanic black children was not mediated entirely by lower access to preemptive transplantation. The results were similar to those of the primary analysis, with an HR of 1.27 (95% CI, 1.12 to 1.42) for death in non–Hispanic black children compared with non–Hispanic white children who did not receive preemptive

Table 1. Characteristics of patients by race and ethnicity at time of first RRT and their absolute risk of death

Characteristic	Non–Hispanic White Children, *n*=5942	Non–Hispanic Black Children, *n*=3045	Hispanic Children, *n*=3136	*P* Value
Median age [IQR], yr	14.5 [10.5–16.5]	15.5 [12.5–17.5]	14.5 [11.5–17.5]	<0.001
Men, % (*N*)	55.0 (3270)	54.4 (1656)	53.6 (1682)	0.44
Cause of ESRD, % (*N*)				<0.001
CAKUT	47.7 (2836)	24.4 (742)	34.3 (1077)	
FSGS	11.9 (708)	25.2 (766)	12.7 (399)	
GN	22.9 (1363)	25.9 (790)	26.5 (832)	
Hypertension	2.6 (154)	7.5 (229)	4.3 (135)	
Diabetes	0.6 (38)	1.4 (43)	0.6 (18)	
Neoplasms	2.2 (131)	1.6 (49)	1.7 (53)	
Other	12.0 (712)	14.0 (423)	19.8 (622)	
Insurance, % (*N*)				<0.001
None	4.4 (260)	6.9 (209)	13.9 (437)	
Medicaid	36.6 (2177)	58.1 (1770)	53.5 (1678)	
Median income [IQR], $	51,396 [41,503–66,495]	40,988 [32,526–54,078]	46,517 [37,227–58,141]	<0.001
Dialysis type[a]				<0.001
Hemodialysis	55.7 (2542)	69.4 (2003)	63.5 (1807)	
Peritoneal dialysis	44.3 (2023)	30.6 (884)	36.5 (1039)	
BMI category				
Underweight	10.5 (625)	9.7 (296)	9.9 (310)	<0.001
Normal weight	73.1 (4342)	67.0 (2040)	74.0 (2321)	
Obese	16.4 (975)	23.2 (720)	16.1 (505)	
No. of transplants during follow-up				<0.001
Zero	1053 (17.7)	1040 (34.2)	878 (28.0)	
One	4221 (71.0)	1770 (58.1)	2089 (66.6)	
Two or more	668 (11.2)	235 (7.7)	169 (5.4)	
Cause of death[b]				0.001
Cardiovascular	175 (31.7)	192 (38.6)	69 (34.2)	
Infectious	89 (16.1)	75 (15.1)	50 (24.8)	

IQR, interquartile range; CAKUT, congenital anomalies of the kidney and urinary tract.
[a]Missing in *n*=135.
[b]Missing in *n*=349.

transplants and a HR of 0.62 (95% CI, 0.53 to 0.72) for Hispanic children (Table 2).

In additional subgroup analysis, we also did not find a statistically significant interaction by age (as a continuous or categorical variable), body mass index (BMI) category, cause of ESRD, insurance status, or calendar year of dialysis initiation (before or after 2006) in either non–Hispanic black or Hispanic children (all $P>0.05$). We did find geographic variations in the risk of death among black ($P<0.01$ for interaction between black race and residence in the south) but not Hispanic children. Whereas the risk of death was statistically significantly higher in non–Hispanic black children in the west (HR, 1.66; 95% CI, 1.17 to 2.40), Midwest (HR, 1.30; 95% CI, 1.01 to 1.66), and northeast (HR, 2.03; 95% CI, 1.43 to 2.87) census tracts, the risk of death was not significantly higher in the south (HR, 1.16; 95% CI, 0.98 to 1.36). There was no interaction between geographic region of residence and Hispanic race (all $P>0.05$), such that the risk of death was consistently lower in Hispanic children compared with non–Hispanic white children across all regions of the United States.

Table 2. Relative risk of death in Cox models

Overall Cohort, *n*=12,123	Non–Hispanic Black Children HR (95% CI)	Non–Hispanic White Children HR (95% CI)	Hispanic Children HR (95% CI)
Unadjusted model	1.71 (1.54 to 1.91)	1.0	0.77 (0.67 to 0.89)
Adjusted model	1.36 (1.21 to 1.52)	1.0	0.66 (0.57 to 0.77)
Adjusted model with transplant as time-dependent covariate	0.99 (0.88 to 1.12)	1.0	0.59 (0.51 to 0.68)
Dialysis as first RRT, *n*=10,433	1.27 (1.12 to 1.42)	1.0	0.62 (0.53 to 0.72)

All models adjusted for age, sex, cause of ESRD, calendar year, insurance type, median neighborhood income, and BMI *z* score unless otherwise specified.

Table 3. Follow-up and outcomes partitioned between dialysis and transplant follow-up time according to race and ethnicity

Subgroup	Dialysis, 35,835 person-yr	Transplant, 54,539 person-yr
Non–Hispanic white children		
Follow-up time, person-yr (% of total)	13,481 (29.6)	32,087 (70.4)
Deaths, *N*	537	177
Death rate per 100 person-yr	3.98	0.55
Adjusted HR (95% CI)[a]	1.00 (reference)	1.00 (reference)
Non–Hispanic black children		
Follow-up time, person-yr (% total time)	13,286 (56.4)	10,263 (43.6)
Deaths, *N*	551	78
Death rate per 100 person-yr	4.15	0.76
Adjusted HR (95% CI)[a]	0.96 (0.85 to 1.09)	1.21 (0.90 to 1.61)
Hispanic children		
Follow-up time, person-yr (% total time)	9068 (42.7)	12,190 (57.3)
Deaths, *N*	210	47
Death rate per 100 person-yr	2.32	0.39
Adjusted HR (95% CI)[a]	0.57 (0.48 to 0.67)	0.66 (0.48 to 0.93)

[a]All models adjusted for age, sex, cause of ESRD, calendar year, insurance type, median neighborhood income, and BMI category unless otherwise specified.

DISCUSSION

Black and Hispanic adults treated with dialysis have been shown to have longer survival compared with non–Hispanic white adults, despite potential adverse social and socioeconomic positions that may predispose to poorer health outcomes, including lower access to transplantation.[8–11,24,26,29,31–33] Although studies in the pediatric population have also shown marked disparities in access to transplantation in non–Hispanic black and Hispanic children and worsened graft survival in non–Hispanic black children,[24,26,29,34] our study is novel in its focus on the risk of death by race and ethnicity in children treated with dialysis and transplantation using data from a large United States cohort. We found that the risk of death was significantly higher in non–Hispanic black children beginning RRT compared with non–Hispanic white children but that access to transplantation seemed to mediate the differential risk of mortality. However, Hispanic children had a consistent survival advantage compared with non–Hispanic white children, despite their known lower access to transplantation.[24] This finding was contrary to our hypothesis but is consistent with the better survival that has been observed in Hispanic adults treated with RRT. These observations were consistent across all subgroups of interest that were examined in our study, including age, BMI category, cause of ESRD, calendar year, and treatment modality.

Our study highlights the important contribution of transplantation to the inequities in survival of non–Hispanic black children with ESRD. There was a higher overall relative risk of death in non–Hispanic black (versus non–Hispanic white) children during the full duration of follow-up in our study, which was attenuated from 1.36 to 0.99 with adjustment for transplant as a time-dependent covariate. Furthermore, non–Hispanic black children spent the least amount of follow-up time with a functional allograft (44% in non–Hispanic black children versus 70% for non–Hispanic white children and 57% for Hispanic children). When we examined the risk of death in children in analyses separated according to time attributed to dialysis or transplant, we did not find a statistically significant difference in the risk of death of non–Hispanic black versus non–Hispanic white children, suggesting that black and non–Hispanic white children fare similarly on dialysis or with transplant, contrary to our hypothesis. These results suggest that the lower access to transplantation in non–Hispanic black children and conversely, better survival conferred by higher access to transplantation in non–Hispanic white children[24] are the major explanations for our findings. This is consistent with the fact that the risk of death was not higher in non–Hispanic black versus non–Hispanic white children in the south, where many states have shorter than average wait times and a higher number of pediatric–quality cadaveric kidneys per pediatric candidate.[34] Our results suggest that substantial improvements in the parity of mortality outcomes by race may be possible with the adoption of additional strategies to equalize access to kidney transplantation in non–Hispanic black children and improve allograft survival among those who do receive transplants.[34] The extent to which racial disparities in access to kidney transplantation persist under the new organ allocation system should be examined in the near future when data become available.

Prior studies in the adult dialysis population have noted the importance of age as a determinant of the presence or absence of an observed survival advantage for black patients.[6,8,33,35] In particular, younger black adults <50 years of age have been observed to have a similar or higher risk of death compared with white adults in the same age range, whereas among older patients on dialysis, the risk of death is lower among blacks.[6,8,33,35] Several reasons have been postulated for the variation in survival rates across the age spectrum, including the presence of greater inequities in socioeconomic status and access to health care in younger versus older black adults.[6,8] Our data are consistent with prior reports of the presence of significant effect modification by age in black adult patients on dialysis and extend these

observations to children <18 years of age, in whom the observation of better survival in non–Hispanic black children is not just absent but reversed.[6] Given the lower overall burden of comorbid conditions among children with ESRD (such as diabetes, malignancy, or advanced coronary artery disease), this finding may suggest that differences in the survival of older adults treated with dialysis could be related to the presence or severity of such comorbid conditions.

We also observed a consistently lower risk of death in Hispanic children in our study, despite their lower access to transplantation. Although the reasons for the survival advantage of Hispanic children are unclear, our findings may inform the likelihood of prior proposed hypotheses for the survival advantage of adult Hispanic patients with ESRD. Some studies have suggested that the longer survival of Hispanic patients may be due to lower burden of atherosclerotic disease at the time of ESRD onset in the Hispanic population.[36,37,38] However, in our study, Hispanic children did not have a statistically significantly higher risk of cardiovascular-related death, and children are generally less likely than adults to die of atherosclerotic disease given the duration of time needed for such disease to develop. Because the overall survival of children with ESRD is higher compared with that of adults with ESRD,[39] the likelihood of survivor bias would be low in a pediatric ESRD cohort. Other hypotheses that have been proposed to explain the survival advantage of Hispanic patients treated with dialysis have included the salmon bias and the healthy migrant hypothesis, where sicker migrants may return to their country of origin and therefore, their deaths may not be accounted for in studies, whereas healthier migrants tend to immigrate to the United States and contribute to the better survival of Hispanic patients.[40] However, given that our study focuses on children who are more likely to have been born in the United States and stay in this country, the salmon bias and the healthy migrant hypothesis seem less plausible as explanations for the observed Hispanic survival advantage in children.

The strengths of our study include the large size of the cohort, the contemporary nature of the data, and a relatively large number of clinical outcomes, particularly given the relative youth of our cohort members. Limitations include the observational nature of these data, potential errors in data used for determination of race and misclassification of ethnicity, and missing data in the USRDS, which may have caused some misclassification of transplant status or excluded some children from our study. We do note that there are racial differences in the most common causes of ESRD in children, which may contribute to some of the observed racial differences in survival of children, although we have adjusted for cause of ESRD in our models. However, it is possible that residual confounding may be present, despite our adjustment for important potential confounders.

In conclusion, we observed a significantly higher risk of death in non–Hispanic black versus non–Hispanic white children initiated on RRT over the last two decades that seems mediated by differences in access to kidney transplant. In contrast, we noted a significantly lower risk of death in Hispanic children treated with RRT that was independent of age, BMI, cause of ESRD, geographic location, or treatment modality. Our study suggests a critical need to develop strategies to ensure parity in access to transplantation for non–Hispanic black children with ESRD and the need for additional studies to understand the reasons for the survival advantage of Hispanic children with ESRD.

CONCISE METHODS

Study Population

We performed a retrospective cohort study of children between the ages of 2 and 19 years old who required their first RRT between January 1, 1995 and December 31, 2011 using data from the USRDS, the national ESRD registry. We included only children whose initial onset of ESRD fell within our study period defined by availability of a Centers for Medicare and Medicaid Services (CMS) ESRD Medical Evidence Report (Form CMS-2728-U3) filed within 6 months of the first ESRD service date (n=14,024) (Figure 1). Children under the age of 2 years old were excluded, because standards for BMIs are not available for this age group from the Centers for Disease Control and Prevention (CDC), and BMI was a covariate of interest because of its known association with the likelihood of transplantation and risk of mortality in children.[4,41] We excluded patients whose forms had missing BMI (n=442) or missing median income (n=454) (Figure 1).

Predictor and Covariates of Interest

Race was abstracted from the Patient Files in the USRDS, and children were first categorized by ethnicity (Hispanic versus non-Hispanic). Subsequently, among the non-Hispanic children, race was categorized as non-Hispanic black or non-Hispanic white. If Hispanic ethnicity was unknown, but race was known, these children were classified as non–Hispanic black or non–Hispanic white children. We chose

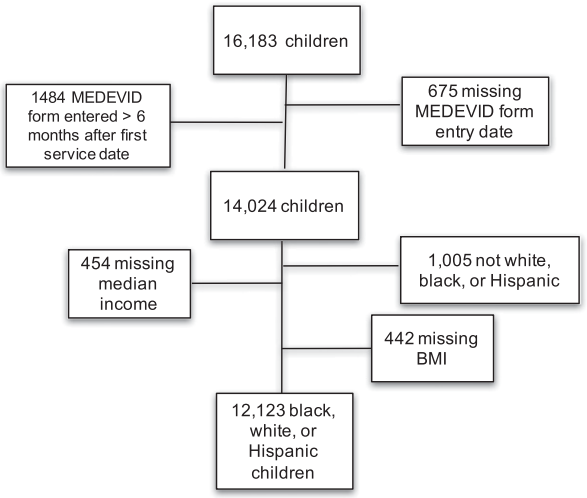

Figure 1. Derivation of the cohort. Inclusion and exclusion criteria for cohort included in our analysis.

non–Hispanic white children as the reference comparator in this study due to the known differences in survival of Hispanic adults treated with dialysis compared with non–Hispanic white adults. Children with unknown or other race were excluded (n=1005).

Patient demographic characteristics (age at incident ESRD, race, and sex), cause of ESRD, insurance coverage (Medicaid, none, or other) as an indicator of lower income status, zip code, date of ESRD onset, and BMI at incident ESRD were abstracted from the CMS-2728 Form (Medical Evidence [MEDEVID]) and Patient Files in the USRDS. BMI values were age and sex standardized to z scores using the 2000 CDC standards for United States children.[41] We defined underweight as BMI<5th percentile for age (corresponding to a z score <-1.64) and obese as BMI≥95th percentile for age (corresponding to a z score ≥ 1.64) according to the CDC criteria because of a known U–shaped association between BMI and mortality from prior studies in children treated with RRT.[41] We used zip code to determine median household income of patients' neighborhood using median income values from the American Community Survey between 2006 and 2010 as a continuous variable.[42] Initial ESRD treatment modality (transplant versus dialysis) was determined at the first ESRD service date as listed in the MEDEVID File. We determined the date of transplant procedures using USRDS Patient and Transplant Files, which contain data reported by transplant centers to the United Network for Organ Sharing.

Outcome Ascertainment

We abstracted death dates from the USRDS Patient Files and ascertained deaths up to June 30, 2012. Cause of death was determined from the USRDS Patient Files and categorized as cardiovascular, infectious, or other.

Statistical Analyses

Association between Race and Risk of Death

We assessed the association between race and risk of all-cause mortality using a Cox proportional hazards model adjusted for age (as a continuous variable), sex, cause of ESRD, Medicaid status, median neighborhood income, calendar year of ESRD onset (to account for potential secular trends in survival), and BMI category. We did not censor patients at the time of transplantation in our primary analysis, because transplantation is expected to improve outcomes and a very common occurrence in children. To examine whether the association between race and risk of death was potentially mediated by transplantation, we used the same multivariable Cox proportional hazards model and further adjusted for transplant as a time-dependent covariate.

Association between Race and Mortality According to Treatment Modality

We assessed the association between race and risk of death in subgroup analysis among those who were treated with dialysis as the first modality of RRT. In sensitivity analysis, we repeated our time–dependent Cox models, partitioning the duration of follow-up to time attributed to dialysis versus time attributed to the presence of a functional allograft to separately examine the risk of death by treatment modality.

Association between Race and Mortality in Subgroup Analyses

To determine whether racial disparities in survival may be amplified within particular subgroups, we tested for interactions between race and prespecified factors of interest, including age (categorized as <13 versus ≥13 years old to account for potential differences in mortality risk in adolescents who may be prone to nonadherence),[43] BMI category, initial RRT modality, cause of ESRD, and calendar period of follow-up (before or after 2006 to assess for the potential effect of Share 35 implementation in September of 2005).[24] We also tested for the presence of interaction by initial treatment modality (hemodialysis versus peritoneal dialysis versus transplant) and insurance status to examine risk of death. In sensitivity analysis, we also tested for interaction between race and age as a continuous variable. P values <0.05 were considered statistically significant for interaction terms.

Finally, because of known variations in transplantation and mortality risk by geographic region in the United States, we performed stratified analysis of the association between race and mortality by United States census tracts (using patients' zip codes).[44] We chose to use these relatively wide geographic divisions to assess any potential differences in mortality risk by geography, because some states may not have transplant or dialysis centers that treat children with RRT and given the likelihood that some children may travel to different states to receive pediatric subspecialty care.[45,46]

With the exception of conversion of BMI into standardized BMI z scores, which was performed using a Statistical Analysis System Tool provided by the CDC,[45] all data analyses were conducted using Stata 13. The Committee on Human Research of the University of California, San Francisco does not consider this work to be human subjects research.

ACKNOWLEDGMENTS

This work was supported by National Institutes of Health (NIH) grants KL2 TR00014 (to E.K.), K23 HL131023 (to E.K.), and K24 DK85153 (to K.L.J.). The work was also supported by a Satellite Dialysis Clinical Investigator Grant of the National Kidney Foundation to E.K. This publication was also supported by the National Center for Advancing Translational Sciences, NIH through University of California San Francisco-Clinical and Translational Sciences Institute grant UL1 TR000004.

Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. The interpretation and reporting of the data presented here are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the US Government.

DISCLOSURES

None.

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See related editorial, "Lesson Learned in Mortality and Kidney Transplant Outcomes among Pediatric Dialysis Patients," on pages 1334–1336.