THE UNIVERSITY OF CHICAGO

# TRANSPLANT CENTER PRACTICES AND THE SURVIVAL BENEFIT OF ORGAN TRANSPLANTATION

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Dedicated to the over 100,000 patients currently waiting for organ transplantation in the United States

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### *Code*

Interested readers can find all analysis code online

**Ch 2:** `https://github.com/08wparker/mixed_effects_survival_benefit_heart_tx`

**Ch 3:** `https://github.com/juliagegeran/geo_var_heart_tx_list`

**Ch 4:** `https://github.com/08wparker/survival_benefit_kidney`

# ABSTRACT

Deceased donor organs are an absolutely scare healthcare resource, meaning demand vastly exceeds a fixed supply with a hard limit. Allocation of donor organs requires difficult choices between thousands of waiting candidates who would benefit from transplantation. But allocation does not occur in a vacuum- transplant programs link donor organs and needy patients. Understanding how allocation rules shape their treatment and selection practices is key to designing effective systems. This three manuscript dissertation explores the relationship between transplant center practices, policy, and lives saved in heart and kidney allocation. In the introductory **Chapter 1**, we outline the broader issue of the allocation of absolutely scarce healthcare resources and discuss the current ethical framework for deceased donor organ allocation in the U.S. In **Chapter 2**, we create a novel mixed-effects model of the survival benefit of heart allocation, the key empirical outcome for the assessment of a transplant allocation system. We find that 5-year survival benefit associated with heart transplant varied across transplant centers, and high survival benefit centers performed heart transplant for patients with lower estimated waiting list survival without transplant. In **Chapter 3**, we describe how a new heart allocation policy was associated with widespread shifts in transplant center practice that threaten to undermine the effectiveness of the new system. Finally, in **Chapter 4** we apply and extend the model from Chapter 2 to deceased donor kidney allocation. We develop a tool that can 1) improve shared decision-making between transplant programs and patients when making accept-reject decisions and 2) identify medically urgent transplantation candidates to align kidney allocation policy with federal law. Incorporating survival benefit into deceased donor organ allocation could save more lives and reduce racial/ethnic disparities in transplantation.

# CHAPTER 1

# INTRODUCTION

## 1.1 Absolutely scarce healthcare resources

Absolutely scarcity occurs when there is high demand for a healthcare resource that vastly exceeds a fixed supply [Persad et al., 2009]. The scarcity may be short-lived, such as when a natural disaster or pandemic overwhelms the healthcare system or when there is a limited supply of a highly effective vaccine for a novel respiratory virus in a pandemic. But absolute scarcity is persistent, as with the chronically insufficient supply of deceased donor organs for transplantation. Regardless of the duration of the supply deficit, the allocation of absolutely scarce healthcare resources is an inescapable rationing problem. If the resource is life-saving, absolute scarcity means some patients will die for want of the resource, regardless of allocation system design. In the U.S. political system, absolute scarcity leads to central control of absolutely scarce resources and central authorities making rationing choices according to specific protocols [Piscitello et al., 2020; Dooling, 2021; OPTN, 2021b]. These protocols, either implicitly or explicitly, are built on specific ethical principles.

### *1.1.1 Ethical principles*

> *To achieve a just allocation of scarce medical interventions, society must embrace the challenge of implementing a coherent multi-principle framework rather than relying on simple principles or retreating to the status quo*
>
> Principles of Allocation of Scarce Medical Interventions. Persad G, Wertheimer A, Emanuel EJ. Lancet 2009

There are many compelling, broadly recognized ethical principles specifically relevant to allocating absolutely scarce healthcare resources. Persad divides these into four major categories: 1) Treat people equally, 2) Maximize benefits, 3) Prioritize the worst-off, and 4) Reward social usefulness (**Table 1.1**). Allocation protocols are the operational approach to

satisfy a specific ethical principle. For example, random assignment with a lottery would treat people equally (ignored when the need for the resource began). Mass-casualty triage systems explicitly prioritize those with the highest chance of survival with treatment to save the most lives. COVID-19 vaccine allocation plans that start with healthcare workers do so because of the principle of instrumental value, i.e., protecting healthcare workers from COVID-19 will have multiplier effects for the rest of society.

Table 1.1: **Ethical principles and example systems**

| **Ethical Principle** | **Example protocol** |
|---|---|
| *Treat people equally* | |
| By time of need | First-come, first-served |
| Ignoring when need began | Lottery |
| *Maximize benefits* | |
| Save lives | Mass-casualty triage |
| Save life-years | Life-years from Transplant (LFYT) proposal |
| Maintain societal function | Essential worker priority for COVID-19 vaccines |
| *Prioritize the worst-off* | |
| Youngest-first | Italian ICU triage system |
| Sickest-first | Medical urgency rankings in organ allocation |
| Disadvantaged-first | SVI*-based vaccine allocation |
| *Social usefulness* | |
| Instrumental value | Healthcare worker priority in vaccine allocation |
| Reciprocity | Prior living kidney donors |

Summary table of principles discussed in Daniels [2007]; National Academies of Sciences, Engineering, and Medicine [2020]; McClung [2020]; Persad et al. [2009, 2020]. * SVI- Social vulnerability index, a measure of community vulnerability to natural disasters.

### *1.1.2 Tradeoffs between ethical principles*

Absolute scarcity generates immediate conflict between these principles. For example, strict adherence to the principle of treating people equally requires ignoring all other considera-

tions. If candidates for a scarce resource have widely varying levels of benefit, then a lottery will be inefficient in distributing the resource. From the perspective of saving the most lives, it would be unacceptable to design a COVID-19 vaccine distribution system that gave an elderly resident of a long-term care facility and a 25-year-old healthy person who works from home equal access.

Another immediate conflict arises between the treat people equally principle and the youngest-first principle. Proponents of youngest-first allocation argue that younger adults are worse off because they have not had an opportunity to live through all life's stages, justifying unequal distribution by age according to the concept of Prudential Lifespan Equity [Daniels, 2007]. However, concerns over age-discrimination reduced youngest-first to a secondary role in US ventilator allocation protocols [Piscitello et al., 2020] and no role in COVID-19 vaccine or organ allocation [Dooling, 2021; OPTN, 2021b].

The magnitude of the tradeoffs between principles is fundamentally an empirical question. U.S. liver allocation uses the Model for End-Stage Liver Disease to rank-order candidates according to medical urgency in a sickest-first system [OPTN, 2021b]. Theoretically, this could be inefficient if the survival benefit of liver allocation declined for the very sickest. However, Luo et al. [2018] demonstrated empirically that the sickest candidates receive the greatest benefit. Therefore in liver allocation, there is no conflict between the rule of rescue and maximizing benefits.

In contrast, sickest-first ventilator rationing under Crisis Standards of Care would be very inefficient [Committee on Guidance for Establishing Crisis Standards of Care for Use in Disaster Situations and Institute of Medicine, 2012]. Assuming a patient has 0% survival without a ventilator, the benefit of treatment is a simple function of expected survival with a ventilator. In this scenario, sickest-first would *minimize* benefits to the population.

The usefulness of empirical methodology goes beyond quantifying tradeoffs between ethical principles. In the next section, we argue that empirical outcomes are fundamental to

both the articulation of a multi-principled ethical framework *and* an associated practical allocation protocol.

### *1.1.3 Developing practical allocation protocols*

Empirical data is critical for the development of a practical, algorithmic allocation protocol. Deriving a protocol from "first principles" only works if consequences are irrelevant, e.g., a pure lottery or first-come, first-served system. Even then, the specific circumstances of the shortage limit the possible normative ethical framework. For example, consider attempting to strictly adhere to the treat people equally principle in two different ventilator allocation scenarios: a pandemic and a natural disaster. In a pandemic, patients arrive in a steady but relentless sequence. First-come, first-served is unavoidable, as it is impossible to run a lottery on the entire set of patients at need simultaneously. In contrast, a natural disaster leading to power loss and forces rationing over the set of patients currently receiving ventilation. A lottery protocol is easy to accomplish in this scenario, whereas first-come, first-served is impossible.

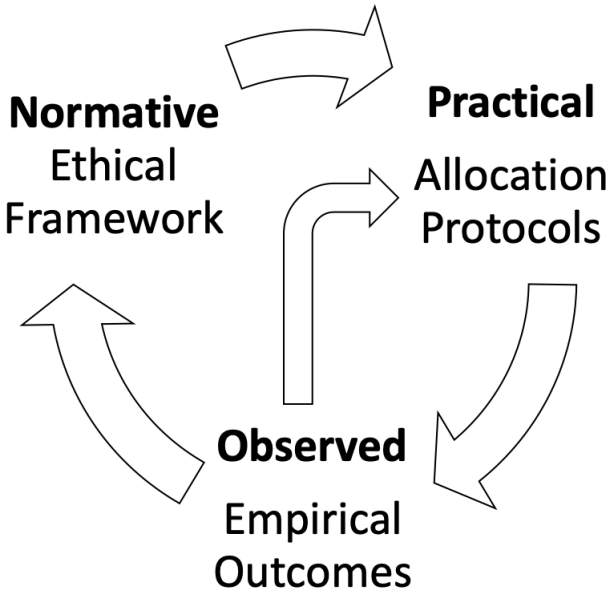
If the ethical framework has *any* component of consequentialism (even if restricted to ensuring recipients have positive benefit from the resource), results from empirical studies will be critical. Problem-specific population characteristics and outcome distributions are required if the principle of maximizing benefits is a component of the framework. Saving the most lives in organ allocation requires identifying the candidates with the largest survival benefit from transplantation. We take on this complex empirical problem for heart transplantation in **Chapter 2** and kidney transplantation in **Chapter 4**.

In a *multi-principled* framework, empiricism takes on an even more prominent role. The empirical details of the scenario determine the subset of relevant principles and limit how any protocol could combine them. Furthermore, empirical data constraints the degree to which the protocol can successfully weigh principles or construct a sensible lexical rank-ordering. In

other words, the details of the rationing problem dictate the set of constrained optimization solutions.

Fundamental empirical questions permeate every aspect of constructing an ethical framework. A lottery might be just as efficient as a system designed to maximize benefits if the prioritization scheme/score is inaccurate, dissolving the need to articulate a relative weight of either principle. Instrumental value, the concept of prioritizing "socially useful" people because of the so-called "multiplier" effects by keeping them healthy and functional, rests entirely on a very specific empirical claim that appeals to maximizing benefits. The magnitude of equity corrections that prioritize the disadvantage depends on the severity of the baseline structural inequities in society. Therefore, empirical methodology plays a role in not just fine-tuning the practical allocation protocol, but also in the construction of the underlying ethical framework **Figure 1.1**.

Figure 1.1: **Role of empirical methodology in the allocation of absolutely scarce healthcare resources**




This dissertation contains three empirical papers that perform the role of observed outcomes in **Figure 1.1**, directly assessing allocation protocols used for deceased donor organ

allocation with respect to the ethical principles specified by the US government.

## 1.2 Deceased donor organ allocation

The quintessential example of an absolutely scarce healthcare resource is deceased donor organs [Sheehy et al., 2003; SRTR, 2019]. Just 1 in 5 candidates listed for deceased donor kidney transplantation in 2016 received a transplant within three years [Hart et al., 2021]; candidates are more likely to die or be delisted than receive a transplant. Per the 1984 National Organ Transplant Act (NOTA), a non-governmental organization receives the Organ Procurement and Transplant Network (OPTN) contract to manage the organ supply centrally. The United Network currently holds the OPTN contract for Organ Sharing (UNOS). In 1999, the Department of Health and Human Service issued a sweeping Final Rule [24 C.F.R. § 121.8] on NOTA.

### *1.2.1 Ethical Principles in the Final Rule*

While the Final Rule is not a complete ethical framework (see Ross et al. [2012]), it does provide the OPTN with specific language on how allocation systems should function. The Final Rule invokes the ethical principles of saving the most lives and prioritizing the sickest first, stating the OTPN should rank candidates from "most to least medically urgent" while "taking into account... that life-sustaining technology allows alternative approaches.". Treating people equally who have equivalent medical urgency and potential benefit from an organ is also a part of the Final Rule. Allocation protocols must "reduc[e] the inter-transplant program variance to as small as can reasonably be achieved" across all measurable performance indicators.

However, for nearly 20 years, the developed organ allocation protocols have blatantly ignored the implications of the principles described in the federal regulation. One particularly egregious example is the lack of geographic sharing of organs. The Final Rule states that the

OPTN should "distribut[e] organs over as broad a geographic area as feasible." Still, for years the OPTN allocated organs according to arbitrary "Donor Service Areas," a process shown to create dramatic disparities in survival and cost lives ([Gibbons et al., 2000]). Ultimately, it took a series of lawsuits initiated by disadvantaged patients to force the OPTN to comply with federal regulations.

## 1.3 Dissertation structure

This dissertation assesses heart and kidney allocation policy compliance with the Final Rule using empirical techniques. The dissertation contains three complete manuscripts which have an overlapping methodology and content areas.

**Chapter 2** and **Chapter 3** assess the heart allocation protocol with respect to the Final Rule principles of saving the most lives and prioritizing the sickest first. In **Chapter 2**, we build a novel mixed-effects model of the survival benefit of heart transplantation that accounts for the clustering of patients within transplant centers and time-dependent covariates [Parker et al., 2019]. We apply this model to heart allocation, determining the association between transplant center practices and the survival benefit. In **Chapter 3** we study the impact of a significant change in heart allocation policy on transplant center practices with a mixed-effect discrete choice model [Ran et al., 2021].

In **Chapter 4**, we extend the survival benefit model developed in Chapter 2 and apply it to kidney allocation. We demonstrate wide variation in the survival benefit of kidney transplantation between centers and candidates, suggesting the waiting time-based kidney allocation system does not maximize the number of lives saved. We show how easily modifiable aspects of the kidney allocation protocol violate the principle of treating people equally, creating significant racial disparities in access to transplantation.

# CHAPTER 2

# ASSOCIATION OF TRANSPLANT CENTER WITH SURVIVAL BENEFIT AMONG ADULTS UNDERGOING HEART TRANSPLANT IN THE UNITED STATES

## Abstract

**Importance** In the United States, the number of deceased donor hearts available for transplant is limited. As a proxy for medical urgency, the US heart allocation system ranks heart transplant candidates largely according to the supportive therapy prescribed by transplant centers.

**Objective** To determine if there is a significant association between transplant center and survival benefit in the US heart allocation system.

**Design, Setting, and Participants** Observational study of adult candidates for heart transplant listed on the national transplant registry from January 2006 through December 2015 with follow-up complete through August 2018.

**Exposure** Transplant center.

**Main Outcomes and Measures** The survival benefit associated with heart transplant as defined by the difference between survival after heart transplant and waiting list survival without transplant at 5 years. Each transplant center's mean survival benefit was estimated using a mixed-effects proportional hazards model with transplant as a time-dependent covariate, adjusted for year of transplant, donor quality, ischemic time, and candidate status.

**Results** Of 29,199 candidates (mean age, 52 years; 26% women) on the transplant waiting list at 113 centers, 19,815 (68%) underwent heart transplant. Among heart transplant recipients, 5389 (27%) died or underwent another transplant operation during the study period. Of the 9384 candidates who did not undergo heart transplant, 5669 (60%) died (2644 while on the waiting list and 3025 after being delisted). Estimated 5-year survival was 77% (interquartile range [IQR], 74% to 80%) among transplant recipients and 33% (IQR, 17% to 51%) among those who did not undergo heart transplant, which is a survival benefit of 44% (IQR, 27% to 59%). Survival benefit ranged from 30% to 55% across centers and 31 centers (27%) had significantly higher survival benefit than the mean and 30 centers (27%) had significantly lower survival benefit than the mean. Compared with low survival benefit centers, high survival benefit centers performed heart transplant for patients with lower estimated expected waiting

list survival without transplant (29% at high survival benefit centers vs 39% at low survival benefit centers; survival difference, -10% [95% CI, -12% to -8.1%]), although the adjusted 5-year survival after transplant was not significantly different between high and low survival benefit centers (77.6% vs 77.1%, respectively; survival difference, 0.5% [95% CI, -1.3% to 2.3%]). Overall, for every 10% decrease in estimated transplant candidate waiting list survival at a given center, there was an increase of 6.2% (95% CI, 5.2% to 7.3%) in the 5-year survival benefit associated with heart transplant.

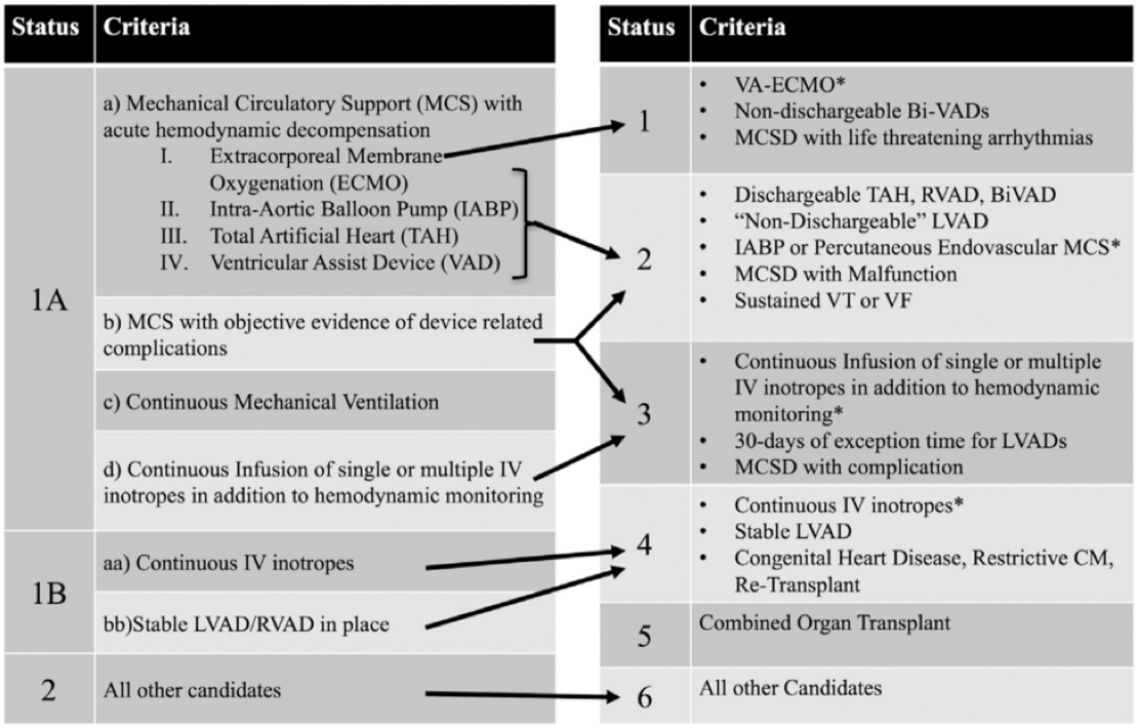
**Conclusion** The 5-year survival benefit associated with heart transplant varied across transplant centers, and high survival benefit centers performed heart transplant for patients with lower estimated waiting list survival without transplant.

## 2.1 Introduction

Heart transplantation remains the definitive treatment for end-stage heart failure. Demand greatly exceeds supply and median waiting time is over 9 months [Colvin et al., 2021]. Federal regulations require the Organ Procurement and Transplant Network to make the "best use" of donor hearts by ranking candidates from "most to least medically urgent" [OPTN, 2021a].The heart allocation protocol is therapy-based, meaning it uses treatment intensity as a surrogate for medical urgency, relying on centers to select sick candidates and use advanced heart failure therapies appropriately.

In 2016, the OPTN thoracic committee identified "major problems" with the US heart allocation system [OPTN/UNOS Thoracic Committee, 2016]. Driven by expanding use of high-dose inotrope and continuous-flow left ventricular assist device (LVAD) therapies, the plurality of adult heart transplant candidates were "Status 1A", a priority intended for a small minority of the most critically ill candidates [Parker et al., 2017b; Dardas et al., 2012]. In competitive organ markets, centers more frequently used Status 1A qualifying high-dose inotropes and intra-aortic balloon pumps (IABP) on candidates who are not in cardiogenic shock [Parker et al., 2018]. In response, the OPTN updated the heart allocation system in October 2018, increasing the number of Status levels from three to six and implementing a cardiogenic shock requirement to restrict access to the top priority Status levels (**Figure**

Figure 2.1: **Schematic depiction of the shift from the current adult heart allocation system to the modified system**




Status 1A exception candidates were re-assigned to Status 3, Status 1B exceptions to Status 4. *Cardiogenic shock requirement applies.Constructed with permission directly from OPTN policy. VT = ventricular tachycardia, VF = ventricular fibrillation, CM = cardiomyopathy, IV = intravenous.

**2.1**) [OPTN/UNOS Thoracic Committee, 2017].

While the new OPTN policy is intended to improve heart allocation, the association between center candidate selection and management practices on heart allocation effectiveness has not been well-studied. This registry cohort study estimated survival benefit of heart transplantation (defined as the difference between a patient's expected survival with and without transplant) for each transplant center in the US, comparing the three-tier system with the new six-tier Status candidate rankings.

## 2.2 Methods

### *2.2.1 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 identified all adult ($\geq$ 18 years of age at listing) heart-alone candidates listed in the United States from January 1st, 2006 to December 31st, 2015. This decade follows the last major heart allocation policy change [Schulze et al., 2014] and modern continuous-flow LVADs were in widespread use [Slaughter et al., 2009]. For each candidate, we constructed a time series with records for initial listing, changes in Status or therapeutic support, transplantation (if allocated a heart), last follow-up visit, re-transplantation, or death through August, 2018. Death records were supplemented from the linked Social Security Death Master File to capture the outcomes of candidates who were delisted alive. Re-transplantation was also treated as a terminal event, standard practice when estimating benefit of an organ transplant [Schnitzler et al., 2005]. Candidates who received multi-organ transplants, were listed at centers with less than 10 adult transplants during the entire study period, were never activated for transplant on the list, or had data entry errors (date of death/removal before listing date) were excluded from the analysis ( see **Figure 2.2** for study flow chart).

We constructed a novel longitudinal dataset from the SRTR database that recorded all the clinical changes candidates underwent on the wait-list prior to transplantation (see example

in **Table 2.1**).

Table 2.1: **Sample of the records from a single patient on the heart transplant wait-list**

| **Time Start** | **Time stop** | **Transplant** | **Dead** | **Three-Status and justification** | **Six-status** |
|---|---|---|---|---|---|
| 0 | 36 | 0 | 0 | Status 1B (inotropes) | 4 |
| 36 | 42 | 0 | 0 | Status 1A - (Exception) | 3 |
| 42 | 141 | 0 | 0 | Status 1B (inotropes) | 4 |
| 141 | 148 | 0 | 0 | Status 1A - (High dose inotropes) | 4 |
| 148 | 150 | 0 | 0 | Status 1A - (High dose inotropes) | 4 |
| 150 | 178 | 0 | 0 | Inactive | 4 |
| 178 | 182 | 0 | 0 | Status 1A (MCS for shock) | 3 |
| 182 | 198 | 0 | 0 | Inactive | 3 |
| 198 | 209 | 0 | 0 | Status 1A - (MCS complication) | 3 |
| 209 | 3863 | 1 | 1 | Status 1A - (MCS complication) | 3 |

The patient was initially listed status 1B with IV inotropes and spent days 0-35 at six-status 4 before transitioning to status 1A justified by an exception (six-status 3) for days 36-41. After 209 days on the list and several more status changes, the patient was transplanted and lived until day 3863 before dying.

When candidates are removed from the list without transplantation, we carried forward their status from the previous observed period. Because many candidates are deactivated from list before dying, this assumption allows the model to appropriately capture the risk of each active wait-list status.

### *2.2.2 Survival benefit model*

The primary outcome was the survival benefit associated with heart transplantation as quantified by estimated improvement in absolute five-year survival gained by receiving a heart transplant. To estimate the primary outcome of survival benefit from transplant,we fit a mixed-effects Cox proportional hazard model with transplantation treated as a time-dependent predictor variable [Ripatti and Palmgren, 2000; Austin, 2017; Therneau et al., 2003; Therneau, 2018]. In order to allow candidate risk of mortality to vary by center both pre- and post-transplant, the model used both a random intercept and a random transplant effect. The model equation for patient $j$ listed at center $i$ is

$$h_{ij}(t) = h_0(t) * exp(\beta_{0i} + \beta_{1i} tx_{ij}(t) + X_{ij}\beta + \Phi(X_{ij} * tx_{ij})) \tag{2.1}$$

With random effect structure

$$\beta_{0i} = \nu_{0i} \tag{2.2}$$

$$\beta_{1i} = \beta_1 + \nu_{1i} \tag{2.3}$$

$$(\nu_{i0}, \nu_{i1}) \sim N(0, \Sigma) \tag{2.4}$$

$$\Sigma = \begin{pmatrix} \sigma_0^2 & \sigma_{01} \\ \sigma_{01} & \sigma_1^2 \end{pmatrix} \tag{2.5}$$

This model has the following terms

- a random intercept for each center $\beta_{0i}$ which allows each center to have a distinct baseline hazard $h_0(t)exp(\beta_0)$
- a random effect $\beta_{1i}$ for the time-dependent transplant variable $tx_{ij}(t)$
- a vector of candidate covariates $X_{ij}(t)$ and their interaction terms with transplant (coefficients $X_{ij}(t) * tx_{ij}(t)$)
- A baseline hazard $h_0(t)$ which is not included in the partial likelihood function and not initially estimated.

Candidate covariates $X_{ij}(t)$ included candidate time-dependent Status (1A, 1B, or 2), year of listing (before or after 2010), and donor risk index $\geq 5$ (calculated using the method of Weiss et al. [2012] using donor age, race, blood urea nitrogen, creatinine, and ischemic time) to account for the significant variability in waiting time and donor quality across the country [Colvin et al., 2021; Dardas et al., 2012, 2017]. Candidate and donor fixed category race variables as recorded by transplant providers in the SRTR dataset were used

in the study because racial mismatch is a known risk factor for post-transplant mortality [Weiss et al., 2012]. Because centers are responsible for listing candidates likely to benefit from heart transplantation and treating them with the appropriate indicated supportive therapy, we deliberately chose to not add candidate covariates other than wait-list Status into the model, instead allowing variation in candidate characteristics and pre-transplant center treatment choices to be captured by the center random effects. In order to estimate the magnitude of the center random effects, we calculated the median hazard ratio for both the wait-list and transplant effects in the model [Bengtsson and Dribe, 2010].

### *2.2.3 Case-mix adjusted center-specific estimates of survival benefit*

Building on standard practices in hospital outcomes reporting [Shahian et al., 2005; Krumholz et al., 2008, 2013], we generated case-mix adjusted center-specific estimates of the five-year survival benefit associated with heart transplantation, adjusting for the covariates $X_{ij}$ above. After estimating the model by maximum partial likelihood using the coxme package [Therneau, 2018], we estimated the five-year survival benefit of transplantation for each recipient using the following procedure:

1. for each recipient, we calculated the hazard function under transplant $h_{ij}(t|tx = 1, X_{ij})$ for all points in time after transplant (e.g. $t > T_{transplant}$) and waiting ($h_{ij}(t|tx = 0, X_{ij})$) using the model estimates of fixed effects ($\hat{\beta}$ and $\hat{\Phi}$), an estimate of the baseline hazard function ($\hat{h}_0$) [Therneau, 2018], and the Empirical Bayes estimates of intercept and transplant effect $\hat{\nu}_{0i}$ and $\hat{\nu}_{1i}$ for their center of transplantation $i$

$$\hat{h}_{ij}(t|wait, X_{ij}) = \hat{h}_0(t) * exp(\hat{\beta}_{0i} + X_{ij}\hat{\beta}) \tag{2.6}$$

$$\hat{h}_{ij}(t|transplant, X_{ij}) = h_0(t) * exp(\hat{\beta}_{0i} + \hat{\beta}_{1i}tx_{ij}(t) + X_{ij}\hat{\beta} + \hat{\Phi}(X_{ij} * tx_{ij})) \tag{2.7}$$

The estimate of the baseline hazard is from an extension of the Nelson-Aalen estimator

of the baseline hazard function to the case of covariates described by Cox and Oakes (1984, Section 7.8). For all patients in the risk set $R(t)$ alive at a given time $t$ from initial listing

$$\hat{h}_0(t) = \frac{d(t)}{\sum_{R(t)} exp(\hat{\beta}_1 tx_{ij}(t) + X_{ij}\hat{\beta} + \hat{\Phi}(X_{ij} * tx_{ij}))} \tag{2.8}$$

where $d(t)$ are the number of deaths in that interval. Note this estimate is constructed for $(\nu_{0i}, \nu_{1i}) = (0, 0)$ (the mean center).

2. Use the estimated hazard functions to construct hypothetical "waiting forever" survival function and "observed" transplant survival functions with or without transplant (see examples in **Figure 2.4**). We reset survival to equal 100% at time $t = T_{transplant}$, making the estimates conditional upon survival to transplant (suppressing hat notation)

$$S_{ij}(t|wait, X_{ij}) = exp(-\int_{T_{tx}}^{t} h_0(t) * exp(\beta_{0i} + X_{ij}\beta)dt) \tag{2.9}$$

$$S_{ij}(t|transplant, X_{ij}) = exp(-\int_{T_{tx}}^{t} h_0(t) * exp(\beta_{0i} + \beta_{1i} tx_{ij}(t) + X_{ij}\beta + \Phi(X_{ij} * tx_{ij}))dt \tag{2.10}$$

3. Finally, the absolute 5-year survival benefit estimate for candidate $j$ transplanted at center $i$ is calculated by simple subtraction

$$B_{ij}(t = 5\ years) = S_{ij}(t = 5\ years|tx = 1, X_{ij}) - S_{ij}(t = 5\ years|wait, X_{ij}) \tag{2.11}$$

Completing this procedure for each recipient using the random effects from the center they were actually transplanted at yields the marginal observed five-year survival benefit distribution. This would not acutally "case-mix" adjust the estimates, as the average center benefit

$B_{ij}(t)$ would reflect the distribution of covariates of recipient-donor pairs $X_{ij}(t)$ actually transplanted at that center. Therefore, we gave each center the hypothetical "opportunity" to transplant each recipient, estimating 113 distributions of recipient five-year benefits by applying each center's Empirical Bayes estimate of intercept and transplant random effect to each of the 19,815 recipients and following the five-year survival benefit procedure described above (see **Figure B.2**). To summarize each center's effect on five-year survival benefit, we calculated the mean of each center's distribution and 95% percent confidence intervals using the variance of the distribution of five-year survival estimates for the entire study population and number of transplants performed at each center during the study period (**Figure 2.3**).

To identify centers with significantly higher or lower survival benefit associated with heart transplantation, standard errors of each center estimate were calculated using the variance of the five-year survival benefit distribution and number of transplants performed at each center during the study period. A center with an estimate above or below the mean center at a $p < 0.05$ level was considered to have significantly higher or lower survival benefit associated with transplantation. To test for a violation of the proportional hazards assumption that could confound the association between center and survival benefit, we performed a Schoenfeld test on post-transplant survival by the level of center benefit.

### *2.2.4 Secondary Outcomes*

Secondary outcomes were characteristics of transplanted recipients at high and low benefit centers, including Status and proportion of recipients treated with Status 1A qualifying IABPs or high-dose inotropes who did not meet hemodynamic requirements for cardiogenic shock. Additional secondary outcomes included age, gender, race, diagnosis, blood type, diabetes status, functional status on the Karnofsky scale [Karnofsky and Burchenal, 1949], cardiac index, pulmonary capillary wedge pressure, Status 1A justification (acute mechanical circulatory support (MCS), MCS with complication, mechanical ventilation, high-dose

inotropes and hemodynamic monitoring, or exception), and payor (Medicare, Medicaid, private, or other).

Secondary outcomes were described and compared between centers with significantly lower and higher survival benefit. For continuous variables, mean and standard deviation were calculated and group comparison testing p-values calculated using Student's t-test. For categorical variables, number (%) were calculated and group comparison testing p-values calculated with Fisher's exact test.

### *2.2.5 Survival benefit under the new 6-status heart allocation system*

We also fit a second mixed-effects Cox model to estimate the between-center variation in heart transplant survival benefit under the six-status system [OPTN/UNOS Thoracic Committee, 2017]. Broadly, the new six status system splits Status 1A qualifying therapies into three groups (the new Status 1-3), distinguishes between severity of mechanical circulatory support complications, and imposes a recurrently verifiable cardiogenic shock requirement for a subset of candidates. We coded each candidate according to the priority status they would have received under the current six-status system using their most recent hemodynamic data for all time points after listing . Following previously published approaches, we applied the cardiogenic shock requirement conservatively, assuming a patient met criteria for cardiogenic shock if hemodynamic data were missing. See **Appendix: Application of the Cardiogenic Shock Requirement** for more details. Absolute five-year survival benefits were calculated using the same procedure described above.

### *2.2.6 Sensitivity Analyses*

We performed four sensitivity analyses to test the underlying assumptions of our model. First, to test the assumption of Gaussian random center effects, we fit a fixed-effects model where center wait-list and post-transplant risk were treated as fixed-effects. Second, to ensure

our modeling choices were not leading to confounding by temporal or donor factors, we fit a mixed-effects model with all donor and ischemic time variables (donor age, race, blood urea nitrogen, creatinine, and ischemic time in hours) modeled independently and listing year instead of transplant year. Third, we added candidate demographic variables (age, gender, body mass index (BMI), diagnosis, blood type, and cross match requirement) to isolate the contribution of candidate demographic variation to the between-center variation in the survival benefit of transplant. Fourth, we added bridge-to-transplant (BTT) LVAD and UNOS region to the model to quantify the contribution of variation in LVAD utilization to the between-center variation in survival benefit.

All statistical testing was two-sided with a p-value threshold of $< 0.05$. Because of the potential for type 1 error due to multiple comparisons, findings for secondary analyses and other analyses should be interpreted as exploratory. All analyses were performed using R 3.4.3 (The R Foundation for Statistical Computing 2017).

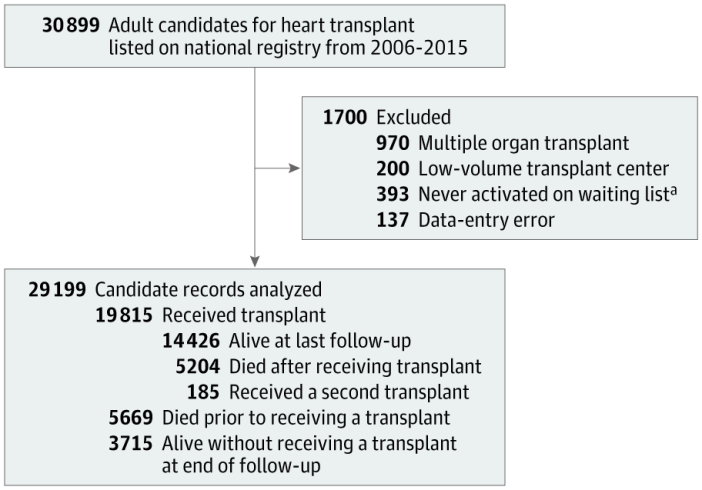
## 2.3 Results

### *2.3.1 Study Population*

During 2006-2015, there were 30,899 adult candidates registered for heart transplantation in the US. We excluded 970 for multi-organ transplantation, 200 for listing at one of 33 low volume centers, 393 who were never activated on the list, and 137 with data entry errors (**Figure 2.2**). The remaining 29,199 candidates (mean age, 52; 26% women) were listed at 113 centers and 19,815 (68%) received a heart transplant (see full characteristics in **Table 2.2**).

Among transplant recipients, 5,389 (27%) died or were re-transplanted during the study period and 14,426 (73%) remained alive at last follow-up. Of the 9,384 candidates who did not receive a transplant, 5,669 (60%) died (2,644 while on the wait-list and 3,025 after

Figure 2.2: **Flowchart of the Study Population and Outcomes**




Study follow-up extended until August 2018. *a*- patients who were registered for heart transplant with an inactive status and who were never converted to an active status

delisting) and 3,715 (40%) were alive but had not received a transplant by the end of follow-up. Surviving patients were followed for a mean of 5.4 years before censoring.

Table 2.2: **Characteristics of US Adult Heart Transplant Candidates listed from 2006-2015**

| | **Overall** (N = 29,199) | **Not transplanted** (N = 9,384) | **Transplanted** (N = 19,815) |
|---|---|---|---|
| Age at listing | 52.38 ± 12.52 | 52.35 ± 12.58 | 52.39 ± 12.49 |
| Body Mass Index | 27.56 ± 5.12 | 28.35 ± 5.30 | 27.19 ± 4.99 |
| Male | 21741 (74.5) | 6946 (74.0) | 14795 (74.7) |
| Diabetes | 8392 (28.7) | 2950 (31.4) | 5442 (27.5) |
| Durable BTT LVAD | 6327 (21.7) | 1710 (18.2) | 4617 (23.3) |
| Race | | | |
| White | 19555 (67.0) | 6193 (66.0) | 13362 (67.4) |

Characteristics of US Adult Heart Transplant Candidates (continued)

| | **Overall** (N = 29,199) | **Not transplanted** (N = 9,384) | **Transplanted** (N = 19,815) |
|---|---|---|---|
| Black | 6247 (21.4) | 2201 (23.5) | 4046 (20.4) |
| Hispanic | 2251 (7.7) | 689 (7.3) | 1562 (7.9) |
| Other | 1146 (3.9) | 301 (3.2) | 845 (4.3) |
| Diagnosis | | | |
| Dilated cardiomyopathy | 12339 (42.3) | 3651 (38.9) | 8688 (43.8) |
| Ischemic cardiomyopathy | 10881 (37.3) | 3499 (37.3) | 7382 (37.3) |
| Restrictive cardiomyopathy | 2773 (9.5) | 907 (9.7) | 1866 (9.4) |
| Other | 3206 (11.0) | 1327 (14.1) | 1879 (9.5) |
| Renal Function | | | |
| GFR <30 ml/min/1.73 mˆ2 | 1456 (5.0) | 833 (8.9) | 623 (3.1) |
| GFR >= 30 & <60 ml/min/1.73 mˆ2 | 11603 (39.7) | 3792 (40.4) | 7811 (39.4) |
| GFR >= 60 ml/min/1.73 mˆ2 | 16010 (54.8) | 4704 (50.1) | 11306 (57.1) |
| Unknown | 130 (0.4) | 55 (0.6) | 75 (0.4) |
| Functional Status* | | | |
| Limited Impairment, 10-30% | 9577 (32.8) | 3203 (34.1) | 6374 (32.2) |
| Moderate Impairment, 40-60% | 10137 (34.7) | 3093 (33.0) | 7044 (35.5) |
| Severe Impairment, 70-100% | 8818 (30.2) | 2828 (30.1) | 5990 (30.2) |
| Unknown | 667 (2.3) | 260 (2.8) | 407 (2.1) |
| Blood Type | | | |
| A | 11073 (37.9) | 3006 (32.0) | 8067 (40.7) |
| AB | 1345 (4.6) | 247 (2.6) | 1098 (5.5) |

Characteristics of US Adult Heart Transplant Candidates (continued)

| | **Overall** (N = 29,199) | **Not transplanted** (N = 9,384) | **Transplanted** (N = 19,815) |
|---|---|---|---|
| B | 3957 (13.6) | 1058 (11.3) | 2899 (14.6) |
| O | 12824 (43.9) | 5073 (54.1) | 7751 (39.1) |
| Primary Payor | | | |
| Medicaid | 3457 (11.8) | 1124 (12.0) | 2333 (11.8) |
| Medicare | 8971 (30.7) | 3155 (33.6) | 5816 (29.4) |
| Other | 1258 (4.3) | 390 (4.2) | 868 (4.4) |
| Private | 15513 (53.1) | 4715 (50.2) | 10798 (54.5) |
| Status and Justification at Initial Listing | | | |
| Status 1A | | | |
| MCS for shock | 3359 (11.5) | 965 (10.3) | 2394 (12.1) |
| MCS complication | 571 (2.0) | 145 (1.5) | 426 (2.1) |
| Mechanical ventilation | 209 (0.7) | 117 (1.2) | 92 (0.5) |
| High dose inotropes | 2616 (9.0) | 595 (6.3) | 2021 (10.2) |
| Exception | 374 (1.3) | 99 (1.0) | 275 (1.4) |
| Status 1B | | | |
| Low dose inotropes | 8315 (28.5) | 2251 (24.0) | 6064 (30.6) |
| Stable VAD | 3474 (11.9) | 1046 (11.1) | 2428 (12.3) |
| Exceptions | 325 (1.1) | 89 (0.9) | 236 (1.2) |
| Status 2 | 9956 (34.1) | 4077 (43.4) | 5879 (29.7) |
| Hemodynamics | | | |

| Characteristics of US Adult Heart Transplant Candidates (continued) | | | |
|---|---|---|---|
| | **Overall** | **Not transplanted** | **Transplanted** |
| | (N = 29,199) | (N = 9,384) | (N = 19,815) |
| Pulmonary Capillary Wedge Pressure, mm Hg | 20.12 ± 8.77 | 19.97 ± 8.85 | 20.19 ± 8.73 |
| Mean Pulmonary Artery Pressure, mm Hg | 29.98 ± 10.41 | 30.27 ± 10.90 | 29.85 ± 10.17 |
| Cardiac Index L/min/m2 | 2.17 ± 0.65 | 2.20 ± 0.66 | 2.16 ± 0.65 |

For categorical variables, n (%) are presented. For continuous variables, mean± SD are presented. *Functional status measured on the Karnofsky Performance Scale. BTT = Bridge-to-transplant, LVAD = Left-ventricular assist device, GFR = Glomerular filtration rate as estimated by the revised Modification of Diet in Renal Disease (MDRD) equation

### *2.3.2 Between-center Variation in the Survival benefit associated with Heart Transplant*

Full model results on log hazard scale are shown in **Table 2.3**. Averaged across the entire recipient population, heart transplantation was associated with a mean hazard ratio (HR) for death of 0.24 compared to waiting without transplant (interquartile range [IQR] 0.14-0.35). When model estimated log hazard ratios were combined with a non-parametric estimate of the baseline hazard function as described in equation 2.9 (**Figure B.1**), the mean absolute improvement in five year survival was 44% (IQR 27-59%), increasing from 33% (IQR 17-51%) without transplant to 77% (IQR 74-80%) with transplant.

Adjusted for Status, candidate risk of death without transplant varied by center from a HR of 0.71 to a HR of 1.63 relative to the mean center. The median hazard ratio was

Table 2.3: **Mixed-effect model results**

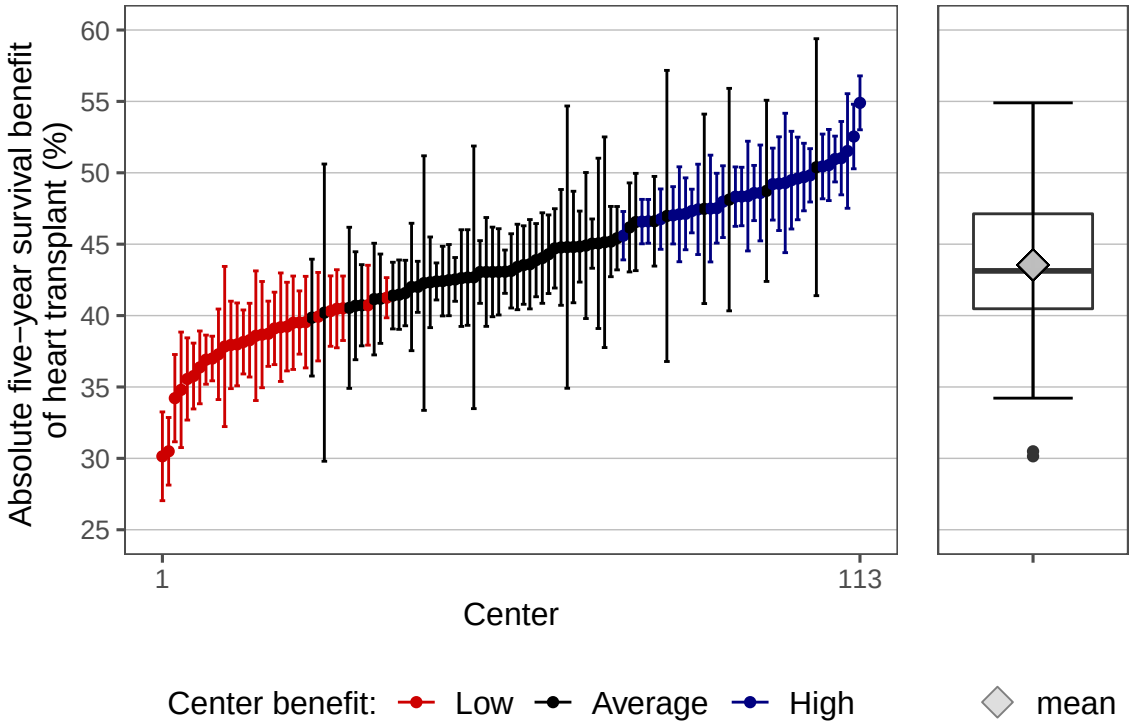
| **Fixed Effects Covariate** | **log hazard ratio** | **95% CI** |
|---|---|---|
| Status 1B | -0.942 | (-1.00, -0.88) |
| Status 2 | -1.36 | (-1.43, -1.28) |
| Transplant | -1.95 | (-2.04, -1.87) |
| Transplant: Status 1B | 0.90 | (0.82, 0.99) |
| Transplant: Status 2 | 1.32 | (1.20, 1.45) |
| Transplant before 2010 | -0.05 | (-0.11, 0.01) |
| Donor Risk Score >5 | 0.26 | (0.21, 0.32) |
| **Random effect** | **variance** | |
| Intercept | $\sigma_0^2 = 0.050$ | |
| Transplant | $\sigma_1^2 = 0.057$ | |
| Correlation | $\rho_{01} = -0.509$ | |

Base case is a candidate waiting at Status 1A after 2010. The random intercept and slope in this model were strongly negative correlated (-0.509), indicating that center-specific hazard ratio of transplantation decreased with increased center-specific wait-list risk. The variance in the survival benefit of transplant (wait-list subtracted from transplant) was 0.161 on log hazard ratio scale.

1.24, indicating that the risk of death without a transplant was 24% higher when comparing a random lower risk center to a higher risk center. The reduction in mortality risk from heart transplantation also varied significantly by center, HR range 0.71 to 1.68 relative to the mean center. The median hazard ratio for the transplant effect was 1.26, indicating that the risk of death with transplant was 26% higher at a random higher risk center compared to a lower risk center.

In combination, these center effects led to wide variation in the case-mix adjusted survival benefit associated with heart transplantation: the mean improvement in estimated five-year survival ranged from 30% to 55% by center, IQR [40% - 47%] (**Figure 2.4**, **2.3**).

Figure 2.3: **Between-Center Variation in the Adjusted 5-Year Survival Benefit Associated With Heart Transplant**

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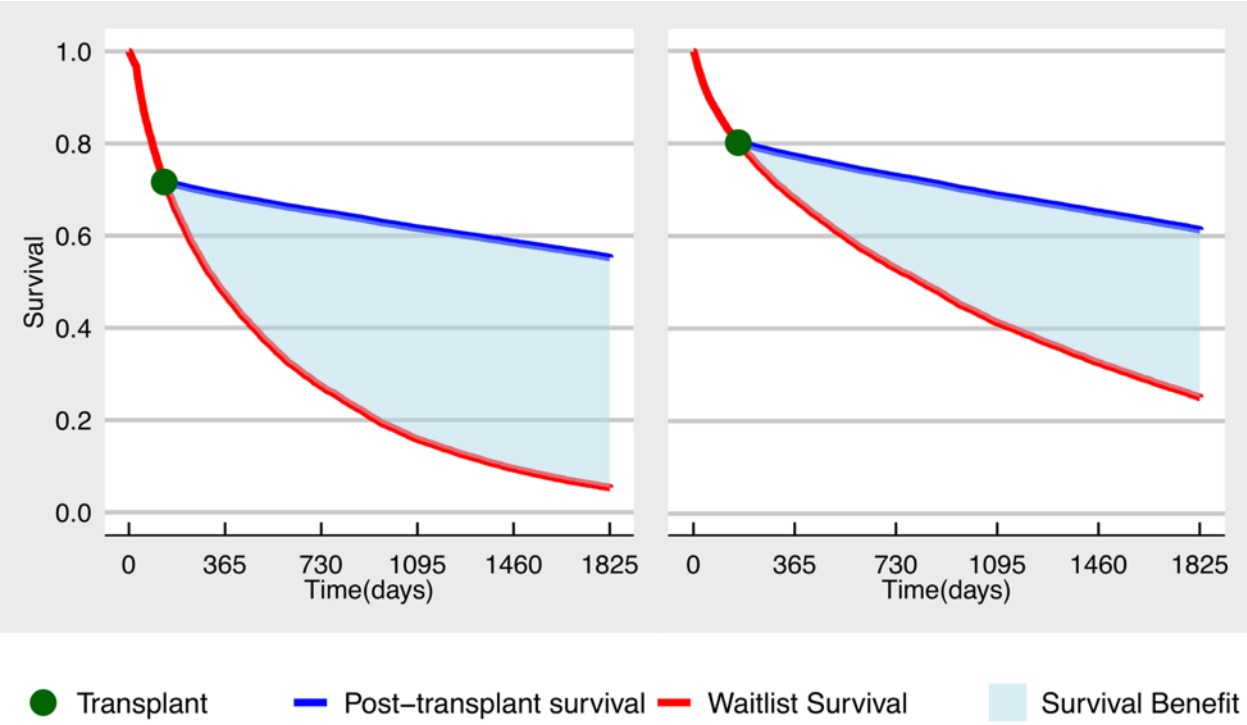
Caterpillar plot (left) of estimates of each center's mean absolute 5-year survival benefit, case-mix adjusted for time from listing to transplant, waiting list status, year of listing, donor quality, and ischemic time. The 95% CIs were constructed using the variance of the distribution of 5-year survival estimates for the entire study population and the number of transplants performed at each center during the study period. Compared with the mean center, 31 centers (27%) had significantly higher survival benefit (blue) and 30 centers (27%) had lower survival benefit (red). The adjusted 5-year survival benefit varied substantially by center, ranging from 30% to 55%, median of 43% (interquartile range [IQR], 40%-47%) (box plot, right).

### *2.3.3 Medical Urgency and Post-transplant survival of Transplant Recipients at High and Low Survival Benefit Centers*

For every 10% decrease in expected candidate five-year wait-list survival without transplantation, there was a 6.2% increase in estimated five-year survival benefit with transplant (95% CI 5.2% to 7.3%). In contrast, there was no significant relationship between a center's mean post-transplant survival and benefit (1.5% increase in survival benefit for every 10% increase

Figure 2.4: **Survival benefit of transplantation for a Status 1A patient at a high and low benefit center**

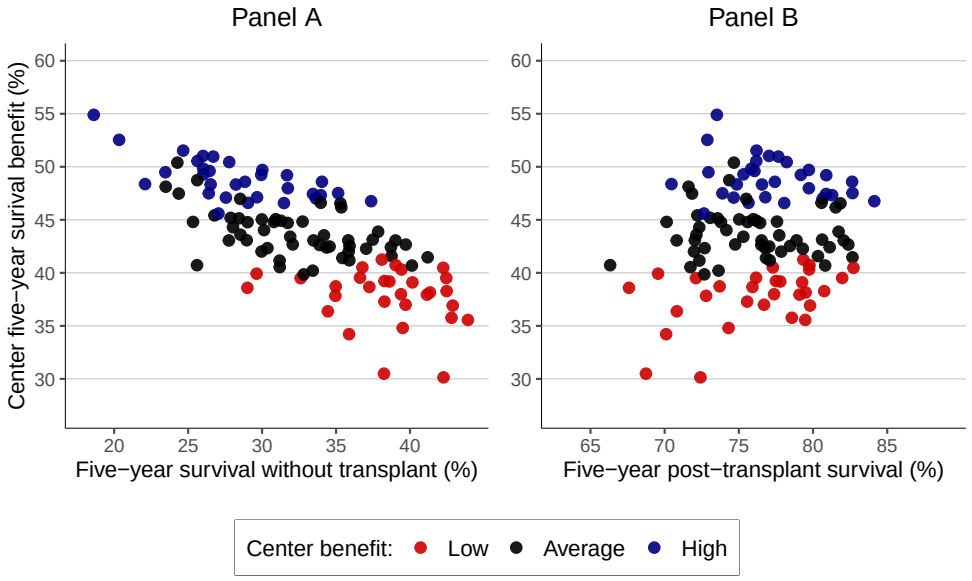



The high-benefit center (left panel) prioritizes candidates at higher risk of wait-list mortality and therefore transplantation at this center lowers risk more than the mean center. Specifically, candidates listed by this center have a risk of death 63% higher than the mean center (relative HR 1.63) and transplant lowers the risk of mortality 29% more than at the mean center (HR 0.71). The combination of these two effects leads to a large 5-year survival benefit, improving survival (conditional upon reaching transplant) from 6.1% to 75% (+69% absolute gain) for this particular Status 1A patient transplanted after waiting 135 days. In contrast, the patients transplanted at the low-benefit center (right panel) are at lower risk of dying on the wait-list at baseline and transplantation at this center lowers risk less than the mean center. Specifically, candidates listed by this center have 26% lower risk of death than candidates at the mean center (HR 0.74) and transplant offers 60% less improvement in mortality risk than at the mean center (HR 1.60). The combination of these two effects leads to a smaller 5-year survival benefit, improving survival from 28% to 75% (+46% absolute gain) for this particular Status 1A patient transplanted after waiting 162 days.

in post-transplant survival, 95% CI -3.8% to 0.83%) (**Figure 2.5**).

Compared to the mean center, 31 centers (27.4%) had significantly higher survival benefit

Figure 2.5: **Relationship Between Candidate Survival on the Waiting List, Post-transplant Outcomes, and the Benefit of Heart Transplant for Each US Heart Transplant Center**.




There was a significant association between the status-adjusted medical urgency of candidates listed by each center (as measured by the risk of death on the waiting list) and the benefit of transplant measured by 5-year survival benefit (panel A). For every 10% decrease in expected candidate waiting list survival, there was an increase of 6.2% (95% CI, 5.2% to 7.3%) in estimated survival benefit associated with heart transplant. In contrast, there was no significant association between survival after transplant and center survival benefit (survival difference, 1.5% [95% CI, -3.8% to 0.83%]) (panel B)

and 30 centers (26.5%) had significantly lower benefit. At five-years, Status-adjusted post-transplant survival was not significantly different at high and low-benefit centers (77.6% vs. 77.1%, +0.5%; 95% CI, -1.3% to 2.3%) and the Schoenfeld test for a difference in proportional hazards assumption violation between high and low benefit centers was not significant ($p = 0.45$). Estimated candidate survival without transplant was lower at high-benefit centers (29% vs 39%, -10%; 95% CI, -12% to -8.1%), leading to a +10.6% absolute improvement in survival benefit (48.6% vs 38%, +10.6%; 95% CI, 9.3% to 12%).

Compared to low-benefit centers, high-benefit centers used Status 1A qualifying therapies less frequently (50% vs. 63% of recipients, -13%; 95% CI, -15% to -11%) and were less likely

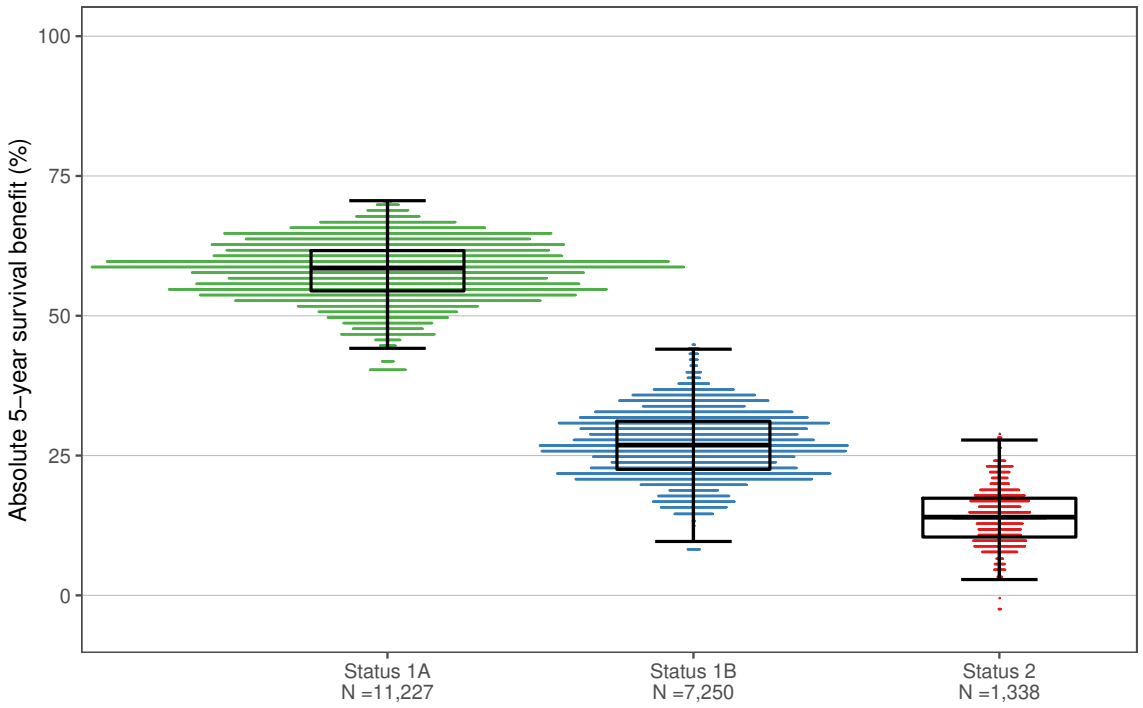
to treat candidates who did not meet hemodynamic requirements for cardiogenic shock with Status 1A qualifying IABPs or high-dose inotropes (25% vs. 31% of recipients, -5.1%; 95% CI, -7.2% to -3%). At the time of transplant, Status 1A recipients at high benefit centers had higher pulmonary capillary wedge pressures (mean 20.1 vs. 18.9 mmHg, +1.2; 95% CI, 0.7 to 1.6; percentage less than 15 mmHg 25% vs. 32%, -7.1%; 95% CI, -9.2% to -4.9%), and worse functional status (55% vs. 42% requiring continuous hospitalization, +13%; 95% CI, 11% to 15%) than low-benefit centers. High-benefit centers transplanted more recipients with acute hemodynamic decompensation requiring mechanical support (38% vs. 31%, +7%; 95% CI, 5% to 9%) and used the "device-related complication" justification less often (20% vs. 37%, -17%; 95% CI, -19% to -15%). At high benefit centers, 35% of Status 1A recipients had a BTT LVAD at the time of transplant compared to 48% of recipients at low benefit centers (difference -14%; 95% CI, -16% to -12%).

### *2.3.4 The Association of Status and Survival Benefit in Three and Six-Tier Allocation Systems*

Under the prior three-status heart allocation system, the most common Status at transplant was 1A (N =11,227, 57%) and heart transplantation for a Status 1A candidate conferred a mean five-year survival benefit associated with 58%, (IQR 54- 62%). Status 1B was the next most common (N = 7,250, 37%) with a mean five-year survival benefit associated with transplant of 27%, (IQR 23- 31%). There were only 1,338 candidates at Status 2 at the time of transplant (7%) with mean five-year survival benefit associated with transplant of 14%, (IQR 10- 17%) (**Figure 2.6**). Overall, within a given priority Status at transplantation, the standard deviation in five-year survival benefit was 5.5% with the majority (76%) of the variation amongst recipients attributable to center-level effects and the remaining 24% attributable to variation in transplant year, waiting time, donor quality and ischemic time.

When retrospectively re-classifying recipients from 2006-2015 based on new Status 1-6

Figure 2.6: **Dot and box plots of estimated 5-year survival benefit associated with heart transplant for adult recipients by 3-status at transplant**




In the box plots, the middle line represents the median, the hinges represent the upper and lower bounds of the interquartile range (IQR), the whiskers represent the smallest and largest observations within 1.5 times the IQR of the hinges, and the points represent outliers beyond the whisker range. There were 11,227 transplant recipients with status 1A and the median benefit from transplant was 59% (IQR, 54%-62%); 7250 transplant recipients with status 1B and the median benefit from transplant was 27% (IQR, 23%-31%); and 1338 transplant recipients with status 2 and the median benefit from transplant was 14% (IQR, 10%-17%).

system, 6,255 Status 1A recipients met Status 3 criteria (56%), 1,254 met Status 2 criteria (11%), and 255 met Status 1 criteria (2%). A total of 3,462 (31%) of Status 1A recipients would have been downgraded to Status 4 because of a violation of the cardiogenic shock requirement at the time of transplant. All 7,250 Status 1B recipients were re-assigned to Status 4. Two-hundred and twenty eight (22%) low priority Status 2 (three-status system) recipients would have been assigned to the higher Status 4 because of restrictive cardiomyopathy, congenital heart disease, hypertrophic cardiomyopathy, or amyloidosis. Model results are

Table 2.4: **Mixed-effect model results with candidates reclassified according to the six-status system**

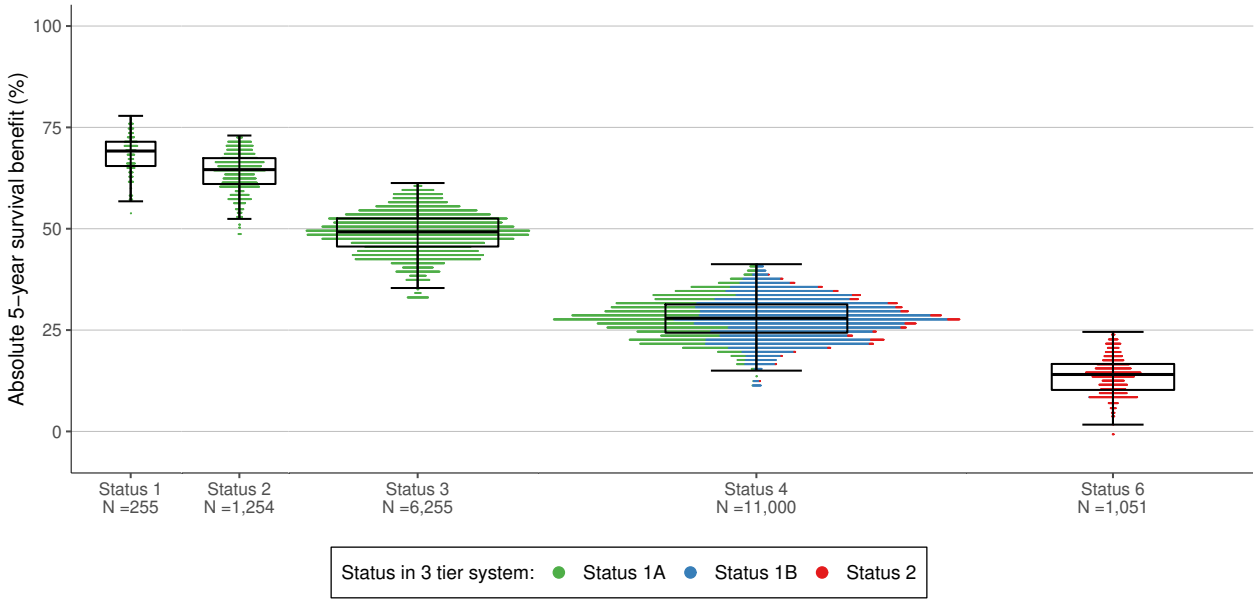
| **Fixed Effects Covariate** | **log hazard ratio** | **95% CI** |
|---|---|---|
| Status 2 | -0.87 | (-1.04, -0.69) |
| Status 3 | -1.53 | (-1.69, -1.36) |
| Status 4 | -2.17 | (-2.32, -2.02) |
| Status 6 | -2.61 | (-2.78, -2.45) |
| Transplantation | -2.92 | (-3.2, -2.65) |
| Transplant: Status 2 | 0.74 | (0.44, 1.04) |
| Transplant: Status 3 | 1.25 | (0.97, 1.53) |
| Transplant: Status 4 | 1.85 | (1.58, 2.12) |
| Transplant: Status 6 | 2.29 | (1.99, 2.58) |
| Donor Risk Score >5 | 0.26 | (0.21, 0.32) |
| Transplant before 2010 | -0.05 | (-0.11, 0.01) |
| **Random effect** | **variance** | |
| Intercept | $\sigma_0^2 = 0.038$ | |
| Transplant | $\sigma_1^2 = 0.045$ | |
| Correlation | $\rho_{01} = -0.386$ | |

Base case is a candidate waiting at Status 1 requiring ECMO, non-dischargeable bi-VAD support, or life-threatening arrhythmias.Compared to the three-status model (**Table 2.3**), the calculated variance in the survival benefit of transplant decreased by 29% from 0.161 to 0.115 on log hazard ratio scale.

reclassifying candidates into six-status tiers are shown in **Table 2.4**. The median hazard ratio for risk of death without a transplant was 1.2 and the median hazard ratio for the risk of death with a transplant was 1.22, both indicating less between-center variation in risk in either state compared to the model containing only status 1A, 1B, and 2 (**Table 2.3**).

Estimated five-year survival benefit associated with transplant ranged from of 68% (Status 1) to 14% (Status 6) (**Figure 2.7**). Compared to the three-status system, the within-status standard deviation of five-year survival benefit decreased from 5.5% to 4.9% but the majority (66%) was still attributable to centers. The between-center variance in the survival benefit of transplant on the log hazard ratio scale transplant decreased from 0.161 to 0.115, corresponding to a reduction in the between-center variance of absolute five-year survival

Figure 2.7: **Distribution of 5-year survival benefit associated with heart transplant for adult recipients by 6-status at transplant**




After re-classification, there were 255 transplant recipients with status 1 and a median benefit from transplant of 69% (IQR, 65%-71%); 1254 transplant recipients with status 2 and a median benefit from transplant of 65% (IQR, 61%-67%); 6,255 transplant recipients with status 3 and a median benefit from transplant of 49% (IQR, 46%-53%); 11,000 transplant recipients with status 4 and a median benefit from transplant of 28% (IQR, 24%-31%); and 1,051 transplant recipients with status 6 and a median benefit from transplant of 14% (IQR, 10%-17%)

benefit from 23% to 16%.

### *2.3.5 Sensitivity Analyses*

The full results of the all robustness checks described in section 2.2.6 are in **Appendix B**. To achieve convergence, the fixed-effects model was constrained to centers with at least 20 observed deaths, which resulted in the exclusion of 9 centers and 260 patients (**Table B.1**). The distribution of center benefit from transplant was visually roughly Gaussian and the Shapiro-Wilk test for non-normality was not significant (p = 0.18, **Figure B.3**). The Spearman correlation between random effect and fixed center estimates was very high

(Spearman correlation = 0.97, **Figure B.4**). Additionally, there was a strong association between center wait-list risk and transplant benefit similar in magnitude to the random-effects model (**Figure B.5**).

In the model containing expanded donor factors, listing year, and candidate demographic variables, the between-center variance in the survival benefit of transplant was 0.14 on the log hazard ratio scale (**Table B.2**). In the model including the BTT LVAD and UNOS region, compared to no BTT LVAD, the presence of a BTT LVAD was associated with lower risk of death wait-list without transplant (log hazard ratio compared to no LVAD -0.49, 95% CI -0.55, -0.42) and lower benefit of from heart transplant (log hazard for interaction between transplant and LVAD 0.68, 95% 0.59, 0.77) (**Table B.3**). In contrast, no UNOS region had a significantly different survival benefit from the mean. The between-center variance in the survival benefit of transplant was 0.12 on log hazard ratio scale, compared to 0.16 in the original model. Finally, in the in the model containing expanded donor factors and listing year, the between-center variance in survival benefit of transplant was 0.15 on the log hazard ratio scale compared to 0.16 in the original three-status model (**Table B.4**).

## 2.4 Discussion

In this registry cohort study of 29,199 adult heart transplant candidates, wide between-center variability was observed in the survival benefit associated with heart transplantation. High-benefit centers had an estimated absolute 5-year survival benefit that was 10.6% higher than low-benefit centers by achieving good post-transplant outcomes for patients with lower cardiac indices, higher pulmonary capillary wedge pressures, worse functional status, and lower estimated five-year survival without transplant. The estimated association between center of listing and survival benefit was lower in the new six-status candidate classification scheme.

Previous estimates of heart transplant survival benefit [Schnitzler et al., 2005; Singh

et al., 2014; Smits et al., 2013] have not considered transplant candidate listing and management practices, implicitly assuming that candidates are the same at each center and receive equivalent benefit from transplantation. The novel mixed-effects approach identified a large group of "low-benefit" centers that prioritized less medically urgent candidates with a lower risk of death without transplant and less potential benefit than the mean recipient. The specific management practices these centers employ support the explanation these centers are more likely to select stable candidates and escalate supportive therapies as needed to achieve Status 1A. Low-benefit centers frequently treated candidates without shock with high-dose inotropes and balloon pumps and used the device-related complication indication for LVAD candidates (who have low urgency without transplant [Wever-Pinzon et al., 2013]). These results suggest that the between center practice variation in the three-status system may have not been consistent with the Final Rule requirement to "avoid grouping together patients with substantially different medical urgency" [24 C.F.R. § 121.8].

The study results also suggest that the priority reassignments in the new six-status system may reduce the variability in survival benefit, potentially through the limited incorporation of objective medical acuity criteria and disease-specific status adjustments. There were relatively few candidates that would have been assigned to the top Status 1-2, which theoretically would alleviate waiting times for the most urgent heart transplant candidates. However, there are reasons the new system may not produce dramatic improvements. There was still significant within-status variation in survival benefit attributable to center practices, implying the six-statuses still do not meet Final Rule guidelines that call for "a sufficient number of categories... to avoid grouping together patients with substantially different medical urgency" [24 C.F.R. § 121.8]. Furthermore, even this limited improvement is contingent on stable utilization of the current set of advanced heart failure therapies by transplant centers. After the last major heart allocation policy change in 2006, there were major national and regional shifts in transplant center practices attributed to increased competition

for donor hearts and new technology [Parker et al., 2018; Nativi et al., 2010; Schulze et al., 2014]. Applying the new cardiogenic shock criteria conservatively a third of Status 1A recipients would not qualify for Status 1-3. The shock criteria will increase heart allocation to those with the most urgent need only if these more stable candidates are actually listed at the lower Status 4 designation. Adding more tiers and complexity to the therapy-based system may simply create more loopholes and inefficiency for transplant programs to manipulate.

In other organ allocation systems, the Final Rule requirements have been met with the implementation of scores based on objective clinical measurements. In liver transplantation, transitioning from a therapy-based system to MELD eliminated unnecessary intensive care unit stays [Snyder, 2010] and allowed identification and transplantation of the sickest candidates based on objective medical criteria [Merion, 2005], likely saving thousands of lives since its implementation in 2002. Whether the new six-status allocation system properly allocates organs in the current era of highly effective LVAD devices as a bridge or alternative to heart transplantation [Krim et al., 2015; Truby et al., 2018] remains to be determined.

In addition, it is appropriate for an allocation system to incentivize programs to list and to transplant candidates whom they believe will have good post-transplant outcomes. The finding that post-transplant outcomes were not significantly different between centers could be interpreted to mean that regulation of these endpoints by the OPTN and CMS [Center for Medicare and Medicaid Services, 2017] has been successful.

### *2.4.1 Limitations*

This study has several limitations. First, increased candidate wait-list mortality risk at a center may be reflective of sub-optimal pre-transplant management rather than the severity of illness in the center's candidate population. However, this is unlikely as high-benefit centers transplanted recipients with objectively worse physiologic data at the time of transplantation. Furthermore, high-benefit centers had no significant difference in post-transplant outcomes

when compared to low-benefit centers despite sicker candidate clinical and physiologic profiles at transplant, suggesting the medical care of the transplant recipient at high-benefit centers is not significantly below average. Second, the benefit associated with heart transplantation clearly extends beyond a five-year survival improvement. Five-year survival benefit was chosen because of the duration of follow-up available for the candidates listed during study period and the restrictions of the semi-parametric survival Cox proportional hazards model approach. Different time frames or survival benefit hazard ratios relative to the mean center may be more appropriate for use in the actual regulation of programs. Third, the efforts to "case-mix" adjust each center's survival benefit estimate may be inadequate, potentially biasing the results of individual centers. Specifically, the models may not be fully capturing donor quality as the donor risk index has limited accuracy [Weiss et al., 2012] or completely accounting for the temporal effects of changing technologies and treatments. However, the sensitivity analysis performed with individual donor factors and a more granular listing year variable had similar between-center variation in the survival benefit of transplant (**Table B.4**), suggesting these factors are not significantly confounding the results of the principal analysis. Fourth, the between-center variation in survival benefit observed in this study may be attributable more to geographic variation in candidate demographics, rather than center selection and treatment practices. However, the minimal reduction in the between-center variation in survival benefit observed after the inclusion of several important demographic variables (**Table B.2**) suggests that the results cannot be attributed simply to variability in potential heart transplant candidates across the country. Fifth, support with BTT LVADs was associated with lower estimated wait-list mortality and lower survival benefit from heart transplantation (**Table B.3**). This finding is consistent with the low wait-list mortality risk for BTT LVAD candidates observed in the French national transplant registry [Jasseron et al., 2017]. These results suggest that, along with practices like the use of high-dose inotrope and balloon pumps in candidates without shock, between-center variation in BTT

LVAD utilization may explain part of the association between transplant center and survival benefit. The allocation system may have to be altered to properly account for BTT LVAD support and maximize the survival benefit gains from heart transplant.

### *2.4.2 Conclusion*

In this registry-based study of heart transplant candidates in the US, the 5-year survival benefit associated with heart transplantation varied across transplant centers. High survival-benefit transplant centers save more lives by listing medically urgent candidates with low wait-list survival and achieving the same post-transplant survival as low benefit centers. The new six-status allocation system has the potential to save more lives, but only if transplant center practices do not evolve in response.

# CHAPTER 3

# BETWEEN-CENTER VARIATION IN HIGH-PRIORITY LISTING STATUS UNDER THE NEW HEART ALLOCATION POLICY

> While physicians' fiduciary duty to "do all they can" for their patients is understandable, the practice of initiating, augmenting, or maintaining therapeutic measures that are not otherwise indicated for the sole purpose of advancing a patient's status on the waitlist is contrary to the OPTN's ethical principles of organ allocation, and is thus not ethically supported by the transplant system
>
> -OPTN/UNOS Ethics Committee, 2018.

## 3.1 Abstract

Under the new US heart allocation policy, transplant centers listed significantly more candidates at high priority statuses (Status 1 and 2) with mechanical circulatory support devices than expected. We determined whether the practice change was widespread or concentrated among certain transplant centers. Using data from the Scientific Registry of Transplant Recipients, we used mixed-effect logistic regression to compare the observed listings of adult, heart-alone transplant candidates post-policy (December 2018 to February 2020) to seasonally matched pre-policy cohort (December 2016 to February 2018). US transplant centers (N = 96) listed similar number of candidates in each policy period (4,472 vs. 4,498) but listed significantly more at high priority status (25.5% vs. 7.0%, p < .001) than expected. Adjusted for candidate characteristics, 91 of 96 (94.8%) centers listed significantly more candidates at high-priority status than expected, with the unexpected increase varying from 4.8% to 50.4% (interquartile range [IQR]: 14.0%-23.3%). Centers in OPOs with highest Status 1A transplant rate pre-policy were significantly more likely to utilize high-priority status under the new policy (OR: 9.7, 95% CI 6.3 - 15.0, p = .01 compared to transplant rate <70%). The new heart allocation policy was associated with widespread and significantly variable changes in transplant center practice that may undermine the effectiveness of the new system.

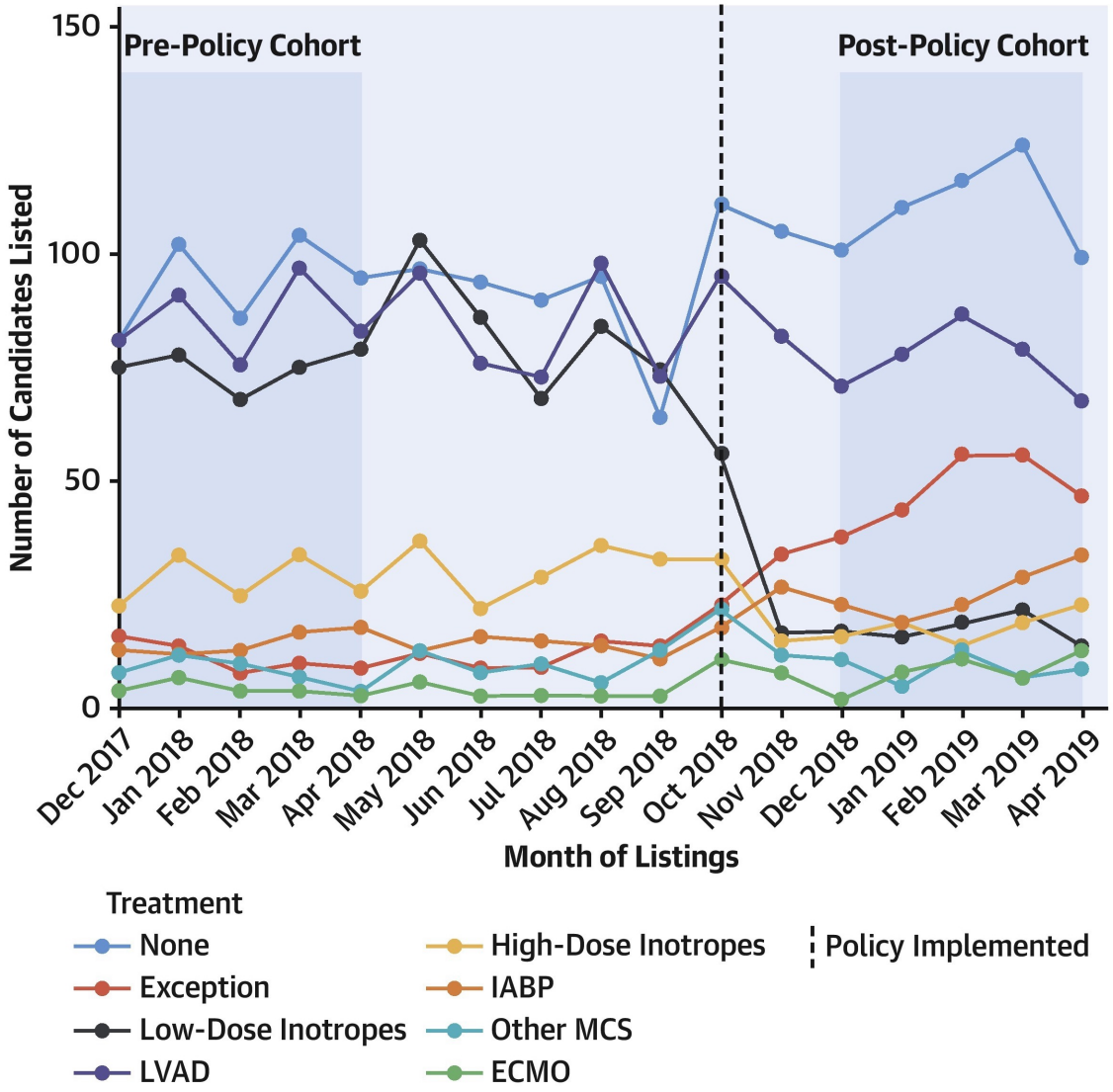
## 3.2 Introduction

In October 2018, the Organ Procurement and Transplant Network (OPTN) implemented a new heart allocation policy designed to improve compliance with the U.S. Department of

Health and Human Services Final Rule on organ transplantation [24 C.F.R. § 121.8]. In addition to increasing the geographic sharing of donor hearts, the policy expanded the number of therapy-based Status levels from 3 to 6, intending to improve candidate risk stratification, reduce exception requests, and accommodate changing mechanical circulatory support (MCS) practices [OPTN/UNOS Thoracic Committee, 2017]. The Status tier changes were intended to decompress the highest priority status level by splitting Status 1A into Status 1-3 and adding strict hemodynamic requirements. The OPTN further enhanced the priority of Status 1 and 2 by assigning these tiers a larger first geographic allocation circle compared to Status 3 (500 nautical miles compared to 250 nautical miles). If treatment practices remained stable, only 6% of candidates were expected to be initially listed at Status 1 or Status 2 [Parker et al., 2020a]. However, transplant centers used exception requests, extracorporeal membrane oxygenation (ECMO), and intra-aortic balloon pumps (IABPs) at much higher rates than anticipated (**Figure 3.1**), listing over 25% of candidates at Status 1 or Status 2 [Parker et al., 2020a; Huckaby Lauren V. et al., 2020; Varshney et al., 2020; Hanff et al., 2020].

However, it is unknown if this practice shift was uniform or concentrated amongst a subgroup of centers. Past heart allocation policy changes have had widely variable effects across the country. The first expansion of geographic sharing of donor hearts in 2006 was associated with marked regional differences in left ventricular assist device (LVAD) use as a bridge to transplant [Schulze et al., 2014]. Under the old heart allocation system, transplant centers in large urban areas and competitive Organ Procurement Organizations (OPOs) were more likely to use IABPs or high-dose inotropes when their candidates did not meet cardiogenic shock hemodynamic criteria [Parker et al., 2018]. Substantial between-center variation in listing practice under the new heart allocation policy without meaningful difference in candidate characteristics would suggest concerning disconnection between medical severity and access to transplantation.

Figure 3.1: **Trends in Treatments Used to List Adult Heart Transplant Candidates During the Transition to the New Heart Allocation Policy**




The new heart allocation system significantly expanded the geographic sharing of donor hearts, effectively giving the new Status 1 and 2 levels even higher priority. Therefore, understanding why and how centers are changing their practices in response to the new heart allocation policy is critical to ensure the broad and fair distribution of donor hearts. In this observational cohort study, we aimed to

1. confirm that the high Status 1 and Status 2 listing rates have persisted over time

2. estimate each center's expected and observed high-priority status listing rate

3. identify local OPO characteristics associated with between-center variation in policy response

## 3.3 Methods

### *3.3.1 Data source and study population*

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services, provides oversight to the activities of the OPTN and SRTR contractors. Since this was a secondary analysis of a prospectively obtained de-identified cohort, this study was deemed exempt by the University of Chicago Institutional Review Board.

We identified all adult, active, heart-only candidates newly added to the wait-list between December 1, 2016 and February 28, 2020 in the SRTR dataset. We constructed a study population from two seasonally matched cohorts from before and after the implementation of the new policy. The pre-policy cohort consists of all qualifying candidates listed between December 1, 2016 and February 28, 2018. The post-policy cohort consists of qualifying candidates listed between December 1, 2018 and February 28, 2020 (**Figure 3.2**). We excluded candidates listed inactive, for multi-organ transplant, or by a small transplant center with fewer than 10 candidate listings per year in either the pre-policy or post-policy periods. To assess for large changes in the volume of listings in each policy period, we compared center listing volumes in the two cohorts using a mixed-effect Poisson regression.

### *3.3.2 Classification of Status 1-6 and Primary outcome*

The primary outcome of this study was the probability of high-priority status listing, defined as initial listing at Status 1 or Status 2. The new allocation system divides the old Status 1A group into Status 1, 2, and 3. We designated only Status 1 and 2 as high-priority because these statuses have larger geographic priority than Status 3 (500 nautical miles compared to 250 nautical miles) and because of previously described increases in ECMO and IABP utilization (Status 1 and 2 qualifying therapies) and decreases in high-dose inotrope use (Status 3 qualifying therapy) [Parker et al., 2020a; Huckaby Lauren V. et al., 2020; Varshney et al., 2020; Hanff et al., 2020]. Candidates in the post-policy cohort had their official status assignment at the time of listing directly extracted from the SRTR dataset. To determine the expected distribution of candidates under the new allocation policy, we classified pre-policy candidates into Status 1-6 using the treatments and hemodynamic values recorded in their listing justification forms. Importantly, we retrospectively applied the hemodynamic portion of the cardiogenic shock criteria to the pre-policy cohort. Pre-policy candidates were reclassified into Status 1-4 if they received qualifying therapeutic intervention and met necessary hemodynamic requirements (if applicable). Candidates originally assigned to Status 1A by exception requests are reclassified into Status 3. This reclassification method was previously employed in OPTN's simulations and several other observational studies, full details of our reclassification procedure are available in the **Appendix A**.

### *3.3.3 Model of center listing practices*

As candidate-level transplant data are clustered within transplant centers, we analyzed estimated the probability of high-status listing using a mixed-effects logistic regression model with a center-level random intercept and random policy effect. For center $i$ listed at center $j$.

$$log(\frac{P(Y_{ij}=1)}{(1-P(Y_{ij}=1)}) = \beta_{0i} + \beta_{1i} * Policy_{ij} + X_{ij}\beta \tag{3.1}$$

With random effect structure

$$\begin{aligned} \beta_{0i} &= \beta_0 + \nu_{0i} \\ \beta_{1i} &= \beta_1 + \nu_{1i} \\ (\nu_{i0}, \nu_{i1}) &\sim N(0, \Sigma) \\ \Sigma &= \begin{pmatrix} \sigma_0^2 & \sigma_{01} \\ \sigma_{01} & \sigma_1^2 \end{pmatrix} \end{aligned} \tag{3.2}$$

This model has the following terms

- an indicator term for the time period of listing $Policy_{ij} \in (0, 1)$
- fixed-effect intercept $\beta_0$ and policy effect $\beta_1$
- a random intercept for each center $\nu_0$ which allows each center to have a distinct pre-policy high-status listing rate
- a random policy effect $\nu_{1i}$ which allows the policy to have heterogenous effects across centers
- A correlation structure $\Sigma$ that allows for unstructured correlation between the random effects
- A vector of candidate covariates $X_{ij}$ that are likely to influence the listing status choosen by the transplant center

This model structure allows the pre-policy probability of high-status listing and post-policy probability of high-status listing to vary at the center level and for the pre and post-policy probability of high status listing at a given center to be correlated.

The candidate covariates $X_{ij}$ included demographic, medical and socioeconomic candidate-level characteristics between policy periods that might explain changes in transplant center practices. Specifically, candidate characteristics $X_{ij}$ included age, race, history of smoking, educational status, state of employment at the time of listing, blood type, body mass index(kg/$m^2$), diagnosis, renal function (mL/min/1.73$m^2$), history of diabetes, functional status, cardiac index(mL/kg/$m^2$), pulmonary capillary wedge pressure (mmHg), and payor. Functional status was recorded on Karnofsky 11-point performance status scale [Karnofsky and Burchenal, 1949]. Body mass index, pulmonary wedge pressure, and cardiac index were treated as quartiles to capture non-linear relationships with the outcome. Continuous variables were mean centered and the most prevalent category was chosen as the base level for each discrete variable. We performed a Chi-square test to assess whether the distribution of candidates across status assignments differed across policy periods.

### *3.3.4 Case-mix adjusted center high status listing rates*

We computed case-mix adjusted pre and post policy high-status listing rates by extending Center for Medicare and Medicaid services methodology for hospital reporting [Shahian et al., 2005; Shahian and Normand, 2008; Krumholz et al., 2008]. After estimation of equation (3.1) via maximum likelihood [Hedeker et al., 2000], we generated predicted probabilities of high status listing for every candidate in the dataset using the estimated fixed effect coefficients and the empirical bayes (median) of the center effects

$$p_{ij0} = \frac{1}{1 + exp(\hat{\beta}_0 + \hat{\nu}_0 i + X_{ij}\hat{\beta})} \tag{3.3}$$

$$p_{ij1} = \frac{1}{1 + exp(\hat{\beta}_0 + \hat{\nu}_0 i + X_{ij}\hat{\beta} + \hat{\beta}_1 + \hat{\nu}_1 i)} \tag{3.4}$$

We then calculated "expected" probabilities for each patient in the pre and post period with just the fixed effects alone, removing the center effects from the equation.

$$e_{ij0} = \frac{1}{1 + exp(\hat{\beta}_0 + X_{ij}\hat{\beta})} \tag{3.5}$$

$$e_{ij1} = \frac{1}{1 + exp(\hat{\beta}_0 + X_{ij}\hat{\beta} + \hat{\beta}_1)} \tag{3.6}$$

For a given center $i$, a observed to expected rate $r_i \in (0, \infty)$ is calculated by the ratio of the predicted and expected probabilites of all $j$ patients listed at that center

$$r_i = \frac{\sum_j p_{ij}}{\sum_j e_{ij}} \tag{3.7}$$

To put this quantity based on a probability scale, a final case-mix adjusted probability is calculated by multiplying the observed to expected rate by the average rate of the outcome in the entire population, or

$$\bar{p}_i = r_i * Pr(Y_i j = 1) \tag{3.8}$$

To calculate a case-mix adjusted rate for each policy period, we computed an $r_{0i}$ with candidates listed pre-policy and an $r_{1i}$ for candidates listed post policy, then multiplied by the corresponding population mean.

$$\bar{p}_{i0} = r_{i0} * Pr(Y_i j = 1 | policy = 0) \tag{3.9}$$

$$\bar{p}_{i1} = r_{i1} * Pr(Y_i j = 1 | policy = 1) \tag{3.10}$$

We generated standard errors for (3.9) and (3.10) via bootstrapping resampling within centers [Efron, 1979; Field and Welsh, 2007].

### *3.3.5 Explanatory center-level variables*

We investigated three potential transplant center and OPO characteristics for association with listing behavior in the post-policy period: transplant center volume, the level of competition in the OPO, and Status 1A transplant rate in the pre-policy period. We measured local competition for organs by the number of transplant centers in an OPO. An OPO was considered competitive if it consisted of three or more transplant centers, a level of competition previously associated with more aggressive treatment practices [Parker et al., 2018]. Finally, a high rate of transplantation at Status 1A candidates in an OPO indicates that candidates listed at high-priority status had greater access to deceased donor organs. We hypothesized that high Status 1A transplant rate in the pre-policy period would predict larger practice changes in post-policy period as centers sought to maintain high transplant rate for their most prioritized candidates. We added these covariates to model (3.1)

$$log(\frac{P(Y_{ij}=1)}{(1-P(Y_{ij}=1)}) = \beta_{0i} + \beta_{1i} * Policy_{ij} + X_{ij}\beta + \alpha W_i * Policy_{ij} \tag{3.11}$$

Where $W_i$ are the potential modifiers of the policy effect described above. The random effect structure of this model was the same as in (3.2).

## 3.4 Sensitivity Analyses

We performed two sensitivity analyses. First, we computed the odds ratio of high-priority status listing during the first and second half of the post-policy study period, using seasonally matched pre-policy cohorts as reference, to determine whether the impact of the allocation policy changed over time. Then, we changed the outcome of (3.1) to determine the association between policy period and probability of exception for high priority statuses (i.e. Status 1A pre-policy, Status 1 and 2 post-policy), adjusting for candidate characteristics.

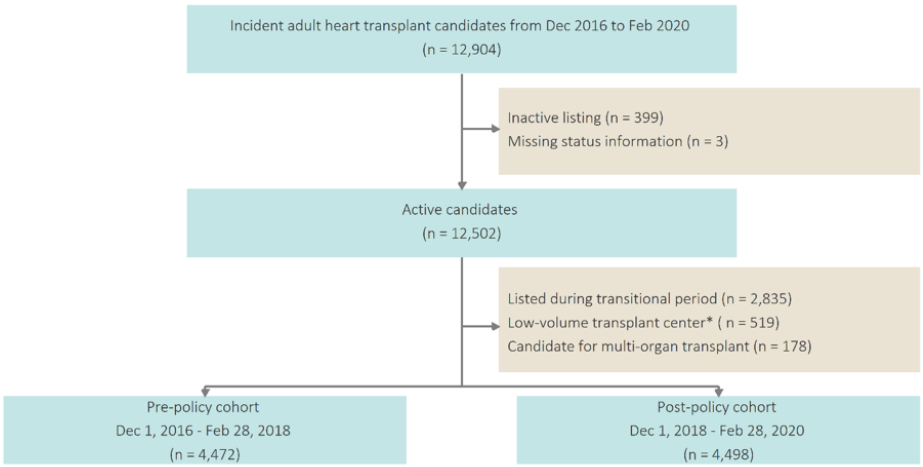
All analyses were conducted using R version 3.6.1 (The R Foundation for Statistical Com-

puting, Vienna, Austria) and Stata version 16 (Stata-Corp, LLC, College Station, Texas). All statistical testing was 2-sided with a p-value threshold of $< 0.05$.

## 3.5 Results

### *3.5.1 Study cohort characteristics*

Figure 3.2: **STROBE Patient selection Flow diagram**




A transplant center is considered low-volume and its listed candidates dropped from analyses if the center had fewer than 10 active listings per year in 2017, 2018, or 2019, or those with fewer than 10 active listings in total in either of the two policy eras (Dec 1, 2016 - Feb 28, 2018, or Dec 1 ,2018 - Feb 28, 2020)

A total of 12,904 active, adult heart-only candidates were listed from December 1st, 2016 and February 28th, 2020. We excluded 399 candidates for inactive listing, 3 candidates for missing data, 519 candidates listed at low volume centers, and 178 multi-organ candidates. There were 4,472 patients in the seasonally matched pre-policy period (December 1st, 2016 to February 28th, 2018) compared with 4,498 in the post-policy period (December 1st, 2018 to February 28th, 2020) (**Figure 3.2**). The number of candidates listed at each transplant center did not differ significantly between policy period on average (rate ratio = 1.00, 95% CI: 0.99 – 1.00). **Table 3.1** compares candidate characteristics between the pre-policy and

post-policy cohort.

Overall, candidate characteristics remained largely unchanged across policy periods. Candidates listed in the post-policy period had a slightly lower cardiac index (absolute difference, -0.03 L/min/m2; 95% CI: -0.05 L/min/m2 to -0.01 L/min/m2), and worse functional status (absolute difference in % with severe impairment, +3.3%; 95% CI: 1.2% to 5.4%). Mean pulmonary capillary wedge pressure was comparable between the two policy periods (absolute difference, -0.2 mmHg; 95% CI: -0.58 mmHg to 0.15 mmHg).

### *3.5.2 Distribution of Priority Statuses in the Pre and Post Policy Period*

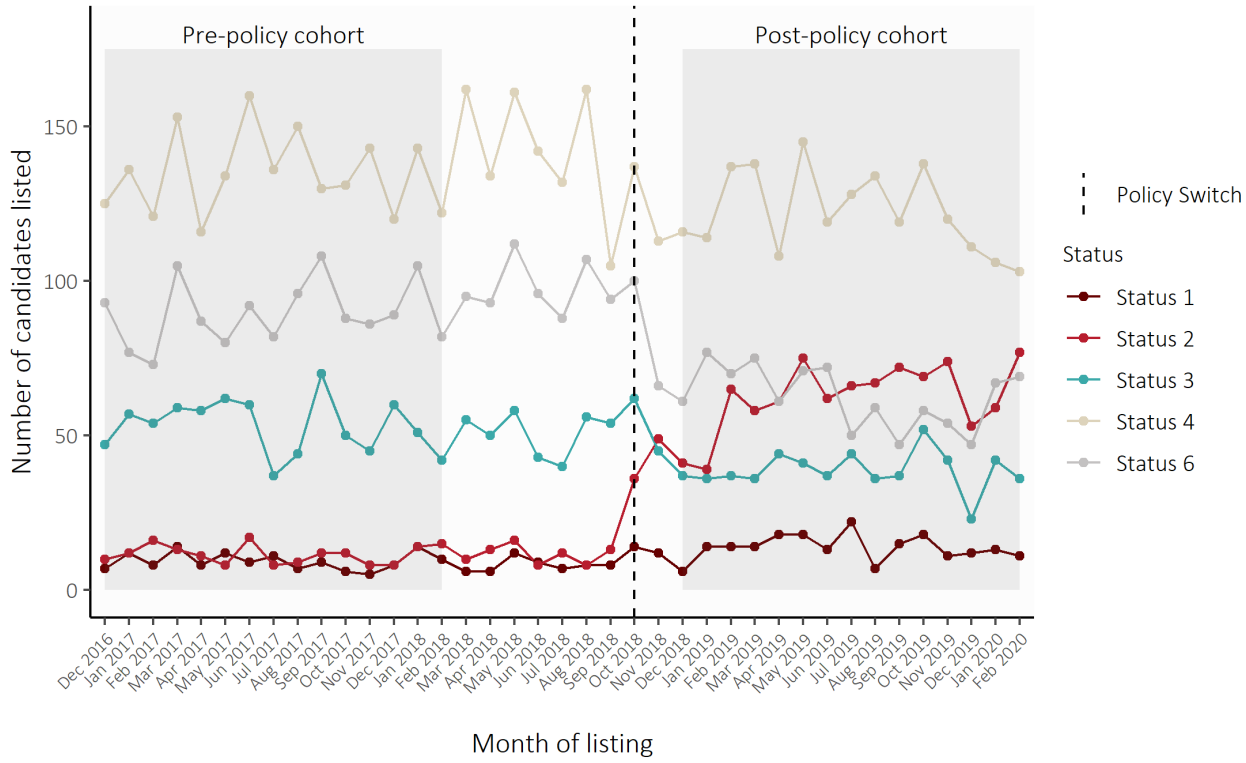
Trends in expected and observed Status 1-6 listings during the transition to the new heart allocation policy are depicted in **Figure 3.3**. After applying the new status justification to candidates listed in pre-policy period, the expected status distribution was 140 Status 1, 173 Status 2, 796 Status 3, 2,020 Status 4, and 1,343 Status 6. The observed status distribution after implementing the new policy was 206 Status 1, 938 Status 2, 580 Status 3, 1836 Status 4, and 938 Status 6, ($p < 0.001$ compared to expected by $\chi^2$ test, **Figure 3.4**). There were more high-priority listings than expected, with +1.4% more in Status 1 (95% CI: 0.7% to 2.2%) and +17% more in Status 2 (95% CI: 15.7% to 18.3%). In contrast, there were -4.91% fewer Status 3 (95% CI: -6.39% to -3.42%), -4.35% Status 4 (95% CI: -6.4% to -2.3%), and -9.2% Status 6 listings (95% CI: -11% to -7.4%). Status 5 is for multi-organ candidates who were excluded from the analysis.

### *3.5.3 Justification for high-status listing in the post-policy period*

Among the 313 candidates who met Status 1 or Status 2 criteria in the pre-policy cohort, centers listed 75 with ECMO, 99 with IABP, 32 with LVAD with device malfunction, and 107 with other MCS. There were 91 Status 1A exception requests. Among the 1,144 candidates listed Status 1 or 2 in the post-policy cohort, centers listed 112 with ECMO, 462 with IABP,

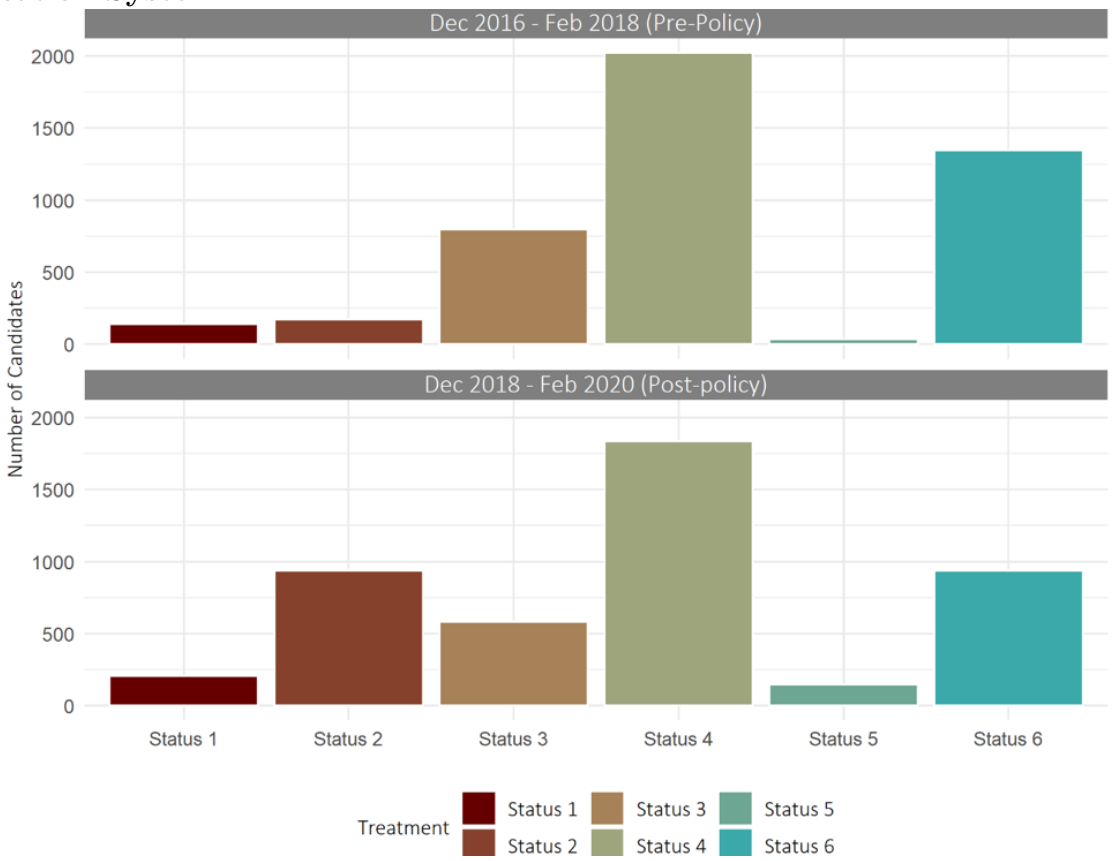
25 with LVAD with device malfunction, and 139 with other MCS. There were 64 Status 1 exception requests and 342 Status 2 exception requests (**Figure 3.5**). Transplant centers used ECMO 1.48 times more often (95% CI 1.10- 2.02), IABP 4.6 times more often (95% CI 3.73 – 5.82), and exception requests 4.4 times more often (95% CI 3.52- 5.63) than expected.

Figure 3.3: **Trends in expected and observed priority statuses during transition to the new heart allocation policy**




Trends in the number of adult heart transplant candidates listed each month, as stratified by Status at initial listing. Colors correspond with observed status assignment in the post-policy period (after Oct 2018), and reclassified expected status assignment in the pre-policy period (before Oct 2018). Status 5 is for multi-organ transplant candidates, which were excluded from the analyses. Dashed line represents October 2018, when the new allocation policy was implemented.

Figure 3.4: **Expected and Observed Status Distribution in the New U.S. Heart Allocation System**

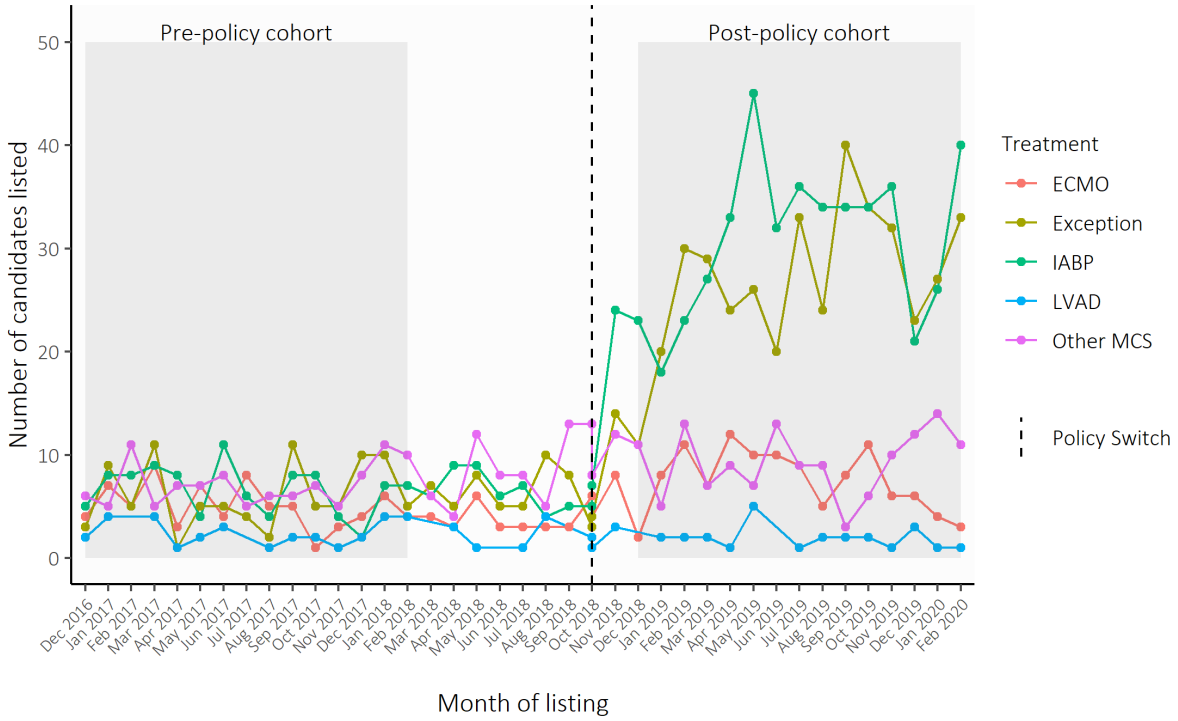



Histogram of the Expected and Observed Status Distribution in the New U.S. Heart Allocation System. Colors correspond with observed status assignment in the post-policy period (after Oct 2018), and reclassified expected status assignment in the pre-policy period (before Oct 2018). Status 5 is for multi-organ transplant candidates, which were excluded from the analyses. $p < 0.001$ for significantly different observed distribution compared to expected by $\chi^2$ test.

### *3.5.4 Between-center variation in high-priority status listing across policy periods*

In total, 7% of candidates met high-priority status criteria (Status 1 and 2) in the pre-policy cohort compared to the 25% candidates listed at high-priority in the post-policy cohort. Accounting for center-effects with the mixed-effects logistic regression but before adjustment for candidate covariates, the odds of listing at high-priority status were 5-fold higher in the

Figure 3.5: **Trends in high-priority status MCS justifications and exceptions during transition to the new heart allocation policy**




Trends in the number of adult heart transplant candidates listed at high-priority statuses in each month, as stratified by treatment at initial listing. Prior to the implementation of the new allocation policy in October 2018, colors correspond to the treatments candidates reclassified as Status 1 and 2 or qualified for Status 1A through exception requests. After October 2018, colors correspond to the treatments used to justify Status 1 and Status 2 listings. Dashed line represents October 2018, when the new allocation policy was implemented. ECMO: extra-corporeal membrane oxygenation; IABP: intra-aortic balloon pump; LVAD: left ventricular assistive device (with device malfunction to qualify for Status 1 or 2); Other MCS: other mechanical circulatory support.

post-policy period than expected (OR 5.23, 95% CI 4.26-6.42 estimated with mixed-effect model without any candidate level covariates). After estimating model (3.1) controlling for candidate level variables, the odds was 6-fold higher (adjusted OR 6.35, 95% CI: 5.08-7.94) ( **Table 3.2**). The base case in model **Table 3.2** is patient with blood type A, male, height <167cm, weight < 72kg, BMI 24-28 kg/$m^2$, non-diabetic, non-smoking, functional status 40%, white, private insurance, with post-secondary education, GFR $\leq$ 47.6 mL/min/1.73 $m^2$, with dilated cardiomyopathy.

Table 3.2: **Mixed-effects logistic regression model of high-status listing**

| **Fixed Effect** | **log odds ratio** | **lower 95% CI** | **upper 95% CI** |
|---|---|---|---|
| Post-policy listing | 1.848 | 1.626 | 2.071 |
| Age at listing | -0.000 | -0.007 | 0.006 |
| Female | -0.052 | -0.212 | 0.108 |
| Race | | | |
| Black | -0.141 | -0.320 | 0.038 |
| Hispanic | 0.079 | -0.174 | 0.331 |
| Other | 0.120 | -0.215 | 0.456 |
| History of smoking | -0.170 | -0.317 | -0.024 |
| Working for income | | | |
| Missing | -0.121 | -0.624 | 0.382 |
| Yes | -0.064 | -0.248 | 0.120 |
| Education level | | | |
| High school | 0.068 | -0.085 | 0.222 |
| Less than high school or other | 0.117 | -0.168 | 0.402 |
| Weight (kg) | | | |
| 72-84 | 0.334 | 0.084 | 0.583 |
| 82-97 | 0.034 | -0.309 | 0.377 |
| >97 | 0.243 | -0.214 | 0.700 |
| Missing | 1.92 | -0.639 | 4.480 |
| Height (cm) | | | |

Mixed-effects logistic regression model of high-status listing (continued)

| **Fixed Effect** | **log odds ratio** | **lower 95% CI** | **upper 95% CI** |
|---|---|---|---|
| 168-175 | 0.007 | -0.196 | 0.212 |
| 175-181 | 0.045 | -0.201 | 0.292 |
| >181 | -0.046 | -0.325 | 0.231 |
| BMI (kg/m2) | | | |
| <24 | 0.118 | -0.064 | 0.300 |
| 29-31 | -0.005 | -0.197 | 0.188 |
| >32 | -0.087 | -0.297 | 0.122 |
| Missing | 0.412 | -0.392 | 1.216 |
| Blood type | | | |
| AB | 0.052 | -0.280 | 0.384 |
| B | 0.185 | -0.021 | 0.390 |
| O | -0.023 | -0.178 | 0.133 |
| Diagnosis | | | |
| Ischemic cardiomyopathy | -0.038 | -0.220 | 0.144 |
| Other | -0.239 | -0.467 | -0.011 |
| Restrictive cardiomyopathy | -0.192 | -0.413 | 0.028 |
| Renal Function | | | |
| 47.6 – 62.5 | -0.144 | -0.340 | 0.051 |
| 62.5 – 79.8 | -0.167 | -0.365 | 0.032 |
| >79.8 | 0.085 | -0.114 | 0.284 |
| History of DM | -0.181 | -0.344 | -0.018 |
| Functional Status | | | |
| Limited Impairment | -2.580 | -2.859 | -2.301 |

Mixed-effects logistic regression model of high-status listing (continued)

| **Fixed Effect** | **log odds ratio** | **lower 95% CI** | **upper 95% CI** |
|---|---|---|---|
| Moderate Impairment | -2.466 | -2.739 | -2.194 |
| Unknown | -1.125 | -1.695 | -0.555 |
| Cardiac Index (L/min/m2) | | | |
| 1.75 - 2.10 | -0.652 | -0.849 | -0.455 |
| 2.10 - 2.51 | -0.724 | -0.935 | -0.514 |
| >2.51 | -0.457 | -0.663 | -0.251 |
| Missing | 0.170 | -0.158 | 0.499 |
| Pulmonary capillary wedge pressure (mmHg) | | | |
| <11 | -0.246 | -0.491 | -0.000 |
| 18-24 | 0.490 | 0.277 | 0.703 |
| >24 | 0.702 | 0.494 | 0.910 |
| Missing | 1.437 | 1.159 | 1.715 |
| Payor | | | |
| Medicaid | -0.280 | -0.504 | -0.056 |
| Medicare | -0.257 | -0.429 | -0.086 |
| Other | 0.140 | -0.202 | 0.482 |
| Intercept | -1.873 | -2.258 | -1.488 |

| **Random effect** | **variance** |
|---|---|
| Intercept | $\sigma_0^2 = 0.609$ |
| Policy | $\sigma_1^2 = 0.382$ |
| Covariance | $\sigma_{01} = -0.199$ |

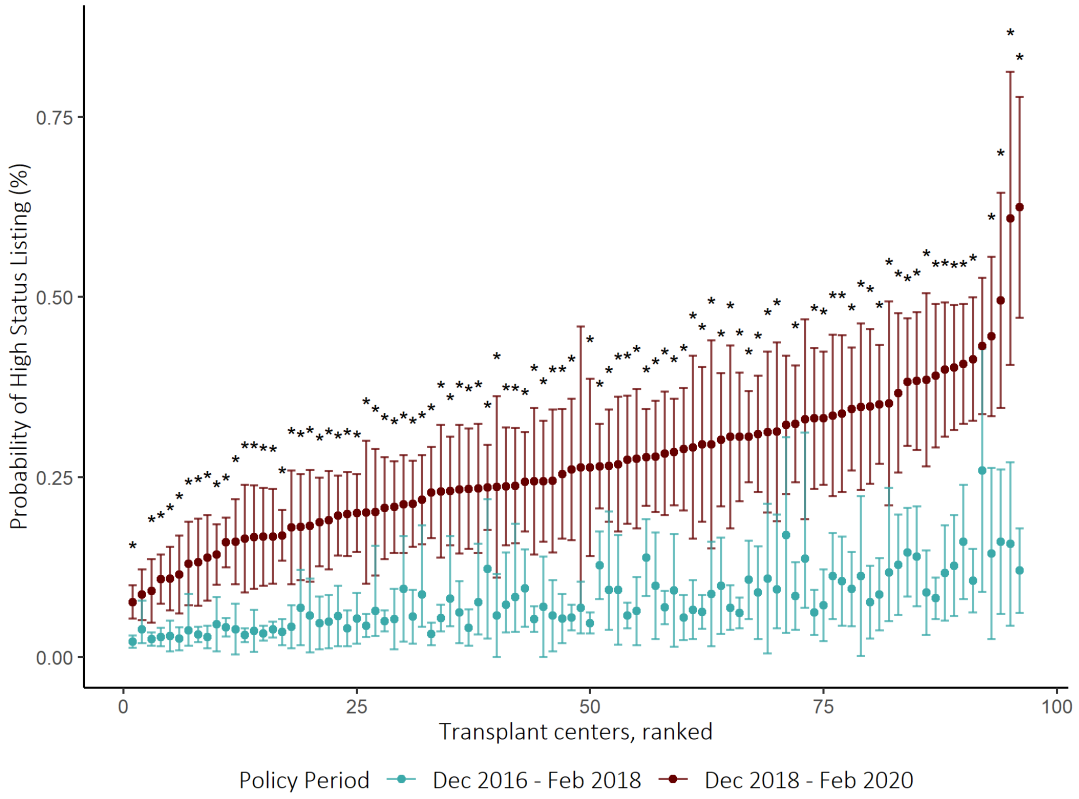
After case-mix adjustment, the expected pre-policy high-priority status listing rate varied from 2.1% to 25.9% (IQR: 4.9% to 9.9%) across centers. The observed high-status listing rates in the post-policy period varied from 7.6%, to 62.4% (IQR: 20.0% to 32.5%). Ninety-one (94.8%) centers listed significantly more patients at high-priority status than expected (**Figure 3.6**). The observed rate of high-priority status listing exceeded expectations by substantially different rates between transplant centers, ranging from +4.8% to +50.4%, (Inter-quartile range: 14.0% to 23.3%). A total of 88 centers (92%) listed 10% more candidates at high status than expected and 39 centers (41%) listed 20% more candidates at high status than expected.

**Figure 3.7** compares the geographic variation in the rate of high-priority status listing before and after implementing the new heart allocation policy. After adjusting for candidate-level characteristics and weighting by listing volume at constituent transplant centers, the rate of high-priority status listing increased in all OPOs. While the magnitude of the increase differs substantially across the country, there is no obvious geographical pattern (**Figure 3.8**). Areas of the greatest rates of high-priority status listing in the post-policy period not only include densely populated urban areas, but also many OPOs with large geographic size and low population density.

### *3.5.5 Association of center and OPO level variables and the change in high-status listing*

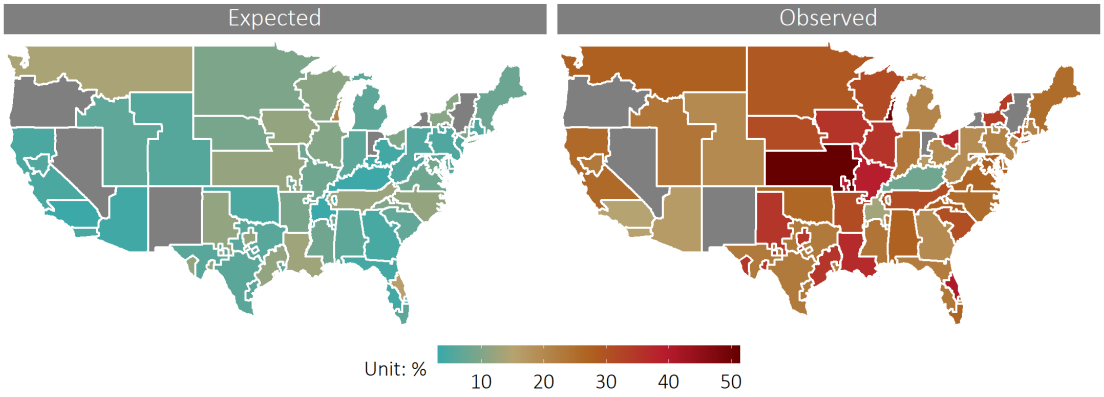
Among the three center-level predictors tested, only Status 1A transplant rate in the pre-policy period was significantly associated with greater chance of high-priority status listing than expected (**Table 3.3**). The odds of high-priority status listing was 9.73 times (OR: 9.73; 95% CI: 6.67 to 14.19) higher for transplant centers in OPOs with a high pre-policy Status 1A transplant rate (>82%), in comparison to 5.53 times for those in OPOs with low (<72%) of Status 1A transplant rates (OR: 5.53; 95% CI: 3.89 to 7.86), (p=0.01 for

Figure 3.6: **Between-center variation in high-priority status listing after implementation of the new heart allocation policy**



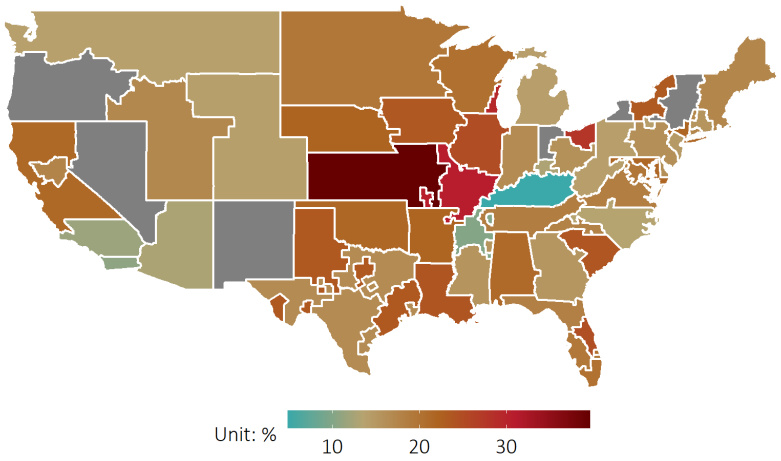

Caterpillar plot showing the estimated probability of being listed at high-priority (Status 1 or Status 2) at each transplant center, adjusting for candidate characteristics. Colors correspond to the predicted rate of being listed in high-priority status based on status reclassification of pre-policy candidates (green) and the rate based on observed utilization of high-priority statuses after the policy change (red). The expected rates (green) represent the counterfactual scenario in which center practices did not change in response to the new heart allocation policy. The 95% CIs were constructed via bootstrapping. Transplant centers were ranked based on predicted probability of high-priority listing after policy update. Asterisks indicate centers with statistically significant change in the estimated probability of listing in Status 1 or 2 before and after implementing the new policy. The observed rate significantly exceeded the expected rate in 91 out of 96 centers (94.8%).

Figure 3.7: **Geographical Variation in high-priority status listing after implementation of the new heart allocation policy**



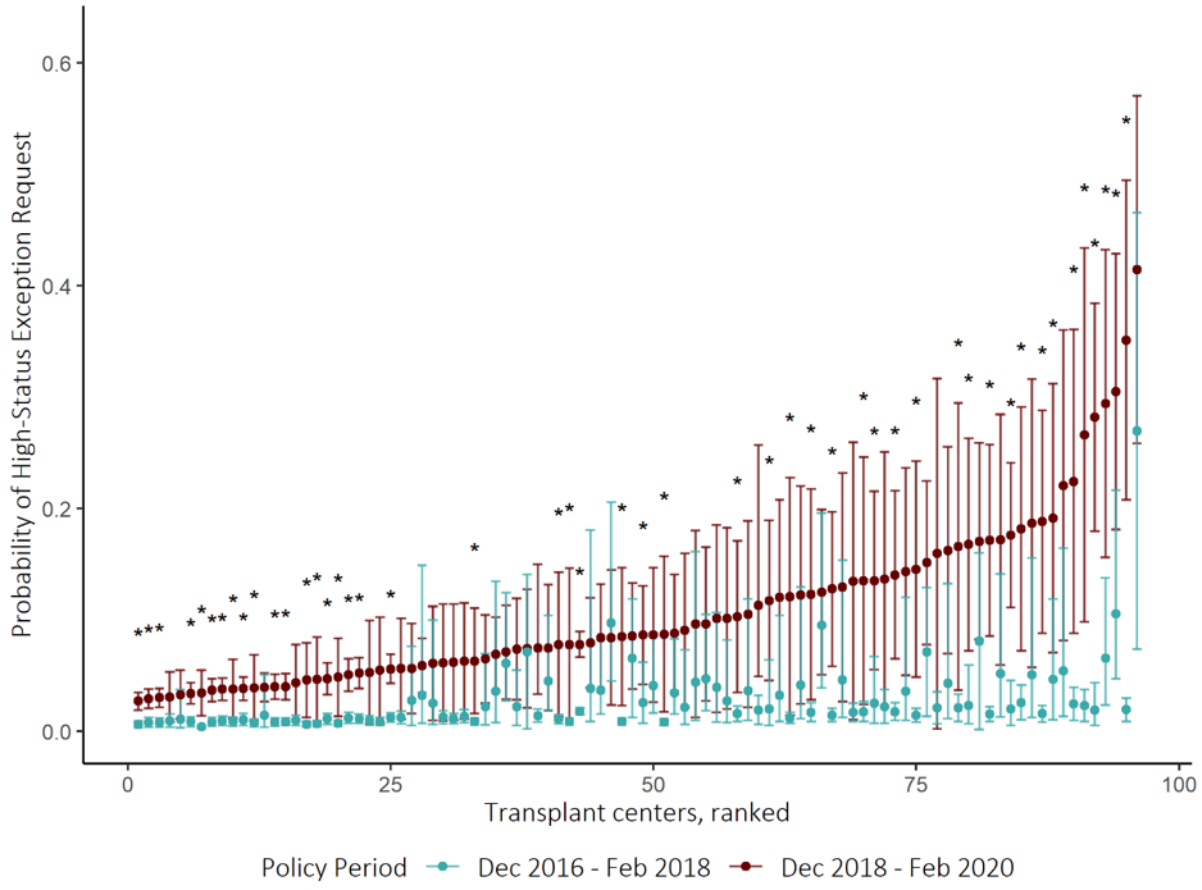

National variation in the rate of being listed at high priority (Status 1 or Status 2), estimated from multilevel logistic regression model adjusted for candidate level characteristics. Rates are aggregated at the Organ Procurement Organization (OPO) level, the first local level of organ allocation in the United States. Colors correspond to the estimated probability the average candidate is listed at high priority status (Status 1 or 2). Map on the left displays the expected rate of high-priority listing in each OPO, generated from applying the new allocation scheme to candidates listed between Dec. 2016 and Feb. 2018. Map on the right displays the case-mix adjusted rates of Status 1 and 2 listing observed at each OPO from Dec. 2018 to Feb. 2020, after the new allocation scheme was implemented.

Figure 3.8: **Excess utilization of high-priority Status in the US after implementation of the new heart allocation policy**




Colors indicate absolute difference between observed utilization of high priority listing status (Status 1 or Status 2) compared to expected rates, as estimated from multilevel logistic regression model, adjusting for candidate level characteristics (**Table 3.2**). Rates are aggregated at the Organ Procurement Organization (OPO) level, the first local level of organ allocation in the United States. The difference is positive for all OPOs. Expected utilization is constructed by applying the new allocation scheme to heart transplant candidates listed prior to the policy's implementation (Dec. 2016 – Feb 2018). The observed utilization of high priority status is the case-mix adjusted rates of Status 1 and 2 listing observed at each OPO from Dec. 2018 to Feb. 2020, after the new allocation scheme has already been implemented.

Figure 3.9: **Between-center variation in probability of exception request for high-priority status after implementation of the new heart allocation policy**




Caterpillar plot showing the estimated probability of utilizing exception request to qualify for high-priority status (Status 1A pre-policy, Status 1 or Status 2 post-policy) at each transplant center, adjusting for candidate characteristics. Colors correspond to the estimated rate of exception request for Status 1A among pre-policy candidates (green) and the rate exception request for Status 1 and 2 combined after the policy change (red). The 95% CIs were constructed via bootstrapping. Transplant centers were ranked based on predicted probability of exception request after policy update. Asterisks indicate centers with statistically significant change in the estimated probability of exception request before and after implementing the new policy. The observed rate significantly exceeded the expected rate in 91 out of 96 centers (94.8%).

interaction).

Table 3.3: **Mixed-effects logistic regression model of high-status listing with center level variables**

| **Fixed Effect** | **log odds ratio** | **lower 95% CI** | **upper 95% CI** |
|---|---|---|---|
| Post-policy listing | 1.708 | 1.357 | 2.060 |
| Center-level policy interaction terms | | | |
| Center volume | -0.005 | -0.013 | 0.003 |
| >3 centers in OPO | -0.031 | -0.373 | 0.311 |
| Status 1A transplant rate | | | |
| 70-75% | 0.141 | -0.292 | 0.575 |
| 75-82% | -0.128 | -0.619 | 0.364 |
| > 82% | 0.568 | 0.135 | 1.000 |
| Candidate covariates coefficients suppressed | | | |
| Constant | -1.888 | -2.276 | -1.501 |
| **Random effect** | **variance** | | |
| Intercept | $\sigma_0^2 = 0.597$ | | |
| Policy | $\sigma_1^2 = 0.280$ | | |
| Covariance | $\sigma_{01} = -0.169$ | | |

### *3.5.6 Sensitivity Analyses*

The relationship between policy change and high-priority status listing was not sensitive to passage of time since policy implementation. In the first half of the post-policy study period (Dec 1, 2018 – July 16, 2019), the odds of high-priority status listing was 5.17 times (95%

CI: 3.99 – 6.69) greater than in seasonally matched pre-policy study period (Dec 1, 2016 – July 16, 2017). In the second half of the post-policy study period (July 17, 2019 – Feb 28, 2020), the odds ratio was 7.92 (95% CI: 5.85 to 10.70).

The effect of policy period on the probability of exception request mirrored its impact on the overall utilization of high-priority statuses. After accounting for candidate characteristics and center-level effects, transplant centers are 5.81 times more likely to utilize exception request at the time of initial listing to qualify for high priority statuses under the new policy (95% CI: 3.73 to 9.04). The probability of using exception request to qualify for high-priority status increased significantly in 47 out of 96 transplant centers. (**Figure 3.9**). The high-priority exceptions increased by substantially different rates between transplant centers, ranging from +2.1% to +33%, (Inter-quartile range: 3.5% to 14.5%).

## 3.6 Discussion

In this study of 8,970 adult heart transplant candidates from 96 transplant centers in the United States, the number of high-priority status (Status 1 or 2) listings was higher than expected after implementation of the new heart allocation policy. The odds of high-priority listing was more than five times greater than expected in the post-policy period, without accompanying explanatory changes in candidate characteristics. Transplant centers all over the country listed more candidates than expected at high-priority status, mainly by using more IABP support and exception requests than anticipated. This practice change was especially pronounced for transplant centers in OPOs with a high Status 1A transplant rate before the policy change, suggesting that the combination of the new status tiers and expanded geographic sharing of donor hearts prompted these centers to dramatically modify their listing practices to continue transplanting high-priority candidates at the same rate. The impact of the policy change on high-priority status listing was not a temporary "bolus effect", but rather was driven by persistent and increasing trends towards more aggressive

treatment practices.

Two of the policy's major intended effects were to alleviate the crowding of candidates "with disparate risks in the most urgent status" and reduce the number of exception requests. Our study suggests that the policy has had limited success in achieving these goals [OPTN/UNOS Thoracic Committee, 2017]. Whereas the previous highest priority Status 1A accounted for 45% of all heart transplant candidates listed in 2016, the new highest priority status (Status 1) only accounts for 4.6% of candidates after the policy update. However, our study shows that "crowding" did not disappear with the new policy. It became a shared phenomenon between Status 1 and 2 and attributable to more ECMO, IABP, and exception requests than expected. In particular, the increase in the number of exception requests varied substantially across transplant centers unaccompanied by changes in candidate characteristics. This observation suggests a mismatch between the requirements for high-priority listing and the perceived urgency of transplantation by the listing physicians. On one hand, exceptions may be serving an essential role in identifying very urgent candidates whose level of urgency is not adequately measured by hemodynamic measures required by the new allocation policy. On the other hand, the large number of exception requests could undermine the gatekeeping effect of cardiogenic shock hemodynamic requirements by allowing less urgent candidates access to the expanded geographic priority of Status 1 and 2. The motivations underlying the rise in exception requests are not definitively known, and are likely center-specific. Furthermore, data regarding the auditing process of exception requests in terms of percentage of acceptances or denials is not publicly available at time. Either scenario is concerning for the effectiveness of the new status tiers, indicating a limited ability to identify the most urgent heart transplant candidates. Future studies examining reasons for exception request will be critical in understanding the increasing popularity of its usage. The development of evidence-based objective criteria for high-priority listing could reduce the volume of exception requests.

Our results have several important implications for future policy. First, it suggests that the higher rates of aggressive treatment represent deliberate practice changes, rather than artifacts of data collection and codification. Second, although the need to "treat to the priority" has always existed for transplant centers in highly competitive environments, our study suggests that all transplant centers – even those in traditionally non-competitive environments – have started to more aggressively elevate the priority status of their candidates under the new allocation scheme [Stevenson et al., 2016; Parker et al., 2018]. It is likely that high-priority status listing became more valuable under the new allocation scheme due to the expansion in the geographic sharing of donor hearts. The priority for a donor organ is no longer based on OPO affiliation but instead relies on the physical distance between the transplant center and donor hospital. With procurement areas now overlapping for many more centers, the competition for scarce donor hearts may have increased for many transplant centers even though the total number of donors or candidates remained constant within an OPO [Goff et al., 2020].

Finally, while it is undeniable that listing practices were different from expectations under the new allocation policy, it is impossible to judge the motivation behind an individual physician's listing and treatment decision based on registry data. In an allocation system based primarily on therapy, the increased use of exception requests could simultaneously indicate greater extent of "gaming" or effective advocacy for patients denied access to transplantation by the unvalidated, and perhaps excessively strict, hemodynamic requirements [Khazanie Prateeti and Drazner Mark H., 2019]. Similarly, given the decreased likelihood of expedited heart transplant of a patient stable with an LVAD at Status 4, centers may inevitably be motivated to utilize temporary mechanical support strategies in favor of direct transplant. This may be especially true in patients with blood type (Type O) or a larger body mass index, in whom a bridge to transplant strategy in a timely manner becomes a challenge without an exception, use of 30-day time or LVAD-related complication to allow

for an upgrade to Status 3.

Refining the criteria for high-priority status extensions is another area where the allocation policy could be potentially improved. For example, centers could be required to transition patients supported with temporary MCS to durable LVADs after a short interval if medically possible. These potential policy improvements should be the focus of future research. To be clear, our results do not imply that the new heart allocation policy was a failure. Indeed, the recently demonstrated reduction in wait-list mortality implies the policy was an improvement over the status quo [Kilic et al., 2021]. Nonetheless, the marked variation between transplant centers in response to the new allocation policy observed in our study has significant implications for the future of the U.S. organ allocation system and reenforces the fundamental limitations of a primarily therapy-based allocation system [Parker et al., 2019]. While more follow-up is required to closely evaluate the impact of these center practice changes on the critical outcomes of wait-list and post-transplant mortality, work must continue to build an objective, score based allocation system resistant to changes in treatment practices [Jasseron et al., 2017; Hong et al., 2011]. Such a system is vital to direct donor hearts to the most urgent candidates and save the most lives.

### *3.6.1 Limitations*

Our study has a few limitations. First, we had to retrospectively classify candidates into pre-policy candidates into Status 1-6 using treatments and hemodynamics at listing. However, our previously published approach ([Parker et al., 2017a, 2018, 2019]) follows the methodology of the OPTN in simulation studies of the policy [OPTN/UNOS Thoracic Committee, 2017]. Second, our study only controlled for observed candidate characteristics. This means that while the absolute number and observed characteristics of candidates in the two policy periods was similar, the pool of candidates being listed post-policy may have been different in some unmeasured way. We also cannot account for unobserved longitudinal trends in

practice patterns or heart transplant candidate characteristics that are unrelated to the new allocation policy. Unobserved changes in the candidates' clinical or social needs over time could explain some of the increased between-center variation in listing practices. Third, the pre-specified center-level variables we tested for association with high-priority status listing may fail to capture important competitive forces experienced by centers, especially given the transition to the new distance-based donor heart distribution system. Finally, candidates can be initially listed at a low priority status and move up after receiving additional therapy. Since we only examined the initial status given to newly listed candidates, we did not capture wait-list dynamics in the current study. This should be examined in future work.

## 3.7 Conclusion

Under the new heart allocation policy, almost all U.S. transplant centers listed more candidates at high priority status than expected, but there was substantial variability between centers. Centers in OPOs with a high Status 1A transplant rate in the pre-policy period changed their practices more than average, potentially continuing to transplant high-priority candidates at high rates. The widespread higher than expected utilization of high-priority listing statuses could prevent fair ranking of candidates based on the urgency of need, and compromise the fair and efficient distribution of scarce donor hearts.

| | **Dec 2016 - Feb 2018 (Pre-Policy) n=4,472** | **Dec 2018 - Feb 2020 (Post-policy) n=4,498** | **Difference * [Confidence Interval]** |
|---|---|---|---|
| Age at Listing (SD) | 53 (13) | 53 (13) | -0.4 [-1 to 0.2] |
| Female (%) | 1156 (26) | 1200 (27) | 0.8 [-1.0% to 2.6%] |
| History of Diabetes | 1300 (29) | 1278 (28) | -0.7% [-2.6% to 1.2%] |
| Race/Ethnicity | | | |
| White | 2818 (63) | 2723 (61) | -2.5% [-4.5% to -0.5%] |
| Black | 1072 (24) | 1156 (26) | 1.7% [-0.1% to 3.5%] |
| Hispanic | 380 (8) | 430 (10) | 1.1% [-0.1% to 2.3%] |
| Other | 202 (5) | 189 (4) | -0.3% [-1.1% to 0.5%] |
| Smoking History (%) | 1992 (45) | 1870 (42) | -3% [-5.0% to -1.0%] |
| Working for Income (%) | 870 (20) | 1039 (24) | 3.6% [ 1.9% to 5.3%] |
| Education Status (%) | | | |
| College | 2566 (57) | 2480 (55) | -2.2% [-4.3% to -0.1%] |
| High School | 1642 (37) | 1618 (36) | -0.7% [-2.7% to 1.3%] |
| Less than high school or other | 264 (6) | 400 (9) | 3% [ 1.9% to 4.1%] |
| BMI (kg/m2) | 27.86 (4.94) | 28.10(5.20) | 0.24 [0.02 to 0.46] |
| Blood Type (%) | | | |
| A | 1692 (38) | 1676 (37) | -0.6% [-2.6% to 1.4%] |
| AB | 213 (5) | 204 (5) | -0.2% [-1.1% to 0.7%] |
| B | 638 (14) | 656 (15) | 0.3% [-1.2% to 1.8%] |
| O | 1929 (43) | 1962 (44) | 0.5% [-1.6% to 2.6%] |
| Diagnosis (%) | | | |
| Dilated cardiomyopathy, non-ischemic | 1947 (44) | 1940 (43) | -0.4% [-2.5% to 1.7%] |
| Ischemic cardiomyopathy | 1354 (30) | 1239 (28) | -2.7% [-4.6% to -0.8%] |
| Restrictive cardiomyopathy | 618 (14) | 700 (16) | 1.7% [ 0.2% to 3.2%] |
| Other | 553 (12) | 619 (14) | 1.4% [ 0.0% to 2.8%] |
| Creatinine | 66 (35) | 67 (41) | 0.8 [-0.8 to 2.4] |
| Functional Status | | | |
| Limited Impairment (70-100)% | 1096 (25) | 975 (22) | -2.8% [-4.5% to -1.1%] |
| Moderate Impairment(50-60%) | 1065 (24) | 923 (21) | -3.3% [-5.0% to -1.6%] |
| Severe Impairment ($\leq$40%) | 2212 (49) | 2373 (53) | 3.3% [ 1.2% to 5.4%] |
| Unknown | 99 (2) | 227 (5) | 2.8% [ 2.0% to 3.6%] |
| Cardiac Index, mL/kg/m2 | 2.18 (1) | 2.15 (1) | -0.03 [-0.05 to -0.01] |
| PCWP, mmHg | 18 (9) | 18 (9) | -0.2 [-0.6 to 0.2] |
| Payor | | | |
| Medicaid | 609 (14) | 615 (14) | 0.1% [-1.3% to 1.5%] |
| Medicare | 1493 (33) | 1364 (30) | -3.1% [-5.0% to -1.2%] |
| Other | 175 (4) | 273 (6) | 2.2% [ 1.3% to 3.1%] |
| Private | 2195 (49) | 2246 (50) | 0.9% [-1.2% to 3.0%] |
| Pertinent Justification at Listing | | | |
| ECMO | 75 (2) | 112 (2) | 0.8% [ 0.2% to 1.4%] |
| LVAD | 1229 (27) | 1105 (25) | -2.9% [-4.7% to -1.1%] |
| Other MCS | 107 (2) | 139 (3) | 0.7% [ 0.0% to 1.4%] |
| High-dose inotropes | 445 (10) | 210 (5) | -5.3% [-6.4% to -4.2%] |
| Low-dose inotropes | 206 (5) | 462 (10) | -18.6% [-20% to -17%] |
| Exception Requests | 141 (3) | 852 (19) | 15.8% [14% – 17%] |
| None | 1192 (27) | 1371 (30) | 3.8% [1.9% – 5.7%] |
| 90-Day wait-list Outcomes | | | |
| Mortality | 137 (3) | 68 (2) | -1.6% [ -2.2% to -1%] |
| Transplantation | 1539 (34) | 2226 (50) | +15.1% [ 13% to 17%] |

Table 3.1: **Candidate characteristics in the study cohort**

# CHAPTER 4

# SAVING MORE LIVES WITH DECEASED DONOR KIDNEY ALLOCATION

## 4.1 Abstract

Deceased donor organs are the definitive treatment for end-stage organ failure, but unfortunately, this life-saving treatment is absolutely scarce. The organ shortage is most severe for deceased donor kidney transplantation. Only a quarter of candidates receiving a transplant within five years of listing, and a newly listed candidate is more likely to die or be removed from the list than receive a transplant. Despite this, the current kidney allocation system largely ignores medical urgency, and transplant programs discard 1 in 5 deceased donor kidneys recovered for transplantation due to perceived low benefit. We use modern survival analysis methodology to model the survival benefit of deceased donor kidney transplantation and present the results in an easy-to-use web application. This model has the potential to 1) improve shared decision-making between transplant programs and patients when making accept-reject decisions and 2) identify medically urgent transplantation candidates to align kidney allocation policy with federal law. Incorporating survival benefit into deceased donor kidney allocation has the potential to save more lives and reduce racial/ethnic disparities in kidney transplantation.

## 4.2 Introduction

Deceased donor organs are absolutely scarce. Thousands of patients fortunate enough to get listed will die on the waiting list every year, 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" [24 C.F.R. § 121.8]. 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 [Krakauer et al., 2005a; Egan et al., 2006; Merion et al., 2005; Singh et al., 2014; Parker et al., 2019], kidney transplantation dramatically improves recipient survival compared to remaining on dialysis [Wolfe et al., 1999; Schnitzler et al., 2005; Orandi et al., 2016; Cohen et al., 2017]. 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 [United States Renal Data System, 2020].

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 [Hart et al., 2021], a rate far higher than Europe [Aubert et al., 2019]. While centers have been more likely to accept hepatitis C-positive donors over time, donors with a lower Kidney Donor Profile Index (KDPI) score have a substantially higher probability of discard. Less than 5% of kidneys from a donor with a KDPI percentile of $< 35\%$ were discarded compared to 20% of kidneys from a donor with KDPI 35-85% and 60% of D kidneys from donors with KDPI$> 85\%$ [Hart et al., 2021]. 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 5-years post-transplant compared to waiting for a better organ for the vast majority of patients [Merion, 2005; Massie et al., 2014; Bowring et al., 2018]. 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 [Wey et al., 2018]. 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 model of deceased donor kidney transplantation (DDKT) that improves upon the existing literature by using modern survival analysis methodology to account 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-transplant period, specifically designed so the model output would easily translate into an accessible end-application that presents more information than KDPI and allows transplant programs and patients to compare deceased donor kidney offers. We developed this improved survival benefit model of deceased donor kidney transplantation 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 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 would 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 lives saved with transplantation 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 [Hart et al., 2021; Melanson et al., 2017], significant structural inequities remain embedded in the system. Black patients are less likely to be listed for transplantation and have less than half the chance of receiving preemptive transplantation compared to White patients [Zhang et al., 2018; King et al., 2019]. 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 [Kulkarni et al., 2019]. Therefore, determining how incorporating survival benefit into the Kidney Allocation System could mitigate or exacerbate structural racism in kidney transplantation is critical.

## 4.3 Methods

### *4.3.1 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 extracted the candidate covariates included in the Estimated Post-Transplant Survival Model (EPTS): age, dialysis time, diabetic status, and history of previous organ transplant [OPTN/UNOS, 2021a]. 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 are not recorded by transplant programs.

For candidates that survived long enough to receive 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 [Massie et al., 2014]. The first observation begins at the time

Table 4.1: **Sample of four patient records in final analytic dataset**

| Patient | Center | Age | Dialysis years | time start | time stop | Status | KDRI | Ischemic Time | Dead |
|---|---|---|---|---|---|---|---|---|---|
| 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 | 1.59 | 12 | 0 |
| 480003 | 78 | 79 | 8.79 | 2570 | 2720 | Transplant | 1.59 | 12 | 0 |
| 480003 | 78 | 79 | 8.79 | 2720 | 4001 | Transplant | 1.59 | 12 | 0 |
| 500064 | 351 | 50 | 3.02 | 0 | 206 | Waiting | | | 0 |
| 500064 | 351 | 50 | 3.59 | 206 | 236 | Transplant | 1.1 | 14 | 0 |
| 500064 | 351 | 50 | 3.59 | 236 | 386 | Transplant | 1.1 | 14 | 0 |
| 500064 | 351 | 50 | 3.59 | 386 | 2476 | Transplant | 1.1 | 14 | 1 |
| 648174 | 33 | 74 | 0.80 | 0 | 117 | Waiting | | | 1 |

- 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 with 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

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 4.1**)

### *4.3.2 Survival benefit model*

The primary outcome was the survival benefit of deceased donor kidney transplantation at 5-years post-transplantation estimated with a mixed-effects Cox proportional hazard model with transplant treated as a time-dependent predictor variable [Parker et al., 2019; Ripatti and Palmgren, 2000; Therneau et al., 2003]. This model accounts for the non-proportional hazard of transplantation by estimating the hazard of death in four distinction time periods:

1) pre-transplant, 2) within 30 days post-transplant, 3) day 30-180 post-transplant a nd 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 [Bae et al., 2019]. 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 partial likelihood with the `coxme` package in `R` [Therneau, 2018].

To calculate the absolute estimated survival with and without transplantation, we multiplied each patient's time-dependent predicted hazard ratio with an extension of the Nelson-Aalen estimator of the baseline hazard (**Figure C.1**) following the approach described in **Chapter 2**. This technique allows the survival benefit to be quantified on a clinically relevant and intuitive scale. We calculated the 5-year survival with and without transplant and survival benefit for all recipients in our study cohort and then estimated the mean, median, and intraquartile range of all three outcomes. See **Appendix C** for technical description of the model and additional methodology.

### *4.3.3 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 survival benefit. To specifically evaluate the compliance of the top

20% KDPI to the top 20% EPTS policy with the Final Rule, we compared the survival benefit 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 survival benefit of a preemptive transplant compared to the benefit of transplanting a patient on dialysis.

### *4.3.4 Association of transplant center with survival benefit*

Following the approach employed by the Center for Medicare and Medicaid Services [**??**], we used the empirical Bayes estimates of each center's intercept and transplant effect to calculate the average survival benefit across kidney transplant programs, case-mix adjusting for donor variables. Specifically, we estimated the survival benefit 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 incredibly large pool of potential candidates for transplantation [Saran et al., 2020].

### *4.3.5 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 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 period of time before receiving a deceased donor kidney transplant (see **Appendix C** for details)

### *4.3.6 Association of race/ethnicity with survival benefit*

We calculated the summary statistics of all model covariates by racial/ethnic group and estimated the average survival benefit for first-time solid organ recipients by racial/ethnic group for our study cohort. 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 prior to the start of dialysis) for each racial/ethnic group from 2000-2010.

All analyses were performed 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.

## 4.4 Results

### *4.4.1 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 2051 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 4.2**, **Table 4.3**). 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.

### *4.4.2 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

Table 4.2: **Candidate characteristics at 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 4.3: **Recipient characteristics at time of transplantation**

| **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 (%)

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 C.2**). The full model results are in **Table C.1** 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 5-years. For the N = 64,589 in the study cohort, transplantation was associated with an improvement in estimated 5-year survival from 50.8% to 82.4%, an absolute benefit of 31.6%. This benefit corresponds to one life saved within 5-years for every 3.16 transplants.

### *4.4.3 The association of survival benefit with medical urgency and Estimated Post-Transplant Survival (EPTS)*

There was wide variation in the survival benefit of transplantation (IQR 24% ,39%), driven by significant variation in risk of death with and without transplantation by candidate characteristics (**Table C.1**). The 25th percentile recipient by survival benefit had an estimated 5-year survival without transplantation of 68% which improved to 91% with transplantation, an absolute survival benefit of 24%. The 75th percentile recipient had a lower absolute estimated 5-year survival without transplantation 37% and with transplantation 76%, however a much larger benefit from transplantation 39% (**Figure 4.1**).

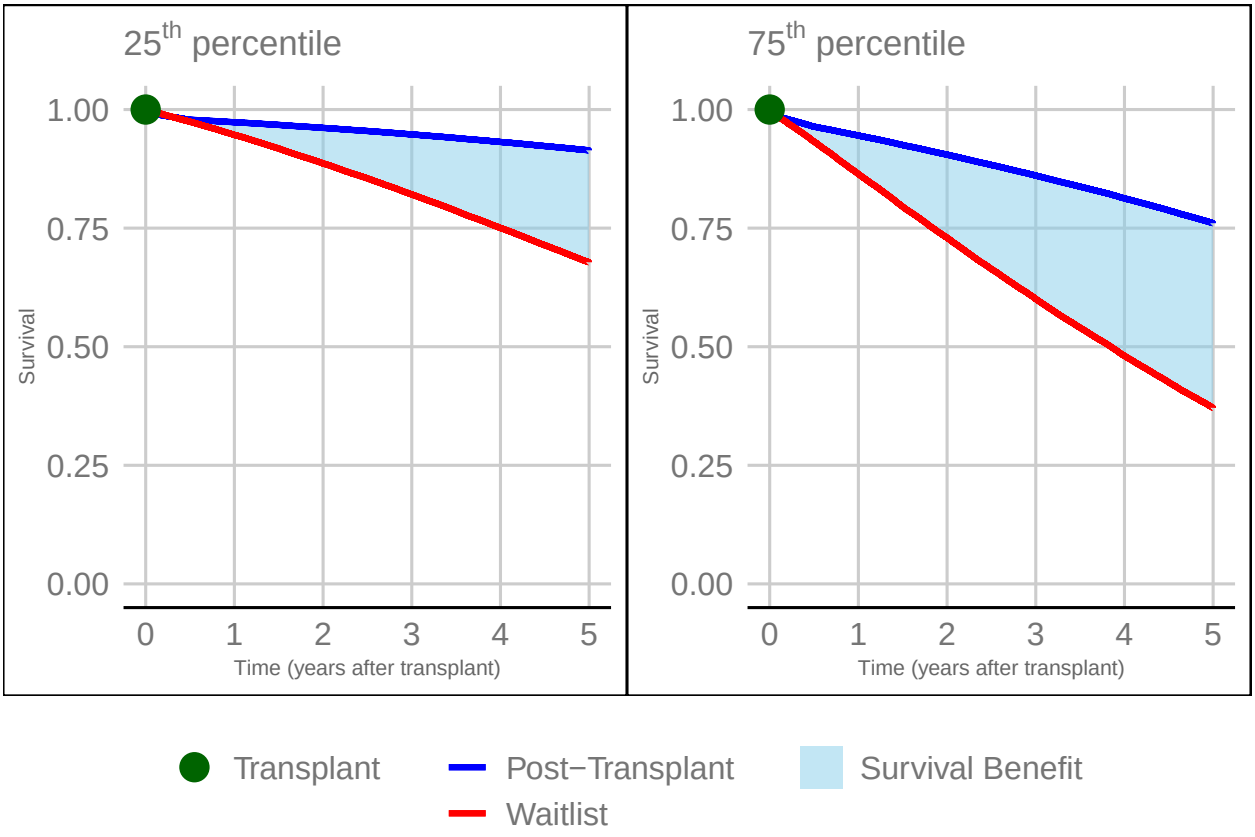
Overall, there was a strong positive correlation between the risk of death without a transplant (medical urgency) and survival benefit ($\rho = 0.83$) (**Figure 4.2**, **Figure 4.3**). The maximum benefit from deceased donor kidney transplantation was a 70% absolute improvement in 5-year survival when 5-year mortality without a transplant was was 93%. This corresponds to a 10 lives saved with every 14 transplants (within the first 5-years).

There was a strong correlation between EPTS score (2019 %) and survival benefit (0.54), meaning that recipients with low EPTS % had *lower* survival benefit (**Figure 4.4**). There was a strong correlation between EPTS scores and 5-year mortality without transplantation

0.79, meaning recipients with lower EPTS % tended to be less medically urgent.

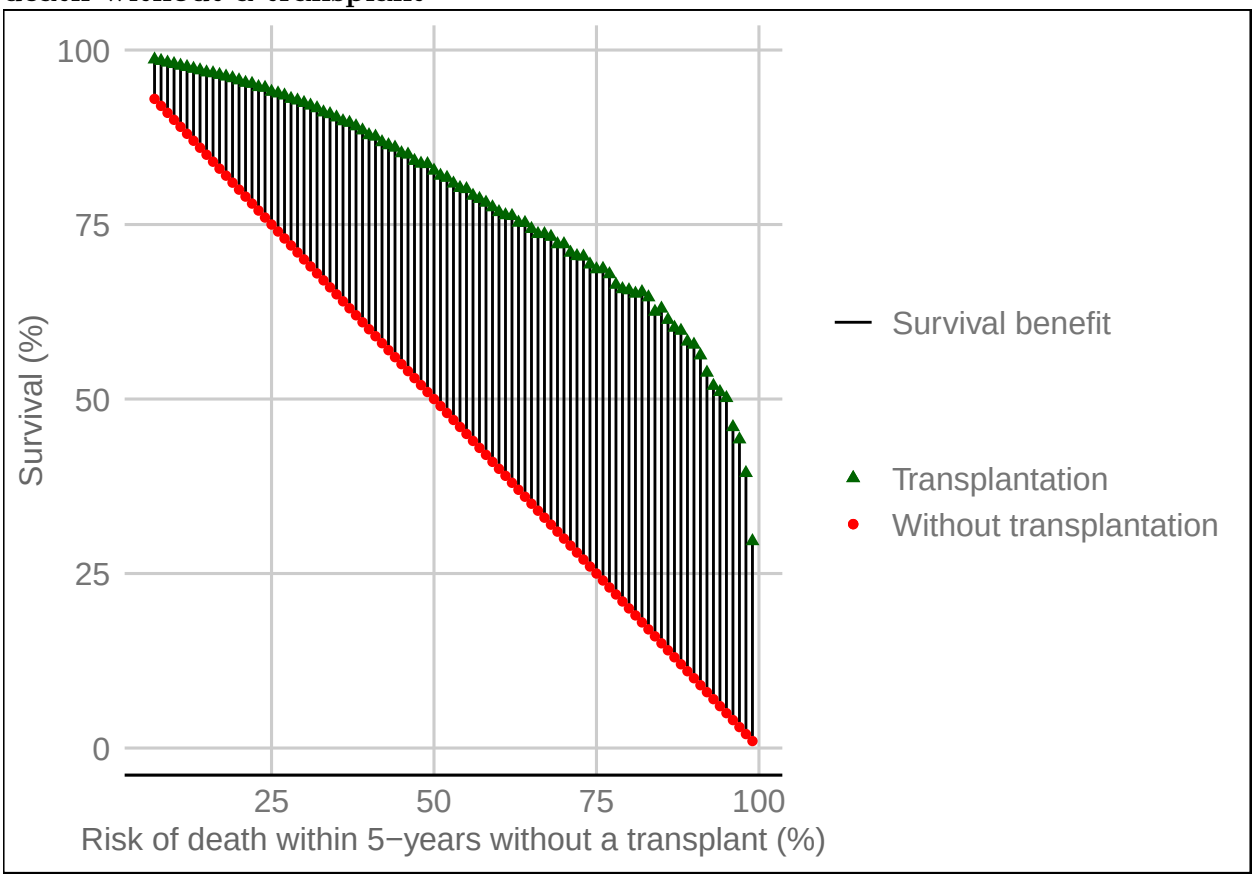
All candidate covariates that generate higher EPTS scores (age, history of diabetes, dialysis time, and history of previous transplant) were associated with greater medical urgency and had strong, independent associations with survival benefit (**Table C.1**). On average, each year of recipient age increased 5-year survival benefit by 0.4%, a history of previous solid organ transplant by 3.1%, and a history of diabetes by 3.2%. Each additional year on dialysis increased 5-year survival benefit by 1.5%. Preemptive transplants were associated with -4.4% less survival benefit at 5-years.

Figure 4.1: **Survival benefit of deceased donor kidney transplantation for the 25th and 75th percentile recipient**



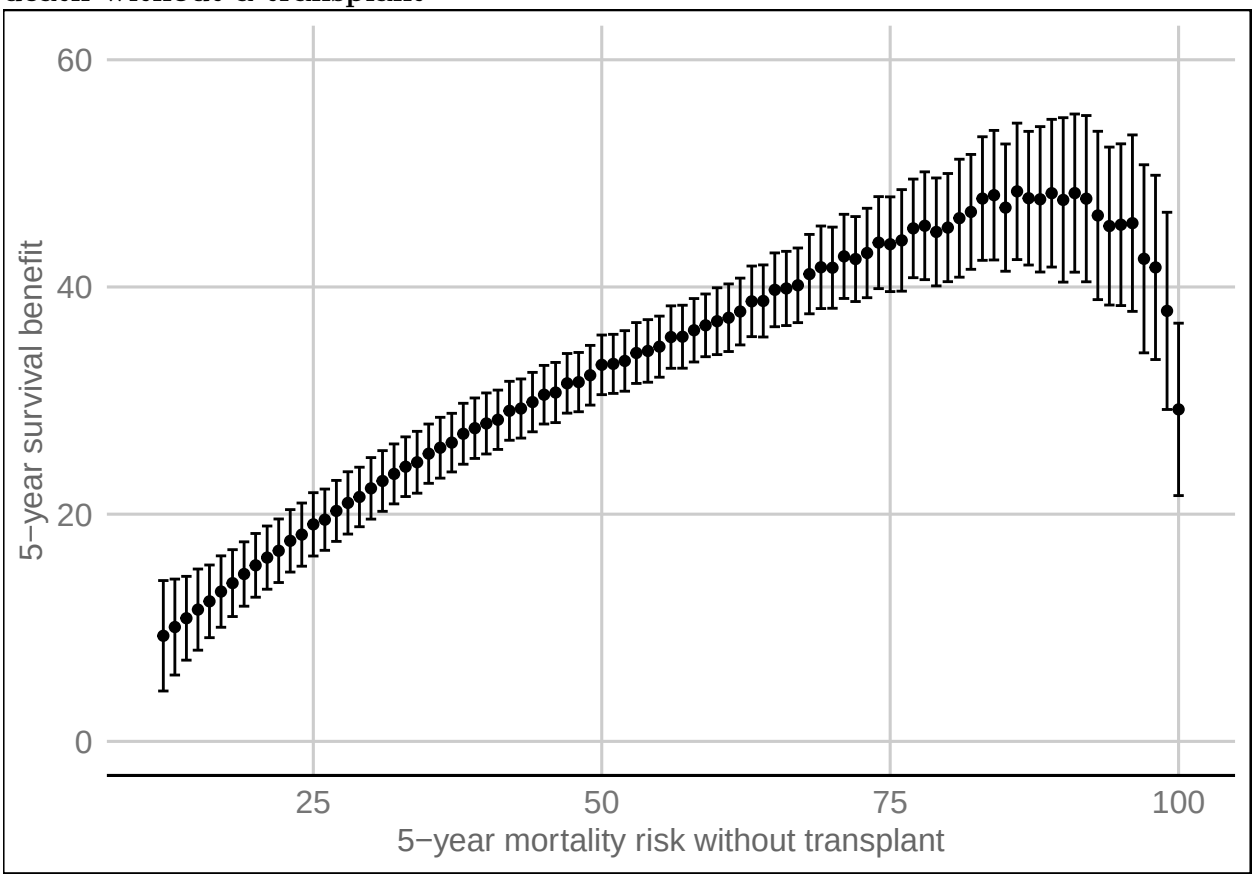

Survival benefit of deceased donor kidney transplantation for the 25th and 75th percentile recipient. The 25th percentile recipient had an estimated 5-year survival without transplantation of 68% which improved to 91% with transplantation. The 75th percentile recipient had a lower absolute estimated 5-year survival without transplantation 37% and with transplantation 76%, however a much larger benefit from transplantation 39%.

Figure 4.2: **Survival benefit of deceased donor kidney transplantation by risk of death without a transplant**



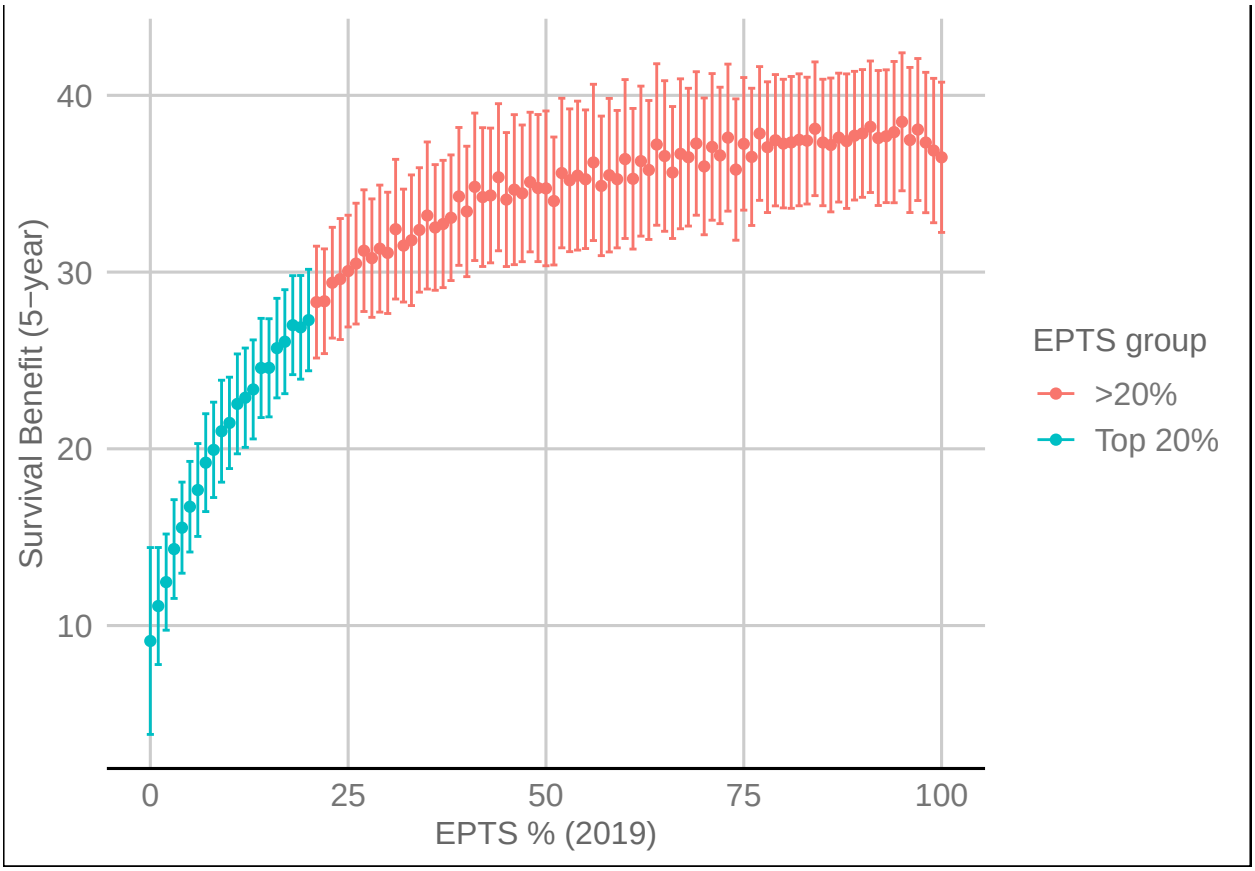

Survival benefit of deceased donor kidney transplantation by risk of death without a transplant. There is a roughly linear relationship between medical urgency and survival benefit until the most urgent candidates (5-year mortality risk without a transplantation > 75%). Only for the most extremely urgent candidates (mortality without transplant > 95%) does the survival benefit of transplantation begin to decline. Survival benefit prediction model available online at `https://wparker-uchicago.shinyapps.io/DDKT_survival_benefit/`.

Figure 4.3: **Survival benefit of deceased donor kidney transplantation by risk of death without a transplant**




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

Figure 4.4: **Survival benefit of deceased donor kidney transplantation by Estimated Post-Transplant Survival (EPTS) percentile**




Survival benefit of deceased donor kidney transplantation 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 $> 20\%$.

## KDPI and EPTS interaction

There was a significant interaction between EPTS and KDPI (**Table 4.4**). Top 20% EPTS recipients (currently receive priority for Top 20% kidneys) gain a 22.5% improvement in 5-year survival with a KDPI 15% kidney compared to a 21% improvement with a KDPI 60% kidney. In contrast, a recipients in the highest risk quartile (EPTS 80-100%) gain 42.9% in 5-year survival with a KDPI 15% kidney compared to 37.2% with a KDPI 60%, a significantly greater benefit from the higher quality graft ($p< 0.01$).

Table 4.4: **Survival benefit by EPTS quintile**

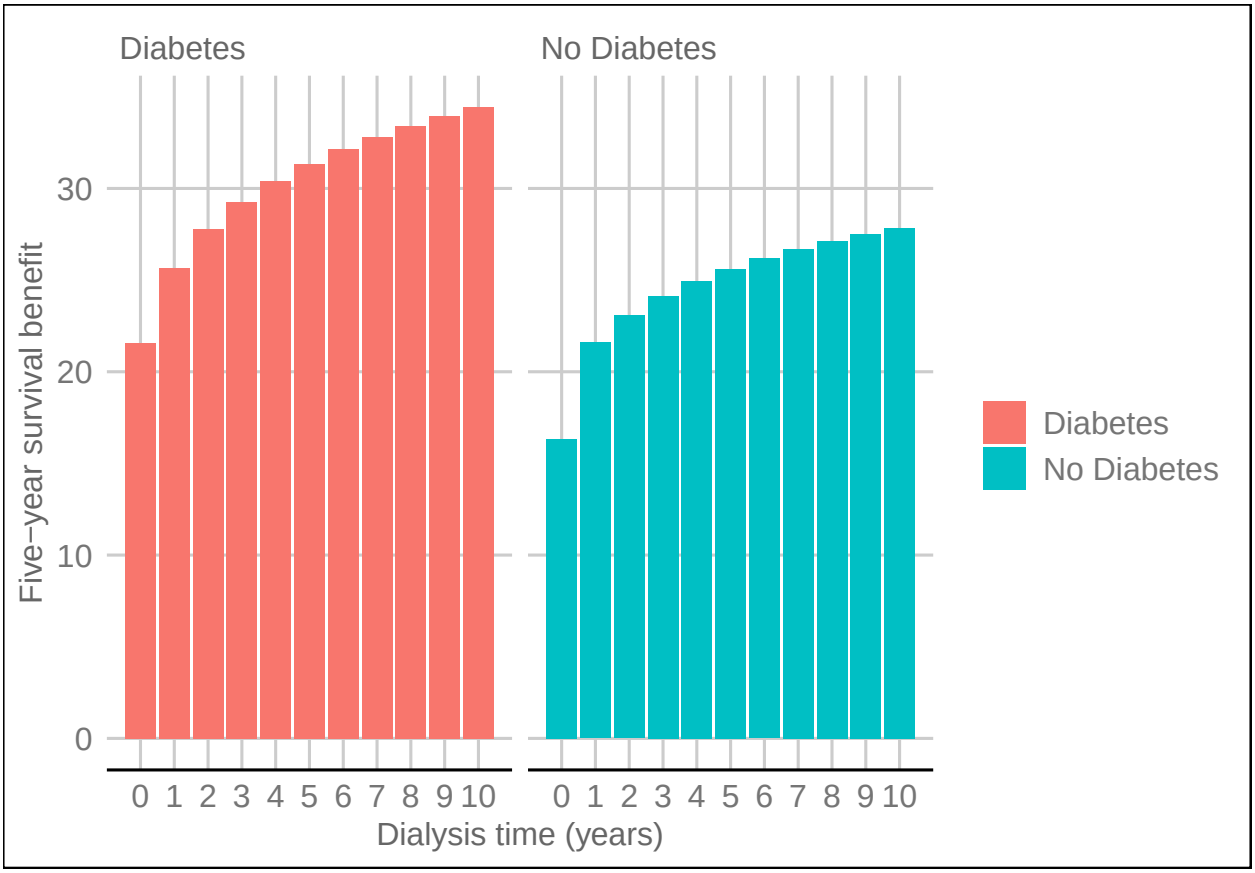
| EPTS | KDPI 15 (%) | KDPI 60 (%) | Absolute difference | 95% CI |
|---|---|---|---|---|
| (0,20] | 22.5 | 21.0 | 1.5 | (1.3,1.8) |
| (20,40] | 33.2 | 30.2 | 3.0 | (2.7,3.3) |
| (40,60] | 37.8 | 33.9 | 3.8 | (3.5,4.1) |
| (60,80] | 40.3 | 35.8 | 4.5 | (4.2,4.8) |
| (80,100] | 42.9 | 37.2 | 5.7 | (5.4,6) |

## 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 C.1**). On average, each year of recipient age increased five-year survival benefit by 0.4%, a history of previous solid organ transplant by 3.1%, and a history of diabetes by 3.2%. Each additional year on dialysis increased five-year survival benefit by 1.5%. Preemptive transplants were associated with -4.4% less survival benefit at five years.

The average five-year survival benefit for a preemptive transplantation in a patient without diabetes was 21.6 (95% CI 20.4%, 22.8%). Preemptive transplantation in patients with diabetes was associated with a five-year survival benefit of 26.6 (95% CI 24.5%, 28.7%) (**Figure 4.5**).

Figure 4.5: **Survival benefit by time on dialysis and history of diabetes**




Five-year survival benefit of deceased donor kidney transplantation by dialysis time and history of diabetes for the median age recipient (55 years old) transplanted after 809 with a 43% donor kidney with 18 hours of ischemic time.

In contrast, the average survival benefit for recipients without diabetes with more than five years of dialysis was 36.7% (95% CI35.9%, 37.5%). For recipients with diabetes and more than five years of dialysis time at transplant, the average survival benefit was 41.5% (95% CI40.3%, 42.7%).

### *4.4.4 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 C.1** for center effects on log hazard scale). The average 5-year risk of death without a transplant ranged from 32% to 66% (IQR [46,54%]).

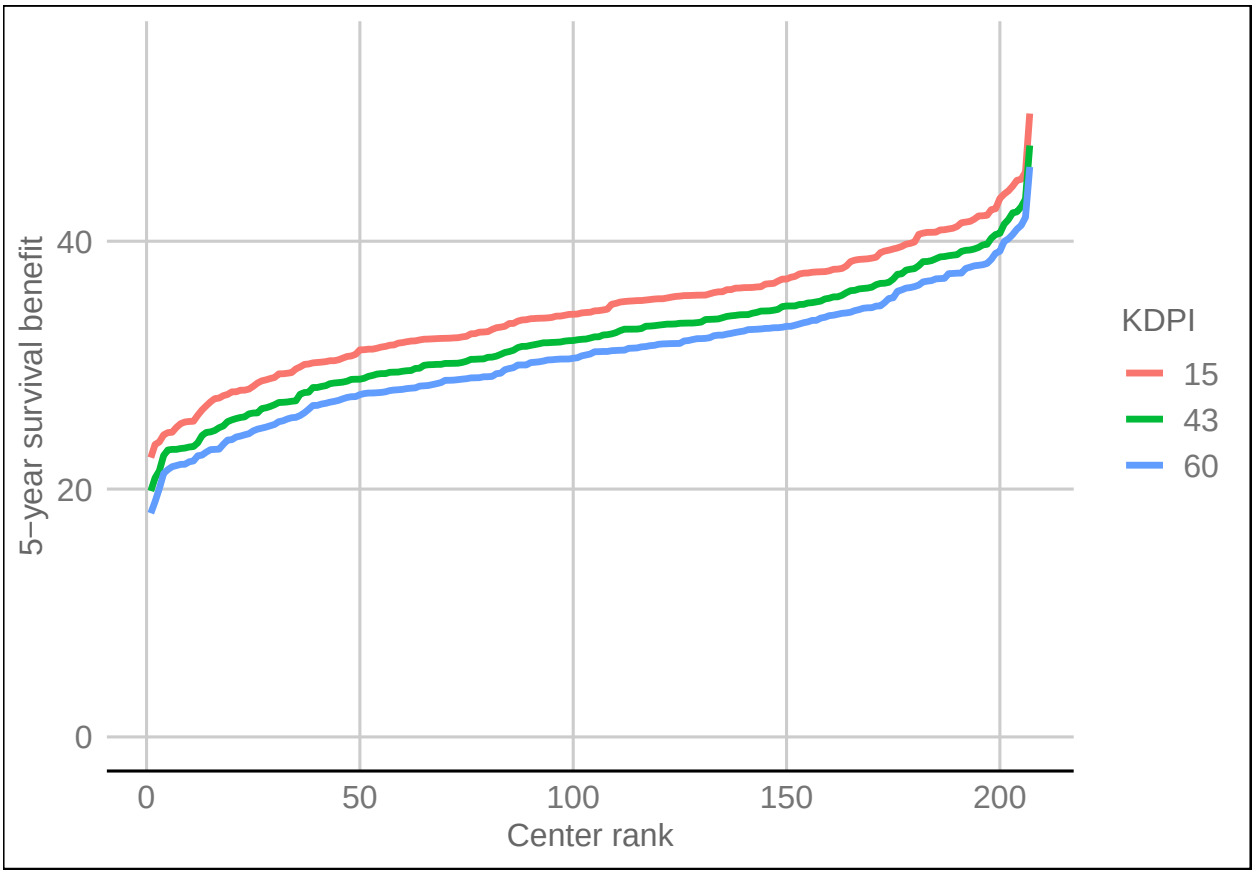
There was less between-center variation in the average 5-year post-transplant survival with a median KDPI kidney (43%), ranging from 70% to 90% (IQR [80,85%]). The correlation between average center risk of death with and without transplantation was strongly positive ($\rho = 0.64$).

The significant between-center variation in the risk of death with and without transplantation and translates into significant between-center in the survival benefit of DDKT (**Figure 4.6**). The 5-year improvement in associated with a median KDPI (43%) donor kidney varied from 20% to 48% (IQR 29,35%). In contrast, the average improvement in survival benefit of a KDPI 15% kidney compared to a KDPI 60% kidney was only 3.5% (IQR 2,4.7%).

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

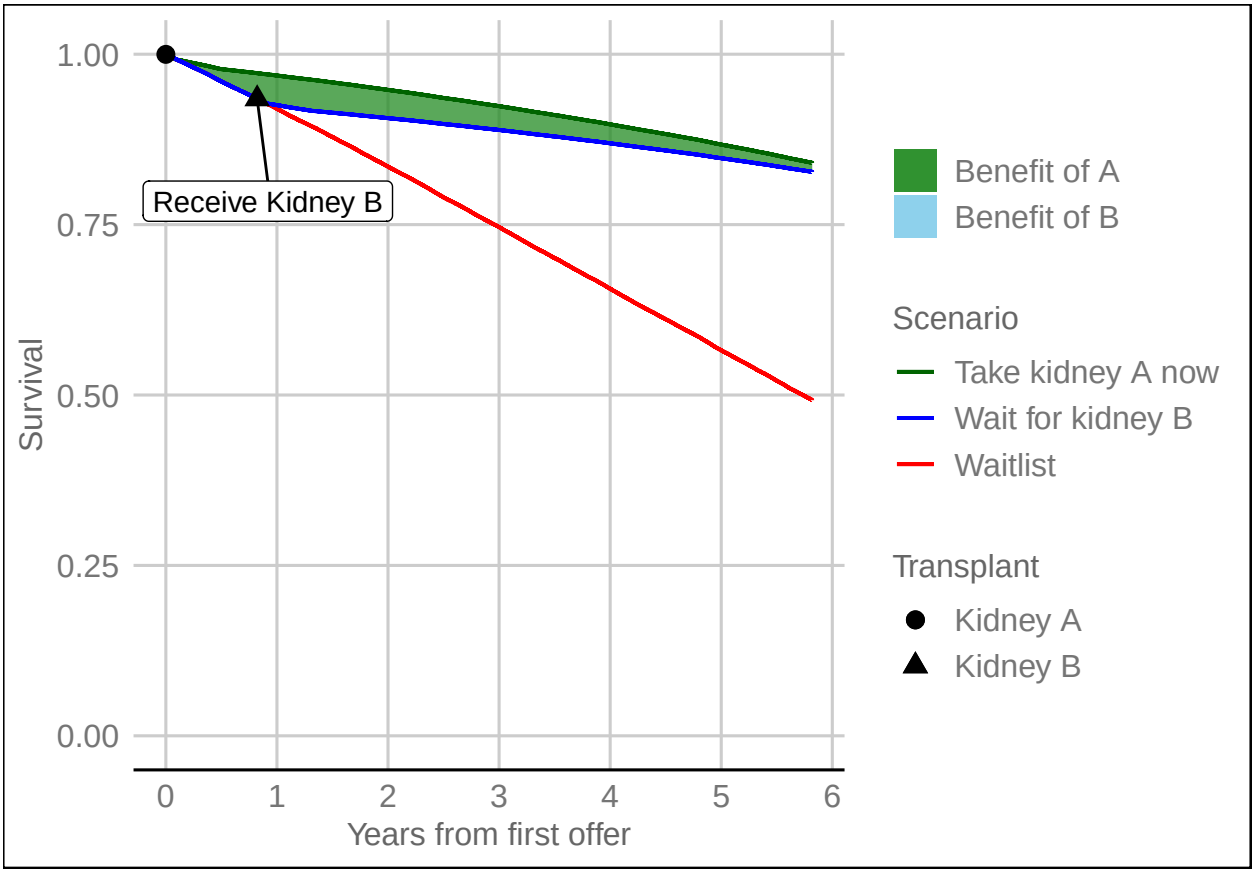
The decision to take an offer or wait for a better one was highly non-linear and both candidates and wait time specific (web application to assist physicians and patients in shared-decision making is available at `https://wparker-uchicago.shinyapps.io/DDKT_survival_benefit_compare/`). For the median 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 4.7**).

Figure 4.6: **Between-center variation in the survival benefit of deceased donor kidney**




5-year survival benefit of deceased donor kidney transplantation with a KDPI 15%, KDPI 43%(median KDPI) and KDPI 60% donor across N = 207 in the US. DDKT transplantation programs in the US. These estimates are generated by averaging the survival benefit of all recipients transplanted at that center, adjusting for KDPI and ischemic time. Center random intercept and transplant effect were estimated with empirical Bayes. The 5-year improvement in associated with a median KDPI (43%) donor kidney varied from 20% to 48% (IQR 29,35%). In contrast, the average improvement in survival benefit of a KDPI 15% kidney compared to a KDPI 60% kidney was only 3.5 (IQR 2,4.7%).

Figure 4.7: **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%. `https://wparker-uchicago.shinyapps.io/DDKT_survival_benefit_compare/`).

### *4.4.6 Survival benefit by race/ethnicity*

Summary statistics for key model variables by race/ethnicity can be found in **Table 4.5**. For adult candidate listed 2005-2010, the median white recipients waited 644 days for transplantation compared 978 days for the median non-white recipient, 334 days longer (p<0.01). White recipients were more likely to transplanted preemptively (15.4% vs. %, 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 4.5: **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 tx. | 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 tx. | 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 5-year survival benefit 29.3%, significantly lower than Black recipients (32.6%), Hispanic recipients (33.1%), and Asian/pacific islander recipients (33.3%) (p<0.01) for all comparisons (**Table 4.6**).

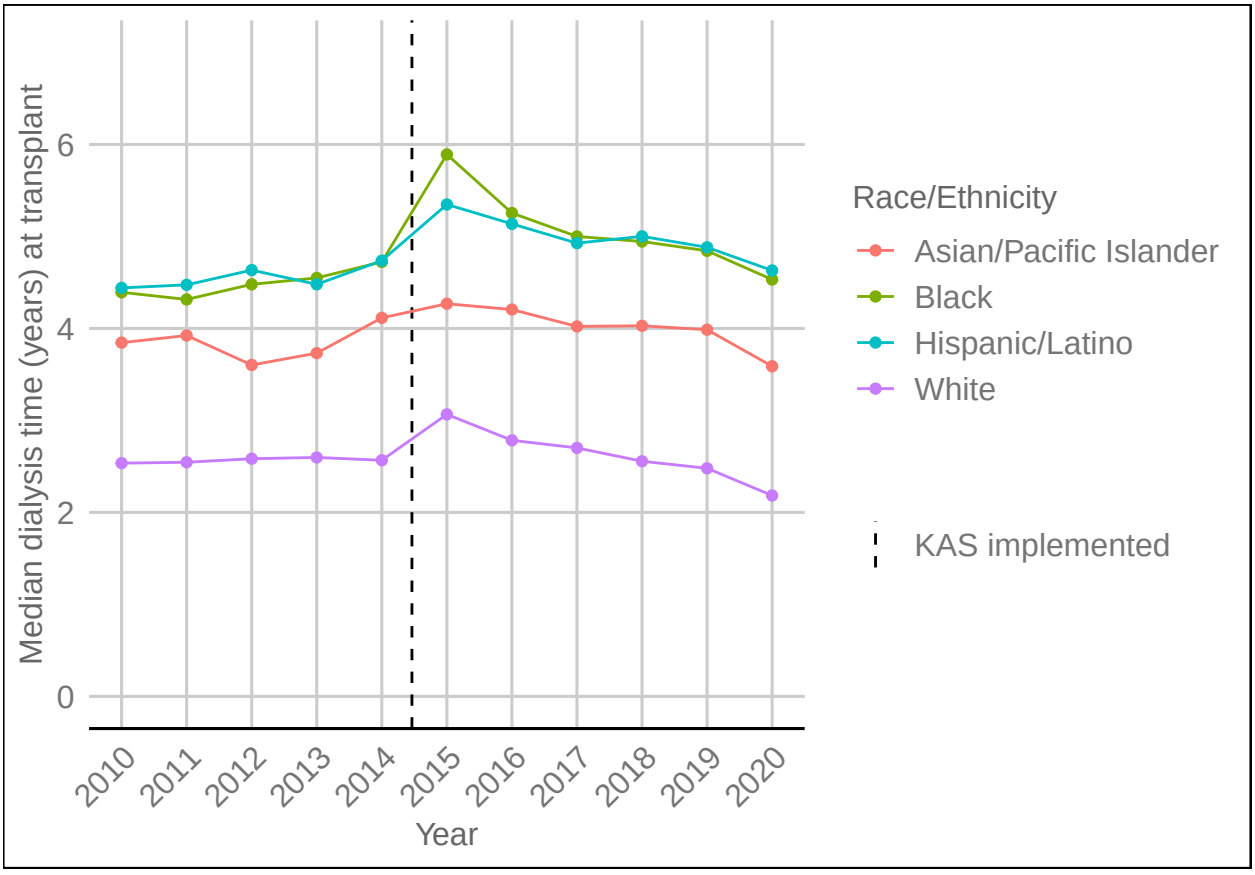
Racial disparities in dialysis time persisted from 2010-2020 despite the implementation of KAS in 2014 (**Figure 4.8**). In 2013, the median dialysis time for a White recipient was 2.6 years compared to 4.5 years for Black recipients. In 2019, the median dialysis time for a White recipient was 2.5 years compared to 4.8 years for Black recipients. The disparity in preemptive transplants increased (**Figure 4.9**). 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.

Table 4.6: **Age-adjusted 5-year mortality without a transplant and survival benefit by racial/ethnic group**

| Race/ethnicity | Mortality without transplant % | Survival benefit % |
|---|---|---|
| Asian/Pacific Islander | 51.2 | 33.3 |
| Hispanic/Latino | 52.7 | 33.1 |
| Black | 52.0 | 32.6 |
| White | 45.4 | 29.3 |

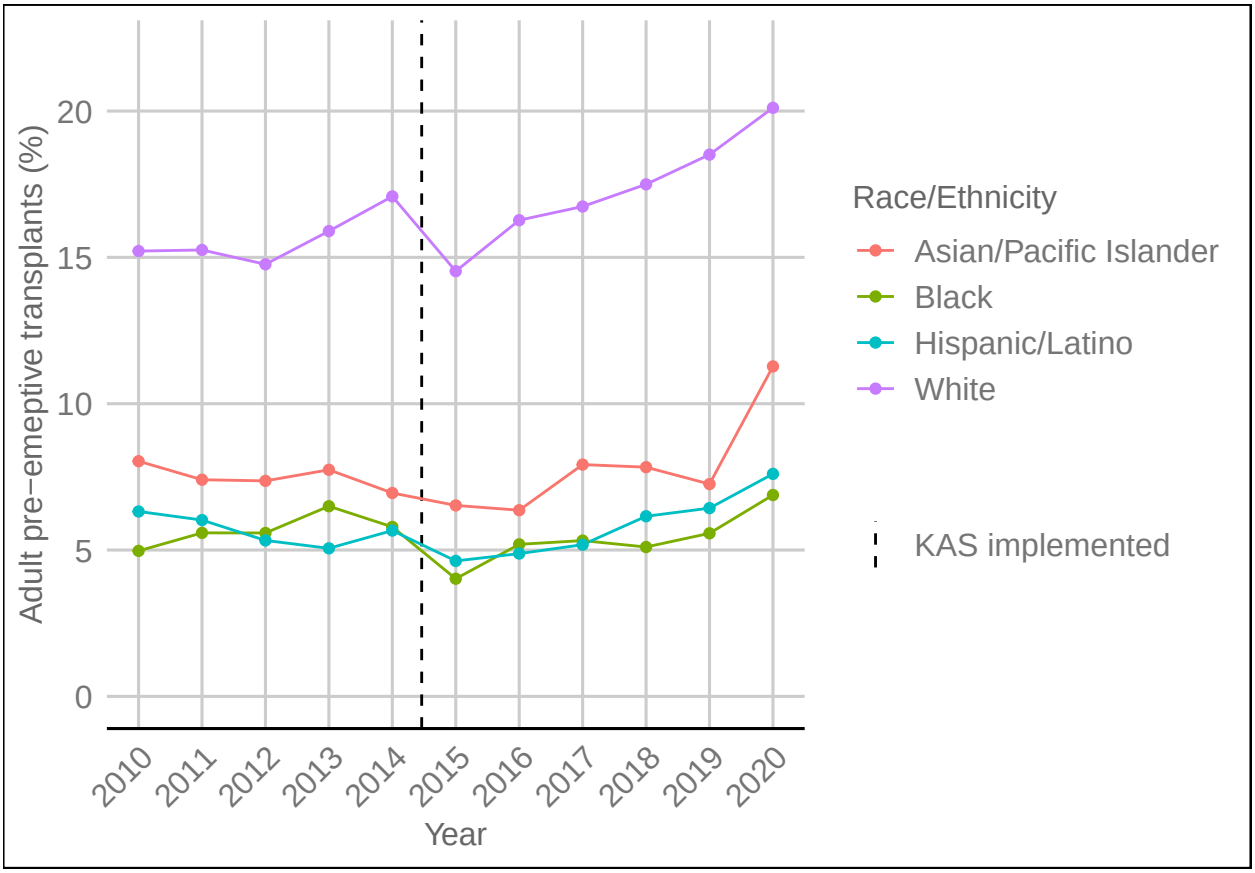
5-year mortality without a transplant (medical urgency) and survival benefit for first time deceased donor kidney transplant recipients by race/ethnicity, age-adjusted using direct-standardization with age bins of (0,30), (30,40), (40,50), (50,60), (70+).

Figure 4.8: **Trends in median dialysis time by race/ethnicity**




Trends in the median dialysis time at transplant by race/ethnicity. Despite the decemeber 2014 change to give candidates credit for pre-listing dialysis time, a large (>2 year) disparity in dialysis time at transplant persists through 2020. Other race/ethnicity groups not shown.

Figure 4.9: **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. [2019].

## 4.5 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.

### *4.5.1 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 by Bae et al. [2019] 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.

### *4.5.2 Lives-saved 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) [Wolfe et al., 2008]. There are two main arguments for the Kidney Allocation System to focus on lives-saved (short-term survival benefit) 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, lives saved on a shorter defined interval 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."

### *4.5.3 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 survival benefits 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 King et al. [2019] 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.

### *4.5.4 Eliminating points for pre-dialysis waiting time*

Ku et al. [2021] have shown that higher eGFR thresholds for Black patients could alleviate disparities in transplantation. 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 survival benefit.

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 elimi-

nating any pre-dialysis waiting time on overall graft survival and lives saved by the system.

### *4.5.5 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 [OPTN/UNOS, 2021a]. Therefore, our survival benefit estimates could be used to balance medical urgency with other ethically relevant factors in scarce resource allocation. Second, our center estimates are not case-mix adjusted for observed candidate covariates to reflect center selection practices. However, the prevalence of chronic kidney disease and potential candidates' demographics vary considerably across the country [Saran et al., 2020], so adjustment for specific candidate covariates (e.g., age) may be appropriate. Third, 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. Finally, we focused on the five-year survival benefit in this study to demonstrate the enormous benefit on a clinically relevant scale. However, policymakers will need to use shorter time frames or hazard ratios to evaluate programs more rapidly in practice.

### *4.5.6 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.

# CHAPTER 5

# SUMMARY AND FUTURE DIRECTIONS

## 5.1 Summary

In this dissertation, we have precisely quantified the survival benefit of heart and kidney transplantation and elucidated the key role that transplant center practices play in saving lives with organ allocation. The therapy-based heart allocation system with discrete categories are subject to manipulation and fail to properly rank order candidates on the wait-list. In kidney allocation, we have demonstrated how current policy completely ignores the Final Rule medical urgency requirement. This is both inefficient and inequitable, as minority candidates are structurally disadvantaged by transplant center practices. The are several clear next steps for this line of research.

## 5.2 Survival benefit under the new heart allocation policy

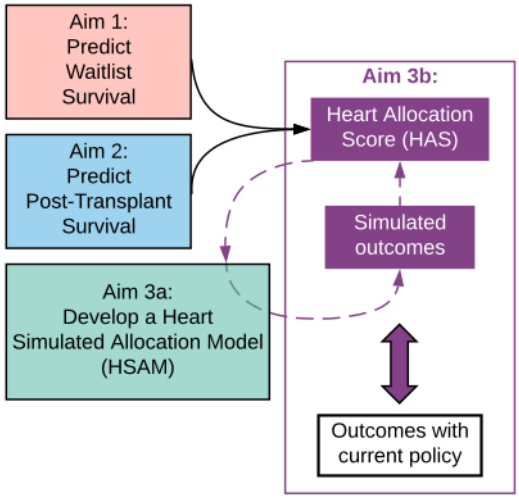
The new heart allocation policy has been in place for over 2 years now, approaching the point where non-biased estimates of post-transplant survival is possible. Therefore, we plan to adapt the mixed-effects approach taken in Chapter 2 to estimate the policy effect on survival benefit. If the new system truly prioritized more urgent candidates as intended, the survival benefit should increase post-policy. We will also assess the survival benefit by Status and compared to the expected distribution in **Figure 2.7**. Our hypothesis is that because of the treatment shifts described in Chapter 3 (see **Figure 3.4**) that there will not be a clear improvement in survival benefit.

## 5.3 A Novel Heart Allocation Score

The fundamental limitations of the therapy-based heart allocation system have created a clear need to develop and simulate a novel Heart Allocation Score (HAS) designed to identify the candidates who experience the greatest survival benefit from heart transplantation. Previous attempts to develop such a score using conventional statistical methods have been unsuccessful because of limited predictive accuracy [Schnitzler et al., 2005; Krakauer et al., 2005b; Smits et al., 2013; Singh et al., 2014].

Machine learning (ML) techniques can find complex interactions between clinical variables and have been shown to outperform conventional regression models in a variety of clinical contexts [Churpek et al., 2016; Rajkomar et al., 2018; Rojas et al., 2018], suggesting a machine learning HAS will succeed where other scores have failed. In addition, a new open-source Heart Simulated Allocation Model (HSAM) is needed to compare policy alternatives because the available simulation program for hearts is closed-source, inflexible, outdated, and structurally unable to simulate a HAS developed with ML. Our overall hypothesis is that a heart allocation score developed with machine learning will lead to policy that optimizes heart allocation. We will test this by pursuing the following aims (**Figure 5.1**)

Figure 5.1: **Proposed development and testing plan for a novel heart allocation score**



1. **Accurately predict waitlist survival**. Identifying candidates at high risk of death without transplantation is a critical task for heart allocation. Using the continuously audited and updated national transplant registry of all heart transplant candidates (N = 109,315), we will develop wait-list survival models using ML techniques and compare to the current therapy-based allocation policy. The most accurate prediction model will form a key component of the HAS and will be an important tool for heart transplant physicians in clinical practice.

2. **Accurately predict post-transplant survival** Several post-heart transplant survival models exist, however the most widely used model was only designed to predict one-year survival and has poor accuracy [Weiss et al., 2012]. Using the comprehensive national transplant registry dataset, we will predict post-transplant survival with ML and compare to the published conventional statistical model. The most accurate prediction model will be the second key component of the HAS and provide an important risk-stratification tool for the transplant community.

3. **Develop a heart allocation simulation model and evaluate a novel HAS policy**

   (a) *Develop a new, open-source heart simulated allocation model (HSAM)* we will build a structurally novel discrete-event simulation capable of fully simulating a HAS policy developed with ML. This aim will be independent of Aims 1 & 2 and serve as the platform for policy analyses (Aim 3b). By sharing our simulation software, we will provide a needed asset to the organ allocation research community which can be used to comprehensively evaluate the performance of any potential heart allocation policy.

   (b) *Develop and evaluate a novel HAS policy.* We will synthesize the results of Aim 1 & 2 to create an objective HAS to rank candidates. The HAS policy will be based

on expected survival benefit from heart transplantation but balanced to ensure fair distribution of hearts. We will compare the novel HAS policy against current policy using HSAM (Aim 3a).

Successful completion of these aims will lead to the foundation of a novel heart allocation system that has the potential to save lives and transform organ allocation policy.

## 5.4 Policy recommendations for the Kidney Allocation System

Incorporating survival benefit into deceased donor kidney allocation would align kidney allocation policy with the Final Rule, save more lives, and reduce racial/ethnic disparities in kidney transplantation. Specifically, our results in **Chapter 4** suggest the following immediate policy changes:

- Require transplant programs to document shared-decision making that includes a discussion of survival benefit before making accept-reject decisions for deceased donor organs
- Instruct the Organ Procurement and Transplant Network to study the following changes to the Kidney Allocation System
  - Eliminate points for pre-dialysis waiting time
  - Eliminate top 20% EPTS priority
- Evaluate transplant centers by survival benefit, not post-transplant survival
  - Create an incentive for centers to select medically urgent candidates with the most to gain from transplantation
  - Applies to all solid organ transplantation

### *5.4.1 Integrating survival benefit directly into kidney allocation*

In chapter 4 we demonstrate how the Kidney Allocation System is non-adherent to the Final Rule and propose eliminating the top 20% EPTS priority and pre-dialysis waiting time points. These policy changes would save more lives with deceased donor kidney transplantation and reduce disparities in transplantation.

However, we don't propose a complete kidney allocation system. Building a new allocation system based entirely around prediction of survival benefit would be a flawed approach as we would be 1) ignoring other ethically relevant principles and 2) rank-ordering candidates based on a model with modest rank-ordering performance (c-stat 0.69).

But it is possible to sketch out several coherent allocation plans based on multi-principled ethical frameworks that would better satisfy the Final Rule than the status quo. Below are a few preliminary frameworks.

#### Medical urgency categories

1. Create bins of medical urgency (e.g. high, medium, low) based on 5-year survival benefit and position more urgent candidates higher up the KAS allocation sequences

2. rank order candidates with urgency bin by dialysis time.

This system would create categories of urgency. For example, candidates with a 5-year survival benefit of over 40% would be "high" priority and positioned high up in the current KAS sequences. This has the benefit of simplicity but the downside of creating arbitrary discontinuities in candidate priority.

#### Equal weight on survival benefit and waiting time

A continuous solution involves equally weighting the principles of treating people equally and maximizing benefits.

$$KAS = (\frac{dialysis\ time\%}{2} + \frac{survival\ benefit\%}{2}) \tag{5.1}$$

In this system a candidate would receive between 0-50 points for dialysis time and 0-50 points for survival benefit. E.g. a candidate with a longer dialysis time percentile of 60% and a high survival benefit of 70% would get a score of 65. This would not categorically deny preemptive transplants, but these candidates would get 0 points from the dialysis time contribution to the score.

## 5.5 Data linkages with the SRTR

While the transplant registry is a complete audited longitudinal record of the wait-list and post-transplant periods, there are two areas of significant potential improvement

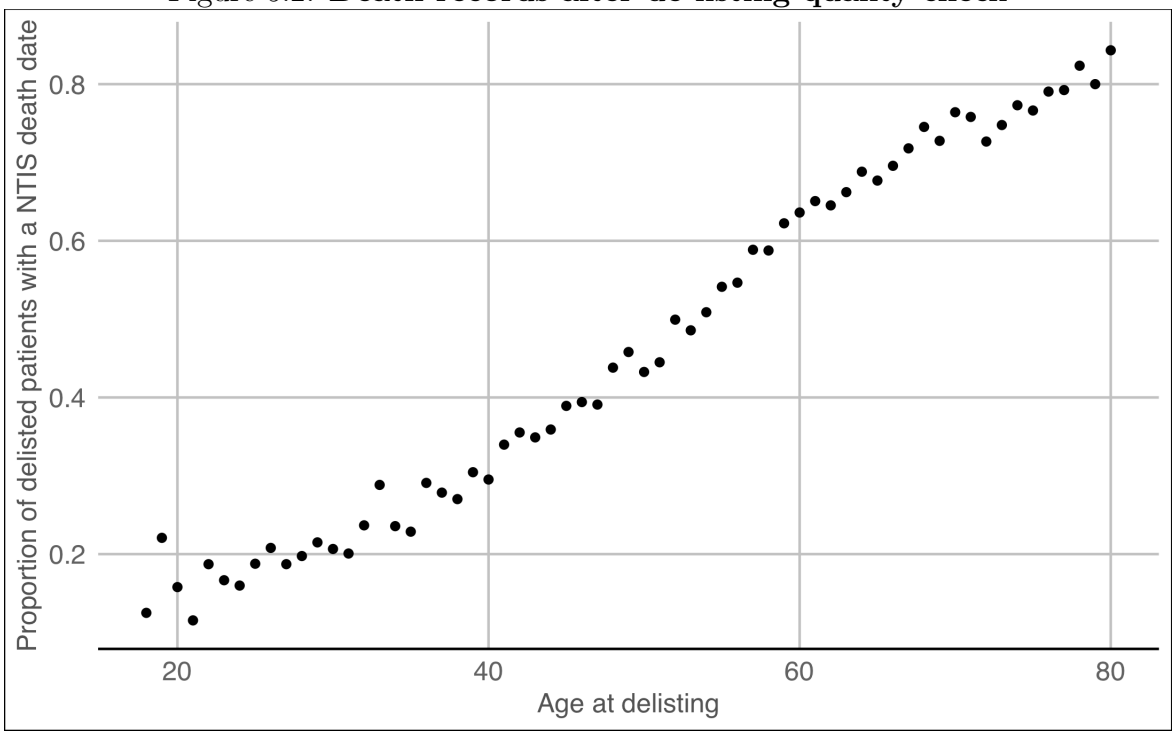
### *5.5.1 Pre-listing databases*

Successful data linkages between the transplant registry and more general datasets of patients with end-stage organ failure (US Renal Disease System and Society of Thoracic Surgeons (STS) databases) could allow for modeling of between-center variation in the wait-listing decision at the center level. This could provide further evidence for the claim

### *5.5.2 Additional sources of deaths*

Transplant center programs have strict reporting requirements for deaths that occur on the waitlist and for deaths in the first-year post-transplantation. Beyond this point, the SRTR relies on a data linkage to the National Technical Information Service (NTIS) death master file which is used to record deaths by the Social Security Administration. This may be missing some patient deaths. In a quality check, we determined the proportion of candidates who had a recorded death date after delisting by age **Figure 5.2** and the proportion of

Figure 5.2: **Death records after de-listing quality check**

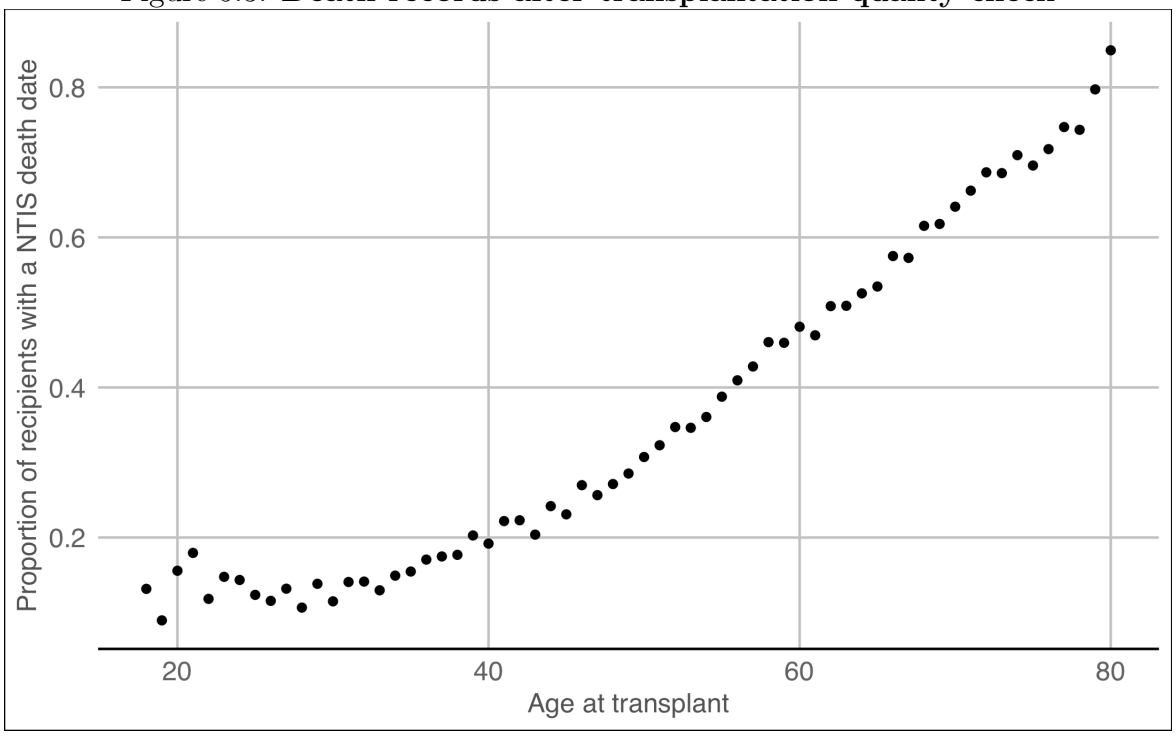



Proportion of adult candidates with a recorded death date after who were alive when they were taken off the wait-list. There is an expected linear relationship with age without any discontinuities to suggest biased data collection.

recipients with a recorded death date **Figure 5.3**, looking specifically for a discontinuity around age 65 at listing (when adjudicating SS claims become more important).

So while it appears unlikely that deaths missed by the NTIS are biasing any coefficients in the models, if deaths after delisting are under counted that generate a source of random error into the measurement of survival benefit. A linkage to the Center for Disease Control's National Death Index may significantly enhance the recording of deaths both pre and post transplantation.

Figure 5.3: **Death records after transplantation quality check**




Proportion of adult candidates with a recorded death date after transplantation. There is an expected linear relationship with age without any discontinuities to suggest biased data collection.

## 5.6 Conclusion

Complex, multi-principled solutions are necessary for the fair and efficient allocation of absolutely scarce healthcare resources via centralized mechanism. Rigorous empirical methodology is critical to translate ethical frameworks into practical allocation protocols. Serious ethically relevant deficiencies in the current deceased donor organ allocation systems exist and novel systems are needed.

# APPENDIX A

# CLASSIFICATION INTO STATUS 1-6 AND APPLICATION OF THE CARDIOGENIC SHOCK REQUIREMENT

We assessed whether or not candidates met the shock requirement according to previously published methodology [Parker et al., 2017a, 2018]. First, we identified candidates subject to the shock criteria based on the listed indication on the Status 1A justification forms. We then classified candidates based as in shock or not based on cardiac index according to the guidance in the policy for cardiac index values obtained in various circulatory support scenarios summarised below in **Figure A.1** [OPTN/UNOS Thoracic Committee, 2017]. Because there were relatively few VA-ECMO and percutaneous mechanical circulatory support candidates (<50 a year pre-policy shift) and these candidates often have missing hemodynamic data, these candidates were conservatively characterized as "in shock." We used Status 1A justification form, transplant candidate registration (TCR), and transplant recipient registration (TRR) hemodynamics. We used inotrope doses available from the Status 1A justification form to apply the minimum dose criteria to the high dose inotrope group. Body weight, height, and cardiac output were used to calculate cardiac index for each patient using the DuBois formula for body surface area [Du Bois and Du Bois, 1989 Sep-Oct]. For candidates with missing cardiac index data or supported with multiple support therapies simultaneously, we considered them as in shock. Because blood pressure readings were only available sporadically for candidates treated with inotropes, we conservatively did not apply this portion of the criteria. For candidates listed with IABP with hemodynamics measured while receiving IABP support, the policy does not offer specific guidance as it requires pre-IABP implantation hemodynamics for qualification. Therefore, we decided to categorize IABP candidates with post-implantation hemodynamics in shock if the cardiac index was $< 2.0\, L/min/m^2$ on IABP support. We based this threshold on the criteria for extension of Status 2, a failure to wean from IABP evidenced by a "Cardiac Index less than $2.0\, L/min/m^2$".

Figure A.1: **The Detailed Cardiogenic Shock Requirements for Intra-Aortic Balloon Pumps and Multiple Inotropes or a Single High Dose Inotrope and Hemodynamic Monitoring**

| Candidate Groups | Status | Initial Listing Criteria |
|---|---|---|
| Intra-Aortic Balloon Pump | 2 | A candidate's transplant program may assign a candidate to adult status 2 if the candidate is admitted to the transplant hospital that registered the candidate on the waiting list, and **is supported by an IABP for cardiogenic shock** as evidenced by either of the following:<br>• Within 7 days prior to IABP support, **all** of the following are true within one 24 hour period:<br>a. Systolic blood pressure less than 90 mmHg<br>b. Cardiac index less than 1.8 L/min/m2 if the candidate is not supported by inotropes or less than 2.0 L/min/m2 if the candidate is supported by at least one inotrope<br>c. Pulmonary capillary wedge pressure greater than 15 mmHg<br>• If hemodynamic measurements could not be obtained within 7 days prior to IABP support, at least one of the following is true within 24 hours prior to IABP support:<br>o CPR was performed on the candidate<br>o Systolic blood pressure less than 70 mmHg<br>o Arterial lactate greater than 4 mmol/L<br>o Aspartate transaminase (AST) or alanine transaminase (ALT) greater than 109 1,000 U/L |
| Multiple Inotropes or a Single High Dose Inotrope and Hemodynamic Monitoring | 3 | A candidate's transplant program may assign a candidate to adult status 3 if the candidate is admitted to the hospital that registered the candidate on the waiting list, and within 7 days prior to inotrope administration or while on inotropes meets all of the following:<br>1. Has one of the following:<br>• Invasive pulmonary artery catheter<br>• Daily hemodynamic monitoring to measure cardiac output and left ventricular filling pressures<br>2. Is in cardiogenic shock, as evidenced by all of the following within one 24 hour period:<br>a. Systolic blood pressure less than 90 mmHg<br>b. Pulmonary Capillary Wedge Pressure greater than 15 mmHg<br>c. Cardiac index of either:<br>• Less than 1.8 L/min/m2 for candidates without inotropic or mechanical support within 7 days prior to inotrope administration<br>• Less than 2.2 L/min/m2 for candidates with inotropic or mechanical support<br>3. Is supported by one of the following:<br>• A continuous infusion of at least one high-dose intravenous inotrope:<br>o Dobutamine greater than or equal to 7.5 mcg/kg/min<br>o Milrinone greater than or equal to 0.50 mcg/kg/min<br>o Epinephrine greater than or equal to 0.02 mcg/kg/min<br>• A continuous infusion of at least two intravenous inotropes:<br>o Dobutamine greater than or equal to 3 mcg/kg/min<br>o Milrinone greater than or equal to 0.25 mcg/kg/min<br>o Epinephrine greater than or equal to 0.01 mcg/kg/min<br>o Dopamine greater than or equal to 3 mcg/kg/min mcg/kg/min |

Table constructed (with permission) directly from the policy details available on the OPTN website

# APPENDIX B

# ADDITIONAL ANALYSIS AND ROBUSTNESS CHECKS FOR ASSOCIATION OF TRANSPLANT CENTER WITH SURVIVAL BENEFIT AMONG ADULTS UNDERGOING HEART TRANSPLANT IN THE UNITED STATES

Table B.1: **Fixed-effect model of the three-status system**. Base case is a candidate waiting at Status 1A.

| **Fixed effect** | **Log hazard ratio** | **Lower 95% CI** | **Upper 95% CI** |
|---|---|---|---|
| Status 1B | -0.95 | -1.01 | -0.89 |
| Status 2 | -1.38 | -1.46 | -1.31 |
| Transplantation | -1.78 | -2.21 | -1.36 |
| Transplantation: Status 1B | 0.92 | 0.83 | 1.01 |
| Transplantation: Status 2 | 1.35 | 1.22 | 1.48 |
| Donor Risk Score >5 | 0.26 | 0.21 | 0.32 |
| Transplant before 2010 | -0.05 | -0.11 | 0.01 |
| center7 | -0.06 | -0.42 | 0.30 |
| center8 | -0.50 | -0.94 | -0.06 |
| center18 | -0.42 | -0.83 | -0.01 |
| center25 | -0.11 | -0.53 | 0.32 |
| center33 | -0.25 | -0.59 | 0.10 |
| center47 | 0.14 | -0.37 | 0.66 |
| center55 | 0.45 | -0.04 | 0.95 |
| center63 | -0.25 | -0.78 | 0.29 |

| **Fixed-effect model of the three-status system** (continued) | | | |
|---|---|---|---|
| **Fixed effect** | **Log hazard ratio** | **Lower 95% CI** | **Upper 95% CI** |
| center64 | 0.17 | -0.27 | 0.61 |
| center65 | -0.50 | -1.01 | 0.02 |
| center67 | -0.17 | -0.58 | 0.25 |
| center72 | 0.10 | -0.28 | 0.47 |
| center78 | -0.04 | -0.39 | 0.30 |
| center79 | -0.11 | -0.52 | 0.31 |
| center91 | -0.17 | -0.59 | 0.25 |
| center94 | -0.65 | -1.14 | -0.15 |
| center96 | -0.25 | -0.68 | 0.17 |
| center108 | -0.22 | -0.58 | 0.15 |
| center119 | -0.04 | -0.41 | 0.33 |
| center128 | -0.56 | -0.97 | -0.15 |
| center131 | -0.49 | -0.87 | -0.11 |
| center136 | -0.30 | -0.67 | 0.06 |
| center141 | -0.02 | -0.36 | 0.33 |
| center147 | -0.19 | -0.69 | 0.30 |
| center149 | -0.30 | -0.83 | 0.24 |
| center165 | -0.47 | -0.94 | 0.00 |
| center171 | -0.71 | -1.15 | -0.28 |
| center178 | -0.59 | -0.98 | -0.19 |
| center183 | -0.38 | -0.78 | 0.03 |
| center185 | 0.23 | -0.25 | 0.71 |
| center190 | 0.05 | -0.34 | 0.44 |

| **Fixed-effect model of the three-status system** (continued) | | | |
|---|---|---|---|
| **Fixed effect** | **Log hazard ratio** | **Lower 95% CI** | **Upper 95% CI** |
| center195 | -0.13 | -0.59 | 0.32 |
| center199 | -0.19 | -0.72 | 0.34 |
| center201 | 0.00 | -0.38 | 0.39 |
| center210 | -0.04 | -0.40 | 0.32 |
| center213 | -0.54 | -1.06 | -0.02 |
| center221 | 0.01 | -0.33 | 0.35 |
| center234 | 0.45 | -0.15 | 1.04 |
| center298 | 0.10 | -0.26 | 0.45 |
| center301 | -0.53 | -0.88 | -0.19 |
| center303 | -0.45 | -0.82 | -0.07 |
| center307 | -0.31 | -0.70 | 0.08 |
| center313 | 0.35 | -0.01 | 0.71 |
| center324 | -0.35 | -0.77 | 0.08 |
| center337 | -0.20 | -0.55 | 0.14 |
| center338 | -0.23 | -0.70 | 0.25 |
| center348 | -0.12 | -0.47 | 0.22 |
| center350 | -0.41 | -0.76 | -0.05 |
| center351 | 0.07 | -0.26 | 0.40 |
| center359 | -0.71 | -1.19 | -0.23 |
| center372 | 0.29 | -0.14 | 0.72 |
| center377 | -0.64 | -1.25 | -0.03 |
| center380 | -0.21 | -0.65 | 0.22 |
| center382 | -0.06 | -0.40 | 0.28 |

| **Fixed-effect model of the three-status system** (continued) | | | |
|---|---|---|---|
| **Fixed effect** | **Log hazard ratio** | **Lower 95% CI** | **Upper 95% CI** |
| center388 | -0.09 | -0.50 | 0.33 |
| center402 | -0.74 | -1.22 | -0.25 |
| center404 | -0.12 | -0.50 | 0.26 |
| center408 | -0.45 | -0.96 | 0.05 |
| center434 | -0.37 | -0.68 | -0.05 |
| center442 | -0.27 | -0.62 | 0.08 |
| center445 | -0.37 | -0.80 | 0.05 |
| center446 | -0.49 | -0.88 | -0.11 |
| center459 | -0.17 | -0.61 | 0.27 |
| center465 | -0.21 | -0.54 | 0.12 |
| center479 | -0.25 | -0.69 | 0.19 |
| center484 | 0.68 | 0.05 | 1.32 |
| center486 | -0.44 | -0.97 | 0.10 |
| center487 | -0.01 | -0.39 | 0.37 |
| center507 | -0.55 | -1.02 | -0.08 |
| center512 | -0.27 | -0.66 | 0.12 |
| center520 | -0.42 | -0.83 | 0.00 |
| center523 | -0.01 | -0.50 | 0.48 |
| center527 | -0.08 | -0.45 | 0.28 |
| center532 | -0.12 | -0.53 | 0.29 |
| center534 | 0.16 | -0.31 | 0.63 |
| center536 | -0.31 | -0.68 | 0.06 |
| center588 | 0.96 | 0.30 | 1.62 |

| **Fixed-effect model of the three-status system** (continued) | | | |
|---|---|---|---|
| **Fixed effect** | **Log hazard ratio** | **Lower 95% CI** | **Upper 95% CI** |
| center595 | 0.03 | -0.43 | 0.48 |
| center615 | 0.18 | -0.30 | 0.65 |
| center620 | -0.04 | -0.37 | 0.30 |
| center633 | 0.07 | -0.34 | 0.48 |
| center640 | -0.40 | -0.77 | -0.04 |
| center642 | -0.55 | -1.02 | -0.09 |
| center643 | -0.10 | -0.42 | 0.22 |
| center645 | 0.17 | -0.23 | 0.58 |
| center648 | -0.15 | -0.73 | 0.43 |
| center656 | 0.40 | 0.06 | 0.74 |
| center667 | -0.32 | -0.72 | 0.09 |
| center670 | -0.06 | -0.72 | 0.60 |
| center675 | 0.03 | -0.34 | 0.40 |
| center688 | -0.67 | -1.23 | -0.12 |
| center690 | -0.51 | -1.00 | -0.01 |
| center696 | -0.49 | -0.87 | -0.11 |
| center700 | -0.32 | -0.71 | 0.07 |
| center701 | -0.64 | -1.13 | -0.15 |
| center703 | -0.69 | -1.10 | -0.28 |
| center708 | -0.19 | -0.62 | 0.24 |
| center733 | -0.16 | -0.59 | 0.27 |
| center736 | -0.32 | -0.69 | 0.06 |
| center742 | -0.06 | -0.64 | 0.52 |

| **Fixed-effect model of the three-status system** (continued) | | | |
|---|---|---|---|
| **Fixed effect** | **Log hazard ratio** | **Lower 95% CI** | **Upper 95% CI** |
| center746 | 0.06 | -0.29 | 0.41 |
| center749 | -0.37 | -0.80 | 0.06 |
| center838 | -0.58 | -1.14 | -0.03 |
| tx:center7 | -0.35 | -0.91 | 0.20 |
| tx:center8 | 0.26 | -0.37 | 0.88 |
| tx:center18 | -0.37 | -0.97 | 0.23 |
| tx:center25 | 0.16 | -0.42 | 0.75 |
| tx:center33 | -0.13 | -0.61 | 0.35 |
| tx:center47 | -0.42 | -1.11 | 0.27 |
| tx:center55 | -0.46 | -1.15 | 0.24 |
| tx:center63 | -0.10 | -0.88 | 0.69 |
| tx:center64 | -0.56 | -1.19 | 0.06 |
| tx:center65 | 0.27 | -0.46 | 0.99 |
| tx:center67 | -0.64 | -1.30 | 0.01 |
| tx:center72 | -0.56 | -1.08 | -0.04 |
| tx:center78 | -0.29 | -0.77 | 0.20 |
| tx:center79 | -0.52 | -1.11 | 0.07 |
| tx:center91 | -0.28 | -0.88 | 0.32 |
| tx:center94 | 0.14 | -0.54 | 0.81 |
| tx:center96 | -0.10 | -0.74 | 0.54 |
| tx:center108 | 0.20 | -0.38 | 0.78 |
| tx:center119 | -0.59 | -1.14 | -0.04 |
| tx:center128 | 0.02 | -0.55 | 0.59 |

| **Fixed-effect model of the three-status system** (continued) | | | |
|---|---|---|---|
| **Fixed effect** | **Log hazard ratio** | **Lower 95% CI** | **Upper 95% CI** |
| tx:center131 | 0.13 | -0.39 | 0.64 |
| tx:center136 | 0.11 | -0.41 | 0.64 |
| tx:center141 | -0.38 | -0.90 | 0.14 |
| tx:center147 | 0.61 | -0.22 | 1.44 |
| tx:center149 | 0.24 | -0.46 | 0.95 |
| tx:center165 | -0.48 | -1.20 | 0.25 |
| tx:center171 | 0.81 | 0.18 | 1.44 |
| tx:center178 | -0.06 | -0.65 | 0.53 |
| tx:center183 | -0.03 | -0.59 | 0.54 |
| tx:center185 | -0.61 | -1.36 | 0.15 |
| tx:center190 | -0.19 | -0.73 | 0.35 |
| tx:center195 | -0.24 | -0.87 | 0.40 |
| tx:center199 | 0.15 | -0.56 | 0.86 |
| tx:center201 | -0.18 | -0.73 | 0.38 |
| tx:center210 | -0.05 | -0.61 | 0.50 |
| tx:center213 | 0.15 | -0.56 | 0.86 |
| tx:center221 | -0.55 | -1.08 | -0.01 |
| tx:center234 | -0.72 | -1.63 | 0.20 |
| tx:center298 | -0.56 | -1.11 | -0.01 |
| tx:center301 | -0.22 | -0.78 | 0.33 |
| tx:center303 | -0.13 | -0.69 | 0.44 |
| tx:center307 | -0.24 | -0.85 | 0.36 |
| tx:center313 | -0.57 | -1.11 | -0.03 |

| **Fixed-effect model of the three-status system** (continued) | | | |
|---|---|---|---|
| **Fixed effect** | **Log hazard ratio** | **Lower 95% CI** | **Upper 95% CI** |
| tx:center324 | -0.04 | -0.66 | 0.58 |
| tx:center337 | -0.46 | -0.98 | 0.06 |
| tx:center338 | -0.77 | -1.53 | -0.01 |
| tx:center348 | -0.62 | -1.17 | -0.07 |
| tx:center350 | -0.21 | -0.75 | 0.32 |
| tx:center351 | -0.43 | -0.93 | 0.07 |
| tx:center359 | 0.16 | -0.44 | 0.76 |
| tx:center372 | -0.48 | -1.11 | 0.16 |
| tx:center377 | -0.13 | -0.97 | 0.72 |
| tx:center380 | -0.68 | -1.30 | -0.06 |
| tx:center382 | -0.09 | -0.57 | 0.40 |
| tx:center388 | -0.12 | -0.73 | 0.49 |
| tx:center402 | 0.28 | -0.36 | 0.92 |
| tx:center404 | -0.35 | -0.87 | 0.18 |
| tx:center408 | 0.15 | -0.52 | 0.83 |
| tx:center434 | -0.16 | -0.63 | 0.30 |
| tx:center442 | -0.57 | -1.18 | 0.04 |
| tx:center445 | -0.42 | -1.04 | 0.21 |
| tx:center446 | 0.60 | 0.06 | 1.14 |
| tx:center459 | -0.11 | -0.73 | 0.52 |
| tx:center465 | -0.46 | -0.95 | 0.02 |
| tx:center479 | -0.20 | -0.82 | 0.41 |
| tx:center484 | -0.61 | -1.55 | 0.33 |

**Fixed-effect model of the three-status system** (continued)

| Fixed effect | Log hazard ratio | Lower 95% CI | Upper 95% CI |
|---|---|---|---|
| tx:center486 | 0.72 | -0.10 | 1.54 |
| tx:center487 | -0.10 | -0.67 | 0.47 |
| tx:center507 | -0.29 | -0.93 | 0.36 |
| tx:center512 | -0.13 | -0.69 | 0.43 |
| tx:center520 | 0.49 | -0.09 | 1.07 |
| tx:center523 | -0.16 | -0.85 | 0.53 |
| tx:center527 | -0.21 | -0.72 | 0.29 |
| tx:center532 | 0.00 | -0.59 | 0.60 |
| tx:center534 | -0.37 | -1.06 | 0.32 |
| tx:center536 | -0.17 | -0.68 | 0.34 |
| tx:center588 | -1.43 | -2.28 | -0.58 |
| tx:center595 | -0.67 | -1.32 | -0.02 |
| tx:center615 | -0.14 | -0.80 | 0.51 |
| tx:center620 | -0.42 | -0.94 | 0.10 |
| tx:center633 | 0.14 | -0.43 | 0.71 |
| tx:center640 | -0.30 | -0.85 | 0.26 |
| tx:center642 | 0.21 | -0.49 | 0.90 |
| tx:center643 | -0.03 | -0.51 | 0.44 |
| tx:center645 | -0.58 | -1.17 | 0.01 |
| tx:center648 | 0.48 | -0.27 | 1.24 |
| tx:center656 | -0.66 | -1.18 | -0.15 |
| tx:center667 | -0.06 | -0.63 | 0.52 |
| tx:center670 | -0.29 | -1.25 | 0.66 |

**Fixed-effect model of the three-status system** (continued)

| Fixed effect | Log hazard ratio | Lower 95% CI | Upper 95% CI |
|---|---|---|---|
| tx:center675 | -0.20 | -0.72 | 0.31 |
| tx:center688 | -0.19 | -0.92 | 0.53 |
| tx:center690 | -0.09 | -0.76 | 0.59 |
| tx:center696 | -0.04 | -0.62 | 0.54 |
| tx:center700 | 0.32 | -0.24 | 0.87 |
| tx:center701 | 0.61 | -0.10 | 1.32 |
| tx:center703 | 0.17 | -0.44 | 0.79 |
| tx:center708 | -0.56 | -1.21 | 0.09 |
| tx:center733 | -0.93 | -1.64 | -0.21 |
| tx:center736 | -0.71 | -1.29 | -0.13 |
| tx:center742 | -0.27 | -1.26 | 0.72 |
| tx:center746 | -0.36 | -0.87 | 0.16 |
| tx:center749 | -0.30 | -0.91 | 0.31 |
| tx:center838 | 0.19 | -0.62 | 1.00 |

Base case is a candidate waiting at Status 1A at a specific center. Model equation is the same as equation 2.1 but with center effects estimated as fixed effects.

Table B.2: **Mixed-effects model with three-status and expanded donor variables and candidate variables**

| **Fixed Effect** | **Log hazard ratio** | **95% CI** |
|---|---|---|
| Status 1B | -0.939 | (-1, -0.877) |
| Status 2 | -1.46 | (-1.53, -1.39) |
| Listing year 2007 | -0.0346 | (-0.164, 0.0944) |
| Listing year 2008 | -0.0893 | (-0.214, 0.0353) |
| Listing year 2009 | -0.135 | (-0.257, -0.0124) |
| Listing year 2010 | -0.226 | (-0.349, -0.103) |
| Listing year 2011 | -0.3 | (-0.428, -0.172) |
| Listing year 2012 | -0.287 | (-0.413, -0.161) |
| Listing year 2013 | -0.375 | (-0.501, -0.248) |
| Listing year 2014 | -0.289 | (-0.413, -0.165) |
| Listing year 2015 | -0.45 | (-0.581, -0.32) |
| Age | 0.0149 | (0.0124, 0.0173) |
| Female | 0.0161 | (-0.0482, 0.0803) |
| BMI <25th percentile | 0.0636 | (-0.00685, 0.134) |
| BMI >75th percentile | 0.0562 | (-0.00631, 0.119) |
| Ischemic Cardiomyopathy | 0.133 | (0.0692, 0.198) |
| Restrictive cardiomyopathy | 0.191 | (0.0891, 0.292) |
| Other Diagnosis | 0.53 | (0.447, 0.614) |
| Cross Match requested | 0.396 | (0.328, 0.465) |
| Blood type: AB | 0.138 | (-0.0252, 0.302) |
| Blood type: B | -0.000891 | (-0.0913, 0.0895) |

Mixed-effects model with three-status + expanded donor and candidate variables (continued)

| **Fixed Effect** | **Log hazard ratio** | **95% CI** |
|---|---|---|
| Blood type: O | 0.00624 | (-0.0526, 0.0651) |
| Transplant | -1.49 | (-1.74, -1.24) |
| Transplant: Status 1B | 0.912 | (0.825, 0.998) |
| Transplant: Status 2 | 1.44 | (1.31, 1.57) |
| Transplant: Listing year 2007 | -0.0342 | (-0.198, 0.13) |
| Transplant: Listing year 2008 | 0.0499 | (-0.113, 0.213) |
| Transplant: Listing year 2009 | 0.11 | (-0.0534, 0.273) |
| Transplant: Listing year 2010 | 0.118 | (-0.0495, 0.286) |
| Transplant: Listing year 2011 | 0.251 | (0.0768, 0.426) |
| Transplant: Listing year 2012 | 0.23 | (0.0537, 0.407) |
| Transplant: Listing year 2013 | 0.436 | (0.257, 0.615) |
| Transplant: Listing year 2014 | 0.411 | (0.229, 0.594) |
| Transplant: Listing year 2015 | 0.693 | (0.5, 0.886) |
| Donor BUN/Cr Ratio | -0.0195 | (-0.0745, 0.0355) |
| Donor Age $\leq$30 | -0.38 | (-0.47, -0.29) |
| Donor Age 30-50 | -0.186 | (-0.287, -0.0851) |
| Donor-Recipient race mismatch | 0.187 | (0.127, 0.247) |
| Ischemic time (hours) | 0.139 | (0.0932, 0.186) |
| Transplant: age | -0.0163 | (-0.0197, -0.0128) |
| Transplant: female | 0.00115 | (-0.0904, 0.0927) |
| Transplant: BMI <25th percentile | -0.125 | (-0.223, -0.0274) |
| Transplant: BMI >75th percentile | 0.123 | (0.0303, 0.216) |
| Transplant: Ischemic cardiomyopathy | 0.117 | (0.0263, 0.208) |

Mixed-effects model with three-status + expanded donor and candidate variables (continued)

| **Fixed Effect** | **Log hazard ratio** | **95% CI** |
|---|---|---|
| Transplant: Other Diagnosis | -0.376 | (-0.505, -0.246) |
| Transplant: Restrictive cardiomyopathy | -0.105 | (-0.253, 0.0423) |
| Transplant: cross match requested | -0.294 | (-0.409, -0.18) |
| Transplant: blood type AB | -0.133 | (-0.338, 0.0712) |
| Transplant: blood type B | 0.0612 | (-0.0604, 0.183) |
| Transplant: blood type O | 0.0848 | (6.94e-05, 0.17) |
| **Random effect** | **variance** | |
| Intercept | $\sigma_0^2 = 0.048$ | |
| Transplant | $\sigma_1^2 = 0.049$ | |
| Correlation | $\rho_{01} = -0.462$ | |

Base case is a male candidate waiting at Status 1A, dilated cardiomyopathy, blood type A, no cross-match requested, BMI 25th-75th percentile. The random intercept and slope in this model were strongly negative correlated (-0.462, indicating that center-specific hazard ratio of transplantation decreased with increased center-specific waitlist risk. The variance of the survival benefit of transplant was 0.143 on log hazard ratio scale, 11% lower than the three-status model.

Table B.3: **Mixed-effects model with three-status, VAD, and region**

| **Fixed Effect** | **Log hazard ratio** | **95% CI** |
|---|---|---|
| Status 1B | -0.914 | (-0.977, -0.852) |
| Status 2 | -1.57 | (-1.65, -1.49) |
| UNOS Region 2 | 0.163 | (-0.0878, 0.414) |
| UNOS Region 3 | 0.102 | (-0.15, 0.355) |
| UNOS Region 4 | 0.242 | (-0.0155, 0.499) |
| UNOS Region 5 | 0.137 | (-0.116, 0.391) |
| UNOS Region 6 | 0.11 | (-0.242, 0.462) |
| UNOS Region 7 | 0.104 | (-0.155, 0.363) |
| UNOS Region 8 | 0.0085 | (-0.294, 0.311) |
| UNOS Region 9 | 0.0338 | (-0.262, 0.33) |
| UNOS Region 10 | 0.151 | (-0.119, 0.42) |
| UNOS Region 11 | 0.133 | (-0.118, 0.384) |
| LVAD | -0.485 | (-0.549, -0.421) |
| Transplant | -2.36 | (-2.62, -2.09) |
| Transplant: Status 1B | 0.913 | (0.827, 1) |
| Transplant: Status 2 | 1.63 | (1.5, 1.76) |
| Transplant: UNOS Region 2 | 0.0861 | (-0.211, 0.383) |
| Transplant: UNOS Region 3 | 0.127 | (-0.174, 0.428) |
| Transplant: UNOS Region 4 | 0.117 | (-0.187, 0.422) |
| Transplant: UNOS Region 5 | -0.0121 | (-0.311, 0.287) |
| Transplant: UNOS Region 6 | -0.516 | (-0.945, -0.0868) |

| Mixed-effects model with three-status, VAD, and region (continued) | | |
|---|---|---|
| **Fixed Effect** | **Log hazard ratio** | **95% CI** |
| Transplant: UNOS Region 7 | -0.0164 | (-0.325, 0.293) |
| Transplant: UNOS Region 8 | 0.0695 | (-0.284, 0.423) |
| Transplant: UNOS Region 9 | 0.0719 | (-0.277, 0.42) |
| Transplant: UNOS Region 10 | 0.0132 | (-0.307, 0.333) |
| Transplant: UNOS Region 11 | 0.0736 | (-0.225, 0.372) |
| Transplant: LVAD | 0.678 | (0.59, 0.766) |
| Donor Risk Score >5 | 0.265 | (0.21, 0.32) |
| Transplant before 2010 | -0.0254 | (-0.0855, 0.0347) |
| **Random effect** | **variance** | |
| Intercept | $\sigma_0^2 = 0.039$ | |
| Transplant | $\sigma_1^2 = 0.039$ | |
| Correlation | $\rho_{01} = -0.56$ | |

Base case is a candidate waiting at Status 1A, UNOS Region 1, without an LVAD.The random intercept and slope in this model were strongly negative correlated (-0.56), indicating that center-specific hazard ratio of transplantation decreased with increased center-specific waitlist risk. The variance of the survival benefit of transplant in the model including UNOS region and LVAD was 0.122 on log hazard ratio scale, 24% lower than the three-status model.

Distribution of 5-year survival benefit if the best and worst center hypothetically had transplanted all recipients during the study time period. The highest benefit center had a mean five-year survival benefit of 55% compared to only 30% at the lowest benefit center. The means and standard deviations of each center's distribution were used to create the point estimates and 95% confidence intervals, with standard errors calculated using the actual number of transplants performed by the center in the study time period.

Figure B.1: **Non-parametric estimate of the baseline hazard function $\hat{h}_0(t)$ for a candidate who has not yet undergone heart transplantation listed at the mean center**

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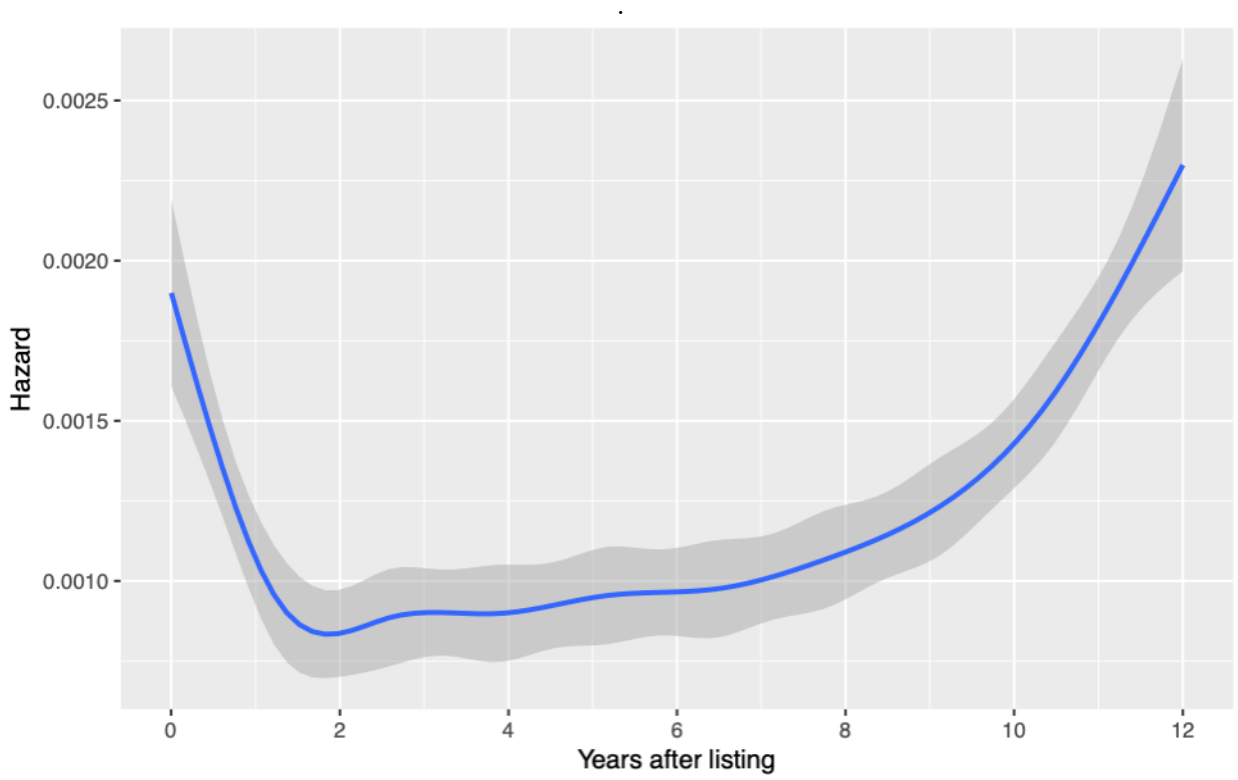



Immediately after listing for heart transplantation, candidates have increased hazard of death. More than 5 years after listing the hazard begins to rise again due to aging and the compounding risks of advance heart failure.

Table B.4: **Mixed-effect model results with three-status and expanded donor factors and listing year**

| **Fixed Effects Covariate** | **log hazard ratio** | **95% CI** |
|---|---|---|
| Status 1B | -0.946 | (-1.01, -0.884) |
| Status 2 | -1.43 | (-1.5, -1.36) |
| Listing year 2007 | -0.0392 | (-0.168, 0.0894) |
| Listing year 2008 | -0.103 | (-0.227, 0.0215) |
| Listing year 2009 | -0.153 | (-0.275, -0.0316) |
| Listing year 2010 | -0.231 | (-0.354, -0.108) |
| Listing year 2011 | -0.312 | (-0.439, -0.184) |
| Listing year 2012 | -0.305 | (-0.43, -0.179) |
| Listing year 2013 | -0.403 | (-0.528, -0.278) |
| Listing year 2014 | -0.335 | (-0.457, -0.213) |
| Listing year 2015 | -0.483 | (-0.612, -0.353) |
| Transplant | -2.4 | (-2.56, -2.25) |
| Transplant: Status 1B | 0.919 | (0.833, 1.01) |
| Transplant: Status 2 | 1.4 | (1.28, 1.53) |
| Transplant: Listing year 2007 | -0.0313 | (-0.195, 0.132) |
| Transplant: Listing year 2008 | 0.0583 | (-0.104, 0.221) |
| Transplant: Listing year 2009 | 0.119 | (-0.0434, 0.282) |
| Transplant: Listing year 2010 | 0.113 | (-0.0538, 0.28) |
| Transplant: Listing year 2011 | 0.257 | (0.0827, 0.43) |
| Transplant: Listing year 2012 | 0.235 | (0.0598, 0.411) |
| Transplant: Listing year 2013 | 0.454 | (0.277, 0.632) |
| Transplant: Listing year 2014 | 0.444 | (0.264, 0.625) |
| Transplant: Listing year 2015 | 0.705 | (0.513, 0.897) |
| Donor BUN/Cr Ratio | -0.0336 | (-0.0882, 0.0209) |
| Donor Age $\leq 30$ | -0.384 | (-0.474, -0.295) |
| Donor Age 30-50 | -0.182 | (-0.283, -0.0816) |
| Donor-Recipient race mismatch | 0.17 | (0.111, 0.229) |
| Ischemic time (hours) | 0.146 | (0.0996, 0.192) |
| **Random effect** | **variance** | |
| Intercept | $\sigma_0^2 = 0.045$ | |
| Transplant | $\sigma_1^2 = 0.057$ | |
| Correlation | $\rho_{01} = -0.481$ | |

Base case is a candidate listed in 2006, waiting at Status 1A, donor ¿50, no race mismatch, ischemic time <1 hour. The random intercept and slope in this model were strongly negative correlated (-0.48), indicating that center-specific hazard ratio of transplantation decreased with increased center-specific waitlist risk. The variance of the survival benefit of transplant was 0.151 on log hazard ratio scale, 6.3% lower than the three-status model.

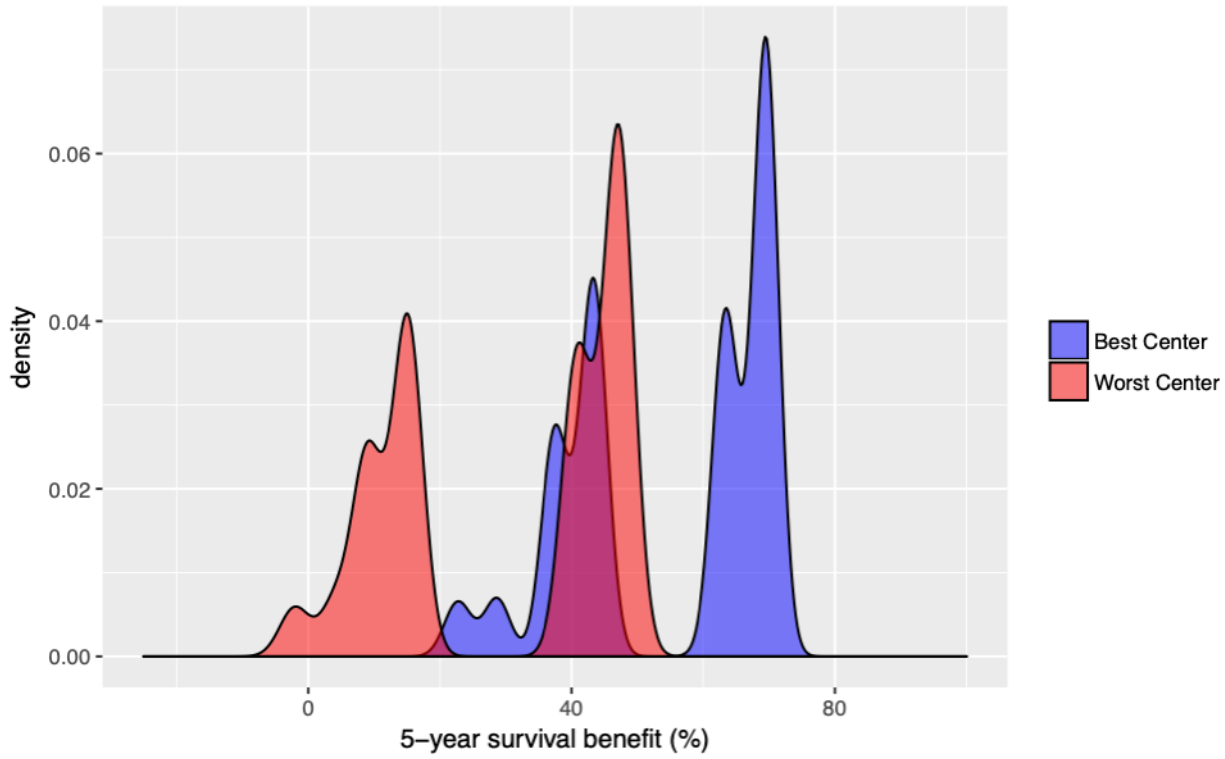
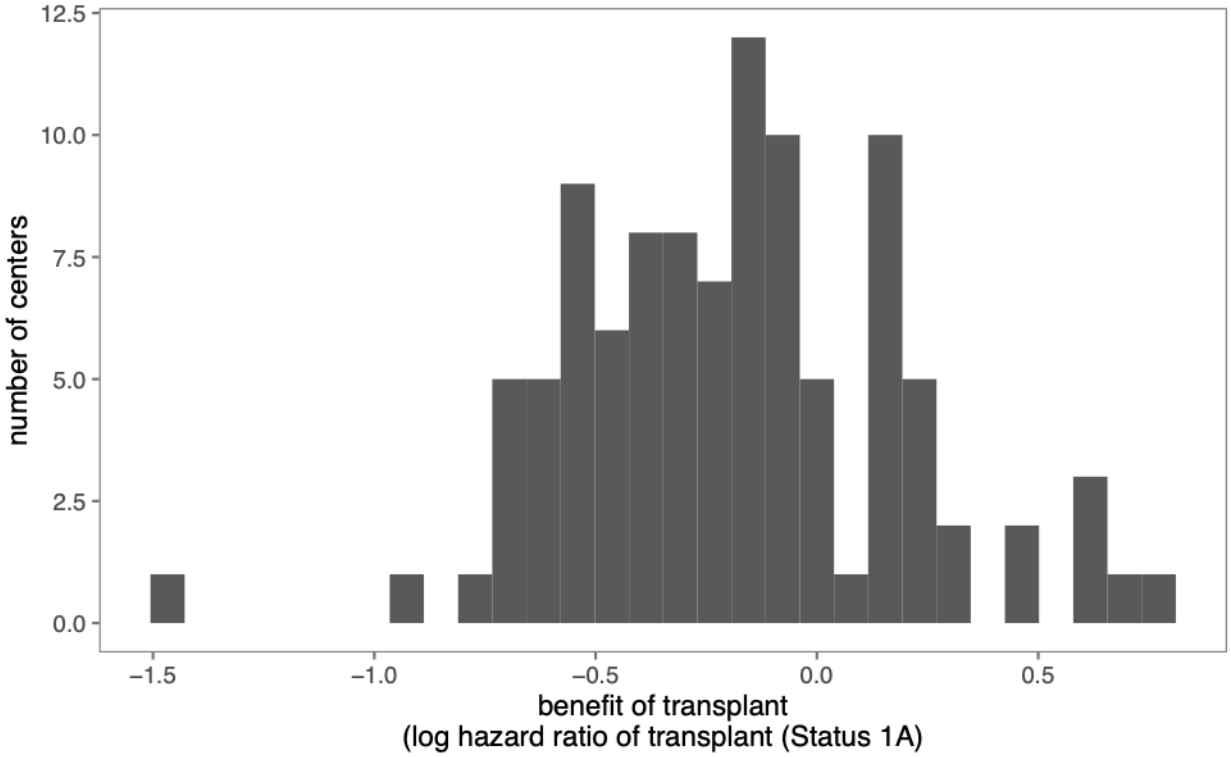


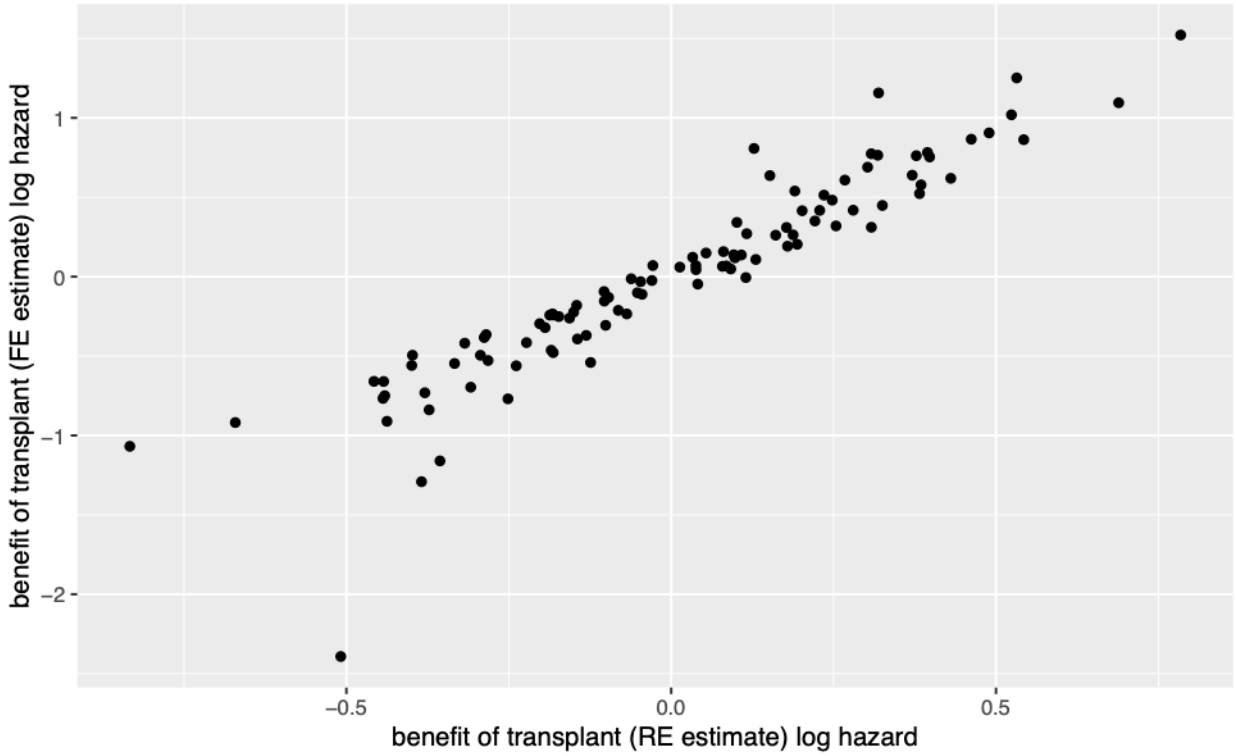

Figure B.2: **Distribution of Five-year Survival Benefit at the Highest and Lowest Benefit Center, 2006-2015**.

Figure B.3: **Histogram of center-specific survival benefits of heart transplantation as estimated by a fixed-effects model**



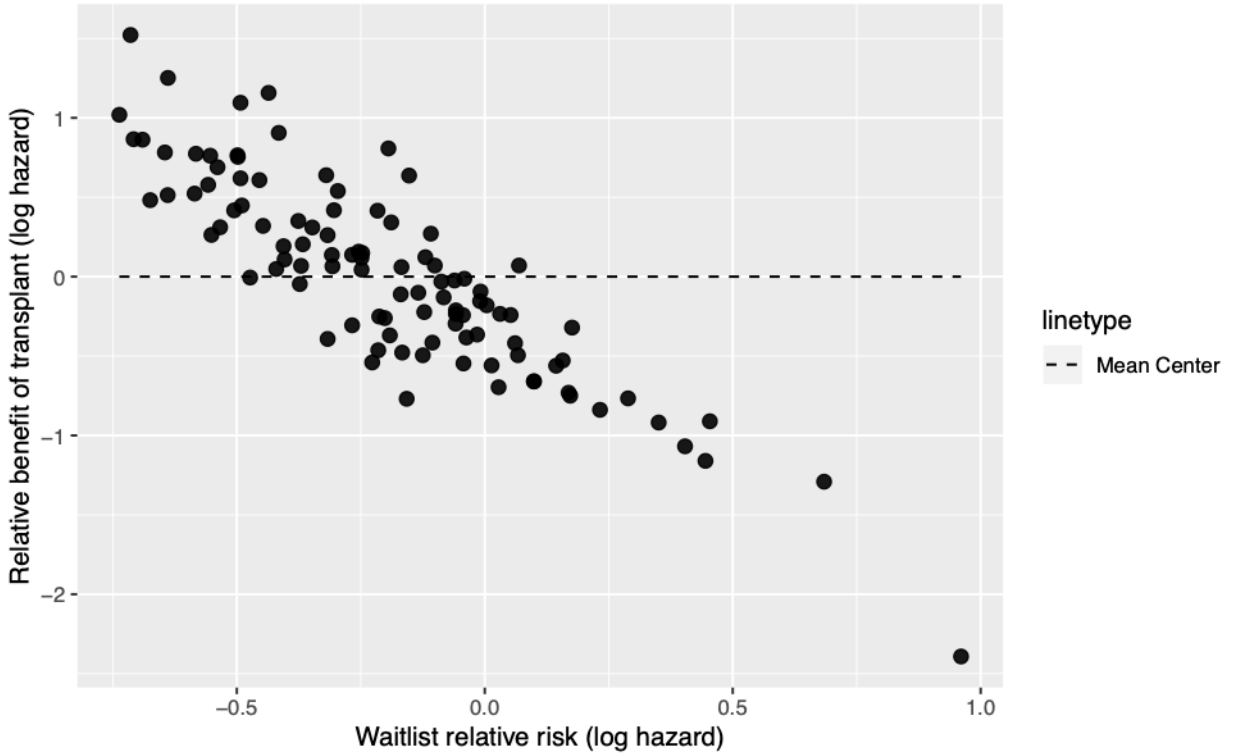

Distribution of center-specific survival benefits for a Status 1A recipient, calculated by subtracting the log hazard of waitlist from the log hazard of transplant at the center. The shapiro-wilk test for non-normality was not significant ($p = 0.18$).

Figure B.4: **Relationship between fixed-effect and random-effect center estimates of survival benefit from heart transplantation**




Scatter plot of center fixed-effect (y-axis) and random-effect (x-axis) estimates of the survival benefit of heart transplantation (on log hazard scale). A spearman correlation between the two was 0.97. The log hazard ratios ore more extreme in the tails for the FE model, a well-known regression effect.

Figure B.5: **Association of center waitlist risk with survival benefit from transplantation in a fixed-effects model**




The association between estimated log hazard of death on waitlist at a given center (x-axis) and log hazard survival benefit (y-axis). A linear association is observed, for every one unit increase in the log hazard of waitlist risk the log hazard of transplant decreased -1.8 (95

# APPENDIX C

# ADDITIONAL METHODOLOGY AND ROBUSTNESS CHECKS FOR SAVING MORE LIVES WITH DECEASED DONOR KIDNEY TRANSPLANTATION

## C.1 Methodology

### *C.1.1 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 deaths after delisting for untransplanted candidates and post-transplant deaths
- Time-dependent indicator variable for transplantation $Tx_i(t)$
  - For each observed transplant:
    - Donor quality $W_j$ (**KDRI Rao**)

* Ischemic time $I_{ikj}$, categorized as (<12 hours, 12-22 hours, >22 hours, or missing)

### *C.1.2 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, extending the model developed in **Chapter 1**.

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

With random effect structure

$$\begin{aligned} \beta_{0i} &= \nu_{0i} \\ \beta_{1i} &= \beta_1 + \nu_{1i} \\ (\nu_{i0}, \nu_{i1}) &\sim N(0, \Sigma) \\ \Sigma &= \begin{pmatrix} \sigma_0^2 & \sigma_{01} \\ \sigma_{01} & \sigma_1^2 \end{pmatrix} \end{aligned} \tag{C.2}$$

this model includes:

- A random intercept $\nu_{0k}$ for each center, representing waitlist risk 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 $\beta_{1k}$, which represents the change in hazard from transplant at a particular center
- A covariance matrix $\Sigma$ for the random effects, which allows for the intercept and transplant effect to be correlated
- Effect of DDKT $\beta_{1k}$ modified by the following interaction effects:
  - Candidate factors $\alpha * X_{ij}$
  - $\Pi$: KDRI $W_j$ and $\gamma$: ischemic time
  - $\zeta$: candidate and donor interactions $W_j * X_{ik}(t)$

Table C.1: **Mixed-effects cox proportional hazards model results**

| 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) |
| 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) |

**Mixed-effects cox proportional hazards model results** (continued)

| Variable | Coefficent | 95% CI |
|---|---|---|
| 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) |

| **Mixed-effects cox proportional hazards model results** (continued) | | |
|---|---|---|
| Variable | Coefficent | 95% CI |
| 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) |
| Random effect | Variance | |
| Waitlist risk ($\nu_0$ ) | 0.04 | |
| Transplant effect ($\nu_1$) | 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

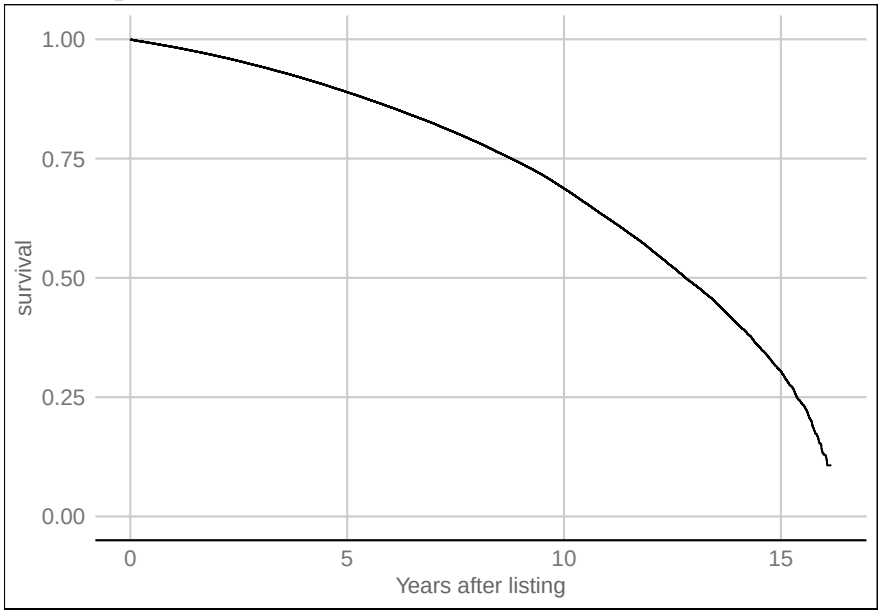
$$Var(\nu_{i1} - \nu_{i0}) = Var(v_{1i}) + Var(\nu_{0i}) - 2 * Corr(v_{1i}, v_{0i}) * \sigma_{v_{0i}} \sigma_{v_{1i}}$$

So for the model estimated above (**Table C.1**), the between-center standard deviation of survival benefit on the log hazard scale is 0.27

## C.2 Absolute survival benefit 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 Parker et al. [2019], 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 C.1**).

Figure C.1: **Non-parametric estimate of the baseline survival function** $\hat{S}_0(t)$




Survival for the base case deceased donor kidney transplantation candidate without transplantation.

To illustrate the full procedure, 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

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

$$\hat{h}_{ijk}(t|waitlist) = \hat{h}_0(t) * (exp(\hat{\beta}_{0k} + X_{ikt}\hat{\beta})$$

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 $t > t_{tx} + 180$

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

3. Calculate the estimated absolute survival benefit at the specified points in time, i.e.

$$Benefit(5-year)_{ijk} = \hat{S}(1825\,days|transplant)_{ijk} - \hat{S}(1825\,days|wait)_{ik}$$

## C.3 Shared decision making tool: Take the offer or wait for a better one?

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

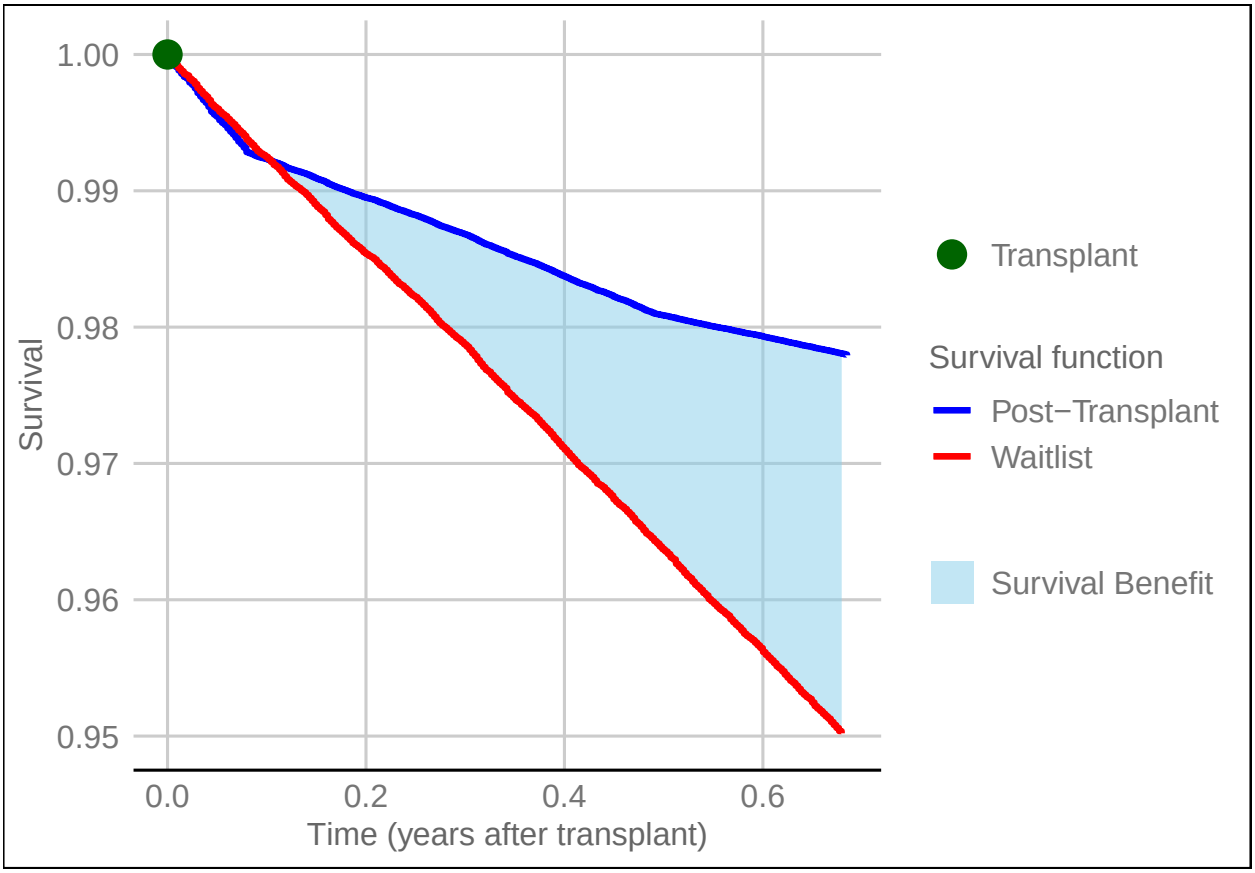
1. Accept kidney $W_j$ after $t_a$ time on the waitlist. This is the same as the standard post-transplant survival function generated by our model

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

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 wait-list 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 $t_b$)

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

Figure C.2: **Non-proportional hazard of deceased donor kidney 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.

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