Supplemental material to:

Bae S, et al. Mortality and Access to Kidney Transplantation in Patients with Sickle Cell Disease-Associated Kidney Failure.

Table of Contents

Supplemental Method. Sequential stratification matching between KT recipients and waitlisted candidates.

In brief, we aimed to emulate the following hypothetical experiment. Two patients with the same age, diabetes status, and history of previous transplant begin dialysis on the same day. On a later day, only one of them receives KT, whereas the other remains on dialysis. We evaluate the survival benefit conferred by KT by comparing how long the KT recipient survived from the date when KT was performed versus how long the patient who remained on dialysis survived from the same date. We repeat this experiment on multiple pairs of patients to establish a statistical inference.

In the current study, we matched KT recipients with controls by age, diabetes, history of previous transplant, and time on dialysis: the four variables that constitute the Estimated Post Transplant Survival (EPTS). Using the date of dialysis initiation as the reference time, we compared the survival from the recipient's receipt of KT within the matched pairs (Supplemental Figure 1, Case 1). For the recipients of a preemptive KT (*i.e.*, KT prior to initiating chronic dialysis), we used the date of waitlist registration as the reference time, and matched a comparable waitlisted candidate who was registered prior to initiating routine dialysis (Supplemental Figure 1, Case 2). For the KT recipients, survival was defined as the time from receipt of KT to death. The waitlisted candidates served as the counterfactual for their matched KT recipients; for the waitlisted candidates, survival was defined as the time from the matched recipient's receipt of KT to the candidate's death, censoring at the candidate's receipt of KT (Supplemental Figure 1, Case 3).

Supplemental Results. Sensitivity analysis on identifying the sickle cell group.

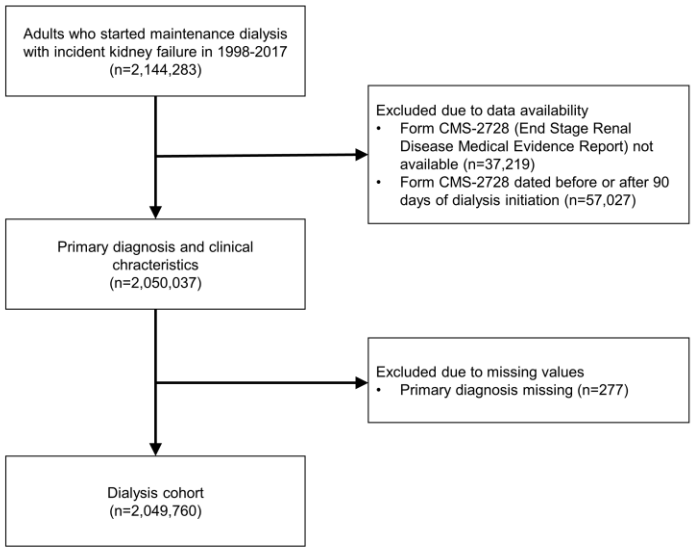
In this study, we identified the sickle cell group using the primary cause of renal failure as reported to the national registries. However, with this method, the control group may include patients who had sickle cell disease as an underlying disease (vs. the primary cause of renal failure). To assess whether this grouping approach has impacted our results, we conducted a sensitivity analysis using an alternative method for identifying the sickle cell group.

The dialysis cohort was studied using the USRDS data, which also provides Medicare claim data of the eligible persons; in our case, Medicare claims between 2001 and 2016 were available. Among the dialysis cohort (n=2,049,760), 1,681,625 (82.0%) started ESKD service between 2001 and 2016, and 514,617 (30.6%) had Medicare as their primary insurance during the first year of ESKD service. In the Medicare primary cohort, 393 patients were originally assigned to the sickle cell group, and 514,224 were to the control. Among them, 364 (92.6%) of the sickle cell group and 1,073 (0.2%) of the control group had Medicare claims with ICD-9-CM diagnosis code 282.6 or ICD-10-CM diagnosis code D57 during the one-year period following the beginning of ESKD service. In other words, the 1,073 (0.2%) patients from the control group appear to have had sickle cell disease as an underlying disease.

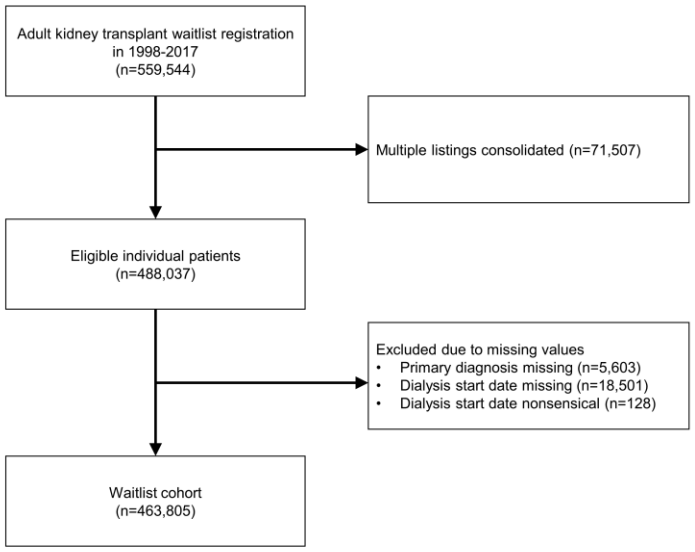
Excluding the control group patients who apparently had sickle cell disease as an underlying disease had a minimal impact on our mortality analysis. The hazard ratio for mortality in the sickle cell disease group (vs. the control group) was 1.10 (95% CI, 0.98 to 1.23) in Model 1, 1.37 (1.22 to 1.53) in Model 2, and 2.25 (2.01 to 2.52) in Model 3 before excluding the affected patients, and 1.10 (0.98 to 1.23) in Model 1, 1.37 (1.22 to 1.53) in Model 2, and 2.27 (2.03 to 2.55) in Model 3 after excluding the affected patients. We were not able to perform the same sensitivity analysis on the other analyses from this study because they used the SRTR data. However, given the very low proportion of the control group patients who had Medicare claims of sickle cell disease, we assume that our main findings will be robust to how the sickle cell group was identified.

Supplemental Figure 1. Patient inclusion flowchart.

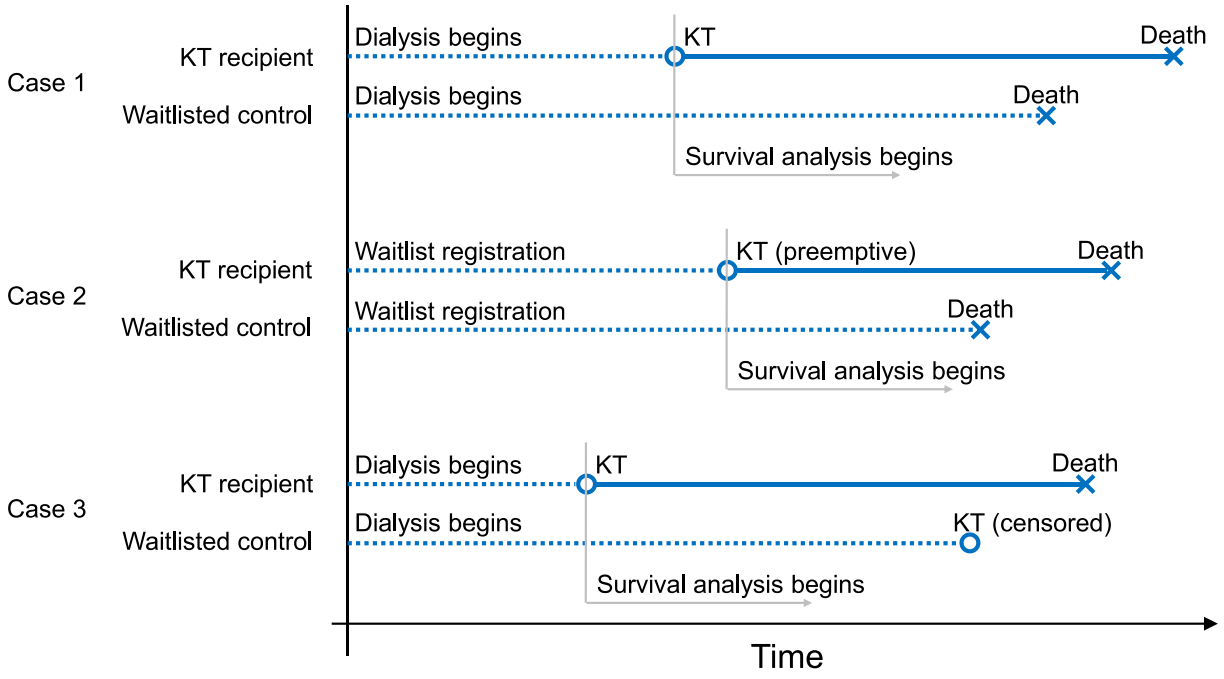
(a) Dialysis cohort



(b) Waitlist cohort



Supplemental Figure 2. Matching transplant recipients with waitlisted candidates via sequential stratification.



KT, kidney transplantation.

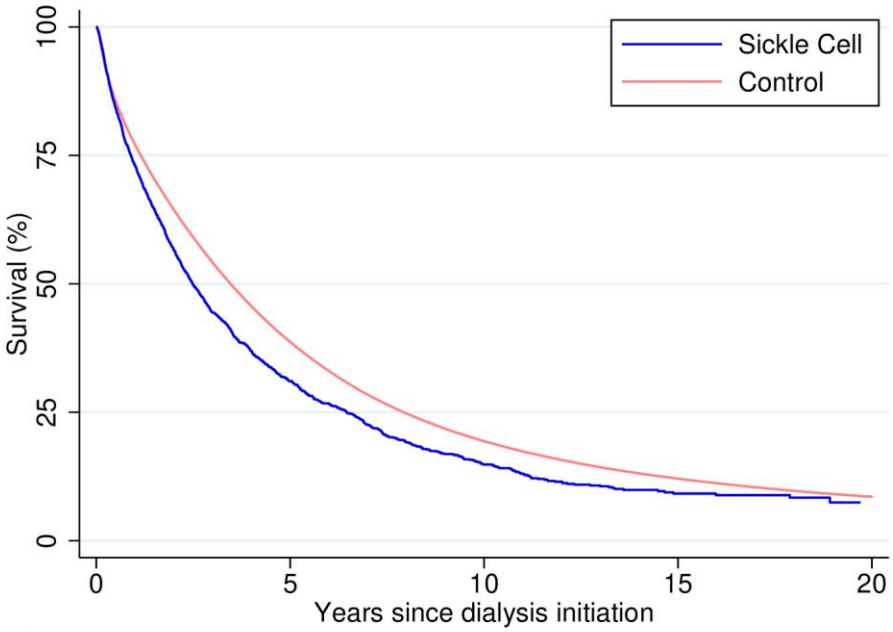
Case 1: we match the KT recipient with a waitlisted control who are similar with the recipient in all of the matching variables as well as has spent longer time on dialysis than the recipient has. Survival analysis begins from the recipient's date of KT.

Case 2: when the recipient underwent preemptive KT (KT before initiating routine dialysis), we used the date of waitlist registration as the reference time.

Case 3: when the waitlisted control has received a KT subsequently, it was treated as a censoring event.

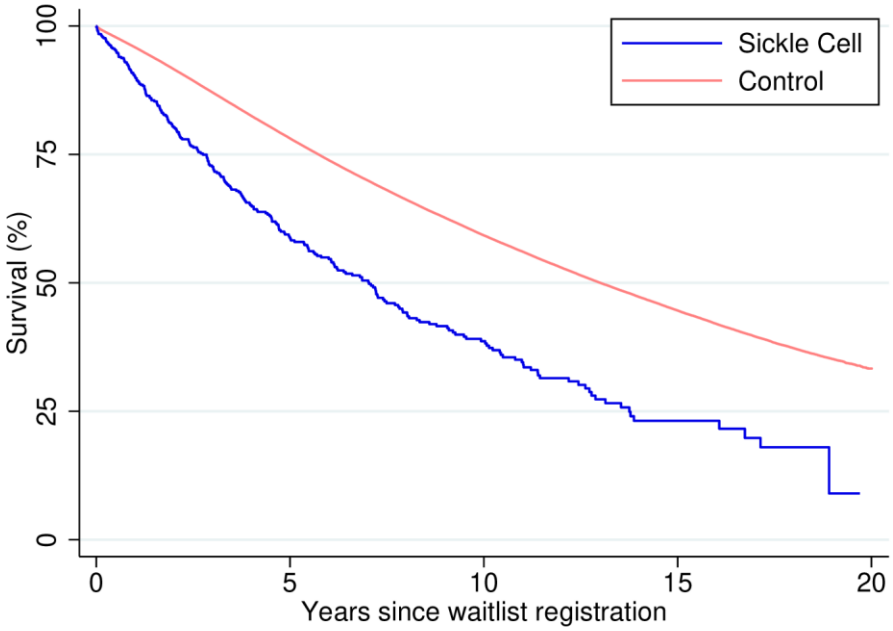
Supplemental Figure 3. Kaplan-Meier curves for dialysis, waitlist, and post-transplant mortality.

(a) Dialysis mortality



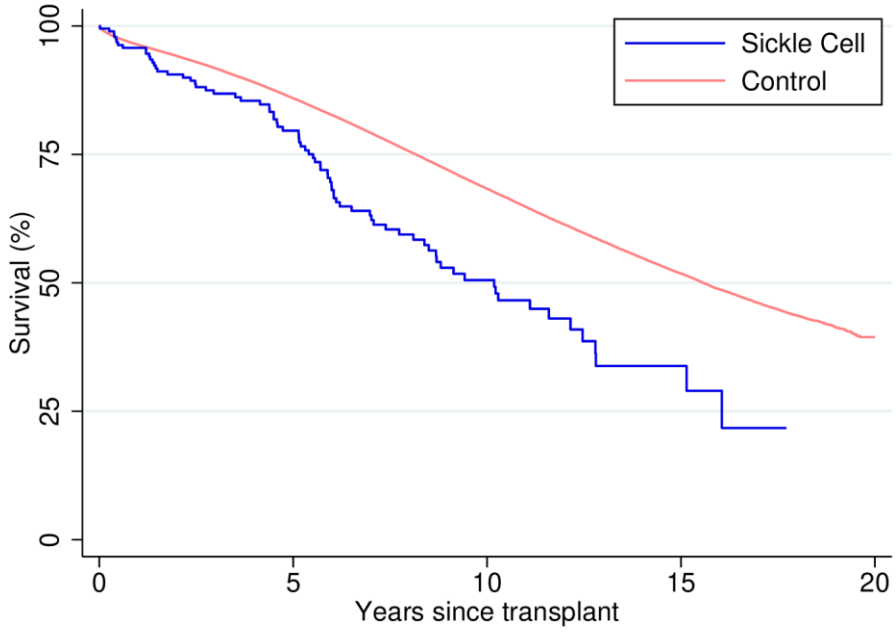
Sample size				
Sickle Cell	1970	443	130	38
Control	2047790	551986	160380	41242

(b) Waitlist mortality



Sample size				
Sickle Cell	507	203	88	22
Control	463298	253843	114352	35832

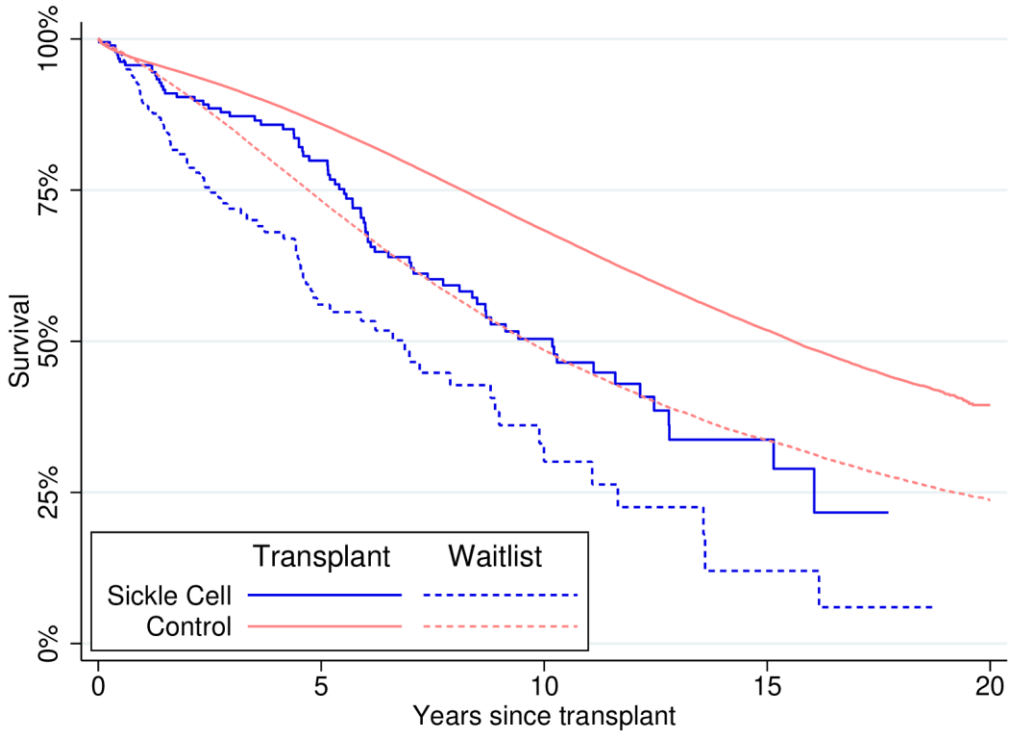
(c) Post-transplant mortality



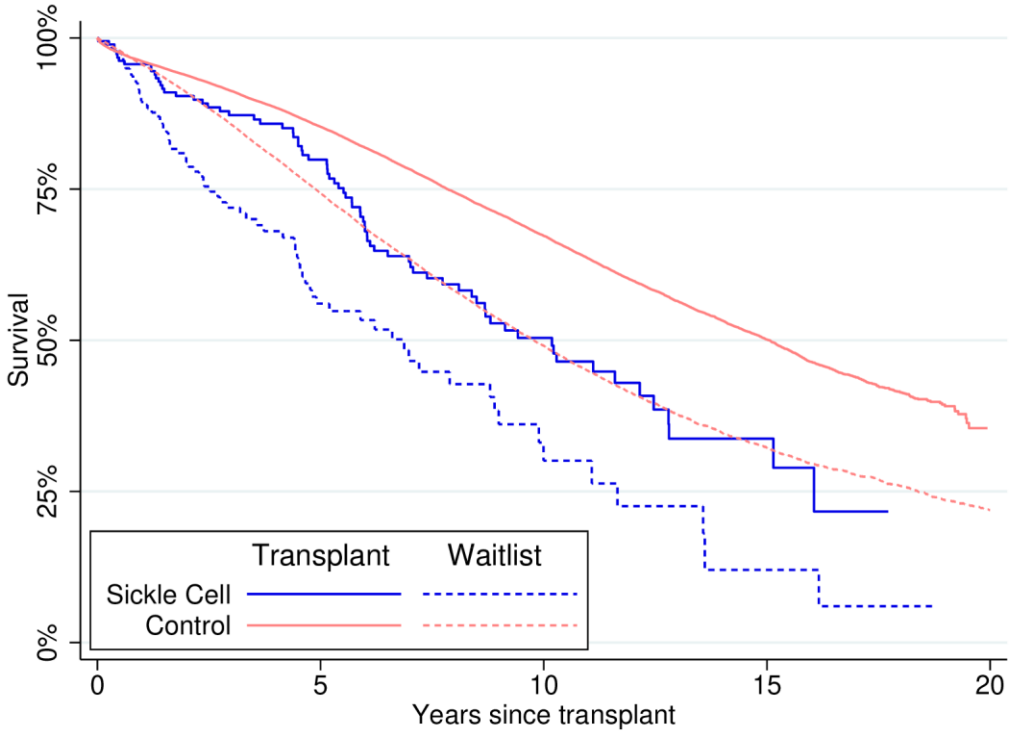
Sample size				
Sickle Cell	192	106	40	7
Control	243040	141502	64138	16771

Supplemental Figure 4. Kaplan-Meier curves for mortality in matched cohorts.

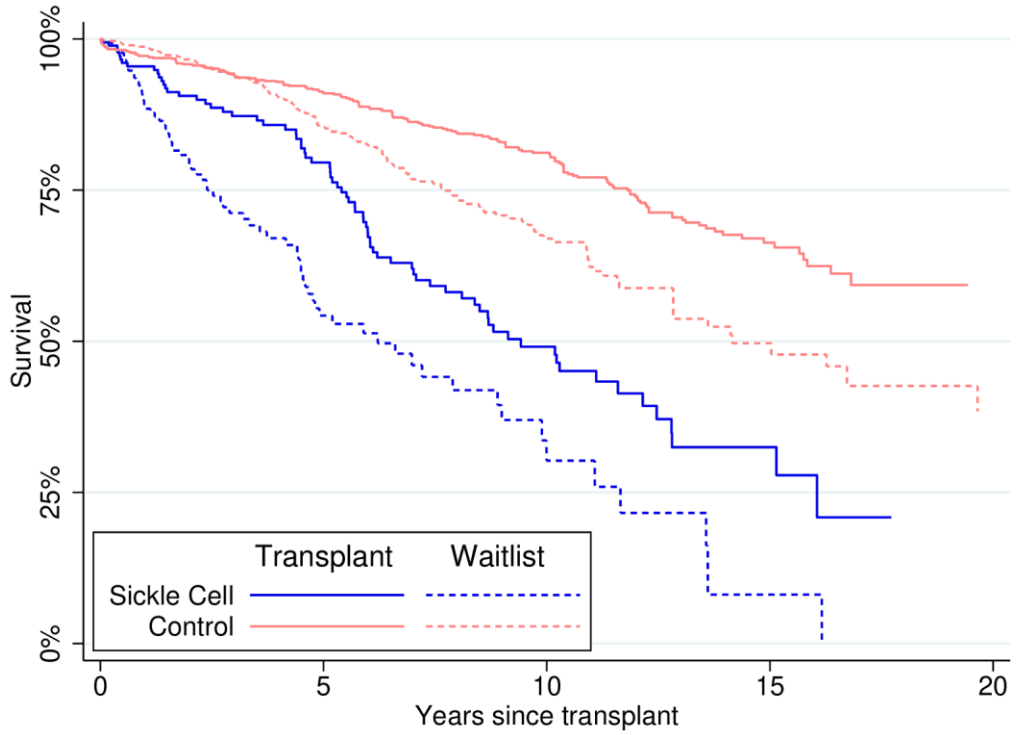
(a) Match Set 1



(b) Match Set 2



(c) Match Set 3


100%
75%
50%
25%
0%
Survival
Transplant
Waitlist
Sickle Cell
Control
0
5
10
15
20
Years since transplant

Supplemental Table 1. Observations with missing covariables

	Dialysis Cohort		Waitlist Cohort	
	Sickle cell (n=1970)	Control (n=2,047,790)	Sickle cell (n=507)	Control (n=463,298)
Age at dialysis initiation, y	0	0	0	0
Female sex	0	0	0	0
Race	0	0	0	0
Comorbidities				
Hypertension	59 (3.0%)	30,104 (1.5%)	110 (21.7%)	114,253 (24.7%)
Diabetes	0	311 (<0.1%)	0	0
Heart disease	0	257 (<0.1%)		
Stroke	61 (3.1%)	31,553 (1.5%)		
Current tobacco user	61 (3.1%)	31,672 (1.5%)		
Body mass index, kg/m^2	39 (2.0%)	30,177 (1.5%)	41 (8.1%)	17,048 (3.7%)
Serum albumin, g/dl	375 (19.0%)	409,086 (20.0%)	77 (15.2%)	83,018 (17.9%)
Hemoglobin, g/dl	529 (26.9%)	264,108 (12.9%)		
Primary insurance	0	0	0	0
Panel reactive antibody, %			0	0
Previous kidney transplantation			0	0

Supplemental Table 2. Population characteristics of matched cohorts.

	Match Set 1				Match Set 2				Match Set 3			
	Sickle Cell		Control		Sickle Cell		Control		Sickle Cell		Control	
	KT	WL	KT	WL	KT	WL	KT	WL	KT	WL	KT	WL
Sample Size	189	189	243043	243043	189	189	62275	62275	181	181	809	809
Age at transplant, y	35 (28-46)	34 (28-46)	49 (38-58)	49 (38-58)	35 (28-46)	34 (28-46)	47 (36-56)	47 (36-56)	35 (28-46)	34 (28-47)	35 (27-47)	35 (28-46)
Female sex	39.2%	52.9%	39.1%	40.4%	39.2%	52.9%	40.3%	41.9%	39.2%	53.6%	39.2%	41.9%
Race												
White	5.3%	1.6%	52.2%	38.4%	5.3%	1.6%	0.0%	0.0%	5.5%	1.7%	0.0%	0.0%
African American	92.6%	96.8%	25.6%	35.1%	92.6%	96.8%	100.0%	100.0%	92.3%	96.7%	100.0%	100.0%
Hispanic/Latino	1.1%	0.5%	14.7%	17.9%	1.1%	0.5%	0.0%	0.0%	1.1%	0.6%	0.0%	0.0%
Other/multi-racial	1.1%	1.1%	7.4%	8.6%	1.1%	1.1%	0.0%	0.0%	1.1%	1.1%	0.0%	0.0%
Panel reactive antibody												
0	43.9%	41.8%	54.0%	54.4%	43.9%	41.8%	48.7%	49.8%	45.9%	40.9%	45.9%	45.6%
1-9	14.3%	7.9%	15.5%	12.0%	14.3%	7.9%	15.4%	11.8%	12.7%	8.3%	12.7%	11.9%
10-79	27.5%	31.2%	21.2%	21.2%	27.5%	31.2%	24.9%	23.9%	28.2%	31.5%	28.2%	24.6%
80-100	14.3%	19.0%	9.2%	12.5%	14.3%	19.0%	11.0%	14.4%	13.3%	19.3%	13.3%	17.9%
Diabetes	1.1%	1.1%	32.2%	32.2%	1.1%	1.1%	34.6%	34.6%	0.6%	0.6%	0.6%	0.6%
Preemptive transplant	9.5%	2.1%	17.7%	4.5%	9.5%	2.1%	8.8%	1.7%	7.2%	1.7%	7.2%	1.5%
Deceased donor	73.5%		67.7%		73.5%		81.8%		74.0%		74.0%	

KT, kidney transplant; and WL, waitlist. Age is shown in median (interquartile range).

Supplemental Table 3. Relative hazard of mortality associated with kidney transplantation in matched cohorts.

	Hazard ratio		P-value for interaction
	Sickle Cell	Control	
Match Set 1	$_{0.36}0.57_{0.91}$	$_{0.53}0.54_{0.55}$	0.8
Match Set 2	$_{0.36}0.57_{0.91}$	$_{0.57}0.58_{0.60}$	0.9
Match Set 3	$_{0.40}0.56_{0.80}$	$_{0.49}0.63_{0.81}$	0.2