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Patients with Sickle Cell Disease who develop End Stage Kidney Disease continue to experience poor survival, a 19- year USRDS Study

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Patients with sickle cell disease (SCD) experience increased morbidity and early mortality, due in part to organ damage, including end stage kidney disease (ESKD)[1]. Decline in kidney function is progressive with initial hyperfiltration, followed by decline in glomerular filtration rate (GFR) and eventual ESKD in adults. Individuals with SCD experience a more rapid decline in GFR than the general African American population and this rapid decline is associated with increased mortality [2,3]. Prior studies suggest the one-year mortality rate after initiating dialysis is higher in patients with SCD but early care by a nephrologist may decrease mortality[4]. Additionally, individuals with ESKD due to SCD (SCD-ESKD) are less likely to receive an arteriovenous fistula (AVF) when initiating hemodialysis (HD)[5,6]

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Authors' Contributions

Project conceptualization: JW, RSZ; data acquisition: JW, RSZ; analysis: JW; interpretation: JW, RSZ, KIA, KL, MY; project administration: RSZ; writing-original draft: JW, RSZ writing review- and editing: JW, RSZ, KIA, JL.

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despite studies demonstrating improved survival when dialyzed with an AVF or graft [7,8]. Finally, referral for transplantation and transplantation rates are lower among individuals with SCD-ESKD despite the improved survival benefit of kidney transplantation[9–11].

It is important to characterize the mortality, and disparities experienced by patients with SCD-ESKD. This data can highlight the need to improve clinical care, monitor kidney disease progression, and develop therapies to prevent SCD-ESKD. Despite improvement in care over the last two decades, the prognosis of SCD-ESKD remains uncertain. This study aimed to characterize the outcomes of individuals with SCD-ESKD from 1998–2017 enrolled in the United States Renal Data System (USRDS) registry. We hypothesized that survival of patients with SCD-ESKD has improved over the course of the last two decades.

We performed an IRB approved retrospective analysis using the USRDS database from 1998–2017. Data including age, sex, race, ethnicity, primary diagnosis, outcome dates, first ESKD treatment modality, and comorbid conditions (atherosclerotic heart disease, congestive heart failure, cerebrovascular disease, diabetes mellitus, peripheral vascular disease, and hypertension) were abstracted from the patient profile using Centers for Medicare and Medicaid Services (CMS) Medical Evidence Form 2278.

Age was summarized by mean (standard deviation), median (interquartile range), and by number and percentage within age groups. Sex, ethnicity, first ESKD modality, dialysis access, duration of pre-ESKD nephrology care, and co-morbid conditions were summarized by number and percentage (Table 1). Groups were divided first by SCD status and then by Black race. Adjusted (Figure 1) and unadjusted (Supplemental Figure) survival and time-to-transplant were calculated using Cox proportional hazards regression model, overall and by year of first ESKD event. For survival, adjusted values were adjusted for age, sex, ethnicity, Black race, initial treatment modality, hemodialysis access type, pre-ESKD nephrology care, and comorbidities. For transplant, due to small numbers in the temporal analysis, adjustment was restricted to demographic variables including age (on a continuous scale), sex, ethnicity, and black race.

Between 1998 and 2017, 2,194,079 patients developed ESKD; 2018 (0.09%) had a diagnosis of SCD. The age at ESKD diagnosis was significantly lower in the SCD-ESKD group than in the non-SCD-ESKD group, both unadjusted (OR: 0.57, 95% CI: 0.55–0.58, for each 10-year increase in age) and when adjusted for sex, race, ethnicity, initial treatment modality, access, nephrology care, and comorbidities (OR: 0.62, 95% CI: 0.60–0.64, for each 10-year increase in age). Twenty percent of patients developed ESKD before the age of 30. Male patients with SCD-ESKD developed ESKD at an earlier age than female patients with SCD-ESKD ($p < 0.001$). Patients with SCD-ESKD had lower adjusted odds of receiving a pre-emptive kidney transplant as compared to being started on dialysis (OR 0.24, 95% CI 0.14, 0.41). Patients with SCD-ESKD were more likely to have ongoing pre-ESKD nephrology care than not having any care (<6 months: OR 1.23, 95% CI 1.01–1.48; 6–12 months: OR 1.33 95% CI. 1.13–1.58; and >12 months: OR 1.43 95% CI 1.22–1.69). The unadjusted hazard ratio of mortality following first ESKD event was higher among SCD-ESKD patients than non-SCD-ESKD patients (HR: 1.21, 95% CI: 1.15–1.27). This hazard of mortality effect was much larger after adjusting for age, sex, ethnicity,

Black race, initial treatment modality and comorbidities (HR: 2.68, 95% CI: 2.55–2.83). Over the nineteen-year study period, the adjusted hazard of mortality improved by 35% (HR 0.65, 95% CI 0.64–0.66) for non-SCD-ESKD and by 30% (HR 0.70, 95% CI 0.58–0.84) for SCD-ESKD. These values were not significantly different between the groups. The unadjusted rate of receiving a transplant was lower among SCD-ESKD patients than non-SCD-ESKD patients by 29% (OR: 0.71, 95% CI: 0.62–0.83). This relative transplant rate was even smaller after adjusting for age, sex, ethnicity, and Black race (HR: 0.49, 95% CI: 0.29–0.84). Over the study period, the adjusted rate of transplant decreased for the non-SCD-ESKD (HR 0.81, 95% CI 0.80–0.82), but this decrease was not statistically significant for the SCD-ESKD group (HR 0.75, 95% CI 0.43–1.32).

Patients with SCD continue to develop ESKD earlier in life, have a higher risk of death, and lower transplant rate than non-SCD-ESKD patients. When adjusting for age, this disparity in survival was magnified as SCD-ESKD patients have a 2.7 times higher hazard of mortality. In contrast to a prior study[4], we found that despite the increase in pre-ESKD nephrology care, mortality remained elevated. It remains alarming that patients with SCD-ESKD were less likely to receive a kidney transplant as compared to non-SCD-ESKD patients. Data remains conflicting as to whether SCD patients have lower overall and graft survival than non-SCD patients; this should not preclude patients from transplant[11–13].

This retrospective study has some limitations. We could not assess the stage of CKD at time of referral. USRDS reports active medications, but we could not evaluate the effect of SCD modifying or renoprotective therapies on progression to ESKD. Large prospective cohort studies are needed to determine the impact of therapies on progression of kidney disease.

This study confirms that patients with SCD who develop ESKD continue to experience disparities in renal outcomes. As patients with SCD-ESKD are at high risk of all-cause mortality, it is important to ensure comprehensive SCD care centers that includes both pediatric and adult hematologists[14]. Ongoing research should identify risk factors for ESKD progression, ensure implementation of monitoring for kidney disease, and determine therapies that prevent the development of ESKD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Sharing:

This study was approved by the institutional review board at the University of Tennessee Health Science Center at Memphis and the USRDS. Data is made available by contacting the USRDS.

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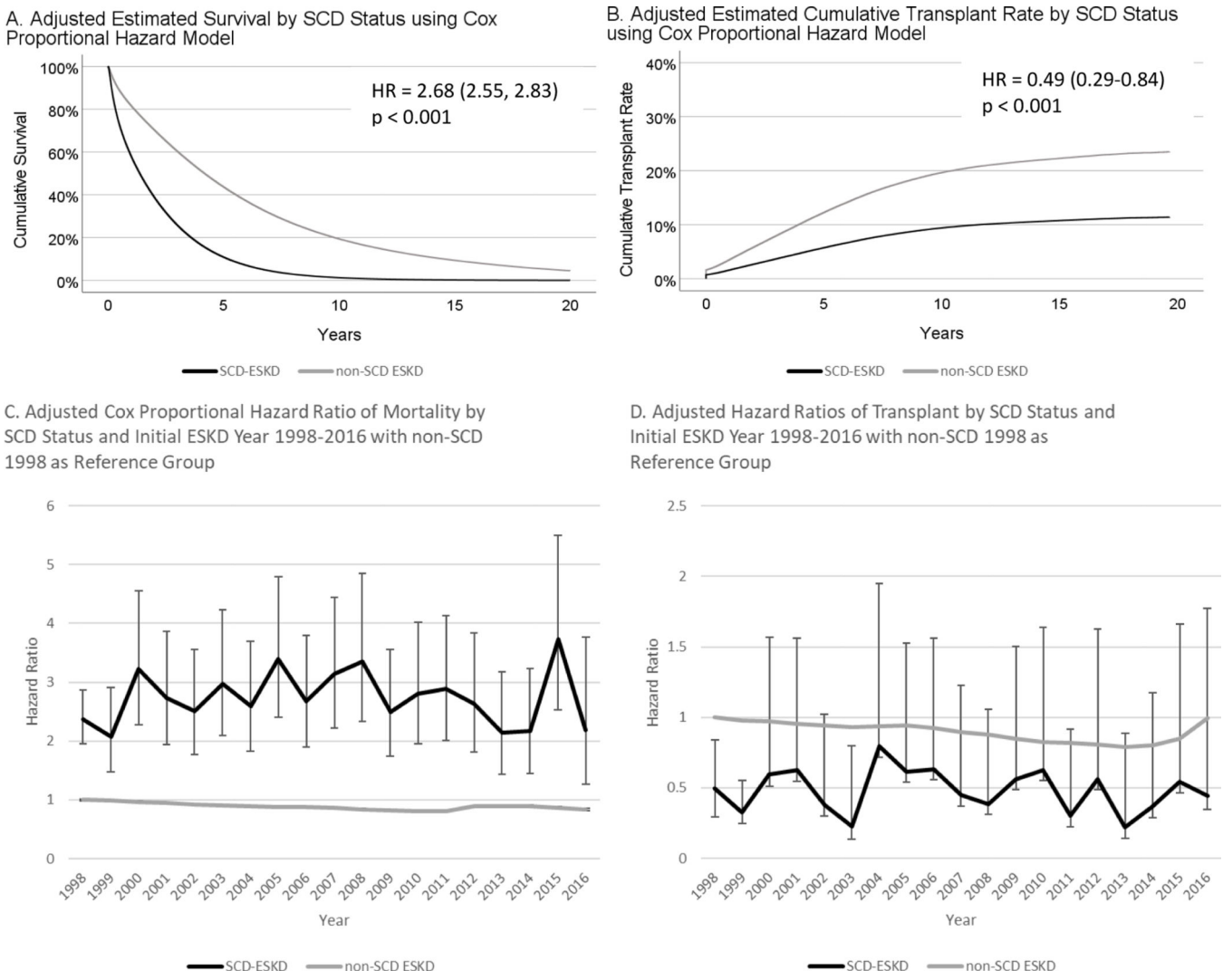

Figure 1.

Adjusted survival† and time-to-transplant‡ comparison overall and over time between sickle cell disease patients with end stage kidney disease (SCD-ESKD) and non-sickle cell disease patients with end-stage kidney disease (non-SCD-ESKD) using Cox proportional hazard model with hazard ratio and 95% confidence intervals overall.

† Adjusted for Age, Sex, Race, Ethnicity, Initial Treatment Modality, Access, Nephrology Care, and Comorbidities

‡ Adjusted for Age, Sex, Race, Ethnicity

Table 1.

Baseline characteristics of patients with end-stage kidney disease (ESKD), with and without sickle cell disease (SCD), and by Black or non-Black race

	SCD				Non-SCD					
	Black		Non-Black		Black		Non-Black			
Number of Patients	**1879**		**139**		**598726**		**1593335**		**Unadjusted OR SCD vs. non-SCD**	**Adjusted[†] OR SCD vs. non-SCD**
Age (years)									[††]0.57 (0.55, 0.58) ***	[††]0.62 (0.60, 0.64) ***
Mean (SD)	43.2 (13.3)		48.9 (16.8)		58.4 (15.5)		63.8 (15.7)			
Median (IQR)	44 (34, 52)		49 (37, 60)		59 (48, 70)		66 (55, 76)			
Age Group										
<18	32	1.7%	<11	N/A	4812	0.8%	16762	1.1%		
18–30	345	18.4%	13	9.4%	23696	4.0%	41084	2.6%		
31–40	405	21.6%	25	18.0%	50556	8.4%	75084	4.7%		
41–50	539	28.7%	34	24.5%	95458	15.9%	159613	10.0%		
51–60	383	20.4%	30	21.6%	141139	23.6%	295856	18.6%		
61–70	130	6.9%	18	12.9%	142396	23.8%	398127	25.0%		
71–80	>11	N/A	<11	N/A	101024	16.9%	396473	24.9%		
>80	<11	N/A	<11	N/A	39645	6.6%	210336	13.2%		
Male Sex	973	51.8%	76	54.7%	307684	51.4%	923885	58.0%	1.18 (1.09, 1.29) ***	1.17 (1.07, 1.27) ***
Hispanic Ethnicity	19	1.0%	42	30.2%	8959	1.5%	296665	18.6%	0.15 (0.10, 0.22) ***	0.95 (0.72, 1.24)
First ESRD Event Modality Type										
Hemodialysis	1638	87.2%	122	87.8%	557154	93.1%	1406547	88.3%	Reference Group	Reference Group
Peritoneal Dialysis	228	12.1%	>11	N/A	35745	6.0%	134963	8.5%	1.58 (1.38, 1.81) ***	1.00 (0.85, 1.17)
Transplant	>11	N/A	<11	N/A	5104	0.9%	49104	3.1%	0.29 (0.17, 0.49) ***	0.24 (0.14, 0.41) ***
Unknown	<11	N/A	<11	N/A	723	0.1%	2721	0.2%		
Initial Hemodialysis Access										
Arterio-Venous Fistula	84	4.5%	<11	N/A	49664	8.3%	149776	9.4%	Reference Group	Reference Group
Graft	71	3.8%	<11	N/A	16811	2.8%	25017	1.6%	3.80 (2.81, 5.15) ***	2.96 (2.18, 4.02) ***
Catheter	836	44.5%	68	48.9%	294325	49.2%	757059	47.5%	1.82 (1.48, 2.26) ***	1.43 (1.15, 1.78) **
None/Other/Unknown	888	47.3%	57	41.0%	237926	39.7%	661483	41.5%		
Pre-ESKD Nephrology Care										

	SCD				Non-SCD					
	Black		Non-Black		Black		Non-Black			
Number of Patients	**1879**		**139**		**598726**		**1593335**		**Unadjusted OR SCD vs. non-SCD**	**Adjusted† OR SCD vs. non-SCD**
None	731	38.9%	46	33.1%	207870	34.7%	535221	33.6%	Reference Group	Reference Group
< 6 Months	152	8.1%	<11	N/A	48983	8.2%	138909	8.7%	0.96 (0.80, 1.16)	1.23 (1.01, 1.48) *
6–12 Months	228	12.1%	>11	N/A	77071	12.9%	211982	13.3%	0.93 (0.79, 1.10)	1.33 (1.13, 1.58) ***
> 12 Months	293	15.6%	16	11.5%	92485	15.4%	307508	19.3%	0.86 (0.74, 1.00)	1.43 (1.22, 1.69) ***
Unknown	474	25.2%	52	37.4%	172293	28.8%	399661	25.1%		
Co-morbid Conditions										
Atherosclerotic Heart Disease	37	2.0%	<11	N/A	46764	7.8%	210243	13.2%	0.16 (0.12, 0.21) ***	0.39 (0.29, 0.54) ***
Congestive Heart Failure	522	27.8%	29	20.9%	168701	28.2%	494474	31.0%	0.87 (0.76, 0.96) **	2.07 (1.87, 2.30) ***
Cerebrovascular Disease	141	7.5%	<11	N/A	56973	9.5%	136861	8.6%	0.80 (0.68, 0.95) *	1.43 (1.21, 1.71) ***
Diabetes Mellitus	75	4.0%	<11	N/A	205068	34.3%	526230	33.0%	0.08 (0.06, 0.10) ***	0.10 (0.08, 0.12) ***
Hypertension	1313	69.9%	79	56.8%	515443	86.1%	1280527	80.4%	0.49 (0.45, 0.54) ***	0.53 (0.48, 0.59) ***
Peripheral Vascular Disease	63	3.4%	<11	NA	54733	9.1%	220991	13.9%	0.24 (0.18, 0.30) ***	0.71 (0.55, 0.91) **

†Adjusted for Age, Sex, Race, Ethnicity, Initial Treatment Modality, Access, Nephrology Care, and Comorbidities

††For an increase in 10 years age

*p < 0.05

**p < 0.01

***p < 0.001