Impact of Age, Race and Ethnicity on Dialysis Patient Survival and Kidney Transplantation Disparities

Connie M. Rhee^a Paungpaga Lertdumrongluk^{a, i} Elani Streja^a Jongha Park^{a, j}
Hamid Moradi^a Wei Ling Lau^a Keith C. Norris^{b, c} Allen R. Nissenson^{c, e}
Alpesh N. Amin^f Csaba P. Kovesdy^{g, h} Kamyar Kalantar-Zadeh^{a, c, d}

^aHarold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology and Hypertension, University of California Irvine Medical Center, Orange, Calif., ^bDrew University of Medicine, ^cDavid Geffen School of Medicine at UCLA and ^dDepartment of Epidemiology, Fielding School of Public Health at UCLA, Los Angeles, Calif., ^eDaVita Inc., El Segundo, Calif., ^fDepartment of Medicine, University of California Irvine Medical Center, Irvine, Calif., and ^gDivision of Nephrology, Memphis Veterans Affairs Medical Center, and ^hDivision of Nephrology, University of Tennessee Health Science Center, Memphis, Tenn., USA; ⁱRoyal Irrigation Hospital, Srinakharinwirot University, Nonthaburi, Thailand; ^jDivision of Nephrology, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Republic of Korea

Key Words

Race · Ethnicity · Disparities · Survival · Transplantation

Abstract

Background: Prior studies show that African-American and Hispanic dialysis patients have lower mortality risk than whites. Recent age-stratified analyses suggest this survival advantage may be limited to younger age groups, but did not concurrently compare Hispanic, African-American, and white patients, nor account for differences in nutritional and inflammatory status as potential confounders. Minorities experience inequities in kidney transplantation access, but it is unknown whether these racial/ethnic disparities differ across age groups. **Methods:** The associations between race/ethnicity with all-cause mortality and kidney transplantation were separately examined among 130,909 adult dialysis patients from a large national dialysis organization (entry period 2001–2006, follow-up through 2009) within 7 age cat-

egories using Cox proportional hazard models adjusted for case-mix and malnutrition and inflammatory surrogates. **Results:** African-Americans had similar mortality versus whites in younger age groups (18–40 years), but decreased mortality in older age groups (>40 years). In contrast, Hispanics had lower mortality versus whites across all ages. In sensitivity analyses using competing risk regression to account for differential kidney transplantation rates across racial/ethnic groups, the African-American survival advantage was limited to >60-years age categories. African-Americans and Hispanics were less likely to undergo kidney transplantation from all donor types versus whites across all ages, and these disparities were even more pronounced for living donor kidney transplantation (LDKT). **Conclusions:** Hispanic dialysis patients have greater survival versus whites across all ages; in African-Americans, this survival advantage is limited to patients >40 years of age. Minorities are less likely to undergo kidney transplantation, particularly LDKT, across all ages.

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Introduction

In the past two decades, numerous kidney disease disparities have been identified among minority dialysis patients [1]. For example, African-Americans comprise 12.6% of the US population [2], but have a 3.5-fold higher incidence of end-stage renal disease (ESRD) versus non-Hispanic whites [3]. African-Americans initiate renal replacement therapies at younger ages [4] and have poorer dialysis performance measures (i.e. lower dialysis doses [5] and arteriovenous fistula placement [6]). Although there is comparatively less data on health care disparities among Hispanic kidney disease patients, studies indicate that they experience a 1.5-fold higher incidence of ESRD [3], less pre-ESRD care [7], and a reduced rate of kidney transplantation [8] versus non-Hispanic whites. Despite these inequities, population-level analyses show that African-American and Hispanic ESRD patients have a lower mortality risk versus non-Hispanic whites [3, 4, 9–11], even after accounting for differences in age and comorbidity status [12].

Recent data suggest that the paradoxical survival advantage among African-Americans and Hispanics may be restricted to particular age groups. In a seminal study comparing African-American versus white dialysis patients, Kucirka et al. [13] reported that African-Americans have increased mortality risk in younger (≤ 50 years) age groups and decreased mortality risk in older (> 50 years) age groups, but did not separately consider Hispanic ethnicity. Subsequently, Arce et al. [14] demonstrated that Hispanics initiating dialysis had lower mortality risk compared to non-Hispanic whites, but the magnitude of survival benefit was less pronounced in older age groups, and was attenuated when differential rates of kidney transplantation by ethnicity were accounted for. In the first study to compare Hispanic versus African-American versus non-Hispanic white dialysis patients, Yan et al. [15] showed that these racial/ethnic subgroups have the lowest, intermediate, and highest mortality risk, respectively, across almost all age groups, except for the youngest (18–30 years) age group in which African-Americans had higher mortality risk versus non-Hispanic whites. However, a key limitation across these collective studies was the inability to account for racial/ethnic differences in nutritional and inflammatory status. Prior studies have shown that adjustment for nutritional and inflammatory markers attenuates the Hispanic survival advantage to the null and may in fact reverse the African-American survival advantage [16]. To date, there has not been direct examination of how age modifies the association between race, ethnic-

ity, and survival after accounting for differences in nutritional and inflammatory status.

One of the most critical inequities experienced by minority dialysis patients is their impaired access to kidney transplantation. Kidney transplantation dramatically improves survival and quality of life, and it is considered the gold standard treatment among ESRD patients [17, 18]. Numerous studies show that African-Americans and Hispanics have decreased access to living donor kidney transplantation (LDKT) and deceased donor kidney transplantation (DDKT), but it is not known if these disparities exist across all categories of age [19–22]. Thus to better inform the field, we sought to examine age as a modifier of the association between African-American and Hispanic race/ethnicity with (1) all-cause death and (2) receipt of kidney transplantation in a contemporary cohort of patients with detailed information on sociodemographics, comorbidities, and laboratory data from a large national dialysis organization.

Materials and Methods

Study Population

We examined data from all individuals with ESRD who underwent hemodialysis or peritoneal dialysis in one of the DaVita Inc. outpatient dialysis facilities during an entry period of July 1, 2001 to June 30, 2006 with follow-up through June 30, 2009. The study was approved by the institutional review committees of the Los Angeles Biomedical Research Institute at Harbor-UCLA and DaVita Clinical Research. Given the large sample size, anonymity of the patients studied, and nonintrusive nature of the research, requirement for consent was exempted.

The baseline quarter was the calendar quarter in which the patient's dialysis vintage was > 90 days. Patients who were ≥ 18 years of age, had a dialysis vintage of > 90 days, received dialysis during the baseline quarter, and of non-Hispanic white, non-Hispanic black, or Hispanic race/ethnicity were included. In this report, the former two groups are referred to as whites and African-Americans, respectively. Asian and American Indian racial groups were not included due to small sample size.

Race/Ethnicity, Demographic and Comorbidity Measures

Creation of the cohort has previously been described [23]. Information on race/ethnicity, primary insurance, marital status, and presence of diabetes at baseline were obtained from the DaVita database. Race/ethnicity was self-reported by dialysis patients according to the race/ethnicity they most closely identified with according to US Census Bureau categorizations [2].

To minimize measurement variability, repeated laboratory and clinical measurements for each patient during the calendar quarter of entry (baseline quarter) were averaged. Dialysis vintage was defined as the time between the first day of dialysis treatment and the study entry date. Posthemodialysis dry weight and baseline height were used to calculate BMI. Data on baseline comorbidities, active

tobacco smoking, and drug and alcohol dependence (current/within the past 10 years) were obtained by linking the DaVita database to US Renal Data System (USRDS) Medical Evidence Form 2728 data using patients' names, dates of birth, and social security numbers.

Laboratory Measures

Blood samples were drawn using standardized techniques in all DaVita dialysis clinics and were transported to the DaVita Laboratory in Deland (Fla.) typically within 24 h, and were measured using automated and standardized methods in the DaVita laboratory. Most laboratory parameters [i.e. urea nitrogen, albumin, creatinine, total iron binding capacity (TIBC), bicarbonate, phosphorous, calcium, and normalized protein catabolic rate (nPCR)] were measured monthly; ferritin and intact parathyroid hormone were measured at least quarterly. Hemoglobin was measured at least monthly in all patients and weekly to biweekly in most patients. Most blood samples were collected before dialysis, except for post-dialysis serum urea nitrogen to calculate urea kinetics.

Outcome Ascertainment

The primary outcomes of interest were (1) all-cause death and (2) receipt of kidney transplantation from all donor types, which were ascertained from the DaVita and USRDS databases. We first evaluated the association between race/ethnicity and all-cause mortality using Cox proportional hazard models in which patients remained at-risk until death or censoring for kidney transplantation or end of the study (June 30, 2009). In sensitivity analyses, we examined mortality risk using competing risk regression according to the Fine and Gray method [13, 24], in which death was the outcome of interest and transplantation was treated as a competing risk as opposed to a censoring event. In contrast to Cox regression mortality hazard ratios which assume that different racial/ethnic groups undergo kidney transplantation at equivalent rates, competing risk regression mortality subhazard ratios account for differential transplantation rates among whites, African-Americans, and Hispanics.

We then examined the association between race/ethnicity and receipt of kidney transplantation from all donor types using Cox proportional hazards models. In secondary analyses, we separately examined categories of kidney transplantation according to donor status: (1) LDKT (including living related and unrelated donors), (2) living related donor kidney transplantation (LRDKT), (3) living unrelated donor kidney transplantation (LUDKT), and (4) DDKT, which were ascertained through linkage to the Scientific Registry of Transplant Recipients database using patients' names, dates of birth, and social security numbers. In kidney transplantation analyses, patients were censored for death events or at the end of the study.

Statistical Analyses

Baseline characteristics within each race/ethnicity and age category were analyzed as proportions, means (SD), or medians according to data type. Crude death and transplantation rates within strata of age and race/ethnicity were calculated as the number of events per 100,000 patient-days of follow-up. We evaluated the association between race/ethnicity and all-cause mortality within 7 age categories (18–30, >30 to 40, >40 to 50, >50 to 60, >60 to 70, >70 to 80, and >80 years). Due to a low frequency of transplantation events within the >80-years age category, the association be-

tween race/ethnicity and receipt of kidney transplantation was estimated within 6 age categories only (18–30, >30 to 40, >40 to 50, >50 to 60, >60 to 70, and >70 to 80). For each analysis, we examined two models with incremental multivariable adjustment for baseline covariates. In case-mix models, we adjusted for covariates employed in prior studies of age, race, ethnicity, and survival [13–15], and in fully adjusted models, we additionally adjusted for markers of nutritional status and inflammation and other confounders of the race/ethnicity-mortality association.

Case-mix adjusted models included age, sex, insurance (Medicare, Medicaid, private, and other), entry calendar quarter, BMI category (<18, 18 to <25, 25 to <30, 30 to <35, ≥35), modality (peritoneal or hemodialysis), diabetes, smoking, alcohol dependence, drug dependence, and 8 baseline comorbidities from the USRDS Medical Evidence Form 2728 (atherosclerotic heart disease, cardiac failure, hypertension, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, malignancy, and nonambulatory state).

Fully adjusted models included all case-mix model covariates plus marital status (married, divorced, single, or widowed), vintage (<6 months, 6 to <24 months, and 2–5 years, >5 years), residual renal function, dialysis dose (single pool Kt/V), serum phosphate, and nutritional status and inflammation surrogates (serum albumin, TIBC, calcium, bicarbonate, creatinine, ferritin, hemoglobin, peripheral white blood cell count, lymphocyte percentage, and nPCR) during the baseline quarter.

There was no missing data with regards to age, sex, diabetes, and vintage. Data for modality was missing for <1% of the cohort. Data for insurance, marital status, and comorbidities had 8.4, 17.3, and 5.1% missing values, respectively. Data for residual renal function, BMI, single pool Kt/V, nPCR, albumin, creatinine, TIBC, bicarbonate, phosphorus, calcium, ferritin, hemoglobin, white blood cell count, and lymphocyte percentage were 18.8, 16.8, 24.4, 24.6, 15.1, 17.3, 18.5, 15.6, 14.9, 14.8, 22.5, 13.8, 16.3, and 21.0%, respectively. For continuous variables, missing covariate data were imputed by the means or medians of the existing values, and for categorical variables a missing indicator was created. Plots of log [–log (survival rate)] against log (survival time) were used to check the proportionality assumption. Statistical analyses were conducted with SAS, version 9.1 (SAS Institute Inc., Cary, N.C., USA).

Results

Cohort Description

The cohort initially included 164,789 patients (online suppl. fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000358497). After excluding patients <18 years of age, those whose vintage was <90 days, and of other or unknown race/ethnicity, the final study cohort consisted of 130,909 patients in 1 of 3 mutually exclusive race/ethnicity categories: whites (49%; n = 64,710), African-Americans (35%; n = 45,718), and Hispanics (16%; n = 20,481).

Table 1 shows patients' baseline demographic, clinical, and laboratory characteristics across race/ethnicity

Table 1. Baseline demographic, clinical, and biochemical characteristics of dialysis patients by age and race/ethnicity

	Age 18–40 years				Age >40 to 60 years				Age >60 years			
	White	AA	Hispanic	p	White	AA	Hispanic	p	White	AA	Hispanic	p
Patients, n	130,909	4,850	6,185	2,776	17,559	19,194	7,690		42,301	20,339	10,015	
Age (mean ± SD), years	61±15	32±6	33±5	31±6	52±6	51±5	51±5	<0.001	74±8	71±7	71±7	<0.001
Women, %	45	42	43	42	41	44	41	<0.001	42	56	50	<0.001
<i>Cause of ESRD, %</i>												
Diabetes	43	28	17	18	46	37	60	<0.001	40	51	66	<0.001
Hypertension	28	9	33	22	13	37	18	<0.001	31	37	21	<0.001
Glomerulonephritis	11	28	24	29	15	11	9	<0.001	9	4	4	<0.001
Cystic disease	3	4	1	2	7	2	3	<0.001	3	1	1	<0.001
Other urologic cause	3	7	1	3	4	1	1	<0.001	3	1	2	<0.001
Other	8	19	19	14	11	9	5	<0.001	9	3	3	<0.001
Missing/unknown	4	5	5	12	4	3	4	<0.001	5	3	3	<0.001
Diabetes, %	56	34	25	25	56	51	71	<0.001	54	68	78	<0.001
<i>Vintage, %</i>												
<6 months	13	13	9	11	13	10	11	<0.001	16	12	13	<0.001
6 to <24 months	31	32	24	27	34	25	28	<0.001	36	28	31	<0.001
2–5 years	35	31	34	35	34	34	37	<0.001	35	35	36	0.02
>5 years	21	24	33	27	19	32	24	<0.001	13	25	20	<0.001
<i>Modality, %</i>												
Hemodialysis	93	85	92	88	88	94	93	<0.001	94	97	95	<0.001
Peritoneal dialysis	7	15	8	12	12	6	7	<0.001	6	3	5	<0.001
<i>Insurance, %</i>												
Medicare	69	60	63	46	54	63	57	<0.001	78	79	67	<0.001
Medicaid	5	5	11	23	4	8	16	<0.001	1	2	10	<0.001
Private	10	12	10	13	13	10	11	<0.001	8	7	11	<0.001
Other	16	23	16	18	29	19	16	<0.001	13	11	12	<0.001
<i>Marital status, %</i>												
Married	49	32	23	37	55	37	57	<0.001	60	39	55	<0.001
Divorced	8	8	3	3	13	11	9	<0.001	6	9	7	<0.001
Single	28	59	73	59	29	48	30	<0.001	10	24	16	<0.001
Widowed	15	0	0	0	3	4	4	<0.001	23	28	22	<0.001
<i>Comorbidities, %</i>												
AHD	21	4	2	1	18	10	10	<0.001	35	21	21	<0.001
Hypertension	80	70	77	68	77	83	80	<0.001	78	85	81	<0.001
Cardiac failure	27	8	11	7	21	21	20	0.1	36	31	31	<0.001
PVD	11	4	2	2	10	6	7	<0.001	18	10	12	<0.001
CVD	7	2	2	1	6	5	4	<0.001	10	10	7	<0.001
COPD	6	1	1	0	5	3	1	<0.001	10	5	3	<0.001
Malignancy	5	1	0	1	4	2	1	<0.001	8	5	3	<0.001
Nonambulatory	3	1	1	1	3	2	2	<0.001	3	4	3	<0.001
Active smoking	5	9	5	2	9	8	2	<0.001	4	3	1	<0.001
Alcohol use	1	1	1	1	2	3	1	<0.001	1	1	1	<0.001
Drug use	1	2	3	2	1	4	1	<0.001	0	0	0	n.a.

Table 1. (continued)

	Age 18–40 years				Age >40 to 60 years				Age >60 years			
	White	AA	Hisp.	p	White	AA	Hisp.	p	White	AA	Hisp.	p
RRF (mean ± SD), ml/min	0.43±1.46	0.48±1.67	0.30±1.31	<0.001	0.66±1.90	0.26±1.10	0.37±1.35	<0.001	0.55±1.63	0.24±1.03	0.40±1.31	<0.001
BMI (mean ± SD)	27.0±7.0	25.7±7.5	28.0±8.8	<0.001	28.6±7.8	28.3±8.0	27.6±6.6	<0.001	26.3±6.2	26.6±6.6	26.1±6.1	<0.001
BMI, %												
<18	4	6	4	<0.001	3	3	2	<0.001	4	5	3	<0.001
18–24.99	41	52	53	<0.001	35	36	37	<0.001	44	41	44	<0.001
25–29.99	29	21	25	<0.001	27	27	33	<0.001	30	29	34	<0.001
30–34.99	15	11	10	<0.001	17	17	16	0.3	14	15	13	<0.001
≥35	11	10	8	<0.001	18	17	12	<0.001	8	10	6	<0.001
spKt/V (mean ± SD)	1.52±0.35	1.52±0.38	1.40±0.34	<0.001	1.49±0.38	1.43±0.32	1.52±0.35	<0.001	1.56±0.36	1.51±0.32	1.61±0.36	<0.001
nPCR, (mean ± SD), g/kg/day	0.94±0.25	0.96±0.26	0.92±0.25	<0.001	0.95±0.26	0.93±0.25	1.02±0.26	<0.001	0.92±0.25	0.90±0.24	1.00±0.26	<0.001
Serum levels (mean ± SD)												
Albumin, mg/dl	3.66±0.47	3.82±0.50	3.79±0.54	<0.001	3.68±0.48	3.71±0.48	3.68±0.49	<0.001	3.60±0.44	3.62±0.44	3.61±0.44	<0.001
Creatinine, mg/dl	8.0±3.4	9.5±3.5	11.9±4.2	<0.001	7.8±3.0	10.1±3.6	8.6±3.1	<0.001	6.4±2.4	8.1±2.9	6.9±2.6	<0.001
TIBC, mg/dl	211±47	216±48	202±43	<0.001	222±50	211±46	215±46	<0.001	214±48	196±44	208±45	<0.001
Bicarbonate, mg/dl	22.6±3.1	22.0±3.4	22.0±3.1	0.005	22.2±3.3	22.3±3.1	22.0±3.1	<0.001	22.9±3.1	23.1±3.0	22.6±3.0	<0.001
Phosphorus, mg/dl	5.5±1.5	6.5±1.8	6.2±1.6	<0.001	5.9±1.6	5.8±1.5	5.9±1.5	<0.001	5.2±1.3	5.2±1.3	5.3±1.3	<0.001
Calcium, mg/dl	9.2±0.7	9.3±0.8	9.1±0.8	<0.001	9.2±0.7	9.2±0.8	9.0±0.7	<0.001	9.2±0.7	9.3±0.7	9.1±0.7	<0.001
iPTH, pg/ml	351±368	448±495	582±556	<0.001	336±358	471±451	346±348	<0.001	251±245	371±342	274±252	<0.001
Alk Phos, U/l	119±89	126±126	123±105	0.3	124±102	129±107	132±94	<0.001	110±69	115±78	122±78	<0.001
Ferritin, ng/ml	496±481	392±405	513±609	<0.001	439±442	533±526	479±462	<0.001	478±447	575±515	512±476	<0.001
Hemoglobin, g/dl	12.0±1.4	12.0±1.5	11.7±1.6	<0.001	12.1±1.5	11.9±1.5	12.1±1.4	<0.001	12.1±1.3	11.9±1.4	12.2±1.3	<0.001
WBC, ×10 ³ /μl	7.5±2.6	7.7±2.5	6.9±2.4	<0.001	7.8±2.7	6.9±2.3	7.6±2.2	<0.001	7.8±2.8	7.0±2.4	7.6±2.3	<0.001
Lymphocyte percentage	21±8	22±8	25±9	<0.001	19±7	24±8	21±7	<0.001	18±7	22±8	20±7	<0.001

There was no missing data with regards to age, sex, diabetes, and vintage. Data for modality was missing for <1% of the cohort. Data for insurance, marital status, and comorbidities had 8.4, 17.3, and 5.1% missing values, respectively. Data for RRF, BMI, spKt/V, nPCR, albumin, creatinine, TIBC, bicarbonate, phosphorus, calcium, ferritin, hemoglobin, WBC, and lymphocyte percentage had 18.8, 16.8, 24.4, 24.6, 15.1, 17.3, 18.5, 15.6, 14.9, 14.8, 22.5, 13.8, 16.3, and 21.0% missing values, respectively. AA = African-American; Hisp. = Hispanic; AHD = atherosclerotic heart disease; PVD = peripheral vascular disease; CVD = cerebrovascular disease; COPD = chronic obstructive pulmonary disease; RRF = residual renal function; iPTH = intact parathyroid hormone; WBC = white blood cell count.

Fig. 1. All-cause mortality hazard ratios (95% CI) across 7 age categories using case-mix (a) and fully adjusted (b) Cox regression models comparing 45,718 African-American and 20,481 Hispanic with 64,710 non-Hispanic white (reference) dialysis patients. Er-

ror bars represent 95% CI. Number of patients per age category: 18–30 years (n = 4,356), >30 to 40 years (n = 9,464), >40 to 50 years (n = 17,670), >50 to 60 years (n = 26,792), >60 to 70 years (30,383), >70 to 80 years (28,446), and >80 years (13,798).

and age categories. Compared to whites, a greater proportion of African-Americans and Hispanics were in younger age categories. Across all ages, African-Americans and Hispanics had a higher prevalence of increased (>5 years) vintage, higher mean serum creatinine, and lower prevalence of vascular disease versus whites. In younger and middle age categories (18–40 and >40 to 60 years), African-Americans had a higher prevalence of Medicaid/Medicare and lower prevalence of private insurance, and Hispanics had a higher prevalence of Medicaid across all age categories versus whites. In middle and older age categories (40–60 and >60 years), Hispanics had a higher prevalence of diabetes and hypertension versus whites and African-Americans. The most prevalent causes of ESRD within racial/ethnic groups varied across age categories. In the younger age category, 40% of Hispanics had diabetes or hypertension as the cause of ESRD, compared to 50% of African-Americans and 37% of whites. However, in the middle and older age categories, 78% and 87% of Hispanics had diabetes or hypertension as the cause of ESRD, respectively, which exceeded or was equivalent to the prevalence in African-Americans and whites. In contrast, in the younger age category, 29% of Hispanic patients had glomerulonephritis as the cause of ESRD, representing the most prevalent etiology of disease, versus 24% in African-Americans and 28% in whites. However, in the

middle and older age categories, 9% and 4% of Hispanic patients had glomerulonephritis, which was lower or equivalent to the prevalence in African-Americans and whites. Patients contributed a total of 363,713 patient-years of follow-up time, during which 72,891 deaths (39,708 whites, 23,262 African-Americans, and 9,921 Hispanics) and 12,677 kidney transplants (6,535 whites, 3,916 African-Americans, and 2,226 Hispanics) occurred (online suppl. tables 1, 2). The median follow-up time was 2.4 years.

All-Cause Mortality by Race/Ethnicity and Age Categories Using Cox Regression

In case-mix analyses, African-Americans had similar all-cause mortality risk in younger age categories (18–30 and >30 to 40 years), but decreased mortality risk in age categories >40 years compared to whites (fig. 1; online suppl. table 3). In fully adjusted analyses, mortality reductions among African-Americans versus whites in the >40- to 80-years age categories were mildly attenuated but remained statistically significant. In case-mix analyses, Hispanics had a lower mortality risk versus whites across all ages, with the most potent survival advantage observed in younger age categories. In fully adjusted analyses, mortality reductions among Hispanics versus whites in the 18- to 80-years age categories were mildly attenuated but remained statistically significant. Compared to

Fig. 2. All-cause mortality subhazard ratios across 7 age categories using case-mix (**a**) and fully adjusted (**b**) competing risk regression models comparing 45,718 African-American and 20,481 Hispanic with 64,710 non-Hispanic white (reference) dialysis patients. Er-

ror bars represent 95% CI. Number of patients per age category: 18–30 years (n = 4,356), >30 to 40 years (n = 9,464), >40 to 50 years (n = 17,670), >50 to 60 years (n = 26,792), >60 to 70 years (30,383), >70 to 80 years (28,446), and >80 years (13,798).

Hispanics, African-Americans had increased mortality risk in the age categories 18–70 years in case-mix analyses, with the greatest survival differences observed in younger age categories (online suppl. fig. 2; online suppl. table 3); results from fully adjusted analyses were qualitatively similar.

All-Cause Mortality by Race/Ethnicity and Age Categories Using Competing Risk Regression

In sensitivity analyses employing competing risk regression, African-Americans had similar, slightly higher, and decreased mortality risk versus whites within the age categories of 18–30, >30 to 40, and >40 years in case-mix analyses, respectively (fig. 2; online suppl. table 4). However, the magnitude of mortality risk reduction in older (>40 years) African-Americans was lower than observed in the Cox regression analyses. In fully adjusted analyses, this mortality risk reduction was further attenuated, such that older African-Americans had similar mortality risk versus whites within age categories of >40 to 60 years. In case-mix and fully adjusted analyses, the degree of survival benefit in Hispanics versus whites was lower than observed in the Cox regression analyses, whereas the degree of heightened mortality risk in African-Americans versus Hispanics was qualitatively similar to the Cox regression analyses.

Kidney Transplantation by Race/Ethnicity and Age Categories

Among a total of 12,677 kidney transplantations, 7,132, 3,347, and 2,198 were from deceased, living, and unknown donors, respectively. Among LDKT, 2,131, 1,208, and 8 were from related, unrelated, and unknown living donors, respectively. When kidney transplantations from all donor types were considered, both African-Americans and Hispanics were less likely to undergo transplantation versus whites across all ages, with greater disparities observed in older age categories in case-mix analyses (fig. 3; online suppl. table 5). Compared to Hispanics, African-Americans ages 18–70 years were also less likely to undergo transplantation in case-mix analyses (online suppl. fig. 3; online suppl. table 5). Results from fully adjusted analyses showed similar findings.

When DDKT only was considered, there were no differences in transplantation among African-Americans versus whites and Hispanics versus whites in the 18- to 30-years age category in case-mix analyses. However, both African-Americans and Hispanics were less likely to undergo DDKT versus whites in the >30- to 80-years age categories in case-mix analyses (online suppl. table 6). Results from fully adjusted analyses showed similar findings. Compared to Hispanics, African-Americans were less likely to undergo DDKT in the >40- to 50-years age category

Fig. 3. Kidney transplantation hazard ratios across 6 age categories using case-mix (a) and fully adjusted (b) competing risk regression models comparing 45,718 African-American and 20,481 Hispanic with 64,710 non-Hispanic white (reference) dialysis patients. Error bars represent 95% CI. Age category >80 not included due to

unstable estimates resulting from paucity of events. Number of patients per age category: 18–30 years ($n = 4,356$), >30 to 40 years ($n = 9,464$), >40 to 50 years ($n = 17,670$), >50 to 60 years ($n = 26,792$), >60 to 70 years (30,383), and >70 to 80 years (28,446).

only in case-mix analyses; however, in fully adjusted analyses, African-Americans were also less likely to undergo DDKT across a wider age spectrum of >30 to 70 years.

Disparities in LDKT across categories of race, ethnicity, and age were even more marked than for DDKT and kidney transplantations from all donor types. In case-mix analyses, African-Americans and Hispanics were less likely to undergo LDKT versus whites across all ages, particularly in older age categories (online suppl. table 7). Compared to Hispanics, African-Americans ages 18–70 years were also less likely to undergo LDKT in case-mix analyses. Results from fully adjusted analyses were qualitatively similar.

When LRDKT was considered, African-Americans and Hispanics were less likely to undergo transplantation versus whites across all ages in case-mix analyses (online suppl. table 8). Compared to Hispanics, African-Americans ages 18–70 years were also less likely to undergo LRDKT in case-mix analyses. Findings in fully adjusted analyses were qualitatively similar, with the exception of an attenuation in the Hispanic versus white LRDKT disparity in the >30- to 40-years age category. When LUDKT was considered, African-Americans and Hispanics were less likely to undergo transplantation versus whites in age categories of 18–70 years in case-mix analyses (online suppl. table 9). However, there were no

differences in LUDKT among Hispanics versus African-Americans across any of the age categories in case-mix or fully adjusted analyses.

Discussion

In this large, contemporary cohort of 130,909 US dialysis patients, we observed that Hispanic dialysis patients had greater survival compared to whites and African-Americans across virtually all age categories. African-Americans had greater survival compared to whites among patients exceeding 40 years of age in standard Cox regression analyses, and the magnitude of survival benefit was attenuated when racial/ethnic differences in kidney transplantation rates were accounted for in competing risk regression analyses. When examining kidney transplantations from all donor types, we observed that African-Americans and Hispanics were less likely than whites to undergo transplantation across all age categories. Disparities across race and ethnicity were particularly amplified for LDKT.

Our findings extend upon three recent USRDS studies suggesting that age is an important modifier of the race-mortality association. In the first of these studies, Kucirka et al. [13] showed that the African-American survival ad-

vantage is restricted to older (≥ 50 years) dialysis patients, and that African-Americans < 50 years of age had greater mortality risk compared to the white reference group which included both non-Hispanics and Hispanics. Hispanic dialysis patients have decreased mortality risk compared to non-Hispanic whites [3, 10, 11], and their inclusion in the white reference group may have contributed to the higher mortality risk observed among younger African-Americans versus whites [15]. Arce et al. [14] then showed that the survival advantage among Hispanic white versus non-Hispanic white dialysis patients attenuated (1) with increasing age and (2) after accounting for differential rates of kidney transplantation across ethnicity, although patients of African-American race were not concomitantly examined. In a subsequent study by Yan et al. [15] that separately considered Hispanic dialysis patients from African-Americans and whites, a similar survival disadvantage was observed among younger African-Americans versus whites, but did not consider racial/ethnic differences in rates of kidney transplantation. Furthermore, data limitations precluded the examination of nutrition and inflammatory status as potential confounders of the age, race/ethnicity, and mortality associations.

We observed several corroborative and novel findings as we sought to address these limitations by (1) concurrently examining race and ethnicity, (2) more comprehensively adjusting for sociodemographic variables (e.g. marital status) and repeated measures of laboratory covariates (e.g. malnutrition and inflammatory covariates) and dialysis treatment characteristics averaged in the baseline quarter [16, 25], and (3) accounting for differential rates of kidney transplantation across race/ethnicity. First, our study provides confirmatory evidence that older African-Americans have increased survival versus whites, which was mildly attenuated with incremental adjustment for nutritional and inflammatory covariates. However, in contrast to the aforementioned studies, we observed a *similar* mortality risk among African-American dialysis patients versus whites in younger age (18–40 years) categories in both case-mix and fully adjusted Cox analyses. The underlying reasons for an attenuated survival advantage in younger African-Americans remains unclear; however, it has been suggested that biologic factors primarily mediate the race/ethnicity-mortality association in older patients [26] in whom Medicare eligibility offsets health care access inequities, whereas socioeconomic status, education, access to health care, and social support networks bear greater importance in younger populations [13, 27, 28]. After accounting for differential kidney transplantation rates across racial/ethnic groups using compet-

ing risks regression, the African-American survival advantage in older age groups was attenuated (and became nonexistent in the 40- to 60-years age group), suggesting that the paradoxical African-American advantage may in part be due to their comparatively lower rates of kidney transplantation versus whites. Further studies are needed to determine the underlying factors driving the differential African-American-mortality association across varying age groups.

Similar to the Arce et al. [14] study, we observed that Hispanic dialysis patients have greater survival compared to whites, particularly in younger age groups, and the degree of this survival benefit was mildly attenuated with adjustment for nutritional and inflammatory markers, as well as in competing risk regression analyses. We also showed for the first time that, among minority dialysis patients, Hispanics have decreased death risk compared to African-Americans across nearly all age categories, which was robust to incremental adjustment for laboratory covariates and after consideration of differential rates of transplantation. It has been posited that the Hispanic survival advantage compared to whites may be due to comparatively lower cardiovascular burden [14, 29], ethnic misclassification, or ‘salmon bias’ in which older ailing Hispanics return to their country of origin, resulting in an underreporting of deaths [30–32]. We also observed that older Hispanics had a markedly higher prevalence of diabetes and hypertension (also as the etiology of their ESRD) compared to their younger counterparts, which may explain the attenuation in the Hispanic survival benefit with increasing age. Further examination of the mechanisms underlying the Hispanic survival advantage compared to whites and African-Americans is needed.

Despite the disproportionate burden of ESRD among racial and ethnic minorities, population-based studies show that African-Americans and Hispanics are substantially less likely to receive DDKT [21] and LDKT compared with whites [19, 20, 22]. LDKT is the treatment of choice for dialysis patients given that it confers greater patient survival and quality of life compared with dialysis, as well as improved early graft function, lower rates of acute rejection, and greater graft and patient survival compared to DDKT [33–37]. To our knowledge, ours is the first study to show that African-Americans and Hispanics are less likely to undergo kidney transplantation across all age categories, and that these disparities are magnified for LDKT and particularly LUDKT. In contrast, racial/ethnic disparities in DDKT were not as marked as for LDKT, and were not consistently observed in younger age groups.

Although our study does not elucidate determinants of inequitable kidney transplantation access, prior data shows that minorities encounter barriers at multiple steps (e.g. donor recruitment and conversion, transplant evaluation, and the kidney transplantation procedure itself), and that these barriers operate at multiple levels (recipients, donors, family and social support networks, health care providers and systems, and communities) [36, 38]. For example, at the recipient and donor level, African-Americans are less likely to identify living kidney donors (particularly unrelated donors [39]) compared to whites [38], which may relate to inadequate education regarding ESRD treatment options [40], lack of medically suitable or willing donors [41], socioeconomic insecurity [42], and cultural beliefs [43]. Given that whites and African-Americans disproportionately contribute to the donor and recipient pools, respectively, genetic dissimilarity may be another factor for reduced DDKT rates among African-Americans and other minorities [44–46]. At the provider level, perceptions about patients' suitability and preferences for LDKT may differ by race/ethnicity, resulting in decreased transplant referral for minorities [47]. At the community level, sparsity of transplant centers in rural locations may contribute to reduced LDKT rates in minorities [48]. Rigorous studies are needed to elucidate mechanisms driving transplantation disparities across age, race, and ethnicity, and to explore interventions targeting these barriers [36, 37, 49, 50].

Our study has several strengths, which include its large sample size, extended follow-up period, and comprehensive availability of detailed sociodemographic, dialysis treatment, and laboratory data, including nutritional and inflammatory status covariates. However, several limitations bear mention. First, the findings presented may not be generalizable to patients from non-large dialysis organizations. Second, we had limited ability to distinguish Hispanic subpopulations which may have had differential severity of disease, survival, and access to transplantation depending on country of origin [51]. Third, we cannot exclude the possibility that the survival advantage observed in older African-Americans may have been due to a natural selection bias of the healthiest patients [13, 27, 28]. Fourth, our data do not distinguish steps at which racial/ethnic and age disparities in the transplantation process may occur, nor the underlying reasons for failure to progress to sequential stages. Fifth, baseline comorbidity data was ascertained from the Medical Evidence 2728 form in which comorbidities may have been underreported and severity of

disease cannot be ascertained. Finally, as with all observational studies, we cannot exclude the possibility of residual confounding.

Conclusion

In conclusion, we observed that the African-American survival advantage was restricted to middle- and older-aged dialysis patients, whereas Hispanics experience greater survival across all ages. We also observed that African-American and Hispanic dialysis patients were less likely to undergo kidney transplantation, particularly LDKT, across all age groups. Awareness of the differential race/ethnicity-mortality associations across age categories in dialysis patients has important implications, as misconceptions regarding survival advantage may diminish the urgency with which providers refer minorities for transplantation. Given the disproportionate burden of ESRD among African-Americans and Hispanics, further mechanistic studies are needed to determine the genetic, biologic, socioeconomic, and psychosocial factors underlying the differential survival and access to transplantation among racial/ethnic groups, and timely interventions and policy-level changes targeting the most vulnerable subgroups are needed.

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Disclosure Statement

K.K.-Z. was medical director of DaVita Harbor-UCLA Long Beach from 2007–2012. A.R.N. is Chief Medical Officer of DaVita Inc. None of the other authors declare any relevant conflicts of interest.

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