Appendix: Saving More Lives with Deceased Donor Kidney Transplantation

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Contents

Data Preparation

Formal Description of the Data

With candidates by i, centers by k, and donors by j, denote the data as:

- A vector of candidate covariates $X_{ik}(t)$, specifically the **EPTS variables** with their corresponding transformations
  - $Max(Age\,(years) - 25, 0)$
  - $log(Years\,on\,dialysis + 1)$
  - $I\{Years, on, dialysis = 0\}$
  - $Diabetes$
  - $Prior\,Solid\,Organ\,Transplant$
- Candidate death status ($Y_{ik} \in (0, 1)$) and follow-up time (T_{ik}). Includes death times after delisting for untransplanted candidates and post-transplant deaths
- Time-dependent indicator variable for transplantation $Tx_i(t)$
  - Donor quality W_j (**KDRI Rao**)
  - Ischemic time I_{ikj}, categorized as (<12 hours, 12-22 hours, >22 hours, or missing)

Table S1: Sample of final analytic dataset

Patient	Ctr.	Current age	Dialysis time (years)	time start	time stop	Status (interval start)	KDRI (linear)	Ischemic Time	Dead (end interval)
470987	41	59	2.06	0	684	Waiting			0
480003	78	72	1.83	0	2540	Waiting			0
480003	78	79	8.79	2540	2570	Transplant (day 0-30)	1.59	12	0
480003	78	79	8.79	2570	2720	Transplant (day 30-180)	1.59	12	0
480003	78	79	8.79	2720	4001	Transplant (day 181+)	1.59	12	0
500064	351	50	3.02	0	206	Waiting			0
500064	351	50	3.59	206	236	Transplant (day 0-30)	1.1	14	0
500064	351	50	3.59	236	386	Transplant (day 30-180)	1.1	14	0
500064	351	50	3.59	386	2476	Transplant (day 181+)	1.1	14	1
648174	33	74	0.80	0	117	Waiting			1

Sample of four patient records in final analytic dataset.

- Patient 470987 waited 684 days before delisting and did not have a recorded death date so was censored at the time of delisting.
- Patient 480003 waited $2,540$ days before transplant a KDRI Rao 1.59 kidney with 12 hours of ischemic time. Patient 480003 was still alive at last follow-up $4,001 - 2,540 = 1,461$ days post-transplant
- Patient 500064 waited 206 days for before DDKT with a KDRI Rao 1.1 kidney with 14 hours of ischemic time. After receiving this transplant, patient 500064 lived $2,476 - 206 = 2,270$ days before

death.

- Patient 648174 waited 117 days before dying without a transplant

Methodology

Mixed-effect Cox Proportional Hazards Model

To estimate the primary outcome of survival benefit associated with DDKT, we fit a mixed-effects Cox proportional hazard model with time-dependent covariates and a non-proportional effect of transplantation [1].

$$\begin{aligned} h_{ik}(t) = & h_0(t) * exp(\beta_{0k} + X_{ik}\beta + \\ & 1\{Transplant\} * (\beta_{1k} + \alpha_1 X_{ik} + \Pi_2 W_j + \zeta_1(W_j * X_{ij}) + \gamma I_{ijk}) + \\ & 1\{Day\ 0-30\ post\ transplant\} * (\beta_2 + \alpha_2 X_{ik} + \Pi_2 W_j + \zeta_2(W_j * X_{ij})) + \\ & 1\{Day\ 30-180\ post\ transplant\} * (\beta_3 + \alpha_3 X_{ik} + \Pi_3 W_j + \zeta_3(W_j * X_{ij})) \end{aligned}$$

$$\begin{gathered} \beta_{0k} = \nu_{k0} \\ \beta_{1k} = \beta_1 + \nu_{k1} \\ (\nu_{k0}, \nu_{k1}) \sim N(0, \Sigma) \\ \Sigma = \begin{pmatrix} \sigma_0^2 & \sigma_{01} \\ \sigma_{01} & \sigma_1^2 \end{pmatrix} \end{gathered}$$

this model includes:

- A random intercept ν_{0k} for each center, representing risk of death without transplantation at that center. Note there is no fixed effect intercept (as this is a proportional hazards model, so the “intercept” is the baseline hazard function $h_0(t)$)
- A random transplant effect β_{1k}, which represents the change in hazard from transplant at a particular center
- A covariance matrix Σ for the random effects, which allows for the intercept and transplant effect to be correlated
- Effect of DDKT β_{1k} modified by the following interaction effects:
  - Candidate factors $\alpha * X_{ij}$
  - Π: KDRI W_j and γ: ischemic time
  - ζ: candidate and donor interactions $W_j * X_{ik}(t)$

Table S2: Mixed-effects cox proportional hazards model results

Table S2A: Fixed Effect Coefficients

Variable	Coefficent	95% CI
Max(age -25, 0)	0.035	(0.034,0.036)
log(years on dialysis + 1)	0.122	(0.1,0.145)
Never dialyzed (pre-emeptive listing)	-0.273	(-0.313,-0.233)
Diabetes	0.829	(0.767,0.891)

Variable	Coefficent	95% CI
History of previous solid organ transplant	0.238	(0.206,0.27)
Transplant and interaction terms	—	—
Transplantation	-1.849	(-1.951,-1.747)
KDRI linear component score	0.459	(0.266,0.652)
Day 0-30 post-transplant	2.815	(2.482,3.149)
Day 30-180 post-transplant	1.28	(1.018,1.541)
ischemic time < 12 hours	-0.036	(-0.068,-0.004)
ischemic time > 22 hours	0.044	(0.012,0.077)
ischemic time not recorded	0.163	(0.092,0.234)
transplantation:Max(age -25, 0):	0.011	(0.009,0.013)
transplantation:log(years on dialysis + 1)	-0.112	(-0.154,-0.069)
transplantation:Never dialyzed	-0.06	(-0.153,0.033)
transplantation:Diabetes	0.277	(0.147,0.407)
transplantation:Previous transplant	0.01	(-0.054,0.073)
Diabetes:Max(age -25, 0)	-0.014	(-0.016,-0.013)
Diabetes:log(years on dialysis + 1)	0.001	(-0.032,0.034)
Diabetes:Never dialyzed (pre-emeptive listing)	0.084	(0.029,0.138)
Diabetes:History of previous solid organ transplant	-0.029	(-0.079,0.02)
KDRI linear score:Max(age-25,0)	0.003	(-0.001,0.007)
KDRI linear score:log(years on dialysis + 1)	0.05	(-0.023,0.124)
KDRI linear score:Never dialyzed	0.048	(-0.123,0.219)
KDRI linear score:Diabetes	-0.162	(-0.245,-0.08)
KDRI linear score:Previous transplant	0.086	(-0.044,0.215)
Day 0-30 post-transplant:Max(age -25, 0):	-0.013	(-0.021,-0.006)
Day 0-30 post-transplant:log(years on dialysis + 1)	-0.456	(-0.586,-0.326)
Day 0-30 post-transplant:Never dialyzed	-0.766	(-1.131,-0.4)
Day 0-30 post-transplant:Diabetes	-0.16	(-0.318,-0.002)
Day 0-30 post-transplant:Previous transplant	0.309	(0.102,0.516)
Day 30-18 post-transplant:Max(age -25, 0):	-0.005	(-0.011,0)
Day 30-18 post-transplant:log(years on dialysis + 1)	-0.327	(-0.427,-0.228)
Day 30-18 post-transplant:Never dialyzed	-0.335	(-0.591,-0.08)
Day 30-18 post-transplant:Diabetes	-0.179	(-0.295,-0.063)
Day 30-18 post-transplant:Previous transplant	0.21	(0.049,0.371)
KDRI linear score:Day 0-30 post-transplant	-0.345	(-0.607,-0.082)
KDRI linear score:Day 30-180 post-transplant	0.083	(-0.108,0.274)
Diabetes:Max(age -25, 0):Transplant	0.001	(-0.002,0.004)
Diabetes:log(years on dialysis + 1):Transplant	-0.043	(-0.099,0.013)
Diabetes:Never dialyzed:Transplant	-0.038	(-0.161,0.084)
Diabetes:Previous transplant:Transplant	-0.146	(-0.239,-0.054)

Table S2B: Center-level random effects

Term	Value
Variance of waitlist risk (ν_0)	0.04
Variance of transplant effect (ν_1)	0.05
Correlation ($Corr(\nu_0, \nu_1)$)	0.12

This fit is from N = 328,529 adult candidates listed for kidney alone deceased donor transplant from 2005 to 2010, there were N = 78,076. The discriminatory accuracy of the model as measured by Harrel's C-statistic was 0.69. The between-center variance in survival benefit of transplant on the log hazard scale ($B_i = \nu_{1i} - \nu_{0i}$)

is the variance of the difference between the two center effects, or

$Var(\nu_{i1} - \nu_{i0}) = Var(v_{1i}) + Var(\nu_{0i}) - 2 * Corr(v_{1i}, v_{0i}) * \sigma_{v_{0i}} \sigma_{v_{1i}}$

For the model estimated here, the between-center standard deviation of the survival benefit on the log hazard scale is 0.27

Lives Saved by Transplant within 5 years (LiST-5) calculation

While a hazard ratio of transplantation for each specific candidate-donor pair can be calculated directly from the coefficients in **Table S2**, an estimate of the baseline hazard function $\hat{h}_0(t)$ is required to calculate the improvement in absolute survival with DDKT. Following the previously published methodology of [1], we construct estimates of survival with transplant $S(t|transplant)_{ijk}$ and survival without transplant $S(t|waitlist)_{ijk}$ from the estimated model coefficients and a Nelson-aalen estimate of the baseline hazard function $\hat{h}_0(t)$ (**Figure S1**).

Specifically, assume candidate X_{ik} has waited t_{tx} days and receives an offer for kidney W_j which will suffer ischemic time I_{ikj} in transit. The model can generate counterfactuals for survival with and without transplant.

1. Calculate the hazard function for the patient with and without transplant
   - **with transplant**:

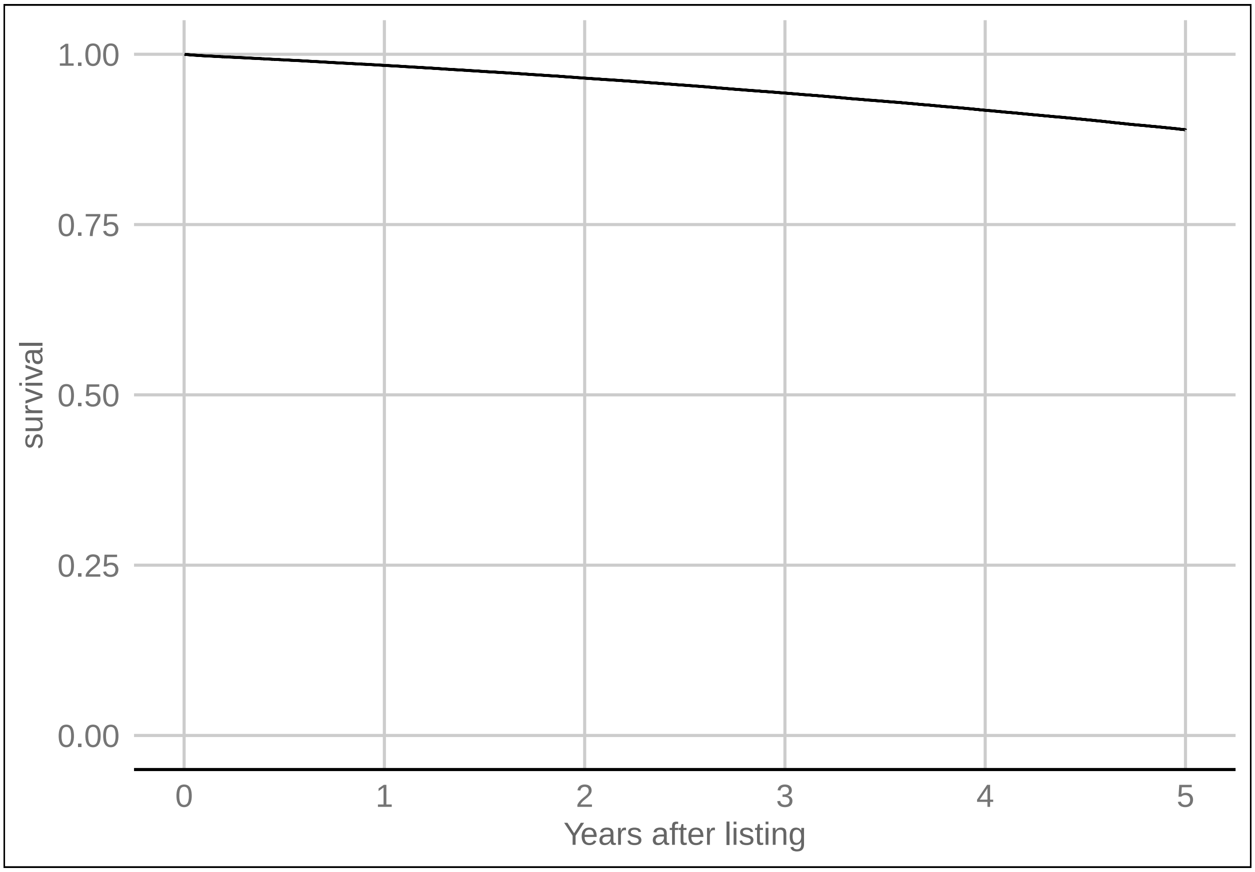
     $\hat{h}_{ijk}(t|transplant) = \hat{h}_0(t) * (exp(\hat{\beta}_{0k} + X_{ikt}\hat{\beta} + \hat{\beta}_{1k} + \hat{\alpha}(X_{ik}))\hat{\Pi} * (W_j) + \hat{\gamma}(I_{ikj})) + \hat{\zeta}(W_j * X_{ik}))$
   - **without transplant**
     $$\hat{h}_{ijk}(t|waitlist) = \hat{h}_0(t) * (exp(\hat{\beta}_{0k} + X_{ikt}\hat{\beta})$$
2. Construct survival functions from the hazard functions, comparing transplantation to waiting without transplantation.
   - **with transplant**:
     $$\hat{S}(t|transplant)_{ijk} = exp(-\int_{t_{tx}}^{t} \hat{h}_{ijk}(t|transplant))dt$$
   - **without transplant**:
     $$\hat{S}(t|wait)_{ik} = exp(-\int_{t_{tx}}^{t} \hat{h}_{ik}(t|wait))dt$$

Note that because the effect of transplantation is non-proportional, the hazard ratio varies inside the integral, i.e. if $t > t_{tx} + 180$

$$\begin{aligned}\hat{S}(t|transplant)_{ijk} = exp(-(& \int_{t_{tx}}^{t_{tx}+30} \hat{h}_{ijk}(t|Day\ 0-30\ post\ transplant) + \\ & \int_{t_{tx}+30}^{t_{tx}+180} \hat{h}_{ijk}(t|Day\ 30-180\ post\ transplant) + \\ & \int_{t_{tx}+180}^{t} \hat{h}_{ijk}(t|Day > 180\ post\ transplant))\ )dt\end{aligned}$$

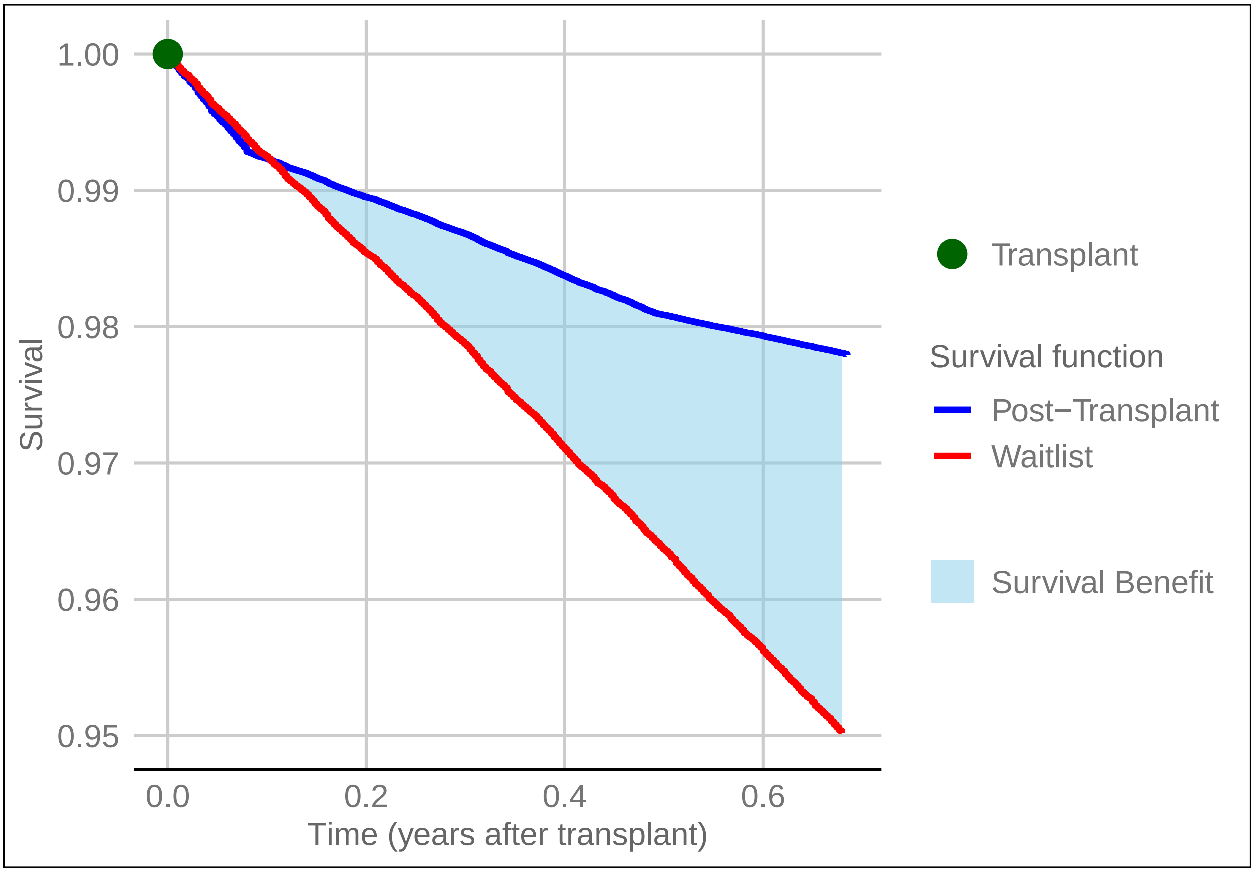
3. Calculate the estimated absolute survival benefit at the specified points in time
   - $LiST-1_{ijk} = \hat{S}(365\,days|transplant)_{ijk} - \hat{S}(365\,days|wait)_{ik}$
   - $LiST-5_{ijk} = \hat{S}(1825\,days|transplant)_{ijk} - \hat{S}(1825\,days|wait)_{ik}$

Figure S1: Non-parametric estimated of the baseline survival function $\hat{S}_0(t)$



Baseline survival function for the model estimated using Cox's extension of the Nelson-Aalen estimator. This represents the survival for the base case deceased donor kidney transplantation candidate (< 25 years old, just started dialysis, without diabetes) in the absence of transplantation during the first five years on the waitlist

Figure S2: The non-proportional effect of transplantation



Visualization of the non-proportional hazard of transplantation for a 55-year old recipient with 3 years of dialysis time transplanted after 700 days of waiting. In the first 30 days post-transplant, the risk of death is actually higher compared to remaining on the wait-list. In days 30-180, the benefit of transplantation outweighs the post-surgical risks. After day 180 post-op, the benefit of transplantation increases further.

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

Formal description

When a candidate receives a deceased donor kidney offer, they have two options:

1. Accept kidney W_j after t_a time on the wait-list. This generates the post-transplant survival function and survival benefit generated by our standard model.

$$\hat{S}(t|accept\, W_j)_{ijk} = exp(-\int_{t_a}^{t} \hat{h}_{ijk}(t|transplant\, W_j))dt$$

2. Reject kidney W_j and wait until time $t_b = t_a + \Delta t$ to get a better kidney W_m. This patient experiences a several discontinuities in estimated hazard, starting off with waitlist risk during the waiting period ($\hat{h}(wait)$ for time (t_a, t_b))and then transitioning to post-transplant risk after accepting the better kidney W_m ($\hat{h}(transplant\, W_m)$ for all time after t_b)

$$\hat{S}(t|wait\, for\, W_m)_{ijk} = exp(-(\int_{t_a}^{t_b} \hat{h}_{ijk}(t|wait)dt + \int_{t_b}^{t} \hat{h}_{ijk}(t|transplant\, W_m)dt))$$

References

1. Parker WF, Anderson AS, Gibbons RD, et al (2019) Association of Transplant Center With Survival Benefit Among Adults Undergoing Heart Transplant in the United States. JAMA 322:1789–1798. https://doi.org/10.1001/jama.2019.15686