Saving More Lives with Deceased Donor Kidney Transplantation

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Abstract

Background

Kidney transplantation is the definitive treatment for end-stage renal disease, but this life-saving treatment is absolutely scarce with demand greatly exceeding the limits of supply. Substantial inefficiencies and inequities in the Kidney Allocation System (KAS), such as high discard rates and ignoring the risk of death on dialysis, exacerbate the harms caused by the kidney shortage.

Objective

The study objective was to generate center and patient specific estimates of the lives saved by deceased donor kidney transplantation with a novel survival benefit model to assess the compliance of kidney allocation policy with the Final Rule.

Methodology

Using the records all adult deceased donor kidney candidates listed from 2005-2010 we developed a novel mixed-effects model of the survival benefit of deceased donor kidney transplantation to estimate the **Lives Saved per Transplant within the first 5 years of kidney transplant (LiST-5)** for a specific center and patient pair.Our model improves upon the existing literature by accounting for center effects, time-dependent covariates, non-proportional hazards, and interactions between candidate and donor variables in a single joint model of the pre and post-transplantation periods.

Results

The study population were the 132,909 candidates (mean age 52 at listing, 60% male) listed for transplant with complete records. By the end of follow-up in March 1st, 2021, 64,589 (48.6 %) were transplanted. Deceased donor kidney transplantation was associated with an improvement in estimated five-year survival from 50.8% to 82.4%, corresponding to a 31.6% absolute improvement in survival at 5-years and 0.316 **Lives Saved per Transplant (LiST-5)**. There was wide variation in the LiST-5 (IQR 0.24 - 0.39) driven by significant variation in the risk of death with and without transplantation by candidate characteristics. Transplanting the median patient without diabetes after the median amount of dialysis time (3.8 years of dialysis) was associated with a LiST-5 of 0.32 compared to a LiST of 0.19 preemptively transplanting the same patient. In 2019, the median dialysis time at transplant for a White recipient was 2.5 years compared to 4.8 years for Black recipients and 19% of White recipients received a preemptive transplant compared to just 6% of Black recipients.

Transplant center effects on LiST-5 were larger than donor effects. For the median recipient, High Kidney Donor Profile Index (KDPI $>$ 85%) kidneys had an estimated LiST-5 of 0.28 compared to a LiST-5 of 0.316 for the median KDPI 43% kidney. In contrast, the LiST-5 from a median KDPI (43%) donor kidney varied from 0.20 to 0.48 (IQR 0.29, 0.35) between transplant centers. The variation in LiST-5 was driven primarily by high benefit centers selecting more medically urgent candidates, as the average five-year risk of death without a transplant ranged from 32% to 66% (IQR [46,54%]). A web-tool to visualize the model results is available at https://wparker-uchicago.shinyapps.io/DDKT_survival_benefit/.

Discussion

Deceased donor kidney transplant candidates have a widely varying risk of death without a transplant. In general, transplanting higher-risk candidates with more dialysis time saves more lives in the first five years. The current Kidney Allocation System ignores the Final Rule requirements to rank-order candidates by medical urgency. Severe racial/ethnic disparities persist within deceased donor kidney allocation, which the OPTN must directly address by radical policy changes such as eliminating pre-dialysis waiting time points. With a shift in focus to survival benefit, deceased donor kidney transplantation can save more lives and improve equity in allocation.

Introduction

Deceased donor organs are absolutely scarce. Thousands of patients fortunate enough to get listed will die on the waiting list every year [1], and countless others who would benefit from a transplant lack access. While efforts to expand the donor pool and encourage transplantation of marginal donors are critical to minimize the shortage, the fact remains that demand for organ transplantation will exceed supply in the U.S. for the foreseeable future. Policymakers at the Organ Procurement and Transplant Network (OPTN) must confront a tragic choice; they must rank order human beings for a life-saving, medically necessary therapy.

The Department of Health and Human Services' Final Rule directs the OPTN to design organ allocation policies "to achieve the best use of donated organs" [2]. Specifically, the OPTN must rank candidates from "most to least medically urgent" while "taking into account... that life-sustaining technology allows alternative approaches." The survival benefit from a transplant, or each candidates' improvement in survival from organ transplantation, represents a direct quantification of the efficiency principles in the Final Rule, statistically quantifying the "lives saved" from each transplant. Like liver, heart, and lung transplantation [3–7], kidney transplantation dramatically improves recipient survival compared to remaining on dialysis [8–11]. Dialysis may be a "life-sustaining measure," but it is much less effective at sustaining life than kidney transplantation.

However, compared to the other solid organ allocation systems, the current Kidney Allocation System (KAS) does not rank-order candidates by medical urgency as required by the Final Rule. KAS ranks candidates mainly by waiting time, with increased priority for hard-to-match highly sensitized patients and candidates with high Expected Post-Transplant Survival (EPTS). The policy does explicitly prioritize candidates without viable options for dialysis access, appreciating that kidney transplantation is acutely life-saving for these candidates. However, this limited policy measure fails to account for the widely varying risk of death while waiting on dialysis [12].

Compounding the fact that the current kidney allocation policy largely ignores medical urgency, U.S. transplant programs discarded 1 in 5 kidneys recovered in 2019 for transplantation [1], a rate far higher than Europe [13]. While centers have been more likely to accept hepatitis C-positive donors over time, donors sorted into a lower allocation sequence by the Kidney Donor Profile Index (KDPI) [14] score have a substantially higher probability of discard [1]. Less than 5% of sequence A and B kidneys (KDPI < 35%) were discarded compared to 20% of sequence C kidneys (KDPI 35-85%) and 60% of sequence D kidneys (KDPI> 85%) [1]. Accepting a "lower quality" kidney- indicated by either Extended Donor Criteria, increased risk for disease transmission (IRD), or Kidney Donor Profile Index (KDPI) over 70%- leads to a significant survival benefit at five years post-transplant compared to waiting for a better organ for the vast majority of patients [15–17]. Similarly, graft survival at three years is higher with accepting a high KDPI now rather than waiting for a better graft, except for very high priority candidates in a high local donor supply environment [18]. The high discard rate reduces both the total lives saved by the system and outcomes for individual patients.

We present a model of the survival benefit of deceased donor kidney transplantation (DDKT) that improves upon the existing literature by accounting for center effects, time-dependent covariates, non-proportional hazards, and interactions between candidate and donor variables. The specific output of our model is the **Lives Saved per Transplant within the first 5 years (LiST-5)** for a specific center and patient pair. Our approach estimates with the lives saved over a defined time interval (5 years) instead of extrapolating out to the total "life-years" gained from a kidney transplant. We designed the model to assess the compliance of kidney allocation policy with the Final Rule and lead to concrete policy recommendations to improve KAS, specifically to address four key aims:

1. **Demonstrate how the current Kidney Allocation System is inconsistent with the Final Rule.** A rigorous survival benefit model with easy to interpret outputs like LiST-5 is necessary to conclusively demonstrate how the current ranking of candidates on the wait-list fails to meet the Final Rule requirements of transplanting the patients with the most to gain.
2. **Improve shared decision-making in accept-reject decisions for deceased donor kidney offers.** Part of the low acceptance rates of higher KDPI kidneys may be that patients and transplant physicians have an incomplete representation of the survival benefit of kidney transplantation relative to remaining on the wait-list. Incorporating accessible representations of survival benefit like LiST-5 could improve shared decision-making between patients and their physicians and can reduce discards.
3. **Improve the evaluation of transplant center performance.** Transplant programs are currently evaluated based on post-transplant survival, not survival benefit. While assessments of post-transplant survival are case-mix adjusted for medical urgency by the SRTR, this is fundamentally different than evaluating centers based on the number of lives saved per kidney transplant. We aimed to demonstrate the potential advantages of assessing program performance based on LiST-5 instead of post-transplant survival.
4. **Determine the potential impact of incorporating survival benefit into kidney allocation on racial/ethnic disparities in kidney transplantation.** While the Kidney Allocation System improved the raw transplantation rates for people from underserved populations who are fortunate enough to gain access to the list [19, 20], significant structural inequities remain embedded in the system. Black patients are less likely to be listed for transplantation [21] and have less than half the chance

of receiving preemptive transplantation compared to White patients [22]. The disparities continue after listing. Transplant programs are more likely to place Black and Hispanic in "inactive" status, and highly-sensitized Black patients are significantly less likely to be transplanted [23]. Therefore, determining how incorporating survival benefit into the Kidney Allocation System could mitigate or exacerbate structural racism in kidney transplantation is critical

Methods

Data Source and Study Population

This study was a secondary analysis of de-identified, pre-collected data and was granted exemption status by the University of Chicago Biological Sciences Division/University of Chicago Medical Center IRB to be performed without patient consent. This study used data from the SRTR (Scientific Registry of Transplant Recipients). The SRTR data system includes data on all donors, wait-listed candidates, and transplant recipients in the United States, submitted by the members of the OPTN. The Health Resources and Services Administration, U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors.

We analyzed the records of all adult ($\geq$ 18 years of age at listing), kidney-alone candidates listed between January 1st, 2005 and December 31st, 2010. We chose 2005-2010 in order to have a full ten years to follow the cohort from the time of listing until transplantation or death. This approach makes the estimate of LiST-5 less likely to be biased by informative censoring. We extracted the candidate covariates included in the Estimated Post-Transplant Survival Model (EPTS): age, dialysis time, diabetic status, and history of previous organ transplant [24]. We included one initial observation per candidate, defining the beginning of the wait-list period as the date of the first registration for candidates with multiple registrations. The observation time interval spans from the date of initial listing until transplant, death (including deaths after de-listing), or last time observed on the wait-list (for untransplanted candidates who do not have a recorded death date). The SRTR dataset includes monthly updates from the National Technical Information Service's (NTIS) Death Master File to capture deaths after de-listing that transplant programs do not report to the OPTN.

For candidates that received a deceased donor kidney transplant, we created 1-3 additional observations with their updated candidate covariates, donor KDPI (mapped to 2019 percentiles), and cold ischemic time to capture the varying risk of death post-transplant over time [16]. The first observation begins at the time of transplant and ends at death or 30 days post-transplant. The second begins at day 30 post-transplant and ends at death or day 180. The last observation spans from day 180 post-transplant to death or last follow-up time. See **Table S1** in the appendix for a more detailed description of the data.

A novel survival benefit model to estimate Lives Saved Per Transplant (LiST)

The primary outcome was the survival benefit of deceased donor kidney transplantation at five years post-transplantation (LiST-5) estimated with a mixed-effects Cox proportional hazard model with transplant treated as a time-dependent predictor variable [6, 25, 26], a single joint model of the pre and post-transplant period. This model accounts for the non-proportional hazard of transplantation by estimating the hazard of death in four distinct periods: 1) pre-transplant, 2) within 30 days post-transplant, 3) day 30-180 post-transplant, and 4) beyond 180 days post-transplantation. The model has a center-level random intercept and random transplant effect, which accounts for the clustering of patients within centers and allows for the risk of death with and without transplantation to vary at the center level.

We restricted the patient-level model covariates to the variables currently readily available at the time of organ allocation: candidate characteristics used in the EPTS score (age, diabetes status, duration of dialysis, and history of previous organ transplantation), donor KDPI, and ischemic time. We included all interaction terms previously found to influence wait-list or post-transplant survival and chose to retain all the interaction terms regardless of significance to control for selection behaviors by transplant physicians [27]. Data from after transplantation, such as the timing of post-transplant graft failure, does not enter into the model. We estimated the model by maximum likelihood with the `coxme` package in `R` [28].

To calculate the absolute estimated survival with and without transplantation, we multiplied each patient's time-dependent predicted hazard ratio with a Nelson-aalen estimate of the baseline hazard (**Figure S1**) [6]. This technique allows quantification of survival benefit on a clinically relevant and intuitive scale (LiST-5). We calculated the five-year survival with and without transplant and survival benefit for all recipients in our study cohort. We then estimated the mean, median, and intraquartile range of all three outcomes. See the **supplemental material** for a technical description of the model, additional methodology, and complete statistical code.

Association of medical urgency and EPTS with survival benefit

We determined the association of five-year mortality without a transplant (medical urgency as estimated by the model) and the OTPN Estimated Post-Transplant Survival score (2019 EPTS percentiles) with LiST-5. To specifically evaluate the compliance of the top 20% KDPI to the top 20% EPTS policy with the Final Rule, we compared the LiST-5 of a 15% KPDI donor kidney to a 60% KDPI donor kidney by EPTS score.

Finally, we determined the association between the candidate variables that compose EPTS (age, dialysis, history of diabetes, and previous transplantation) with survival benefit. Specifically, we calculated the LiST-5 of a preemptive transplant compared to the benefit of transplanting a patient on dialysis.

Association of transplant center with survival benefit

Following the approach employed by the Center for Medicare and Medicaid Services [29, 30], we used the empirical Bayes estimates of each center's intercept and transplant effect to calculate the average LiST-5 across kidney transplant programs, case-mix adjusting for donor variables. Specifically, we estimated the LiST-5 of deceased donor kidney transplantation at each center at KDPI 15%, median KDPI, and KDPI 60% (with median ischemic time). We did not case-mix adjust for candidate covariates because transplant programs are responsible for selecting candidates for the wait-list from a large pool of potential candidates for transplantation [31].

Lives saved by high KDPI kidneys and shared-decision making tool

When considering a deceased donor kidney offer, the proper counter-factual is not waiting indefinitely on dialysis without transplantation. Turning down a particular kidney perceived to be low quality may give a candidate the ability to accept a subsequent offer for a better graft, assuming they survive to receive the next offer. Therefore we applied our model to construct the estimated survival function for waiting a designated time before receiving a deceased donor kidney transplant (see **Supplement** for details).

In 2019, transplant programs discarded 60% of kidneys from deceased donors with KDPI $> 85\%$ despite the high established survival benefit of these organs [1]. We estimate the number of lives saved by KDPI $> 85\%$ donor kidneys in recipients undergoing deceased donor kidney transplantation in 2019.

Association of race/ethnicity with survival benefit

We calculated the summary statistics of all model covariates by racial/ethnic group. We then estimated the average LiST-5 for first-time solid organ recipients by racial/ethnic group. To avoid confounding by differences in age distribution between racial/ethnic groups, we age-adjusted using the direct-standardization by age decile. Because our study cohort was listed before the implementation of the Kidney Allocation System in 2014, we determined trends in the key model covariates of dialysis time and preemptive transplants (transplants performed before the start of dialysis) for each racial/ethnic group from 2000-2010.

We performed all analyses using `R` version 3.6.1 (R Foundation for Statistical Computing). We used

2-sided statistical tests and a p-value of < 0.05 to reject the null hypothesis.

Results

Description of the study population

There were 133,363 adult candidates listed for deceased donor kidney transplantation between January 1st, 2005 and December 31st, 2010. We excluded 454 candidates who were listed at a low volume center and 2,051 for missing data. Out of the remaining 132,909 candidates (mean age 52 at listing, 60% male), 64,589 (48.6 %) had received a transplant by the end of followup (March 1st, 2021) (**Table 1**). Of the remaining 68,320 candidates who did not receive a transplant, 52,431 (77%) died by the end of followup. Mean follow-up for surviving transplant recipients was 10.4 years.

Table 1A: Candidate characteristics at the time of listing

Characteristic	**N = 132,675**[1]
Age	54 (44, 62)
Dialysis time (years)	0.90 (0.12, 2.18)
Listed pre-dialysis	29,656 (22%)
History of diabetes	58,335 (44%)
History of previous organ transplant	20,123 (15%)
EPTS % (2019)	37 (16, 63)
Male gender	79,658 (60%)
Race/ethnicity	
Asian/Pacific Islander	8,815 (6.6%)
Black	42,909 (32%)
Hispanic/Latino	21,805 (16%)
Other	1,842 (1.4%)
White	57,304 (43%)

[1]Median (IQR); n (%)

Table 1B: Recipient characteristics at the time of transplant

Characteristic	**N = 64,589**[1]

Age	55 (45, 63)
Dialysis time (years)	3.5 (1.6, 5.8)
Preemptive transplant	6,362 (9.8%)
History of diabetes	22,879 (35%)
History of previous organ transplant	9,121 (14%)
EPTS % (2019)	45 (20, 75)
Waiting time pre-transplant (days)	984 (509, 1,613)
KDPI % (2019)	43 (21, 66)
Ischemic time (hours)	16 (11, 22)
Male Gender	39,318 (61%)
Race/ethnicity	
Asian/Pacific Islander	4,378 (6.8%)
Black	20,705 (32%)
Hispanic/Latino	9,709 (15%)
Other	856 (1.3%)
White	28,941 (45%)

[1]Median (IQR); n (%)

The survival benefit of deceased donor kidney transplantation

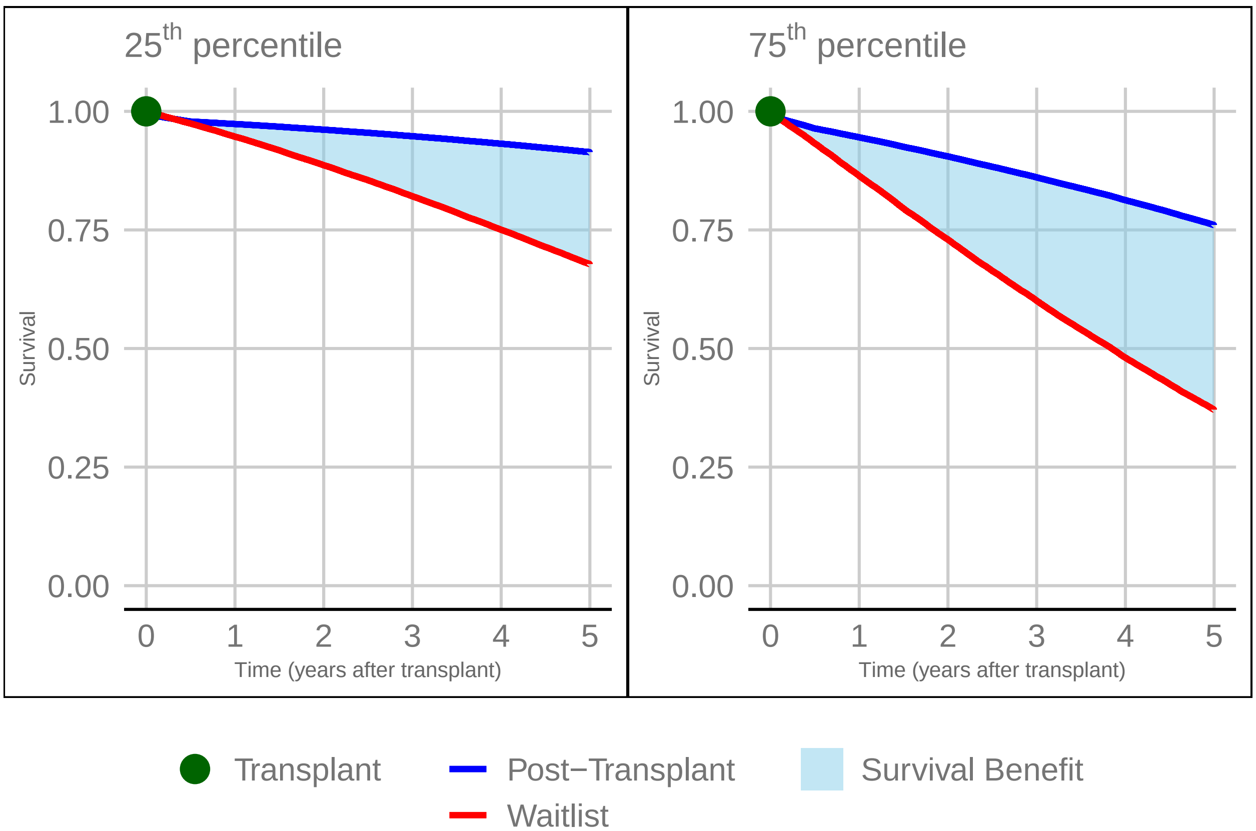
Compared to not receiving a transplant, deceased donor kidney transplantation was associated with an increased risk of death during the first 30 days post-transplantation, median hazard ratio [HR] 1.1 (IQR [0.84 - 1.45]). During day 30-180 post-transplantation, the risk of death was lower with a transplant than waiting, HR 0.4 (IQR [0.3 - 0.53]). Beyond 180 days post-transplantation, the survival benefit of deceased donor kidney transplant continued to increase, HR 0.21 (IQR [0.17 - 0.28]) (**Figure S2**). The full model results are in **Table S2** and the Harrell's c-statistic was 0.69.

The large long-term risk reduction associated with deceased donor kidney transplantation led to a large absolute survival benefit by five years. For the N = 64,589 in the study cohort, transplantation was associated with an improvement in estimated five-year survival from 50.8% to 82.4%, corresponding to a 31.6% absolute improvement in survival at 5-years and 0.316 Lives Saved per Transplant (LiST-5).

The association of medical urgency and post-transplant survival with LiST-5

There was wide variation in LiST-5 (IQR 0.24 - 0.39), driven by significant variation in risk of death with and without transplantation by candidate characteristics (**Table S2**). The IQR of five-year survival without a transplant was (38% ,66%) and the IQR of post-transplant survival was (76% ,92%). The 25th percentile recipient by survival benefit had an estimated five-year survival without transplantation of 68% which improved to 91% with transplantation, a LiST-5 of 0.24. The 75th percentile recipient had a lower absolute estimated five-year survival without transplantation 37% and with transplantation 76%, however a much larger LiST-5 of 0.39 (**Figure 1**)

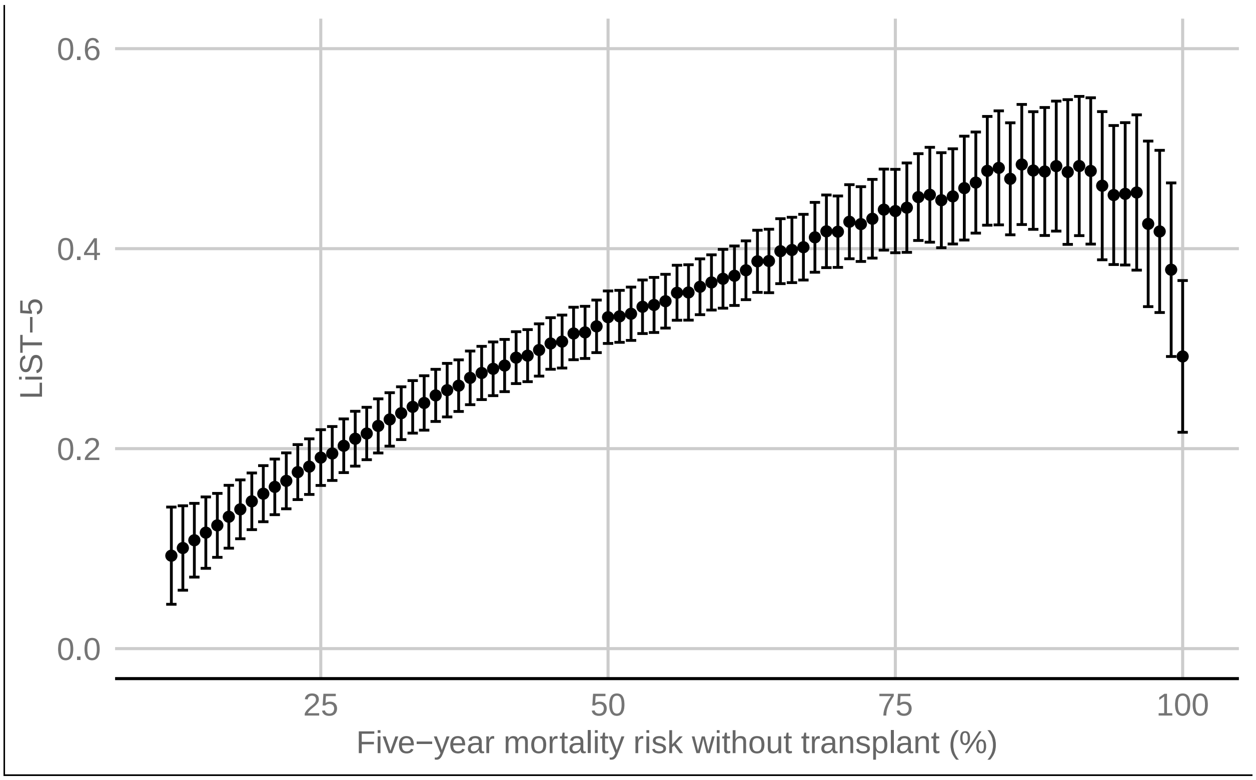
Figure 1: **LiST-5 for the 25th and 75th percentile recipient**



Survival benefit of deceased donor kidney transplantation for the 25th and 75th percentile recipient. The 25th percentile recipient had an estimated five-year survival without transplantation of 68%, which improved to 91% with transplantation, a LiST-5 of 0.24. The 75th percentile recipient had a lower absolute estimated five-year survival without transplantation 37% and with transplantation 76%, however a much larger net benefit from transplantation with a LiST-5 of 0.39

Overall, there was a strong positive correlation between the risk of death without a transplant (medical urgency) and survival benefit ($\rho = 0.83$) (**Figure 2**). The average survival benefit from deceased donor kidney transplantation was highest (0.48 LiST-5) when five-year mortality without a transplant was 86%, corresponding to ten lives saved with every 14 transplants (within the first five years).

Figure 2: **Survival benefit of deceased donor kidney transplantation by risk of death without a transplant**

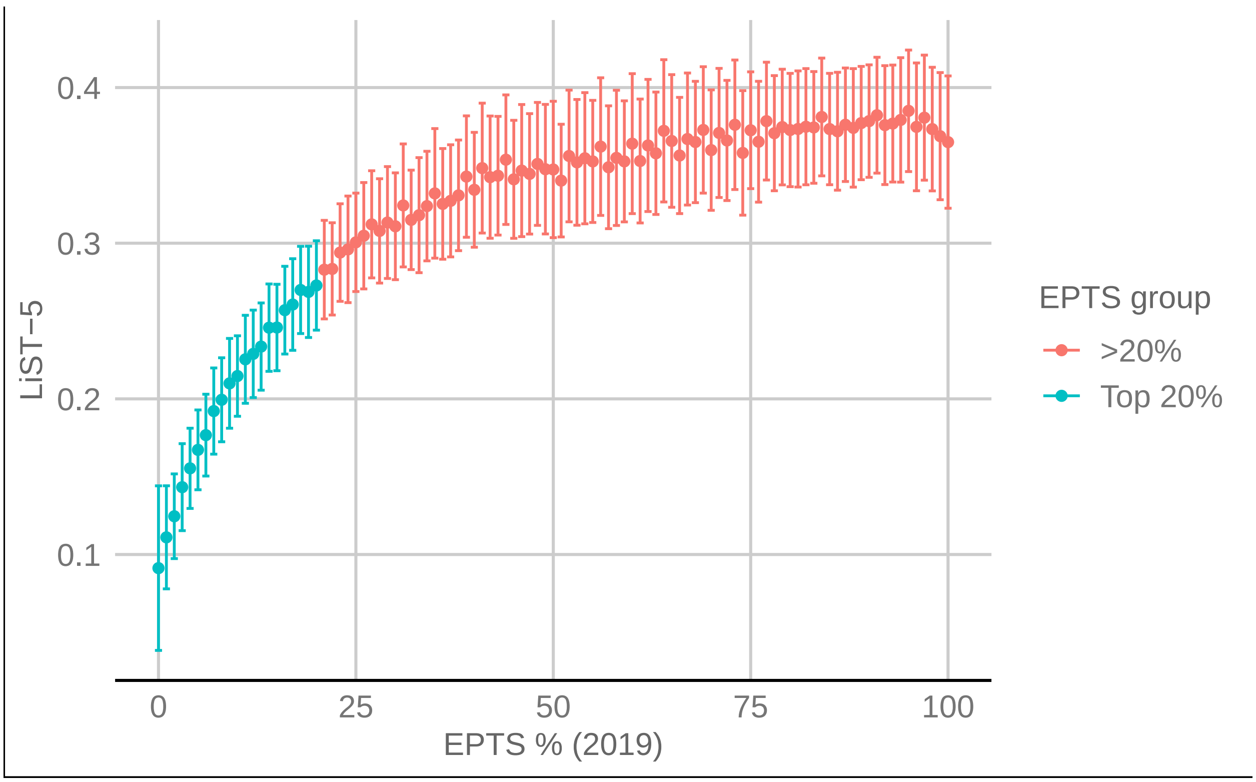


LiST-5 of deceased donor kidney transplantation by the risk of death without a transplant. There is a roughly linear relationship between medical urgency and survival benefit until the most urgent candidates (five-year mortality risk without a transplantation > 75%). Only for the most highly urgent candidates (mortality without transplant > 95%) does the LiST-5 begin to decline because of low expected post-transplant survival.

There was a strong correlation between EPTS score (2019 percentile) and survival benefit (0.54), meaning that recipients with low EPTS % had *lower* survival benefit (**Figure 3**). There was a strong correlation between EPTS scores and five-year mortality without transplantation 0.79, meaning recipients with lower EPTS % tended to be less medically urgent.

There was also a significant interaction between EPTS and KDPI (see **Table 2**, model results in **Table S2**). Top 20% EPTS recipients (currently receive priority for Top 20% kidneys) gain a 22.5% improvement in five-year survival with a KDPI 15% kidney (LiST-5 0.225) compared to a 21% improvement with a KDPI 60% kidney (LiST-5 0.21). In contrast, a recipients in the highest risk quartile (EPTS 80-100%) gain 42.9% in five-year survival with a KDPI 15% kidney (LiST-45 0.429) compared to 37.2% with a KDPI 60% (LiST-5 0.372), a significantly greater benefit from the higher quality graft ($p < 0.01$).

Figure 3: **LiST-5 of deceased donor kidney transplantation by EPTS**



Survival benefit of deceased donor kidney transplantation (LiST-5) by Estimated Post-Transplant Survival (EPTS) percentile (2019 OPTN mapping table). The candidates in the top 20% EPTS (highest expected post-transplant survival) have significantly lower benefit from transplantation when compared to candidates with EPTS > 20%.

Table 2: LiST-5 by EPTS quintile and KDPI

EPTS	KDPI 15 (%)	KDPI 60 (%)	Improvement with lower KDPI kidney	95% CI
(0,20]	0.225	0.21	0.015	(0.013, 0.018)
(20,40]	0.332	0.302	0.03	(0.027, 0.033)
(40,60]	0.378	0.339	0.038	(0.035, 0.041)
(60,80]	0.403	0.358	0.045	(0.042, 0.04.8)
(80,100]	0.429	0.372	0.057	(0.054, 0.06)

In KAS, Candidates with low EPTS (high expected post-transplant survival) are given priority for the top 20% KDPI kidneys. While this policy may extend total graft survival, it lowers the total number of lives saved by the system. Top 20% EPTS candidates have much lower LiST-5 than the top 20% most urgent candidates overall (**Table 3**). Furthermore, the top 20% most urgent candidates experience a greater benefit from lower KDPI kidneys than the top 20% EPTS candidates.

Table 3: LiST-5 Survival Benefit for EPTS top 20% versus 20% most urgent recipients

	KDPI 15 %	KDPI 85%	Improvement with KDPI 15% vs 85%
Top 20% EPTS Recipients	0.22	0.20	+ 0.02
Top 20% Most Urgent Recipients	0.39	0.32	+ 0.07

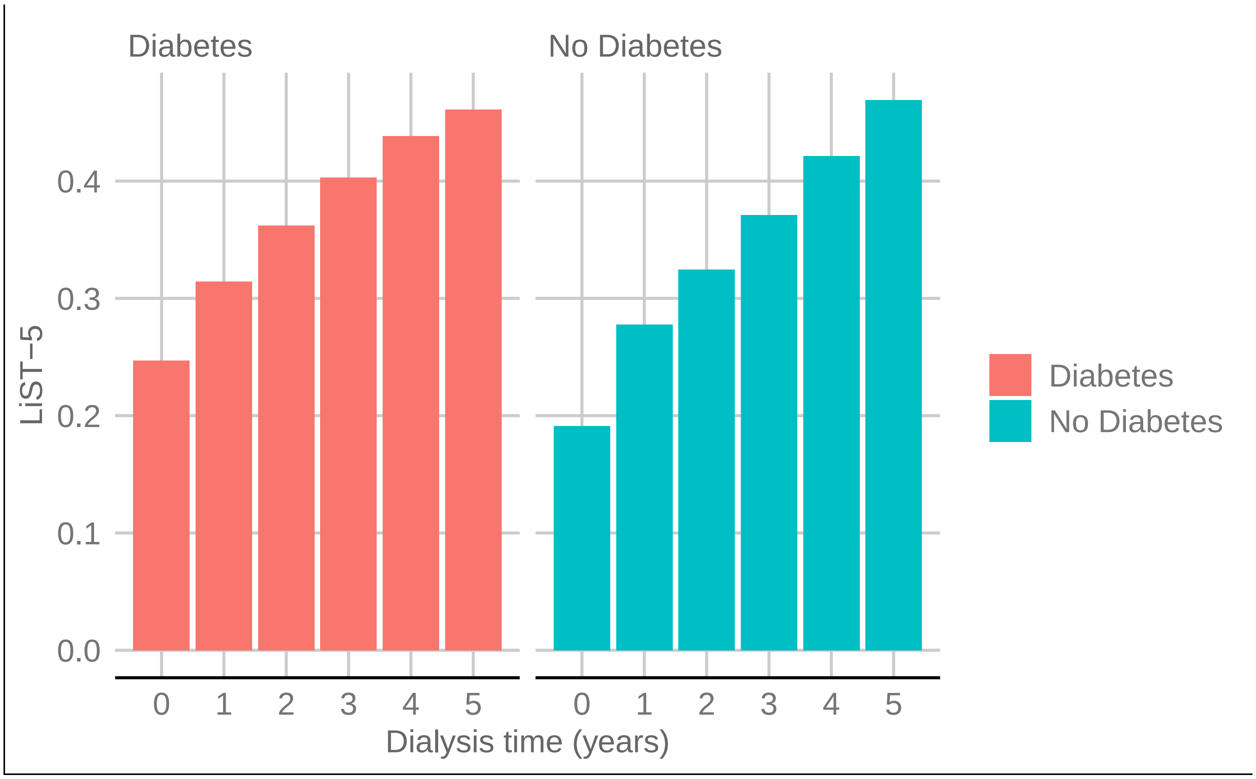
The association of dialysis time and diabetes with survival benefit

All candidate covariates that generate higher EPTS scores (age, history of diabetes, dialysis time, and previous transplant) were associated with greater medical urgency and had strong, independent associations with survival benefit (**Table S2**). On average, each year of recipient age increased LiST-5 by 0.004, a history of previous solid organ transplant by 0.031, and a history of diabetes by 0.032. Each additional year on dialysis increased five-year survival benefit by 0.015. Preemptive transplants were associated with -0.044 lower LiST-5 at five years.

The average LiST-5 for a preemptive transplantation in a patient without diabetes was 0.216 (95% CI 0.204, 0.228). Preemptive transplantation in patients with diabetes was associated with a LiST-5 of 0.266 (95% CI 0.245, 0.287). The average survival benefit for recipients without diabetes with more than five years of dialysis was 0.367 LiST-5 (95% CI 0.359, 0.375). For recipients with diabetes and more than five years of dialysis time at transplant, the average LiST-5 was 0.415 (95% CI 0.403, 0.427).

Transplanting the median patient without diabetes after the median amount of dialysis time (3.8 years of dialysis) was associated with a LiST-5 of 0.32 compared to a LiST of 0.19 preemptively transplanting the same patient (**Figure 4**). This translates over one life saved for every 10 transplants performed in dialysis recipients compared to preemptive transplants.

Figure 4: **LiST-5 by dialysis time**



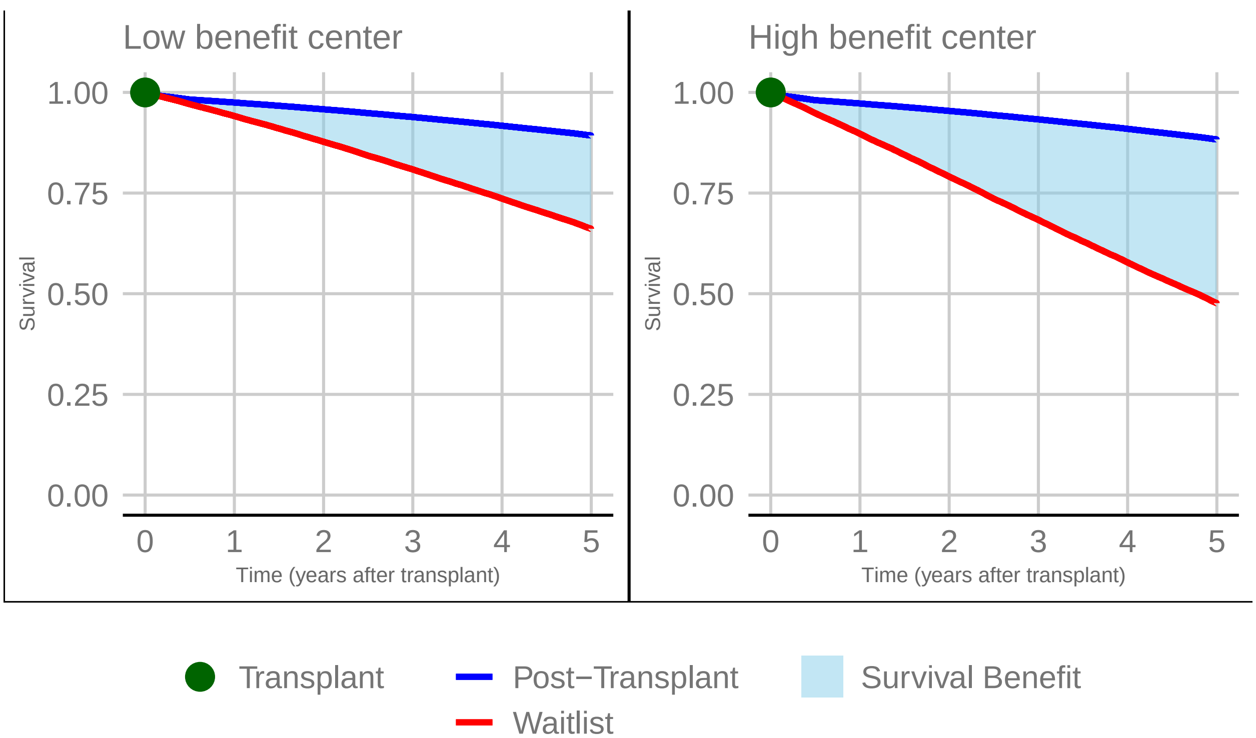
Survival benefit of transplantation for a 55-year-old recipient by time on dialysis with a KDPI 43% kidney and 17.6 hours of ischemic time. Preemptive transplants had 433 days of waiting time pre-transplant.

Between-center variation in the survival benefit

There were large, statistically significant transplant center effects on the risk of death with and without transplantation (see **Table S2B** for center effects on log hazard scale). The average five-year risk of death without a transplant ranged from 32% to 66% (IQR [46,54%]). There was less between-center variation in the average five-year post-transplant survival with a median KDPI kidney (43%), ranging from 70% to 90% (IQR [80,85%]). The correlation between average center risk of death with and without transplantation was strongly positive ($\rho = 0.64$). The significant between-center variation in the risk of death with and without transplantation translates into substantial between-center in the survival benefit of DDKT (**Figure 5**).

The LiST-5 from a median KDPI (43%) donor kidney varied from 0.20 to 0.48 (IQR 0.29, 0.35) between transplant centers. The variation in LiST-5 was driven primarily by high benefit centers selecting more medically urgent candidates, as the average five-year risk of death without a transplant ranged from 32% to 66% (IQR [46,54%]). There was less between-center variation in the average five-year post-transplant survival with (range from 70% to 90%, IQR [80,85%]).

Figure 5: **LiST-5 from transplantation at a high and low benefit transplant center**



Post-transplant survival 5-year post-transplant survival was similar at the high and low benefit centers (88% vs. 89%). However, recipients at the high benefit centers were significantly more urgent (waitlist survival 48% vs. 66%), indicating that the high benefit center was selecting more medically urgent candidates for transplantation. The LiST-5 at the high benefit center was 0.41 compared to 0.23 at the low benefit center.

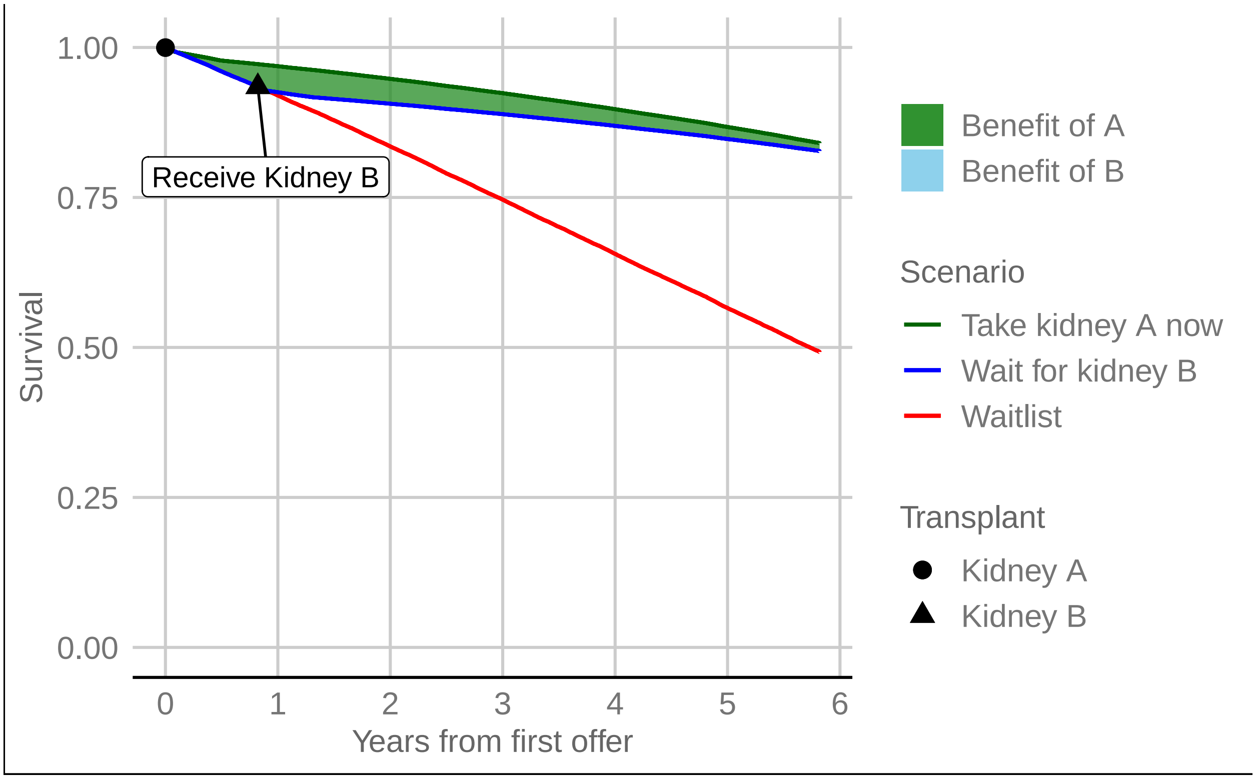
Donor KDPI and survival benefit

There was a small but statistically significant interaction between donor KDPI and survival benefit. For every 1% increase in KDPI, the five-year survival benefit decreased by -0.1%. The average LiST-5 of a KDPI $\geq$ 85% donor kidney was 0.278 (95% CI 0.266, 0.29). In 2019, there were 1,356 transplants performed with KDPI $\geq$ 85% donor kidneys. If these transplants were not performed, an estimated 377 people would die within five years.

Shared-decision making: Take the offer or wait for a better one?

The decision to take an offer or wait for a better one was highly non-linear and both candidates and wait time specific (web application to assist physicians and patients in shared-decision making is available at https://wparker-uchicago.shinyapps.io/DDKT_survival_benefit_compare/). For the median recipient (55 years old, 3.5 years of dialysis at time of first offer), accepting a 60% KDPI Kidney now would increase survival by 57.5 days on average within the first 5 years following transplant compared to waiting 300 days for a 15% KDPI Kidney. The probability the patient dies while waiting for the 15% KDPI kidney is 7%. (**Figure 6**).

Figure 6: **Survival under accepting a 60% KDPI kidney now compared to waiting 300 days for a 15% KDPI kidney for the median recipient without diabetes**



Estimated survival for three scenarios: transplantation now (green), waiting and then undergoing transplantation with a lower KDPI kidney (blue), and waiting indefinitely without transplantation (red). For this 55 year-old patient without diabetes who has 3.5 years of dialysis at time and has waited 809 days on the waitlist, accepting a 60% KDPI Kidney now would increase survival by 57.5 days on average within the first 5 years following transplant compared to waiting 300 days for a 15% KDPI Kidney. The probability the patient dies while waiting for the 15% KDPI kidney is 7%.

Survival benefit by race/ethnicity

Summary statistics for key model variables by race/ethnicity can be found in **Table 4**. For an adult candidate listed 2005-2010, the median white recipients waited 644 days for transplantation compared to 978 days for the median non-white recipient, 334 days longer ($p<0.01$). White recipients were more likely to be transplanted preemptively (15.4% vs. 5.4%, $p < 0.01$) and the median recipient waited 2 fewer years on dialysis prior to transplantation (2.5 vs. 4.4, $p < 0.01$).

Table 4: EPTS characteristics by racial/ethnic group, 2005-2010

Characteristic	Asian/Pacific Islander N = 4,378	Black N = 20,705	Hispanic/Latino N = 9,709	White N = 28,941
Age	56 (45, 63)	52 (43, 61)	53 (42, 61)	57 (47, 65)
Previous transplant	407 (9.3%)	2,370 (11%)	1,067 (11%)	5,184 (18%)
Diabetes	1,573 (36%)	7,554 (36%)	4,160 (43%)	9,112 (31%)
Dialysis (years)	4.1 (2.1, 6.5)	4.4 (2.6, 6.7)	4.7 (2.6, 7.2)	2.5 (0.8, 4.2)
Wait list time	1,108 (511, 1,842)	946 (420, 1,567)	993 (418, 1,785)	644 (239, 1,161)
Preemptive transplant	303 (6.9%)	1,080 (5.2%)	490 (5.0%)	4,444 (15%)

[1] Median (IQR); n (%)

After age-adjustment, the average white recipient in our cohort had a LiST-5 of 0.293, significantly lower than Black recipients (0.326), Hispanic recipients (0.331), and Asian/pacific islander recipients (0.333) (**Table 5**, $p<0.01$) for all comparisons).

Table 5: Age-adjusted five-year mortality without a transplant and survival benefit by racial/ethnic group

Race/ethnicity	Mortality without transplant %	LiST-5
Asian/Pacific Islander	51.2	0.333
Hispanic/Latino	52.7	0.331
Black	52.0	0.326
White	45.4	0.293

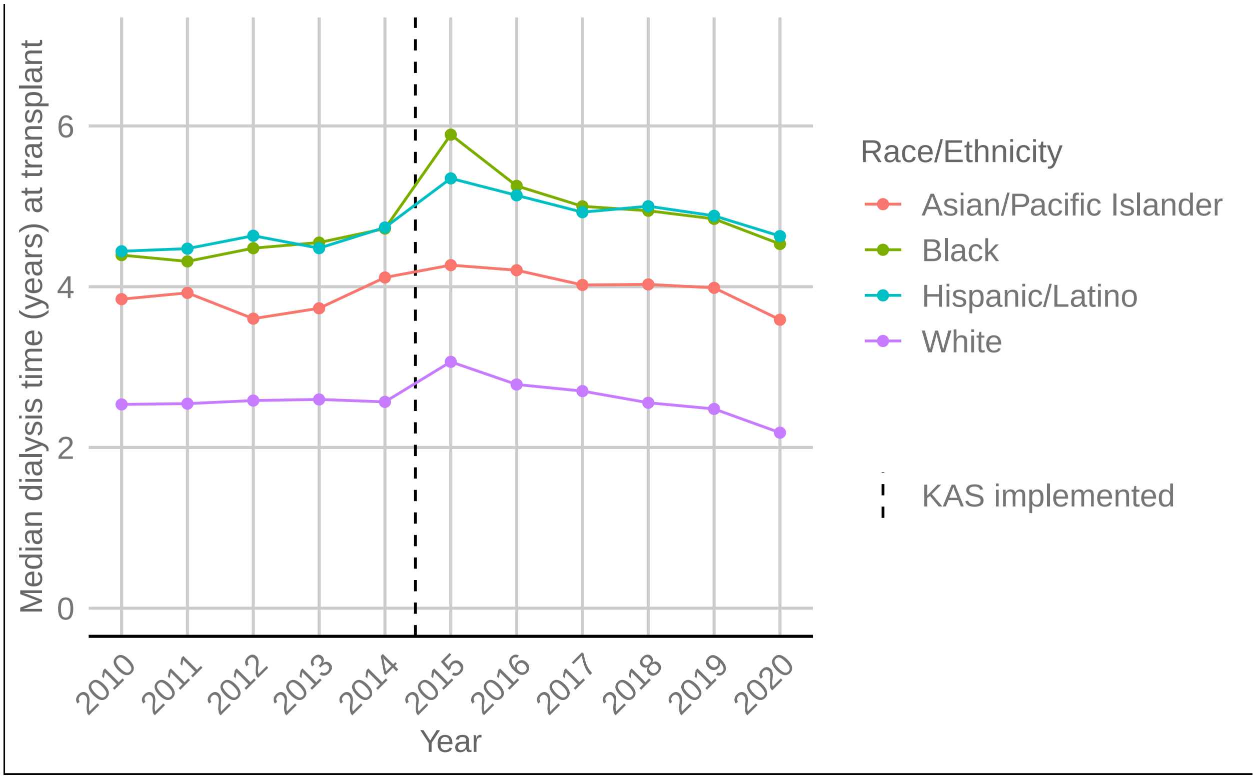
5-year mortality without a transplant (medical urgency) and survival benefit for first-time deceased donor kidney transplant recipients by race/ethnicity, age-adjusted using direct-standardization with age bins of (0,30),(30,40), (40,50), (50,60), (70+).

Racial disparities in dialysis time and preemptive transplantation

Racial disparities in dialysis time persisted from 2010-2020 despite the implementation of KAS in 2014 (**Figure 7**). In 2013, the median dialysis time for a White recipient was 2.6 years compared to 4.5 years for Black recipients. In 2019, the median dialysis time for a White recipient was 2.5 years compared to 4.8 years for Black recipients. The disparity in preemptive transplants increased (**Figure 8**). In 2013, 16% of

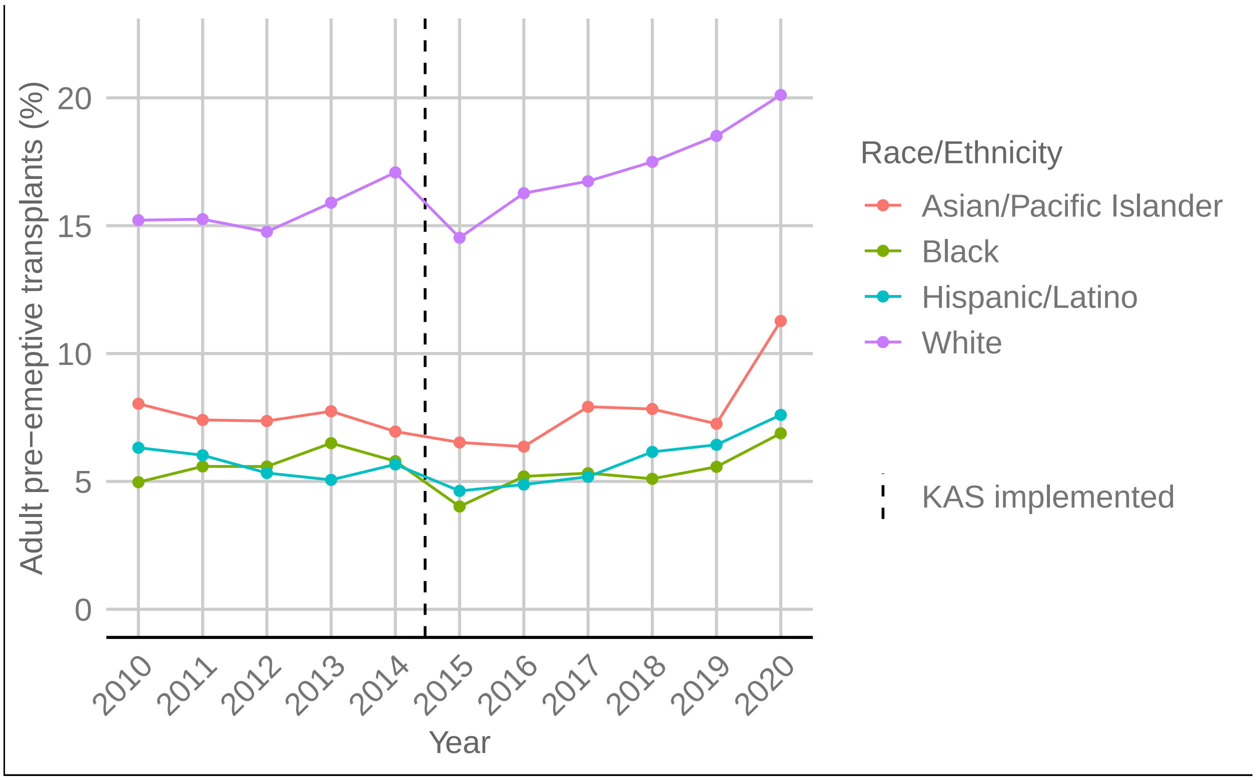
White recipients received a preemptive transplant compared to 6% of Black recipients. In 2019, 19% of White recipients received a preemptive transplant compared to 6% of Black recipients.

Figure 7: **Trends in median dialysis time by race/ethnicity**



Trends in the median dialysis time at transplant by race/ethnicity. Despite the 2014 change to give candidates credit for pre-listing dialysis time, a large (>two year) disparity in dialysis time at transplant persists through 2020. Other race/ethnicity groups not shown.

Figure 8: **Trends in preemptive transplants by race/ethnicity**



Proportion of deceased donor kidney transplants performed preemptively (before the initiation of dialysis) by race/ethnicity over time, as first reported by King et al [22].

Discussion

In this registry cohort analysis, we found significant variation in the survival benefit of kidney transplantation between patients. Older patients, patients with more dialysis time, and patients with diabetes are at high risk of death on the wait-list and have a greater survival benefit from transplantation. Transplanting patients with higher medical urgency would save more lives than transplanting patients with high estimated post-transplant survival. Recipients in the top 20% EPTS category have lower than average survival benefit within the first five years following transplantation. Within five years, candidates are typically better off taking a higher KDPI kidney when offered compared to waiting for a lower KDPI graft. Adjusting for age, non-white recipients have a higher risk of death on the wait-list *and* a larger survival benefit from transplantation, driven by more dialysis time and higher rates of diabetes.

Implications for top 20% EPTS priority

Dialysis may be a life-sustaining therapy, but it is far from perfect. The finding that high-quality kidneys from the top 20% KDPI donors confer *more* survival benefit to medically urgent candidates is consistent with prior results [32] and has immediate policy implications. The current policy of prioritizing the top 20% KDPI kidneys for the top 20% EPTS candidates is inefficient for saving lives. The highest-quality kidneys would save more lives if allocated to higher-risk candidates. While maximizing graft survival is an ethically important consideration, the Final Rule indicates that saving lives by transplanting medically urgent candidates is *at least* as important as total graft years.

Lives-Saved per Transplant within 5-years (LiST-5) vs. Life-years from transplant (LYFT)

Our approach estimates the **lives saved** with each transplant over a defined time interval (5 years) instead of estimating the total "life-years" gained over the length of a kidney transplant. This difference in outcome explains why our model identifies different "high benefit" groups than Life-Years From Transplant (LFYT) [33]. There are two main arguments for the Kidney Allocation System to focus on LiST-5 instead of LYFT, one technical and one normative.

First, calculation of LYFT requires estimation of the long-term benefits of kidney transplantation with minimal data. While younger patients have more potential lifespan and theoretically more potential life-years to gain, the actual calculation of LYFT has to rely on long-term extrapolations well beyond the support of the available data. Specifically, Wolfe et al. assumed that the relative survival benefit of transplant on the log hazard scale remains constant *even after graft failure*. However, it is more likely that after graft failure, the risk of death would regress to the risk of death on dialysis.

Second, LiST-5 better identifies "medically urgent" candidates with high short-term benefits from transplantation. The Final Rule does not contain any text about maximizing total quality-adjusted life-years gained by the system. Instead, the regulation clearly states candidates should be ranked "most to least medically urgent (taking into account…that life sustaining technology allows alternative approaches to setting priority ranking for patients)." We argue that short-term survival benefit achieves this aim of the Final Rule, accounting for the risk of death on dialysis while avoiding futile transplants and making "best use of donated organs."

Racial/ethnic disparities in survival benefit

Applying our model to deceased donor kidney recipients in 2020, we found that non-white recipients have greater age-adjusted LiST-5 than white recipients. This result reflects how the racial disparities in access to transplantation make the system less efficient. Longer dialysis time at listing means non-white candidates are at higher risk of death on the wait-list before transplantation. The current kidney allocation system compounds this disparity by prioritizing candidates with less dialysis time via the top 20% EPTS priority for the top 20% KDPI kidneys.

The persistent racial disparities in preemptive transplantation and median dialysis time are archetypal examples of structural racism in healthcare. There is no explicit racially discriminatory language in the Kidney Allocation System. Nevertheless, non-white recipients wait two years longer on dialysis before receiving a transplant. The OPTN has a moral obligation to modify KAS to counteract this structural disparity. The data in this report and others [22] demonstrate that counting pre-waiting listing dialysis time was insufficient. The recent expansion of geographic sharing may mitigate the disparity somewhat, but the OPTN must study more immediate solutions. For example, eliminating any points for pre-dialysis wait-list time could dramatically improve equity *and*, as shown by our model, save more lives. Thus there would be no equity-efficiency trade-off when addressing racial/ethnic disparities in KAS; correcting the structural racism would save more lives overall.

Eliminating points for pre-dialysis waiting time

Ku et al. have shown that higher eGFR thresholds for Black patients could alleviate disparities in transplantation [34]. However, our results suggest a more radical course of action would reduce disparities in transplantation and save more lives. The predominantly white preemptive transplant recipients have significantly lower LiST-5. If the goal of kidney allocation policy is to save lives, it is neither fair nor efficient to perform low benefit preemptive transplants. It is twice as efficient when the system transplants a patient who has suffered over five years of dialysis and a history of diabetes compared to a non-diabetic preemptive transplant. The OPTN should study the consequences of eliminating any pre-dialysis waiting time on overall graft survival and lives saved by the system.

Limitations

Our study has several limitations. First, our model had a c-statistic of 0.69, which represents good but not excellent discrimination. This suggests that our model should not be used as the only candidate ranking criterion in the kidney allocation system. Limiting the covariates to those currently used in the Kidney Allocation System may have reduced model performance. However, the model has the same accuracy as the EPTS model while predicting risk in 4 distinct time periods [24]. Therefore, our survival benefit estimates could be used to balance medical urgency with other ethically relevant factors in scarce resource allocation. Second, the center estimates presented here are case-mix adjusted for EPTS characteristics, so they capture a mix of center treatment and selection practices on unobserved variables. So increased risk of death (medical urgency) at a transplant center may reflect poor pre-transplantation care rather than truly higher medical risk. However, when transplanted, these higher-risk candidates receive dramatic improvements in survival, indicating high-quality post-transplantation care. In practice, centers should get rewarded for listing and transplanting sicker patients based on observed characteristics, with some accommodation given for the variation in prevalence of chronic kidney disease and potential candidates' demographics vary considerably across the country [31]. In particular, age-adjustment of each center's LiST-5 estimate should be performed. Finally, we focused on the five-year survival benefit (LiST-5) in this study to demonstrate the enormous benefit on a clinically relevant scale. However, policymakers can continuously re-estimate the center effects on the log hazard scale and evaluate programs more rapidly in practice.

Conclusion

Deceased donor kidney transplant candidates have a widely varying risk of death without a transplant. In general, transplanting higher-risk candidates saves more lives in the first five years. The current Kidney Allocation System ignores the Final Rule requirements to rank-order candidates by medical urgency. Severe racial/ethnic disparities persist within deceased donor kidney allocation, which the OPTN must directly address by radical policy changes such as eliminating pre-dialysis waiting time points. With a shift in focus to survival benefit, deceased donor kidney transplantation can save more lives and improve equity.

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