Title
Racial-ethnic disparities in mortality and kidney transplant outcomes among pediatric dialysis patients.

Journal
Pediatric nephrology (Berlin, Germany), 32(4)

ISSN
0931-041X

Authors
Laster, Marciana
Soohoo, Melissa
Hall, Clinton
et al.

Publication Date
2017-04-01

DOI
10.1007/s00467-016-3530-2

Peer reviewed

Pediatr Nephrol
DOI 10.1007/s00467-016-3530-2

ORIGINAL ARTICLE

Racial–ethnic disparities in mortality and kidney transplant outcomes among pediatric dialysis patients

Marciana Laster[1] · Melissa Soohoo[2] · Clinton Hall[3] · Elani Streja[2] · Connie M. Rhee[2,4] · Vanessa A. Ravel[2] · Uttam Reddy[4] · Keith C. Norris[1] · Isidro B. Salusky[1] · Kamyar Kalantar-Zadeh[1,2,4]

Received: 6 July 2016 / Revised: 5 September 2016 / Accepted: 25 September 2016

Abstract
Background Previous studies in adult hemodialysis patients have shown that African–American and Hispanic patients have a lower risk of mortality in addition to a lower likelihood of kidney transplantation. However, studies of the association between race and outcomes in pediatric dialysis are sparse and often do not examine outcomes in Hispanic children. The objective was to determine if racial–ethnic disparities in mortality and kidney transplantation outcomes exist in pediatric dialysis patients.
Methods This was a retrospective cohort analysis of 2,697 pediatric dialysis patients (aged 0–20 years) from a large national dialysis organization (entry period 2001–2011) of non-Hispanic white, African–American, and Hispanic race-ethnicity. Associations between race–ethnicity with mortality and kidney transplantation outcomes were examined separately using competing risks methods. Logistic regression analyses were used to examine the association between race–ethnicity, with outcomes within 1 year of dialysis initiation.
Results Of the 2,697 pediatric patients in this cohort, 895 were African–American, 778 were Hispanic, and 1,024 were non-Hispanic white. After adjusting for baseline demographics, competing risk survival analysis revealed that compared with non-Hispanic whites, African–Americans had a 64 % higher mortality risk (hazards ratio [HR] = 1.64; 95 % CI 1.24–2.17), whereas Hispanics had a 31 % lower mortality risk (HR = 0.69; 95 % CI 0.47–1.01) that did not reach statistical significance. African–Americans also had higher odds of 1-year mortality after starting dialysis (odds ratio [OR] = 2.08; 95 % CI 0.95–4.58), whereas both African–Americans and Hispanics had a lower odds of receiving a transplant within 1 year of starting dialysis (OR = 0.28; 95 % CI 0.19–0.41 and OR = 0.43; 95 % CI 0.31–0.59 respectively).
Conclusion In contrast to adults, African–American pediatric dialysis patients have worse survival than their non-Hispanic white counterparts, whereas Hispanics have a similar to lower mortality risk. Both African–American and Hispanic pediatric dialysis patients had a lower likelihood of kidney transplantation than non-Hispanic whites, similar to observations in the adult dialysis population.

Keywords Race · Ethnicity · African–American · Hispanic · Pediatric · End-stage renal disease · Dialysis · Mortality · Transplant

Electronic supplementary material The online version of this article (doi:10.1007/s00467-016-3530-2) contains supplementary material, which is available to authorized users

✉ Kamyar Kalantar-Zadeh
kkz@uci.edu

[1] David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

[2] Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology and Hypertension, School of Medicine, University of California Irvine, 101 The City Drive South, City Tower, Suite 400, ZOT: 4088, Orange, CA 92868-3217, USA

[3] Department of Epidemiology, UCLA Fielding School of Public Health, Los Angeles, CA, USA

[4] Division of Nephrology and Hypertension, School of Medicine, University of California Irvine, Orange, CA, USA

Introduction

Racial-ethnic disparities exist in end-stage renal disease (ESRD) pediatric patients on dialysis. In 2000, Furth et al. described a 12 % lower likelihood of waitlist activation in African–American pediatric dialysis patients compared with white patients [1]. Despite attenuation in racial disparities in median wait times since 1997,

Published online: 29 October 2016

African–American children are still less likely to receive a kidney transplant than white children [2]. At this time, the median wait time differences between Hispanic vs non-Hispanic children remain largely unknown. However, a 2012 study by Patzer et al. found that both African–American and Hispanic children on the kidney transplant waitlist have longer times to transplant than white children [3].

Currently, there are few studies examining the association among race, ethnicity, and mortality in pediatric ESRD patients. Overall, mortality rates in pediatric dialysis patients aged 0 to 21 years have declined over the past 7 years, after taking into account differences in age, sex, race, ethnicity, primary cause of ESRD, and dialysis vintage [2]. In addition, a study by Ferris et al. using United States Renal Data System information from 1987 to 2002 found that African–American adolescents had lower 10-year survival rates than their white adolescent counterparts [4]. However, no data were available on Hispanic vs non-Hispanic children and mortality rates. These findings contrast with the racial paradoxes seen in adult African–American and Hispanic dialysis patients who demonstrate a survival advantage in comparison with non-Hispanic whites [5]. We thus sought to examine whether racial–ethnic disparities in mortality exist in the pediatric ESRD population and also evaluate disparities in transplantation, with consideration of transplantation and mortality, respectively as competing events.

Materials and methods

Data source and cohort construction

We examined data from incident and prevalent patients with ESRD who underwent dialysis treatment at one of the outpatient dialysis facilities of a large US dialysis organization (LDO) during the study period of 1 July 2001 to 31 December 2011. Information was not available for patients between 1 July 2006 and 31 December 2006.

Construction of this cohort is illustrated in Fig. 1. Patients who were younger than 21 years of age and of non-Hispanic white, non-Hispanic black, or Hispanic race–ethnicity were included in the analytical cohort. In the remainder of this manuscript, the former two groups are referred to as non-Hispanic whites and African–Americans, respectively. After removing patients with missing age information and those aged 21 years or older, 3,170 patients remained. Additional exclusions were made for patients with missing or implausible treatment data on baseline date or dialysis start and for patients with a race defined as "other," due to small sample size. The final study population consisted of 2,697 pediatric dialysis patients, 895 (33 %) of whom identified as African–-American, 778 (29 %) as Hispanic, and the remaining 1,024 (38 %) as white.

Demographic, clinical, and laboratory measures

Information on outcomes, race–ethnicity, and insurance type were obtained from the electronic medical records of the LDO database. Cause of death was categorized according to CMS 2746 ESRD Death Notification form. Race–ethnicity was self-reported by dialysis patients (or caregiver) according to the group with which they most closely identified, and according to US Census Bureau categorizations [6, 7]. A variable to indicate socioeconomic status (SES) was created by linking the zip code of the patients' dialysis centers to the median household income of that zip code; this variable was then stratified into three mutually exclusive groups: high (>$55,000), medium ($35,000–$55,000), and low (<$35,000). Body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared (kg/m^2). Height, weight, and BMI measurements were age- and sex-standardized and presented as percentiles using the 2000 Centers for Disease Control and Prevention (CDC) distribution for United States children. Of note, children < 2 years old did not have a calculated BMI percentile [8]. Low, medium, and high height and BMI groups were based on cutoffs at the 33rd and 67th percentiles of the age and sex standardized values. The height percentile was used in calculation of age- and sex-standardized percentiles for systolic and diastolic blood pressure provided by the National Institutes of Health and National Heart, Lung, and Blood Institute [9]. Hypertension was defined as systolic blood pressure >95th percentile. Cause of ESRD was divided into three mutually exclusive categories: congenital anomalies of the kidney and urinary tract (CAKUT), glomerulonephritis (GN), or other.

Clinical and laboratory measures for each patient were also obtained from the LDO electronic medical records during the study period (1 July 2001 to 31 December 2011). To minimize measurement variability, all repeated measures for each patient during any calendar quarter (i.e., over a 13-week interval) were averaged. Dialysis vintage was defined as the duration of time between a patient's first dialysis treatment and the first day of the baseline calendar quarter in which the patient entered the cohort. The first (baseline) studied quarter for each patient was the calendar quarter in which patient data was first available.

Blood samples were drawn using standardized techniques in all large dialysis organization clinics and were

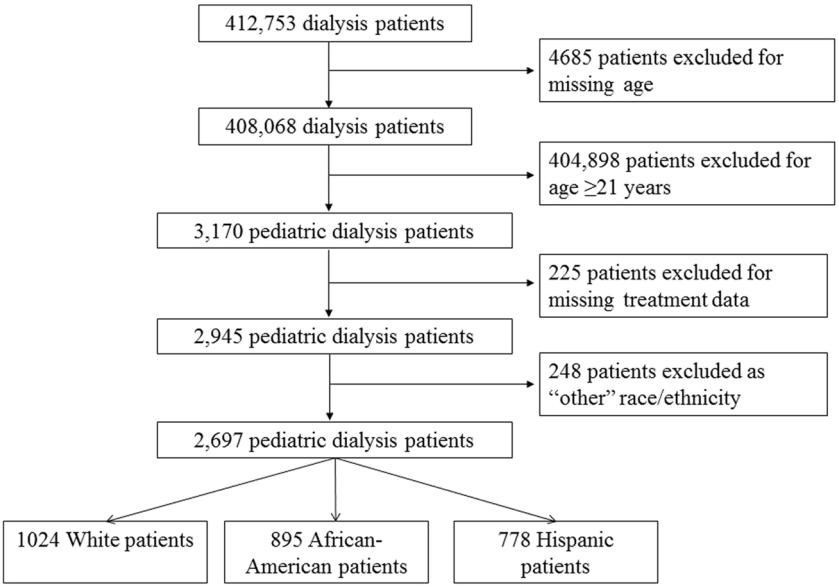

Fig. 1 Cohort construction

transported to a central laboratory in Deland, FL, USA, typically within 24 h, and were measured using automated and standardized methods. Most laboratory parameters (i.e., albumin, bicarbonate, phosphorous, calcium) were measured monthly; ferritin was measured at least quarterly. Hemoglobin was measured at least monthly in all patients but weekly to biweekly in most patients. Delivered dialysis dose was estimated by single-pooled Kt/V (spKt/V) using the urea kinetic model. Low spKt/V was defined by spKt/V <1.8 for patients on peritoneal dialysis and spKt/V <1.2 for hemodialysis patients.

In a subcohort of patients receiving dialysis treatment from July 2001 to June 2006, we obtained blood type (A or A/B, B, O) data through linkage to the candidate waitlist data of the Scientific Registry of Transplant Recipients (SRTR).

Statistical analyses

Baseline characteristics within each racial–ethnic group (Table 1) and age category (Supplemental Table 1) were analyzed as proportions, means (standard deviation), or medians (interquartile range, IQR), as appropriate. Data were compared by racial–ethnic group or age category using analysis of variance or Kruskal–Wallis test for continuous variables or Chi-squared test or Fisher's exact test for categorical variables, where appropriate. The primary outcomes of interest were all-cause mortality and receipt of kidney transplantation. We examined each outcome over two different study periods: over the entire study period for both incident and prevalent patients, and within 1 year of starting dialysis among incident patients. We also investigated potential effect modification on the relationship of race–ethnicity with each outcome over the entire study period across a priori defined subgroups. Subgroups of blood type were evaluated for transplantation outcomes. Interaction terms were evaluated using the Wald test.

For each analysis, we examined three models with incremental multivariable adjustment for baseline covariates. Unadjusted models consisted only of race–ethnicity and the outcome of interest. In minimally adjusted models, we adjusted for patient's sex, age, and vintage, whereas in fully-adjusted models we additionally adjusted for dialysis type, cause of ESRD, and SES. Covariates used for adjustment were chosen based on previous reports [5, 7].

For mortality and transplants occurring over the entire study period, we examined each outcome using competing-risk regression analysis, according to the Fine and Gray method [10]. When examining all-cause mortality, death was the outcome of interest and transplantation was treated as a competing event. Conversely, death was treated as a competing event when we examined transplantation as the outcome of interest. In contrast to Cox regression mortality hazard ratios, competing-risk regression mortality sub-hazard ratios can more appropriately account for informative censoring due to differential transplantation rates among whites, African–Americans, and Hispanics. The association between race–ethnicity and mortality or kidney transplantation within 1 year of starting dialysis was examined using logistic regression among incident dialysis patients only. In sensitivity analyses, we also examined the associations excluding older pediatric

Table 1 Baseline demographic, laboratory, and clinical characteristics of pediatric patients stratified by race–ethnicity

Variable	Total	Race/ethnicity group			*p* value
		White	African–American	Hispanic	
n, %	2,697	1,024 (38.0)	895 (33.2)	778 (28.8)	
Age, *n* (%)					
≤5	126 (4.7)	70 (6.8)	22 (2.5)	34 (4.4)	<0.0001
6-11	147 (5.5)	49 (4.8)	43 (4.8)	55 (7.1)	
12-18	1,120 (41.5)	409 (39.9)	367 (41.0)	344 (44.2)	
19-20	1,304 (48.4)	496 (48.4)	463 (51.7)	345 (44.3)	
Mean age (years)	16.8 ± 4.3	16.6 ± 4.8	17.4 ± 3.6	16.5 ± 4.4	<0.0001
Sex, *n* (%)					
Male	1,490 (55.3)	566 (55.3)	485 (54.2)	439 (56.4)	0.6562
Female	1,207 (44.8)	458 (44.7)	410 (45.8)	339 (43.6)	
Primary insurance, *n* (%)					
Medicare	935 (35.9)	361 (36.1)	363 (42.5)	211 (28.1)	<0.0001
Medicaid	482 (18.5)	109 (10.9)	143 (16.7)	230 (30.6)	
Other	1,188 (45.6)	529 (53.0)	348 (40.6)	311 (41.4)	
Dialysis type, *n* (%)					
Hemodialysis	2,065 (76.6)	770 (75.2)	725 (81.0)	570 (73.3)	0.0004
Peritoneal dialysis	632 (23.4)	254 (24.8)	170 (19.0)	208 (26.7)	
Dialysis vintage category, *n* (%)					
Prevalent	1,005 (37.3)	390 (30.0)	389 (43.5)	226 (29.1)	<0.0001
Incident	1,692 (62.7)	634 (61.9)	506 (56.5)	552 (71.0)	
Vintage (days)	18 (4–351)	19 (4–348)	36 (6–586)	12 (2–191)	<0.0001
Cause of ESRD, *n* (%)					
CAKUT	431 (16.0)	204 (19.9)	120 (13.4)	107 (13.8)	<0.0001
Glomerulonephritis	1,077 (39.9)	384 (37.5)	395 (44.1)	298 (38.3)	
Other	1,189 (44.1)	436 (42.6)	380 (42.5)	373 (47.9)	
Region, *n* (%)					
Midwest	662 (24.6)	297 (29.1)	210 (23.5)	155 (19.9)	<0.0001
Northeast	224 (8.3)	91 (8.9)	92 (10.3)	41 (5.3)	
South	1,109 (41.2)	399 (39.0)	410 (45.9)	300 (38.6)	
West	699 (26.0)	235 (23.0)	182 (20.4)	282 (35.3)	
Socioeconomic status, *n* (%)					
High (≥$55,000)	998 (38.0)	384 (38.2)	348 (39.4)	266 (35.9)	0.0008
Medium ($35,000–< $55,000)	1,155 (43.9)	474 (47.2)	350 (39.6)	331 (44.6)	
Low (<$35,000)	477 (18.1)	147 (14.6)	185 (21.0)	145 (19.5)	
Anthropometric measures, median (IQR)					
Height (percentile)	21 (5–58)	20 (5–56)	34 (9–70)	13 (3–41)	<0.0001
Weight (percentile)	34 (6–74)	31 (7–70)	49 (10–83)	20 (4–62)	<0.0001
BMI (percentile)	51 (13–79)	45 (13–78)	54 (14–84)	50 (12–75)	0.0094
Laboratory measurements, mean ± SD					
Albumin (g/dL)	3.8 ± 0.6	3.8 ± 0.6	3.7 ± 0.7	3.9 ± 0.6	<0.0001
Bicarbonate (mg/dL)	23.0 ± 3.3	23.0 ± 3.5	23.3 ± 3.1	22.7 ± 3.3	0.0018
Hemoglobin (g/dL)	10.9 ± 1.7	10.9 ± 1.7	10.7 ± 1.7	11.1 ± 1.7	<0.0001
Iron (g/dL)	64.1 ± 34.6	64.6 ± 38.0	60.5 ± 30.5	67.5 ± 34.3	0.0003
Calcium (mg/dL)	9.2 ± 0.9	9.3 ± 0.9	9.2 ± 0.8	9.1 ± 0.9	<0.0001
Phosphorous (mg/dL)	5.9 ± 1.7	6.0 ± 1.7	5.8 ± 1.6	5.9 ± 1.7	0.0433
Alkaline phosphatase (U/L)	105 (74–173)	102 (72–163)	100 (72–162)	113 (82–189)	<0.0001
Ferritin (μg/dL)	248 (111–496)	222 (102–465)	296 (138–569)	224 (95–453)	<0.0001
Iron saturation (%)	29.4 ± 14.5	28.9 ± 14.5	29.7 ± 14.2	30.0 ± 14.7	0.1346
Other measurements					
Diastolic blood pressure (percentile), median (IQR)	87 (58–99)	89 (56–98)	90 (63–99)	82 (55–98)	0.0104
Systolic blood pressure (percentile)–median (IQR)	99 (86–100)	99 (86–100)	99 (88–100)	98 (84–100)	0.0467
Hypertensive, *n* (%)	1,269 (62.6)	480 (63.4)	477 (65.9)	312 (57.1)	0.0053
Median weekly Epogen dose, median (IQR)	8,146 (4,667–12,333)	8,529 (4,644–12,879)	8,590 (4,884–13,375)	7,579 (4,475–10,750)	0.0003
Single pooled Kt/V, mean ± SD	1.5 ± 0.4	1.5 ± 0.4	1.5 ± 0.4	1.5 ± 0.4	0.0002
Low spKt/V, *n* (%)	620 (30.4)	208 (28.5)	242 (33.2)	170 (29.4)	0.1151
Low spKt/V HD, *n* (%)	303 (18.3)	84 (14.5)	143 (23.2)	76 (16.6)	0.0003
Low spKt/V PD, *n* (%)	317 (82.6)	124 (82.7)	99 (88.4)	94 (77.1)	0.0736
Blood type, *n* (%)					
A/AB	240 (34.8)	117 (43.2)	70 (28.9)	53 (30.0)	0.0009
B	85 (12.3)	30 (11.1)	39 (16.1)	16 (9.0)	
O	365 (52.9)	124 (45.8)	133 (55.0)	108 (61.0)	

Data presented as means ± standard deviation, median (interquartile range) and number (percentage), where appropriate. Data compared across racial–ethnic groups by analysis of variance or Kruskal–Wallis test for continuous variables or Chi-squared test for categorical variables

BMI body mass index, *CAKUT* congenital anomalies of the kidney and urinary tract, *ESRD* end-stage renal disease

patients (19–20 years), and examined the associations between race-ethnicity and various causes of death, especially cardiovascular mortality.

The proportionality assumption was checked with plots of log [−log (survival rate)] against log (survival time) and proportionality test statements using exposure log–time

interaction. All statistical analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Cohort characteristics

Table 1 displays the characteristics of this population, stratified by race–ethnicity. African–American pediatric patients were more likely to utilize Medicare as their primary insurance, be on hemodialysis at baseline, and had, on average, higher anthropometric and blood pressure measurements than Hispanic and white pediatric dialysis patients. Conversely, Hispanic patients had higher albumin, hemoglobin, and iron levels at baseline. African–Americans were also older than both Hispanic and white patients in this cohort.

Mortality and transplant outcomes

In the overall cohort, there were 310 deaths and 1,017 transplants over a median (IQR) follow-up of 3.0 (1.0–4.5) years. Table 2 shows that, across racial–ethnic subgroups, higher death rates were seen among African–Americans, followed by white and Hispanic patients. African–Americans were also less likely to receive a transplant than both white and Hispanic patients. Additionally, African–Americans had a longer median time interval from dialysis initiation to kidney transplantation than both Hispanics and whites (1,045 days vs 788 and 534 days respectively).

In mortality analyses using competing risk regression, African–Americans had a 73 % higher risk of all-cause mortality compared with white pediatric patients in the unadjusted model (Fig. 2a). After adjusting for baseline demographic covariates, this association was slightly attenuated, yielding a 64 % higher mortality risk for African–American patients (hazards ratio [HR] = 1.64; 95 % CI 1.24–2.17). Conversely, Hispanic patients had better survival than white patients in unadjusted models, although the effect was no longer significant after adjustment for demographic covariates (HR = 0.69; 95 % CI 0.47–1.01).

Both African–American and Hispanic pediatric patients had a lower likelihood of transplantation compared with whites, after accounting for death as a competing event. In the unadjusted model, African–Americans and Hispanics showed a 44 % and 7 % lower likelihood of receiving a transplant compared with whites, respectively (Fig. 2b). After adjustment for demographic covariates, the association for African–Americans was attenuated to a 39 % lower likelihood of transplantation (HR = 0.61; 95 % CI 0.52–0.71), whereas the association for Hispanics was magnified to a 12 % lower likelihood of transplantation (HR = 0.88; 95 % CI 0.76,–1.02).

In analyses of incident dialysis patients examining the association between race–ethnicity and 1-year mortality and transplant after initiating dialysis, African–Americans were more likely to die than whites. However, because of a small number of deaths, the estimates did not reach statistical significance after adjustment for baseline demographics (odds ratio [OR] = 2.08; 95 % CI 0.95–4.58; Fig. 3a). Both African–American and Hispanic incident dialysis patients were less likely to receive a transplant within 1 year of dialysis initiation than white patients, and these associations remained robust after adjustment for baseline demographics (OR = 0.28; 95 % CI 0.19–0.41 and OR = 0.43; 95 % CI 0.31–0.59, respectively) (Fig. 3b).

In examining causes of death, African–American pediatric patients had the highest frequency ($n = 54$, 17 % of deaths) and Hispanic pediatric patients had the lowest frequency of deaths ($n = 17$, 5 %) reported due to

Table 2 Mortality and transplant outcomes of pediatric dialysis patients, stratified by race–ethnicity

Variable	Race–ethnicity		
	White	African–American	Hispanic
n, %	1,024 (38.0)	895 (33.2)	778 (28.8)
Total follow-up time, days, median (IQR)	742 (281–1,433)	1,045 (456–1,798)	821 (421–1,613)
Deaths, *n* (%)	107 (10.5)	146 (16.3)	57 (7.3)
Death rate, per 1,000 person-years, (95 % CI)	40.3 (33.3–48.7)	48.2 (40.9–56.6)	24.4 (18.8–31.7)
Transplants, *n* (%)	420 (41.0)	268 (29.9)	329 (42.3)
Transplant rate, per 1,000 person-years, (95 % CI)	158.1 (143.6–173.9)	88.4 (78.4–99.6)	140.9 (126.5–157.0)
Transplant waiting time, days, median (IQR)	534 (246–1,124)	1,045 (518–1,685)	788 (410–1,418)

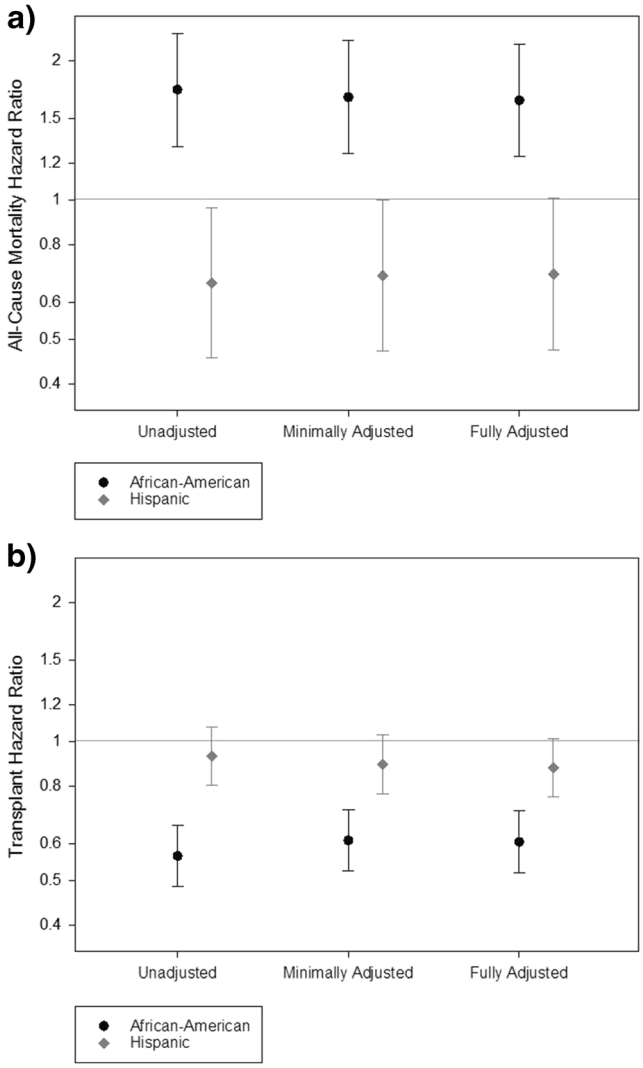

Fig. 2 **a** Hazard ratios for all-cause mortality among African–American and Hispanic pediatric patients compared with white pediatric patients. **b** Hazard ratios for receiving a transplant among African–American and Hispanic pediatric patients compared with white pediatric patients. Fully adjusted covariates: sex, age, vintage, cause of end-stage renal disease, dialysis type, socioeconomic status

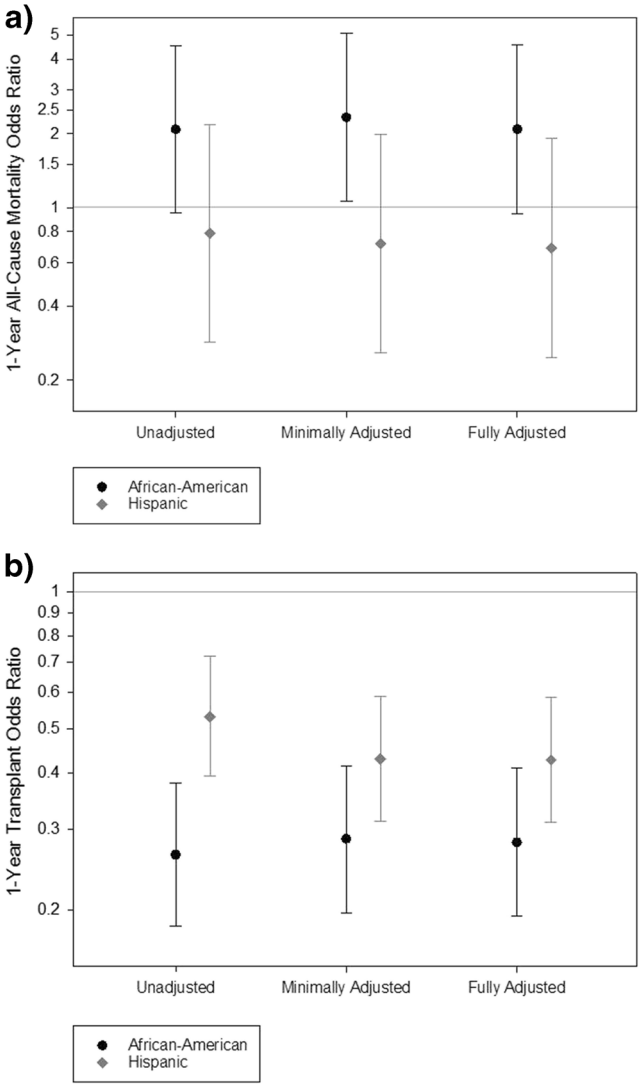

Fig. 3 **a** Odds ratios for mortality within 1 year of starting dialysis for African–American and Hispanic pediatric patients compared with white pediatric patients. **b** Odds ratios for receiving a transplant within one year of starting dialysis for African–American and Hispanic pediatric patients compared with white pediatric patients. Fully adjusted covariates: sex, age, vintage, cause of end-stage renal disease, dialysis type, socioeconomic status

cardiovascular problems. Associations between race-ethnicity and cardiovascular mortality, using kidney transplantation as a competing event, showed similar estimates to that of all-cause mortality in fully adjusted models (African–American HR: 1.64, 95 % CI 1.06–2.53; Hispanic HR: 0.65, 95 % CI 0.36–1.18).

Subgroup analyses

Competing risk hazard ratios for both mortality and transplant outcomes were then examined across a priori selected subgroups of baseline demographic and laboratory variables in the fully adjusted model. In the association of African–American versus white race-ethnicity with mortality outcomes, there was effect modification on the basis of sex. Female African–American patients had a two-fold higher mortality risk than white female patients (HR = 2.08; 95 % CI 1.38–3.12), whereas male African–Americans had a 28 % higher mortality risk (HR = 1.28, 95 % CI 0.87–1.89) than white male patients (p value for the interaction = 0.04; Fig. 4a). Notably, the effect of African–American race-ethnicity on mortality was strongest in the lowest SES group, with a 3.3-fold higher mortality risk (HR = 3.33, 95 % CI 1.48–7.75); however, the interaction of race-ethnicity with SES was not significant (p value for interaction = 0.31). The lack of significant interaction may be attributed to the small sample size and therefore wider confidence intervals in the low SES

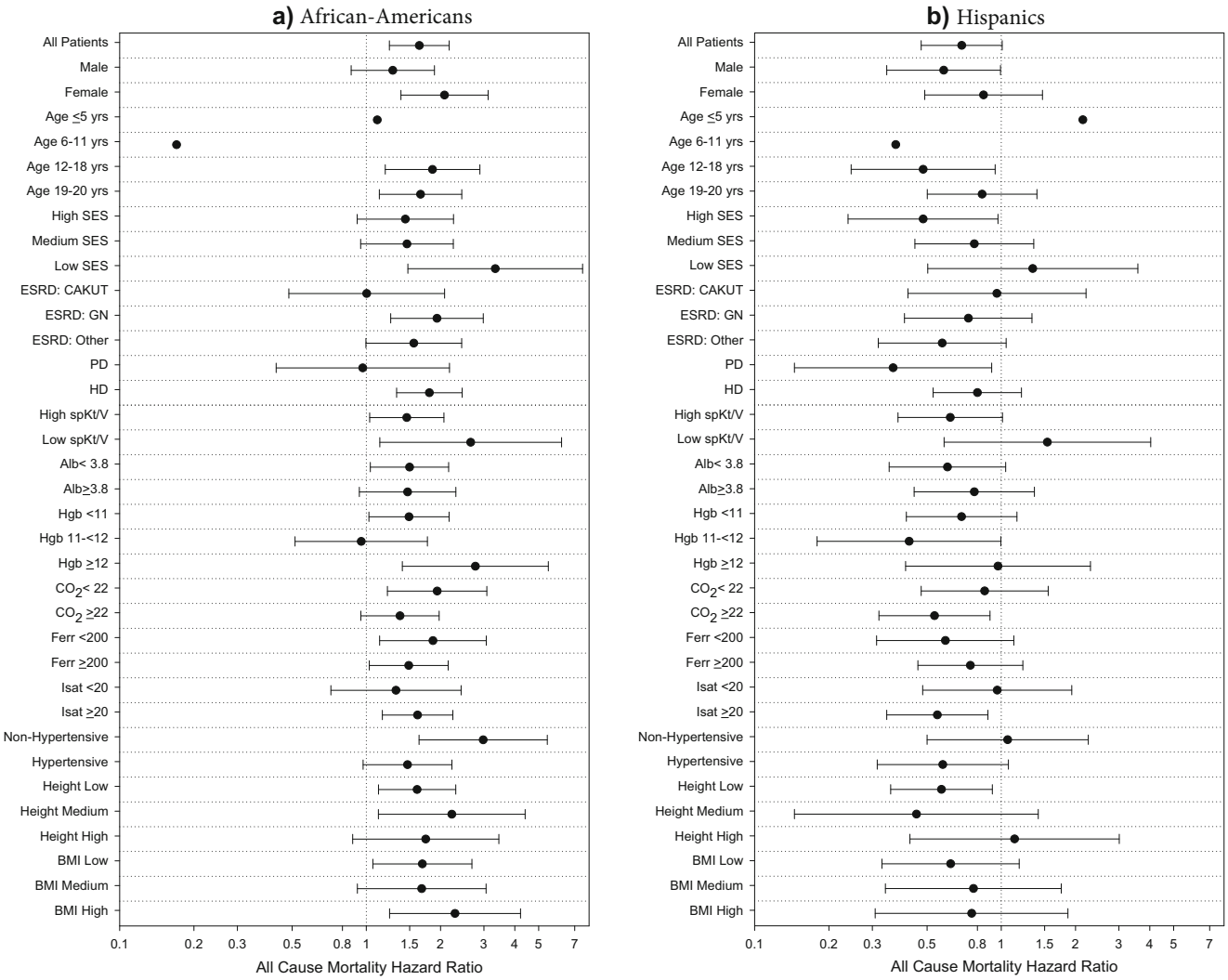

Fig. 4 **a** Subgroup analyses displaying all-cause mortality hazard ratios for African–American pediatric patients compared with white pediatric patients. **b** Subgroup analyses displaying all-cause mortality hazard ratios for Hispanic pediatric patients compared with white pediatric patients. **c** Subgroup analyses displaying transplant hazard ratios for African–American pediatric patients compared with white pediatric patients. **d** Subgroup analyses displaying transplant hazard ratios for Hispanic pediatric patients compared with white pediatric patients. Fully adjusted covariates: sex, age, vintage, cause of end-stage renal disease, dialysis type, socioeconomic status

strata. Across hemoglobin strata, there appeared to be a U-shaped relationship between African–American versus white race-ethnicity and mortality, with those with the lowest (<11 g/dL) and highest (>12 g/dL) hemoglobin strata showing a higher risk of mortality (HR = 1.49, 95 % CI 1.03–2.17 and HR = 2.77, 95 % CI 1.40–5.47 respectively). African–Americans in the strata with normal hemoglobin levels (11–12 g/dL) showed no increase in mortality risk compared with whites (HR = 0.95 95 % CI 0.51–1.77); however, the interaction between race-ethnicity and hemoglobin was not statistically significant (p value for the interaction = 0.18). Across all subgroups, African–Americans had a lower likelihood of transplantation compared with whites. Adolescent African–American patients aged 6–11 years seemed to have a similar likelihood of transplantation compared with white adolescents; however, there was no significant interaction between race-ethnicity and age groups with regard to transplant outcomes (p value for the interaction = 0.19; Fig. 4c).

Across most subgroups, point estimates suggested that Hispanics might have had a lower or similar mortality and likelihood of transplantation compared with white patients, although many of these analyses did not reach statistical significance (Fig. 4b, d). Notably, older Hispanic pediatric patients (19–20 years) were significantly less likely to receive a transplant, whereas younger Hispanic pediatric patients had a similar transplant rate to white patients of the same age group. However, the interaction of race-ethnicity with age group was not statistically significant (p value for the interaction = 0.087).

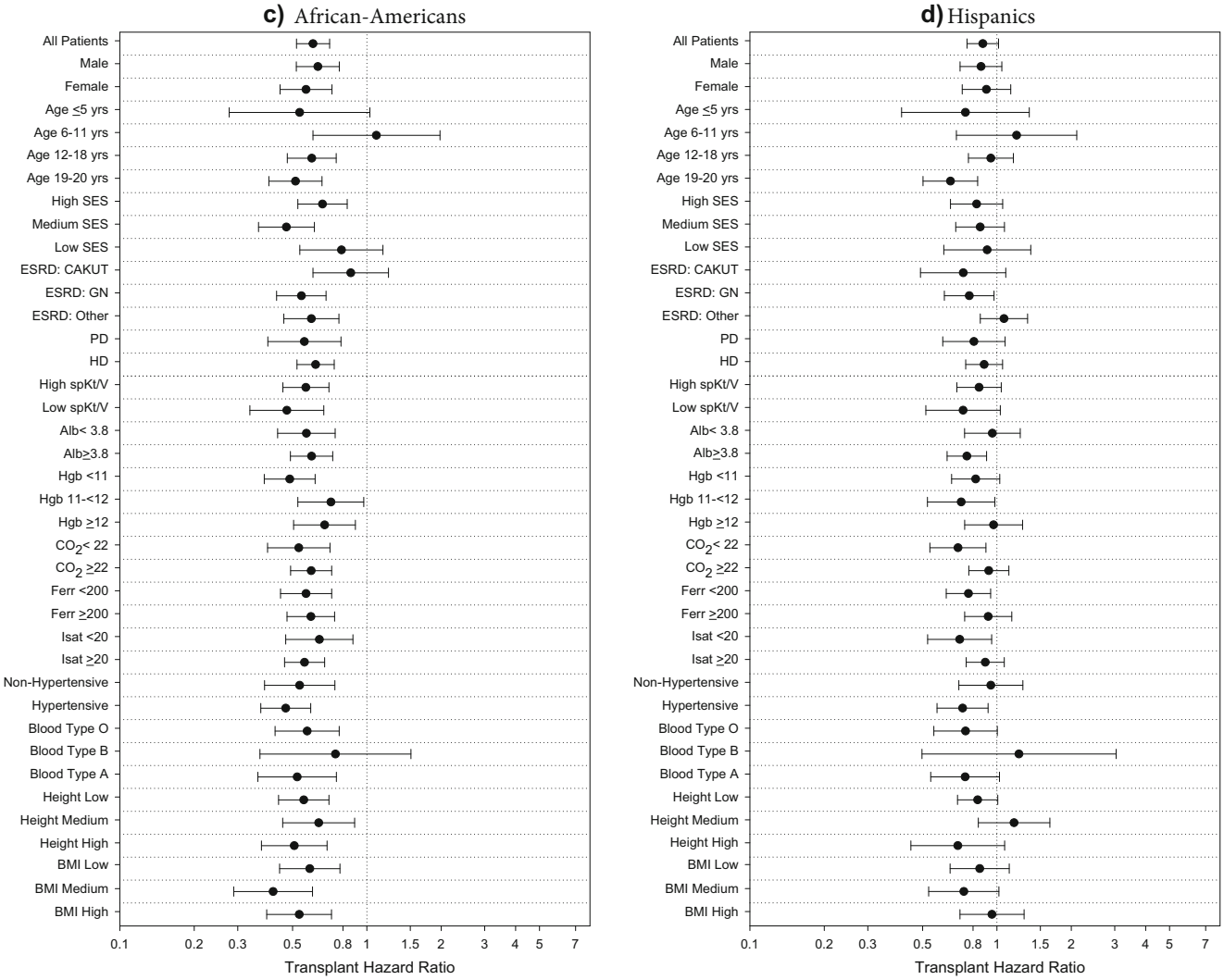

Fig. 4 (continued)

In sensitivity analyses, associations of race-ethnicity with mortality and transplant outcomes were similar after excluding older pediatric patients (age 19–20 years).

Discussion

Racial–ethnic disparities in mortality and kidney transplantation exist in the pediatric dialysis population. African–American children receiving dialysis have a higher risk of mortality and lower likelihood of transplantation than white children. Hispanic children receiving dialysis also display a significantly lower likelihood of transplantation (12 % lower), although no statistically significant difference in mortality compared with white children.

Our study shows that African–American pediatric patients under 21 years of age have a 64 % higher risk of mortality. These differences are most pronounced in the 12–18 and 19–20 age subgroups. A larger sample size is needed to adequately determine the associations between race-ethnicity and mortality and transplant outcomes in patients under 12 years of age. Our findings of worse survival in African–American pediatric dialysis patients contrast that of the larger adult dialysis population [11–13]. However, studies have shown that age does affect racial disparities in survival outcomes in dialysis patients. Among younger adults (<30–50 years) the survival advantage in African–Americans is lost, but does persist for younger Hispanic adults [5, 14, 15]. Previous studies have speculated that the effect of age on racial differences in survival in dialysis patients might be mediated by factors such as nutritional status and health care access [5, 15]. In our study, the higher mortality risk seen among young African–American dialysis patients was exacerbated among those of lower socio-economic status. In addition, previous studies

have postulated that these racial differences in mortality outcomes might be attributed to higher suicide and homicide rates in younger African–Americans [5, 16], or worse pre-dialysis care [17]. Conversely, the survival advantage observed among young Hispanic patients may also be related to better nutritional status or cardiovascular health, as observed in the adult chronic kidney disease and dialysis population [18, 19]. In our cohort, Hispanic pediatric dialysis patients had a higher level of serum albumin and a lower frequency of death owing to cardiovascular problems. In pediatric patients with lower albumin levels, Hispanic and non-Hispanic white children had a similar mortality risk, although in our analyses no significant interaction between albumin and race-ethnicity was detected. Further studies are needed to examine whether these listed factors mediate racial–ethnic disparities in survival in a pediatric dialysis population, or if other factors are at play [16, 20].

Subgroup analyses reveal that although both sexes are at a higher risk of mortality compared with their white counterparts, African–American female patients are disproportionately more affected and display a 2-fold higher mortality risk. Similarly, Ferris et al. showed a significantly lower 10-year survival rate in their female adolescent population [4]. Therefore, female sex may exacerbate the already present racial/ethnic survival disparities in pediatric dialysis patients. Both African–American and non-Hispanic white female patients in our study were more likely to have GN as a cause of ESRD and be hypertensive. However, after adjustment for both these factors, effect modification by sex on the association between African–American race-ethnicity and mortality outcomes persisted. Further investigations should examine the interaction between race-ethnicity and female sex in influencing mortality outcomes in ESRD pediatric patients.

Disparities in mortality persist, despite SES differences in the African–American group. This disparity, albeit slightly attenuated in higher SES brackets, is still persistent across all income levels. African–American children in the highest bracket have a 44 % higher mortality risk and the lowest bracket have a 3.3-fold increase in mortality risk. Therefore, the racial–ethnic disparities in mortality are not fully accounted for by SES, but seem to worsen with lower SES.

Although we did not detect a statistically significant interaction between race-ethnicity and hemoglobin strata, African–Americans had a similar mortality risk to whites in patients with a hemoglobin level that is within the recommended range of 11–12 g/dL. This relationship is also seen in adult hemodialysis patients [21]. Atkinson et al. showed that African–American children on peritoneal dialysis were less likely to achieve hemoglobin values of 11 g/dL or greater compared with white children [22]. Given the presence of racial-ethnic disparities in mortality in children who do not achieve target hemoglobin values, further work is necessary to address the etiologies in disparate hemoglobin values across pediatric racial-ethnic groups.

Similar to findings by Leonard et al., in our study African–American children were found to have less adequate dialysis than white children [23]. However, despite the presence of these differences, in subgroup analysis racial-ethnic disparities in survival persisted among African–American and white patients with appropriate spKt/V values. In addition, African–American children were also found to have lower albumin and increased ferritin levels, which might be indicative of higher degrees of illness and/or inflammation. Nonetheless, African American compared to white pediatric patients had lower rates of survival even within strata of normal albumin and ferritin values.

Our data also confirm the presence of racial–ethnic disparities in kidney transplantation. We found that African–American and Hispanic pediatric dialysis patients have a 39 % and 12 % lower likelihood of transplantation compared with white pediatric dialysis patients. These differences amongst African–American and Hispanic pediatric dialysis patients is consistent with a previous study by Amaral et al., which showed that Hispanic pediatric dialysis patients experienced a greater improvement in transplantation rates after institution of the Share 35, a 2005 policy aimed at offering kidneys from deceased donors under 35 years of age to pediatric patients under 18 years of age [24]. In Hispanic patients compared with white patients, we observed similar transplantation rates in younger pediatric patients, but not in older pediatric patients, which may be attributed to this policy. Other assessments for effect modification of the association between race–ethnicity and transplant outcomes did not reveal any significant findings. Similar to Patzer et al., who found that SES did not modify racial–ethnic disparities in transplantation, we also found transplant rates were consistently lower in African-American and Hispanic pediatric patients across strata of SES [3]. Previous studies have suggested that possible reasons contributing to racial–ethnic differences in access to kidney transplants, beyond socio-economic differences, were decreased access to living related donors, potential physician racial bias in the belief of treatment success and life value, socio-cultural beliefs regarding transplants, lack of education, and/or social support or parental oversight assisting with treatment adherence, and worse pre-dialysis care [3, 25].

The major limitation of this study is the small sample size in the age groups 11 years and younger. This makes it challenging to draw conclusions about mortality and transplantation in these specific age groups, and therefore larger studies are required to further delineate these relationships. Similarly, to assess the impact of peritoneal dialysis, a larger sample size is also needed. Another limitation of this study is the lack of Panel Reactive Antibody (PRA) data and limited blood typing information for the entire cohort. A sub-analysis of 690 patients with available blood typing revealed no significant impact of blood type on transplantation rates, but the small sample size within this subgroup may

limit the ability to detect the impact of blood type, as observed in adult dialysis patients [26]. Finally, we cannot exclude the possibility of residual confounding given the observational nature of the study design.

This study provides an overview of racial–ethnic disparities in mortality, a finding in pediatric patients that deserves further characterization. It also reinforces the persistent disparities in transplantation across racial–ethnic groups. Future studies will need to evaluate if these racial-ethnic disparities in mortality and transplant outcomes persist in the years after implementation of the December 2014 new kidney allocation system [27].

Acknowledgments KKZ had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Compliance with ethical standards

Consent The study was approved by the Institutional Review Committees of the Los Angeles Biomedical Research Institute at Harbor-UCLA, University of California Irvine, and University of Washington. Given the anonymity of the patients studied and non-intrusive nature of the research, the study was exempt from the requirement for consent.

Financial disclosure The work in this manuscript has been performed with the support of the National Institute of Diabetes, Digestive and Kidney Disease of the National Institute of Health research grants R01-DK95668 (KKZ), K24-DK091419 (KKZ), R01-DK078106 (KKZ), and T32-DK104687 (ML). KKZ is supported by philanthropic grants from Mr Harold Simmons, Mr Louis Chang, Mr Joseph Lee and AVEO. CMR is supported by the National Institute of Diabetes, Digestive and Kidney Disease of the National Institute of Health grant K23-DK102903.

Conflicts of interest KKZ has received honoraria and/or support from Abbott, Abbvie, Alexion, Amgen, American Society of Nephrology, Astra-Zeneca, AVEO, Chugai, DaVita, Fresenius, Genetech, Haymarket Media, Hospira, Kabi, Keryx, National Institutes of Health, National Kidney Foundation, Relypsa, Resverlogix, Sanofi, Shire, Vifor, and ZS-Pharma.

References

1. Furth SL, Garg PP, Neu AM, Hwang W, Fivush BA, Powe NR (2000) Racial differences in access to the kidney transplant waiting list for children and adolescents with end-stage renal disease. Pediatrics 106:756–761
2. US Renal Data System (2015) US Renal Data System 2015 Annual Data Report: atlas of chronic kidney disease and end-stage renal disease in the United States. National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda
3. Patzer RE, Amaral S, Klein M, Kutner N, Perryman JP, Gazmararian JA, Mcclellan WM (2012) Racial disparities in pediatric access to kidney transplantation: does socioeconomic status play a role? Am J Transplant 12:369–378
4. Ferris ME, Gipson DS, Kimmel PL, Eggers PW (2006) Trends in treatment and outcomes of survival of adolescents initiating end-stage renal disease care in the United States of America. Pediatr Nephrol 21:1020–1026
5. Rhee CM, Lertdumrongluk P, Streja E, Park J, Moradi H, Lau WL, Norris KC, Nissenson AR, Amin AN, Kovesdy CP, Kalantar-Zadeh K (2014) Impact of age, race and ethnicity on dialysis patient survival and kidney transplantation disparities. Am J Nephrol 39:183–194
6. US Census Bureau. Version current 1 April 2014. Internet: http://www.census.gov Accessed 18 April 2014
7. Federal Office of Management and Budget. Version current 1 April 2014. Internet: http://www.whitehouse.gov/omb Accessed 18 April 2014
8. 2000 CDC growth charts for the United States: methods and development. Available at http://www.cdc.gov/nchs/data/series/sr_11/sr11_246.pdf. Accessed 3 August 2016
9. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (2014) The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 114 [Suppl 2]:555–576
10. Fine JP, Gray RJ (1999) A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 94:496–509
11. Owen WF Jr, Chertow GM, Lazarus JM, Lowrie EG (1998) Dose of hemodialysis and survival: differences by race and sex. JAMA 280:1764–1768
12. Nicholas SB, Kalantar-Zadeh K, Norris KC (2013) Racial disparities in kidney disease outcomes. Semin Nephrol 33:409–415
13. Rhee CM, Kalantar-Zadeh K, Norris KC (2016) Why minorities live longer on dialysis: an in-depth examination of the Danish nephrology registry. Nephrol Dial Transplant 31:1027–1030
14. Yan G, Norris KC, Yu AJ, Ma JZ, Greene T, Yu W, Cheung AK (2013) The relationship of age, race, and ethnicity with survival in dialysis patients. Clin J Am Soc Nephrol 8:953–961
15. Kucirka LM, Grams ME, Lessler J, Hall EC, James N, Massie AB, Montgomery RA, Segev DL (2011) Association of race and age with survival among patients undergoing dialysis. JAMA 306:620–626
16. Kalantar-Zadeh K, Kovesdy CP, Norris KC (2012) Racial survival paradox of dialysis patients: robust and resilient. Am J Kidney Dis 60:182–185
17. Kovesdy CP, Norris KC, Boulware LE, Lu JL, Mz JZ, Streja E, Molnar MZ, Kalantar-Zadeh K (2015) Association of race with mortality and cardiovascular events in a large cohort of veterans. Circulation 132:1538–1548
18. Arce CM, Goldstein BA, Mitani AA, Winkelmayer WC (2013) Trends in relative mortality between Hispanic and non-Hispanic whites initiating dialysis; a retrospective study of the US Renal Data System. Am J Kidney Dis 62:312–321
19. Ricardo AC, Lash JP, Fischer MJ, Lora CM, Budoff M, Keane MG, Kusek JW, Martinez M, Nessel L, Stamos T, Ojo A, Rahman M, Soliman EZ, Yang W, Feldman HI, Go AS, CRIC and HCRIC Investigators (2011) Cardiovascular disease among Hispanics and non-Hispanics in the Chronic Renal Insufficiency Cohort (CRIC) study. Clin J Am Soc Nephrol 6(9):2121–2131
20. Norris KC, Kalantar-Zadeh K, Kopple JD (2011) The role of race in survival among patients undergoing dialysis. Nephrol News Issues 25:13–14,16
21. Streja E, Kovesdy CP, Molnar MZ, Norris KC, Greenland S, Nissenson AR, Kopple JD, Kalantar-Zadeh K (2011) Role of nutritional status and inflammation in higher survival of African American and Hispanic hemodialysis patients. Am J Kidney Dis 57:883–893
22. Atkinson MA, Neu AM, Fivush BA, Frankenfield DL (2008) Disparate outcomes in pediatric peritoneal dialysis patients by gender/race in the End-Stage Renal Disease Clinical Performance Measures project. Pediatr Nephrol 23:1331–1338
23. Leonard MB, Stablein DM, Ho M, Jabs K, Feldman H (2004) Racial and center differences in hemodialysis adequacy in children

treated at pediatric centers: a North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) report. J Am Soc Nephrol 15:2923–2932

24. Amaral S, Patzer RE, Kutner N, Mcclellan W (2012) Racial disparities in access to pediatric kidney transplantation since share 35. J Am Soc Nephrol 23:1069–1077
25. Tjaden LA, Noordzij M, van Stralen KJ, Kuehni CE, Raes A, Cornelissen EA, O'Brien C, Papachristou F, Schaefer F, Groothoff JW, Jager KJ, ESPN/ERA-EDTA Registry Study Group (2016) Racial disparities in access to and outcomes of kidney transplantation in children, adolescents, and young adults: results from the ESPN/ERA-EDTA (European Society of Pediatric Nephrology/European Renal Association-European Dialysis and Transplant Association) Registry. Am J Kidney Dis 67(2):293–301
26. Williams WW, Cherikh WS, Young CJ, Fan PY, Cheng Y, Distant DA, Bryan CF (2015) First report on the OPTN national variance: allocation of A2/A2 B deceased donor kidneys to blood group B increases minority transplantation. Am J Transplant 15:3134–3142
27. OPTN The Organ Procurement and Transplant Network: Kidney Allocation System. Available from: https://optn.transplant.hrsa.gov/learn/professional-education/kidney-allocation-system/ Accessed 10 October 2016