ORIGINAL ARTICLE

Association between ethnicity and kidney transplant waitlist outcomes beyond estimated post-transplant survival score

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SUMMARY

White kidney transplant candidates have the highest pre-transplant mortality rate compared to other ethnicities. The reason for a higher mortality rate is not well-understood. Estimated post-transplant survival (EPTS) score has been used to predict patient survival after transplant and may be associated with pre-transplant survival. First-time kidney transplant candidates listed between 2015 and 2018 were identified from the Organ Procurement Transplantation Network database. Individuals listed for multiple organs, at multiple centers, and age <18 years were excluded. We examined the impact of ethnicity on waitlist mortality and delisting. A total of 114 806 candidates were included. The study population was categorized into four groups which were 43% white, 28% Black, 19.2% Hispanic, and 9.8% "other ethnicities." At 5.2 years, the cumulative incidences of death and delist were 32%, 31%, 29%, and 26%, respectively. Compared to whites, adjusted subdistribution hazard ratio (aSHR) for death and delist among Black, Hispanics, and "other ethnicities" were 0.92 (95% CI 0.89–0.95), 0.89 (95% CI 0.85–0.91), and 0.76 (95% CI 0.72–0.80) after adjustment by EPTS along with other factors, respectively. After adjusting for EPTS score along with additional confounding factors and functional status at initial listing, white ethnicity was independently associated with an increased risk for death and delist.

Introduction

The prevalence of end-stage renal disease (ESRD) in the United States is higher for minority racial/ethnic groups compared with whites [1]. The lack of recognition of chronic kidney disease (CKD), lack of access to medical care, and socioeconomic considerations may contribute to the inequality in CKD and ESRD treatment among these racial/ethnic minorities [2, 3]. Despite the disparity in care, there are studies showing that Black and Hispanic individuals who undergo dialysis have better survival compared to white individuals. This survival paradox phenomenon applies to all age groups of Hispanic dialysis patients, whereas Black patients younger than 50 years have a higher risk of death compared to whites [4–7]. Kidney transplantation is the treatment of choice for most patients with ESRD and is associated with better survival compared with dialysis

[8, 9]. However, racial and ethnic disparities in transplant access exist [10–13]. Compared to other racial groups, white kidney transplant candidates have the highest transplant rate; yet, they have the highest pretransplant mortality rate compared to ethnic minorities [14]. The reason for a higher mortality rate among white candidates is not well-understood.

Kidney transplant candidates often present with multiple comorbidities. Furthermore, up to 20% of individuals evaluated for a kidney transplant are frail, which is associated with an increased risk of mortality [15, 16]. In nonfrail waitlist candidates, a higher comorbidity burden at the time of transplant evaluation is associated with a 66% increase in mortality risk. Comorbidity burden, however, does not further increase mortality risk in candidates who are already frail [17]. Comorbidities and functional status are factors that are used as part of a program decision whether to add candidates to the waitlist. Careful assessment of functional status and treatment of comorbidities among potential transplant candidates may improve waitlist survival. Estimated post-transplant survival (EPTS) score was developed to assign priority in the new kidney allocation system. The score includes candidates' age, duration of dialysis, current diagnosis of diabetes, and prior solid organ transplant in its calculation. EPTS scores range from 0% to 100% with higher EPTS scores predict an estimated lower post-transplant patient survival and largely driven by age and diabetes [18]. Candidates who do not receive a kidney transplant are associated with a higher mortality compared to those with the same EPTS score who receive a kidney transplant [19]. In addition to EPTS score, additional factors such as other comorbidities, frailty, socioeconomic status, ethnicity, and psychosocial support are known to impact transplant outcomes. However, the impact of EPTS score on transplant waitlist outcomes is less well–understood, and it is unknown whether ethnicity affects the survival time on candidates on the waitlist. Here, we report the association of ethnicity and kidney transplant waitlist outcomes beyond the survival prediction by EPTS score.

Materials and methods

Data source and study population

The Organ Procurement Transplantation Network (OPTN) database as of March 20, 2020 was used in this study. All newly listed first-time kidney transplant candidates from January 1, 2015 to December 31, 2018 were included. Individuals listed for multiple organs, at multiple centers, and age at listing <18 years were excluded. This study was institutional review board exempt due to its use of publicly available data and absence of identification of individual candidates.

Demographic and clinical data were collected. Waitlist candidates' characteristics included ethnicity, age at initial listing, gender, cause of ESRD, primary payment, highest educational level, body mass index (BMI), history of diabetes, peripheral vascular disease, previous malignancy, preemptive listing, dialysis vintage, and EPTS score at initial listing. Karnofsky Performance Status was used to assess the baseline functional status of candidates. According to the OPTN database, the term of ethnicity was used. We categorized our study population into four groups according to waitlist ethnicity: (i) white, (ii) Black, (iii) Hispanic, and (iv) "other ethnicities."

Outcome measures

The study population was analyzed to determine the impact of ethnicity adjusted for EPTS on waitlist outcomes. The primary outcome was the cumulative incidence of the composite of either death prior to kidney transplantation or delisting. The secondary outcome was the composite risk for mortality and delisting among candidates' ethnicities.

Statistical analysis

Waitlist characteristics were evaluated using median and interquartile range (IQR) for continuous variables or proportion for categorical variables. Group differences were compared using Kruskal–Wallis or Pearson's chi-squared test as appropriate. Due to the presence of kidney transplant as a competing event for primary outcome, the cumulative incidence function (CIF) was used to estimate the cumulative probability of events over time. The longest possible observation time in this analysis was 1 905 days (from January 1, 2015 to March 20, 2020). Univariate competing risks regression model (Fine-Gray) was used to calculate subdistribution hazard ratio (SHR) and 95% confidence interval (CI) of the composite outcome. In the multivariable model, we adjusted the covariates for EPTS score (model 1) and EPTS score along with gender, primary payment, educational level, peripheral vascular disease, previous malignancy, BMI, and functional status (model 2). All reported P-values were two–tailed, and P-values < 0.05 were considered significant. STATA version 13

(StataCorp, College Station, TX, USA) was used in all statistical analyses.

Results

There were 133 646 newly listed first-time kidney transplant candidates included in this study. We excluded 18 840 candidates (3 980 were under 18 years at listing, 8 497 were listed for multiple organs, 6 299 were listed at multiple centers, and 64 had missing EPTS value). A total of 114 806 candidates were included in our analysis. Majority of candidates reached one of the outcomes (mortality, delist, or kidney transplant) during the early years of follow-up (Fig. S1). Median observation time of the study was 576 (0–1 904) days. The study population was categorized into four groups based on candidates' ethnicity which were 43% white, 28% Black, 19.2% Hispanic, and 9.8% "other ethnicities." Baseline waitlist characteristics were shown in Table 1. White candidates were more likely to be the oldest, whereas Hispanic candidates were more likely to be the youngest at initial listing. Male gender and public insurance were predominant among all ethnicities. White and "other ethnicities" candidates were more likely to have a higher educational level compared to Blacks and Hispanics. Hispanic candidates had the highest proportion of diabetes (53.8%), whereas white candidates had the highest proportion of previous malignancy (12.9%). There was the highest proportion of preemptive listing (47.9%) and the shortest dialysis vintage (384 days) among white candidates, whereas the lowest proportion of preemptive listing (23%) and the longest dialysis vintage (627 days) were observed among Black candidates. There were no clinically significant differences of median EPTS score (40%) and functional status at initial listing among all ethnicities.

Amongst all waitlist candidates, proportion of candidates who received a kidney transplant, died prior to kidney transplant and delisted were 44.4%, 6%, and 14.3%, respectively. Kidney transplant rates among white, Black, Hispanic, and "other ethnicities" were 323, 209, 208, and 196 per 1000 patient-years at risk, respectively. Waitlist mortality rates were 41, 11, 30, and 28 per 1000 patient-years at risk, respectively. Delisting rates were 94, 76, 72, and 60 per 1000 patient-years at risk, respectively (Fig. 1 & Fig. S2). The top reason for delisting (40.6%) was medical deterioration or too sick for transplantation. However, a reason for delisting was not specified for 31.2% of delisted candidates. Candidates who died or delisted were more likely to have an older age, diabetes, and a higher EPTS score compared

to candidates who received kidney transplant. They were more likely to have a shorter dialysis vintage but were less likely to be preemptively listed. Functional capacity at initial listing is not clinically different between groups (Fig. S3). Figure 2 shows the cumulative incidences of the outcomes among white, Black, Hispanic, and "other ethnicities" derived by CIF. At 5.2 years, the cumulative incidences of the composite outcome of death and delist were 32%, 31%, 29%, and 26%, respectively (Fig. 2a). The cumulative incidences of kidney transplant were 57%, 55%, 54%, and 43%, respectively (Fig. 2b).

Using competing risks regression model, all ethnicities were associated with a decreased risk for the composite outcome of death and delist compared to whites. Compared with whites, SHR among Black, Hispanic, and "other ethnicities" were 0.93 (95% CI 0.90–0.76), 0.89 (95% CI 0.86–0.93), and 0.79 (95% CI 0.76–0.83), respectively. After adjustment by EPTS for model 1 analysis, adjusted subdistribution hazard ratio (aSHR) were 0.91 (95% CI 0.88–0.94), 0.88 (95% CI 0.85–0.91), and 0.79 (95% CI 0.74–0.82), respectively. After adjustment by EPTS along with other factors as described in the methods for model 2 analysis, aSHR were 0.92 (95% CI 0.89–0.95), 0.89 (95% CI 0.85–0.91), and 0.76 (95% CI 0.72–0.80), respectively (Table 2).

Discussions

Impact of race/ethnicity on dialysis survival is well-studied. For kidney transplant waitlist candidates, EPTS score has been used to predict patient survival time after transplant and may be associated with pre-transplant survival among candidates who have not yet received a kidney transplant [18, 19]. However, the impact of ethnicity on waitlist survival prediction in addition to EPTS score is unknown. We found that despite white candidates having a higher cumulative incidence of kidney transplantation, they also had a higher cumulative incidence of removal from a transplant waitlist compared to Black, Hispanic, and "other ethnicities" candidates. Waitlist removal was largely driven by delisting more than death. Candidates with a higher EPTS score may be more likely to have a poorer health status because the factors included in EPTS score are frequently associated with other predisposing comorbidities and their complications especially diabetes which is a strong cardiovascular risk. However, EPTS score really includes only four factors that may not reflect the overall patient survival prediction. After adjusting for either EPTS score or EPTS score along with confounding factors including functional status at

Table 1. Baseline candidates' characteristics at initial listing.

Variables	White N = 49,322 (43.0%)	Black N = 32,133 (28.0%)	Hispanic N = 22,064 (19.2%)	Other N = 11,287 (9.8%)	P-value
Median age, years (IQR)	57 (47–65)	53 (43–61)	52 (40–60)	54 (43–63)	<0.001
Male gender, %	63.9	60.1	63.3	59.8	<0.001
Cause of ESRD					<0.001
Glomerular disease	8.9	4.2	6.0	9.5	
Diabetes	12.3	13.1	13.9	12.9	
Hypertension	7.4	14.4	7.9	6.7	
Other	71.4	68.3	72.2	70.9	
Primary payment, %					<0.001
Private insurance	46.2	31.9	34.1	43.3	
Public insurance	53.3	67.9	65.7	56.5	
Other	0.5	0.2	0.2	0.2	
Highest educational level, %					<0.001
Grade school	1.5	2.2	22.1	6.4	
High school	33.4	41.5	42.6	29.0	
College/Technical school	26.5	28.9	18.6	23.8	
Associate/Bachelor's degree	24.0	17.6	9.6	25.7	
Post-college graduate degree	11.3	6.7	2.7	10.9	
Other	3.3	3.1	4.4	4.2	
Median BMI, kg/m^2 (IQR)	28.8 (25.0–33.0)	29.5 (25.6–33.8)	28.3 (24.9–32.0)	26.4 (23.2–30.7)	<0.001
Diabetes, %	40.5	48.4	53.8	50.6	<0.001
Peripheral vascular disease, %	9.9	9.2	10.9	7.3	<0.001
Previous malignancy, %	12.9	6.2	3.7	4.7	<0.001
Preemptive listing, %	47.9	23.0	23.7	33.7	<0.001
Median dialysis vintage at listing in non-preemptively listed, days (IQR)	384 (190–778)	627 (316–1 352)	533 (266–1 104)	462 (234–940)	<0.001
Median initial EPTS, % (IQR)	41 (20–62)	40 (19–65)	41 (15–65)	41 (17–65)	<0.001
EPTS, %					<0.001
0–20%	25.8	27.2	30.4	28.8	
21–40%	24.1	23.1	19.6	20.9	
41–60%	23.2	20.7	20.7	20.8	
61–80%	17.9	17.6	18.9	18.6	
81–100%	9.0	11.4	10.4	10.9	
Functional status (Karnofsky performance status), %					

Table 1. Continued.

Variables	White N = 49,322 (43.0%)	Black N = 32,133 (28.0%)	Hispanic N = 22,064 (19.2%)	Other N = 11,287 (9.8%)	P-value
100% Normal	7.1	5.6	9.9	10.0	<0.001
90% Able to carry on normal activity	24.1	19.6	23.4	28.8	
80% Normal activity with effort	31.0	27.5	23.6	27.1	
70% Cares for self, unable to carry on normal activity or active work	20.4	25.8	25.1	21.0	
60% Able to care for needs, requires occasional assistance	7.7	10.7	8.9	6.4	
50% Frequent medical care, requires assistance	3.5	5.6	4.1	2.8	
40% Disabled, requires special care and assistance	2.3	2.0	1.7	1.4	
30% Severely disabled, hospitalization is indicated	0.7	0.3	0.7	0.3	
20% Very sick, hospitalization necessary	1.1	0.4	0.8	0.6	
10% Moribund	0.2	0.1	0.1	0.1	
Unknown	1.9	2.4	1.7	1.5	

IQR, interquartile range; ESRD, end-stage renal disease; BMI, body mass index; EPTS, estimated post-transplant survival.

initial listing, we found that white ethnicity was an independent risk factor for death and delist compared to Black, Hispanic, and "other ethnicities" candidates.

Reasons underlying the paradoxical survival advantage among minority racial/ethnic dialysis patients have been proposed. The survival advantage may be due to multiple factors [6, 20–25]. Heterogeneity in the cause of ESRD could be one of the factors that contributes to better or worse survival rate among dialysis patients. Black patients who start dialysis due to APOL1-associated kidney disease are more likely to be younger or healthier at the time of dialysis initiation, whereas patients with other predisposing comorbid conditions who develop ESRD may have poorer health status [20]. Socioeconomic factors (e.g. household income, education, and occupation), health care access (e.g. insurance and distance to health care centers), sociocultural and lifestyle factors (e.g. dietary habits, physical activity, tobacco, and alcohol use), and genetic factors potentially affect survival differences among ethnicities [6, 21–23]. Additionally, perceptions of quality of life, coping mechanisms, and preferences for aggressive treatment in chronic illness and the end of life may also play a role in racial/ethnic disparities in survival [24, 25]. All of these reasons may explain the survival advantage among kidney transplant waitlist candidates as well. Ethnicity is a complex construction including genetic, environmental, and sociocultural factors. Combination of these factors contributes to differences in risk for a particular disease, response to treatments, and patient survival among race/ethnicity [26]. Our study shows that the impact of ethnicity on waitlist mortality and delist is not influenced by other risk factors, for example, diabetes, age, and functional status. As a low functional status is well-known to be associated with mortality and adverse outcomes, racial/ethnic disparities in acceptance of disabled patients into the waitlist or delisting may take part in the survival differences. Further studies focusing on these patients may further explain the reason of higher mortality or delist risk among white candidates.

We found that white candidates were less likely to have diabetes, more likely to be listed preemptively, and more likely to have a shorter dialysis vintage when not preemptively listed, which are associated with a better prognosis. White candidates were more likely to have a previous malignancy. Despite pretransplant malignancy is a known risk for recurrent or secondary malignancy post-transplant, graft failure, and death [27, 28], impact of previous malignancy on waitlist survival is unknown. Candidates with a history of malignancy may be listed
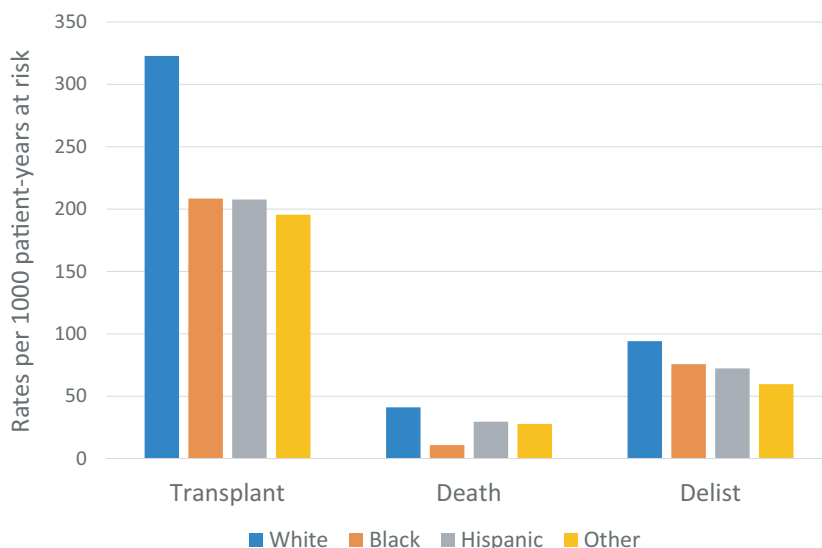
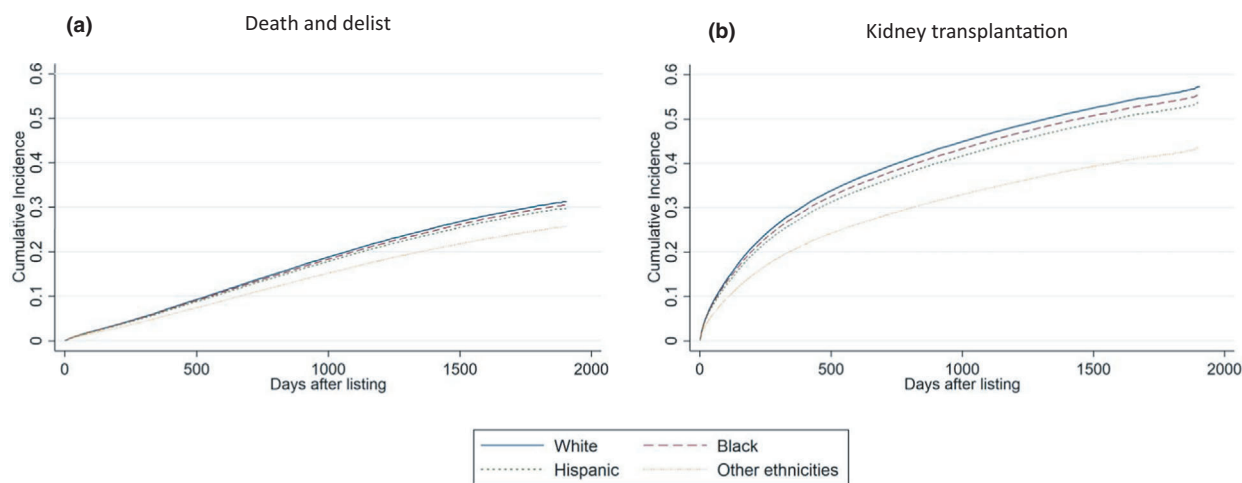**Figure 1** Kidney transplant, death, and delist among candidates' ethnicities.

Figure 2 Cumulative incidences of the outcomes among white, Black, Hispanic, and "other ethnicities" derived by cumulative incidence function. (a) Composite outcome of death and delist. (b) Kidney transplantation.

inactive with a 5-year wait time before being made active and then would not be offered transplant. Candidate health status when inactive listed need to be explored. Survival among patients with previous malignancy depends on types, locations, staging, treatment received, and recurrent malignancy that vary among individuals. Future studies focusing on ethnicity and previous malignancy may confirm the association between these factors and survival among candidates.

As a retrospective database study, there are certain limitations in our study. First, there were no available data on candidates' comorbidity index, an important predictor of patient mortality risk. We cannot prove that survival disparities among candidates' ethnicities are associated with their comorbidities or comorbidity index or not. Further studies including comorbidities and comorbidity index will confirm the impact of race/ethnicity on mortality risk among kidney transplant candidates. Second, white candidates are more likely to be listed preemptively and have a higher rate of living donor kidney transplant (LDKT) [29]. Racial/ethnic difference in patient survival among the remaining candidates who do not receive preemptive LDKT may be affected. Third, patient functional performance

Table 2. Unadjusted and adjusted risk for composite outcome of waitlist mortality and delist associated with ethnicity.

Variables	Univariate analysis		Multivariable analysis			
	SHR	95% CI	aSHR*,‡	95% CI	aSHR†,‡	95% CI
Ethnicity						
White	Reference	-	Reference	-	Reference	-
Black	0.93	0.90–0.96	0.91	0.88–0.94	0.92	0.89–0.95
Hispanic	0.89	0.86–0.93	0.88	0.85–0.91	0.89	0.85–0.91
Other	0.79	0.76–0.83	0.79	0.74–0.82	0.76	0.72–0.80

SHR, subdistribution hazard ratio; aHR, adjusted subdistribution hazard ratio; CI, confidence interval; EPTS, estimated post-transplant survival.

*Adjusted for EPTS score.

†Adjusted for EPTS score, gender, primary payment, educational level, peripheral vascular disease, previous malignancy, body mass index, and functional status.

‡Using kidney transplant as a competing risk.

status usually changes over time. This may be the factor that influences patient survival. Fourth, listing practices vary among transplant centers. Since KAS in 2014 programs are more likely to list those who are not yet on dialysis while deferring those on dialysis until they are fully worked up for transplant as their list date reverts to first day of dialysis. Health status of patients who are listed initially with or without full assessment may be different. Last, we included only candidates that were first-time listed for "kidney only" transplant, at only one center, and age at listing ≥18 years. Results may not be generalizable to all waitlist candidates.

In conclusion, white candidates listed for kidney transplant had a higher rate of death or delist compared to Black, Hispanic, and "other ethnicities" candidates which were 32%, 31%, 29%, and 26%, respectively (median follow-up time of 576 days). After adjusting for EPTS score along with additional confounding factors and functional status at initial listing, white ethnicity was independently associated with 8%, 11%, and 24% increased risk for death or delist, respectively. The outcome of waitlist removal was driven by delist more than death. Ethnicity was an independent risk factor for waitlist candidates' mortality and delist after adjusting for EPTS score.

Authorship

Piyavadee Homkrailas, participated in the research design, performed the data analysis and interpretation, and the writing of paper. Suphamai Bunnapradist, participated in the research design, performed the data analysis and interpretation, the performance of the

research, critical revision of the article and contributed to the writing of paper.

Conflicts of interest

The authors declare no conflicts of interest.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 Number of candidates reached waitlist outcomes.

Figure S2 Kidney transplant, death and delist among candidates' ethnicities.

Figure S3 Characteristics of candidates who received kidney transplant compared to candidates who died or delisted.

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