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Novel Interdisciplinary Approaches To Understanding Kidney Transplantation Outcomes

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NOVEL INTERDISCIPLINARY APPROACHES TO UNDERSTANDING KIDNEY TRANSPLANTATION OUTCOMES

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Abstract

This thesis details 2 studies using novel approaches to understand kidney transplant outcomes: instrumental variables and social network analysis. Together, these studies demonstrate the value of interdisciplinary approaches to advance the field of kidney transplantation.

While some studies have found an association between delayed graft function (DGF) after kidney transplantation and worse long-term outcomes, a causal relationship remains controversial. In our first study, we investigate this relationship using an instrumental variables model (IVM), a quasi-randomization technique for drawing causal inferences. We identified 73,714 adult, deceased-donor, kidney-only transplant recipients from the Scientific Registry of Transplant Recipients (SRTR) between 1997 and 2010. We used cold ischemia time (CIT) as an instrument to test the hypothesis that DGF causes death-censored graft loss and mortality at 1 and 5 years post-transplant, controlling for an array of characteristics known to affect patient and graft survival. We compared our IVM results to a multivariable linear probability model (LPM). DGF occurred in 27% of our sample. Graft loss rates at 1 and 5 years were 6% and 22%, respectively, and 1-year and 5-year mortality rates were 5% and 20%, respectively. In the LPM, DGF was associated with increased risk of both graft loss and mortality at 1 and 5 years ($p<0.001$). In the IVM, we found evidence suggesting a causal relationship between DGF and death-censored graft loss at both 1 year (13.6% increase; $p<0.001$) and 5 years (16.2% increase; $p<0.001$), and between DGF and mortality at both 1 year (7.1% increase; $p<0.001$) and 5 years

(11.0% increase; $p<0.01$). We conclude that instrumental variables analysis supports a causal relationship between DGF and both graft loss and mortality.

Given growth in kidney transplant waiting lists and discard rates, donor kidney acceptance is an important problem. In our second study, we apply tools of social network analysis to examine whether Organ Procurement Organization (OPO) network centrality affects discard rates and recipient outcomes. We identified 96,364 kidneys recovered for transplant from deceased donors in SRTR between 2000 and 2010 and transplanted to adults without previous transplant or 0 HLA mismatches. We constructed the kidney transplant network for each year with each OPO representing a node and each kidney sharing relationship between OPOs representing a directed tie between nodes. The primary exposures were OPO out-degree centrality and in-degree centrality. The primary outcomes were kidney discard, DGF, and 1-year graft loss. We constructed logistic regression models, restricting analysis to observations from the 50% of OPOs with highest discard rate and stratifying remaining OPOs into 2 groups by kidney volume. Models controlled for kidney donor risk index, mean waiting list time, and procurement year and region dummies. Among high-volume OPOs, an increase in one additional OPO to which a kidney was given by a procuring OPO in the procurement year was significantly associated with a 1.8% lower likelihood of discard for a given kidney (OR: 0.982, CI: 0.97, 0.995), but had no association with 1-year graft loss. We conclude that interventions to promote broader inter-OPO sharing should be developed to reduce discard rates.

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Preface

Kidney transplantation is recognized as the treatment of choice for patients with end-stage renal disease (1). This thesis examines novel interdisciplinary approaches to understand kidney transplant outcomes. The first chapter of this thesis leverages instrumental variables analysis, a technique common to the econometric literature, to gain a better understanding of whether delayed graft function (DGF), the most common post-transplant complication, has a causal relationship with kidney transplant recipient outcomes. The second chapter of this thesis leverages social network analysis, a technique common to sociological and organizational behavior literature, to understand whether broader organ procurement organization (OPO) social network connections can lead to decreased discard rates without sacrificing patient outcomes.

A unifying characteristic between these two studies, aside from their interdisciplinary approaches, is the novel way of interpreting cold ischemia time (CIT). CIT is defined as the time from the start of infusion of an organ with cold preservation fluid after an organ is no longer being perfused by a donor until the start of the first vascular anastomosis when the organ is being implanted in a recipient (2). CIT is interesting to the interdisciplinary eye because individuals with unique perspectives can interpret the significance of CIT in different ways. To the cell biologist, CIT can represent a length of accumulation of metabolic waste products that cause cellular damage within an organ. To the surgeon, CIT can represent a measure of donor organ quality while making transplant decisions and a marker of performance in a race against the clock once an organ arrives. To the systems engineer, CIT can represent an inefficiency that needs to

be minimized to maximize overall patient outcomes. Ultimately, to a patient in need of a transplant, CIT can represent the period of excitement, preparation, and joy-tinged apprehension between a long-awaited call and a life-changing surgery.

In this thesis, we approach CIT from 2 different angles. In the first chapter, we look through the lens of an econometrician and view CIT as a source of exogenous variation to draw out causal effects of DGF. In the second chapter, we look through the lens of a sociologist and view CIT as a cost of inter-organizational social interaction. These unique approaches to CIT allow us to draw novel and impactful conclusions on ways to increase kidney supply and improve post-transplant outcomes while demonstrating the value of interdisciplinary approaches to advance the field of kidney transplantation.

Chapter 1: The Causal Effect of DGF on Long-term Kidney Transplant Outcomes Using Instrumental Variables Analysis

Introduction

DGF is an early complication of kidney transplantation that may reflect acute allograft injury and suboptimal early allograft function. DGF results in increased hospital length of stay and costs in the short term (3), but it is unclear if DGF is associated with poor long-term kidney transplant recipient outcomes. Some studies have found that DGF is associated with increased risk of graft loss (4-8) or mortality (9, 10) while others have not found a significant effect (11-15). Determining whether DGF causes worse long-term outcomes would have important implications for the use of DGF as a valid surrogate outcome in transplant clinical trials and for development of therapies to treat DGF.

Plausible biological mechanisms have been described to explain how DGF leads to allograft failure or worse allograft function. Ischemic injury may cause increased HLA expression (16), precipitating rejection and subsequent graft loss. Additionally, maladaptive repair of parenchymal and tubular cells after allograft injury may promote fibrosis and permanent loss of filtration function (17). Alternatively, a relationship between DGF and poor allograft survival might not be causal, since DGF is reversible (18); this relationship could instead be confounded by unobservable characteristics, such as lower intrinsic kidney quality, that cause both DGF and allograft loss.

The use of instrumental variables in multivariable analyses allows one to draw causal inferences with observational data. This technique was developed in economics and has

been widely applied in medical and epidemiological literature (19-24), although rarely in transplantation studies. In traditional linear regression, unobserved variables affecting both exposure and outcomes can confound relationships between these variables (Figure 1). The use of an instrumental variables model (IVM) can overcome this problem by isolating only the variation in the exposure that is not otherwise associated with the outcome. In an IVM, an exogenous instrumental variable is used to predict variation in the exposure variable. These predicted values of the exposure are then used in a regression to determine whether there is a relationship with the outcome of interest. In order for an instrumental variable to be valid, it must be both relevant and exogenous: a relevant instrument is strongly associated with the exposure, and an exogenous instrument is not associated with the outcome except through the pathway of the exposure (25).

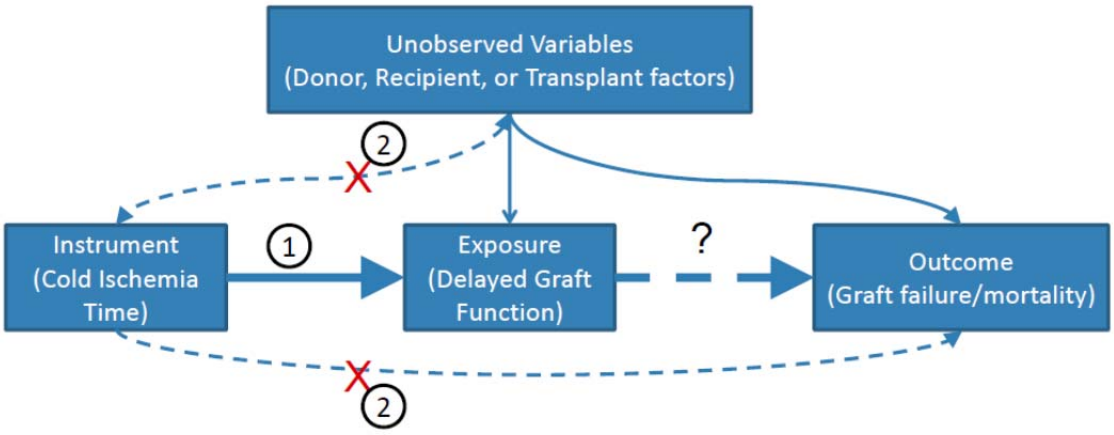


Figure 1. **Instrumental variables analysis**

1. There must be a relevant association between the instrument and the exposure. This bold line indicates that the instrument is relevant.
2. There must not be a relationship between the instrument and the outcome either directly or through association with unobserved variables. The "X" through the thin dotted lines indicates that the instrument is exogenous. Any relationship between the instrument and the dependent variable may only exist through the independent variable.

Statement of Purpose

This study investigated the relationship between DGF and recipient outcomes using CIT as an instrument. DGF stems from ischemic injury to an organ during procurement and transport as well as reperfusion injury in the peri-operative period (26). CIT, a measure of the transport and storage time of an organ, is a relevant instrument for predicting DGF since it has been shown to be an independent risk factor for DGF (27). Additionally, CIT should function as an exogenous instrument, given that CIT is primarily dependent on transport and procurement practices which are unlikely to be related to graft failure or mortality other than through the pathway of DGF. The aim of this study was therefore to determine whether the use of CIT as an instrumental variable supported a causal association between DGF and the outcomes of allograft failure and mortality.

Materials and Methods

Primer on instrumental variables analysis

Instrumental variables regression is a technique that allows one to estimate causal effects with observational data. In traditional linear regression, unobserved variables affecting both exposure and outcome variables can confound relationships between variables. Multivariable linear regression analysis can partially account for this problem by adjusting for many of these confounding variables. However, in certain situations, unobservable confounders, reverse causality, or errors in measurement may still bias the regression model and limit causal interpretation. In the econometrics literature, this definition of bias refers to how, even after accounting for an array of confounders, the

exposure is still associated with the remaining “error term" (also known as residual confounding). Instrumental variables regression overcomes this bias and allows causal interpretation through use of an exogenous instrument.

One can think of the variation in the exposure in such a regression as composed of two components: one which is not associated with the error term; and one which is associated with the error term and therefore pollutes the regression with bias. Instrumental variables regression isolates only the variation in exposure that is not associated with the error term by using an exogenous instrument to predict values of the exposure. This exogenous instrument is completely unrelated to the outcome of interest, and thus, is not associated with an error term. Its only influence on the outcome is through its effect on the exposure variable. The instrument reduces the variation in the exposure variable that is polluted by association with the error term. The remaining variation in the exposure is then used in the multivariable regression with the outcome to produce unbiased estimates of regression coefficients.

Regression coefficients in instrumental variables regression have causal interpretation. An exogenous instrument is used to predict variation in the exposure, independent of variation in the outcome. Thus, any association between the predicted exposure and outcome is a direct *cause* of variation in the exposure only, and the regression coefficients represent how the variation in the exposure *causes* variation in the outcome. Therefore, regression coefficients in instrumental variables regression represent estimates of *causal* effects.

In practice, instrumental variables analysis is commonly calculated using the two-stage least squares regression method. First, an exogenous instrumental variable (*Z*) is used to predict values of the exposure variable (*X*). In this first-stage regression, the instrumental variable is the independent variable and the exposure variable is the dependent variable. Because this exogenous instrument is not correlated with the outcome, the predicted values of the exposure ($\hat{X}$) represent only the variation in the exposure that is not associated with the error term in the original regression (*u*). The predicted values of the exposure ($\hat{X}$) are then used in a regression to determine whether there is a relationship with the outcome of interest (*Y*). In this second-stage regression, the predicted values of the exposure variable comprise the independent variable and the outcome is the dependent variable. One can control for an array of covariates (C_n) in both stages.

First Stage Estimation: $\hat{X} = \beta_Z Z + \beta_n C_n \ldots$

Second Stage Regression: $Y = \beta_{\hat{X}} \hat{X} + \beta_n C_n \ldots + u$

In order for an instrumental variable to be valid, it has to fulfill two assumptions. First, an instrument must be relevant, meaning that it is strongly associated with the exposure. This is usually tested by looking at the first stage of a two-stage least squares regression model. The strength of this relationship can be tested using the general linear test, or F-test, which tests whether the model changes if the instrument is excluded. . An F-statistic > 10 is suggested as a general rule to classify an instrument as relevant (28).

Second, an instrument has to be exogenous, meaning that it cannot be associated with the outcome. This assumption cannot be proven empirically. Instead, one has to rely on theory or knowledge of the subject matter in order to justify why a particular instrument is exogenous. In situations where there are multiple instruments and multiple exposures of interest that are being predicted and if there are more instruments than exposures, one can use a J-test for over-identifying restrictions, which tests whether the second-stage estimates change when instruments are sequentially excluded. However, this test can only rule out instruments that are not exogenous and cannot validate an instrument that is exogenous. Finding an exogenous instrument remains the primary challenge for investigators interested in implementing instrumental variables regression as a tool to make causal inferences. Questioning the exogeneity of an instrument is the major critique of most studies employing this method given the lack of definitive empirical tools to prove the assumption of exogeneity.

In the case of a binary exposure variable, one can think of instrumental variables analysis as a process of pseudo-randomization. One can use variation in the instrument to essentially assign observations to having exposure or no exposure. Because the instrument is strongly associated with the exposure variable, the exposure value assigned by the instrument is likely to match the true exposure value. Because the instrument is exogenous, this assignment is not based on the value of the outcome and is therefore pseudo-random. Instrument variables analysis allows the casual effect to be estimated although the exposure is not randomly assigned.

Participants and study design

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, U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. The data reported here have been supplied by the Minneapolis Medical Research Foundation as the contractor for the SRTR. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by the SRTR or the U.S. Government.

We included all 101,565 adult deceased-donor single primary kidney-only transplant recipients from January 1997 to December 2010 without primary graft failure. We excluded 8,870 recipients with missing CIT, 6,976 recipients who were not on dialysis prior to transplant, and 12,005 recipients with 0 HLA mismatches, given the systematically altered allocation practices of such kidneys that affect both CIT and outcomes. Our final sample was 73,714 observations.

Variables

The primary exposure examined in this study was DGF, as defined by the use of dialysis in the 1st week post-transplant. The primary outcomes included death-censored graft loss and mortality. Graft loss at 1 and 5 years from the transplant date was calculated as

the time to recorded graft failure or the time to the start of a regular course of maintenance dialysis in the SRTR database, whichever was shorter. Patients who died with functioning grafts were not included in either graft loss outcome. Mortality at 1 and 5 years from the transplant date was calculated as the time to death as reported in the Social Security Master Death File with inclusion of additional death dates reported by centers to the OPTN. For the analyses of 5-year mortality and graft loss, we only included the sub-cohort of kidney transplant recipients from January 2000 to December 2006, so that all individuals would have the opportunity for 5 years of follow-up. The instrumental variable was CIT, in hours.

We also included recipient, donor, and allograft characteristics known to affect outcomes as covariates. Recipient characteristics included transplant year, OPO, age, sex, education level (none, grades 0-8, grades 9-12, some college/technical school, associate/bachelor degree, or graduate degree), race (non-Hispanic white, black, Asian, Hispanic, or other), insurance status (public, private, or other), diabetes type (none, type 1, type 2, other type, unknown type, unknown, or missing), days on waiting list, and peak panel reactive antibodies (PRA). Donor characteristics included age, sex, race (non-Hispanic white, black, Asian, Hispanic, or other), history of diabetes, history of hypertension, terminal serum creatinine, cause of death (anoxia, cerebrovascular accident, head trauma, central nervous system tumor, or other), and whether the kidney was a donation after circulatory determination of death (DCDD). Allograft characteristics included number of HLA mismatches and whether the allograft was pumped.

Statistical analysis

To perform IVM analysis, we used a two-stage least squares regression specification: in the first stage, we used CIT as an instrument to predict DGF independent of outcomes; in the second stage, we examined the relationship between predicted DGF values and outcomes. Given that DGF, graft loss, and mortality are all binary variables and that we have included a large number of covariates, the two-stage least squares regression specification was most appropriate for our IVM because it produces estimates that are very similar to nonlinear specifications, such as logistic or bivariate probit (29), yet these estimates are more robust to potential misspecification of the distribution of error terms (30). We compared these IVM results to those from a simple linear probability model (LPM) of the relationship between DGF and outcomes. This LPM was calculated using simple least-squares regression with a binary outcome variable regressed on DGF and all of the covariates included in the IVM.

To assess strength of the IVM, we used the F-test, which examines whether the inclusion of the instrument in the first-stage regression model is relevant. All models adjusted for the recipient, donor and allograft characteristics listed above. Missing data in categorical variables was treated as a separate category using a dummy variable. Observations with missing data in quantitative variables were dropped from the regression model, though this accounted for less than 0.5% of the total sample. All standard errors were heteroskedasticity-robust and clustered around OPO. For ease of interpretation, relative graft loss and mortality rates were approximated from absolute risk differences in the IVM and LPM analyses as 1 + the absolute risk difference divided

by the graft loss or mortality rates among those without DGF in a manner similar to Stukel at al. (23). All analyses were conducted by Neel Butala using STATA 11.0 IC (StataCorp, College Station, TX).

We also conducted several supplemental analyses. In order to remove concerns about the sensitivity of our specification of DGF, we repeated our original analyses using an alternate specification of DGF defined as either dialysis in the 1st week post-transplant or a failure for a recipient's creatinine to decline by 25% or more in the first 24 hours. In order to remove concerns about an alternate pathway between CIT and outcomes, we examined the association between CIT and outcomes among those without DGF in a multivariate linear probability regression using our fully adjusted model. Additionally, we repeated analyses excluding individuals with the top 25% KDRI (31) and stratified our analyses by whether a kidney was pumped.

Results

Baseline characteristics

Descriptive summary statistics classified by median CIT are detailed in Tables A1-A3. CIT in our sample ranged widely and had a median of 17.55 hours (interquartile range 12, 24). Many donor and recipient variables which affect DGF were relatively balanced across median CIT.

DGF occurred in 20,185 participants, which was 27% of the cohort. Death-censored graft loss occurred in 4,382 (6%) individuals by 1 year and 9,252 (22%) individuals by 5 years.

The mortality rates in our sample were 5% at 1 year (n=3,853) and 20% at 5 years (n=9,444).

We assessed the strength of our instruments using the F-test, which examines whether the inclusion of the instrument in the first-stage regression model is relevant. An F-statistic > 10 is suggested as a general rule to classify an instrument as relevant (28). The F-statistics for exclusion of the instrumental variable were 63.56 and 156.80 in the 1-year and 5-year graft loss models, respectively, and 62.48 and 147.02 in the 1-year and 5-year mortality models, respectively. These are all greater than 10, indicating that the instrument was relevant in our models.

Table 1. **Effect of DGF on graft loss and mortality at 1 and 5 years using a conventional linear probability model regression versus an instrumental variable analysis**

Dependent variable	**One year graft loss (N=69,922)**		**Five year graft loss (N=41,138)**		**One year mortality (N=72,879)**		**Five year mortality (N=47,604)**	
Model	*LPM*	*IVM*	*LPM*	*IVM*	*LPM*	*IVM*	*LPM*	*IVM*
DGF coefficient	0.1007	0.1355	0.1248	0.1618	0.0331	0.0711	0.0599	0.1103
(standard error)	(0.0038)	(0.0222)	(0.0047)	(0.0381)	(0.0023)	(0.0149)	(0.0047)	(0.0353)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.002
LPM = Linear Probability Model; IVM = Instrumental Variables Model								
All standard errors are heteroskedasticity robust and clustered by region								
Multiply coefficient by 100 to derive the probability of dependent variable on outcome.								
All models control for the following covariates: transplant year, organ procurement organization, age, sex, educational level, race, insurance status, diabetes type, days on waiting list, peak panel reactive antibodies, and number of HLA mismatches at transplant, donor age, donor sex, donor race, donor diabetes, donor hypertension, whether the kidney was pumped, terminal serum creatinine, donor cause of death, and whether the kidney was a donation after circulatory determination of death.								

DGF and graft loss

DGF was associated with a 10.1% increase in probability of 1-year graft loss ($p<0.001$) in the linear probability model (LPM), which corresponds to an approximate relative risk of 3.98 (Table 1). The magnitude of this effect was larger in the IVM, where DGF was associated with a 13.6% increase in probability of 1-year graft loss ($p<0.001$), corresponding to an approximate relative risk of 5.01. DGF was associated with a 12.5% increase in probability of 5-year graft loss ($p<0.001$) in the LPM, corresponding to an approximate relative risk of 1.69. The magnitude of this effect was larger in the IVM, where DGF was associated with a 16.2% increase in probability of 5-year graft loss ($p<0.001$), corresponding to an approximate relative risk of 1.89.

DGF and mortality

In the IVM, DGF was associated with a 7.11% increase in probability of 1-year mortality ($p<0.001$), corresponding to an approximate relative risk of 2.72 (Table 1). Additionally, DGF was associated with an 11.0% increase in probability of 5-year mortality ($p=0.002$) in the IVM, corresponding to an approximate relative risk of 1.64.

Supplemental results

The rate of DGF as defined by lack of reduction in serum creatinine by 25% in a week was 50.4% (n=28,998) in our sample. Upon repeating our IVM with this alternate specification, we continued to find evidence suggesting a causal relationship between DGF and graft loss at both 1 year (12.0% increase, $p<0.001$) and 5 years (12.9% increase, $p=0.007$) and between DGF and mortality at both 1 year (7.68% increase, $p < 0.001$) and

5 years (8.56% increase, p=0.014). These were similar in magnitude and statistical significance to results using the original specification of DGF, indicating our analysis is robust to this alternate specification.

Upon regressing our outcomes on CIT using only observations without DGF, we found no association between CIT and 5-year graft loss (p=0.221). While we did find a statistically significant association between CIT and 1-year graft loss (b=0.00022, p=0.036) and mortality at 1 year (b=0.00038, p<0.001) and 5 years (b=0.00061, p=0.035), the magnitude of these coefficients were clinically insignificant suggesting these associations were likely a function of our large sample size only and do not refute our assertion that CIT was exogenous.

Upon repeating our original IVM after exclusion of the 20,479 individuals who had a kidney donor risk index (KDRI) greater than 1.155, the 75th percentile in our sample, we continued to find evidence suggesting a causal relationship between DGF and graft loss at 1 year (10.5% increase, p<0.001) and 5 years (10.6% increase, p=0.007) and between DGF and mortality at 1 year (5.94% increase, p=0.001) and 5 years (9.90% increase, p=0.002). These were all similar in magnitude and statistical significance to our original results, indicating our analysis is robust to exclusion of individuals receiving lower quality kidneys.

Approximately 22.2% of our sample (n=16,333) received kidneys that were pumped. Upon repeating our IVM analyses stratifying by whether individuals had received pumped kidneys, we continued to find evidence of a causal relationship between DGF

and graft loss at 1 year (11.6% increase, p<0.001) and 5 years (16.0% increase, p<0.001) as well as between DGF and mortality at 1 year (5.41% increase, p=0.001) and 5 years (12.9% increase, p=0.001) among non-pumped kidney recipients. Among pumped kidney recipients, we continued to find evidence of a causal relationship between DGF and both graft loss (24.9% increase, p=0.007) and mortality (14.5% increase, p=0.006) at 1 year, though we did not find evidence of a causal relationship between DGF and graft loss (6.07% increase; p=0.569) or mortality (9.57% decrease; p=0.369) at 5 years. Our analysis among non-pumped kidney recipients is concordant with our primary results, but among pumped kidney recipients, a causal effect only persists for 1 year outcomes, likely due to loss of statistical power from excluding the majority of our sample (only 6,466 of 41,138 observations remain in 5-year graft loss and only 7,545 of 47,604 observations remain in 5-year mortality models).

Discussion

This study used instrumental variables analysis, a quasi-randomization technique for drawing causal inferences. We used CIT as an instrument for DGF to find evidence suggesting a causal relationship between DGF and both graft loss and mortality at 1 year and 5 years. These effects were robust to exclusion of individuals with high KDRI and pumped kidneys and use of an alternate specification of DGF.

DGF and graft loss

In our study, evidence suggesting a causal relationship between DGF and graft loss was present at both 1 and 5 years in the IVM. These findings are consonant with a 2009

meta-analysis by Yarlagadda et al., which found that patients with DGF had a significantly higher risk of graft loss (RR 1.41, 95% CI: 1.27–1.56) at a mean of 3.2 years of follow-up (32). However, a more recent study by Kayler et al. that used a paired-kidney analysis to examine the impact of CIT-induced DGF on graft failure did not find a difference in graft survival between paired donor transplants with and without DGF when CIT differences were less than 15 hours (33). Of note, in our study, the magnitude of the increase in probability of graft loss at 1 and 5 years as a result of DGF was greater in our IVM analyses (13.55% and 16.18% at 1 and 5 years, respectively) compared to the LPM analyses (10.07% and 12.48%, at 1 and 5 years, respectively) suggesting that other, unaccounted-for variables may be masking the magnitude of the true effect of DGF on graft loss in non-IVM analyses. For instance, kidney transplant recipients who are sicker at baseline may be more likely to get DGF, yet their risk of graft loss may be somewhat mitigated if they receive closer supervision in their post-transplant care than less sick individuals. Such a mechanism could explain the lack of a statistically detectable effect in kidneys with shorter CIT in Kayler et al. While paired kidney analysis controls for unobserved donor characteristics, it does not adjust for unobserved recipient factors confounding the relationship between DGF and graft loss that may have biased this relationship downwards. IVM analysis may offer advantages over a paired kidney analysis in accounting for the effects of confounders.

A potential causal association between DGF and graft loss is supported by experimental studies. Ischemic injury resulting from DGF can cause increased HLA expression or expression of other molecules which may increase graft immunogenicity (16, 34). This

can lead to acute and chronic rejection and subsequent graft loss. Additionally, the addition of severe ischemia-reperfusion injury to a state where one allograft must perform filtration normally done by two kidneys can accelerate permanent nephron loss and contribute to graft failure (35, 36). Furthermore, ischemia-reperfusion injury allows the differentiation of stem-cells into fibroblasts, and other recovering renal cells may acquire the ability to proliferate and synthesize matrix, both which are factors that can lead to fibrosis and subsequent graft loss (17).

DGF and mortality

Evidence suggesting a causal relationship between DGF and death was also present at both 1 and 5 years in the IVM in our study. The meta-analysis by Yarlagadda et al. pooled data from 8 studies and found no significant increase in risk of mortality among those with DGF (32), though one study included in this review by Fontan et al. in 1996 found a relationship between DGF lasting greater than 3 weeks and an excess in mortality (9). A study by Patel et al. published since this review examined 231 high risk deceased-donor kidney transplant recipients who received routine induction therapy with anti-thymoglobulin and found that DGF was associated with a lower 1 year survival rate (99% non-DGF vs. 91% DGF; p=0.001) (37). Additionally, a more recent study by Tapiawala et al. used observations the US Renal Data system between years 1998 and 2004 to examine the relationship between DGF and mortality among those who died with a functioning graft and found that patients with DGF were significantly more likely to die(adjusted HR: 1.53, 95% CI: 1.45-1.63) (10).

DGF can also cause an increase in risk of death through plausible biological mechanisms. DGF can increase mortality because it leads to graft loss and subsequent resumption of dialysis, and survival of patients with a kidney transplant is greater than that of patients on dialysis (38). Additionally, treatment to save failing grafts can predispose to infectious causes of death which lead to poor patient survival after graft loss (39). Among those with a surviving allograft, DGF can cause death through systemic effects, similar to the changes in inflammatory cascades and response to oxidative stress seen in distant organs after acute kidney injury (AKI) (40). Further research is needed to elucidate the precise mechanisms by which DGF can cause mortality in the future.

Implications

Our evidence suggesting that DGF causes a long-term effect in kidneys has important implications for the prognosis of many individuals, given that DGF is the most common immediate post-transplant complication (41). Our results suggest that increased attention should be given to individuals with DGF post-transplant to prevent future graft loss. These patients may benefit from modifications in their induction and maintenance immunosuppression regimens and close monitoring of graft function for several years after discharge (42). The potentially causal association of DGF with graft failure should not suggest an increased rate of refusal of marginal quality organs that may benefit transplant candidates on the waiting list out of fear of DGF, but rather should stimulate development of agents for alleviating effects of ischemia-reperfusion injury and graft failure. Trials evaluating such agents can target DGF as an efficient surrogate outcome for early drug development clinical trials, given the ease and immediacy of

measurement relative to following kidney transplants for several years in order to accumulate graft loss events. Alternatively, patients with DGF can be randomized in treatment trials for testing of clinical management strategies to prevent progression of graft loss. Furthermore, a potential causal effect of DGF on graft loss has important implications for the long-term effects of other types of AKI, given that histological findings on biopsy in kidneys with DGF mimic those found in acute tubular necrosis in native kidneys (43). If the findings concerning the relationship between DGF and graft loss generalize to other types of kidney injury, the results from our study suggest that AKI can potentially cause future chronic kidney disease and add to the growing literature on the long-term effects of AKI (44, 45).

Limitations

Nevertheless, our findings need to be interpreted in light of our limitations. The DGF specification we used wis specific, but not sensitive, and may thus bias our analysis towards an effect (46). However, some patients may require dialysis after transplant for other indications, despite good allograft function, which would bias our analysis towards the null. Our results were also robust to an alternate, more sensitive specification of DGF. Additionally, the two-stage least squares specification for IVM results in artificially large standard errors in settings where binary outcome variables are congregated near 0 or 1, resulting a higher likelihood of rejecting our alternative hypotheses in favor of the null (25). However, we overcame this conservative approach to hypothesis testing with our large sample size, and we found a statistically significant effect in all our IVM analyses. Finally, CIT may not have been a completely exogenous instrument. It is

possible that CIT relates to outcomes through a non-DGF mechanism, such that worse kidneys may be turned down from more centers and take longer to place. Therefore, poor kidney quality could both prolong CIT and associate with allograft failure. However, we adjusted for variables that may reflect kidney quality in our model, which would be expected to lessen the impact of such a mechanism on our results. Additionally, the robustness of our results to exclusion of individuals with a high KDRI, which reflects lower allograft quality, suggests that this mechanism is unlikely. Furthermore, the lack of a clinically significant association between CIT and our outcomes in absence of DGF suggests that the only meaningful relationship between CIT and our outcomes is through DGF. Finally, DGF may have different biological implications among those with pumped kidneys compared to those without pumped kidneys, which may not be completely addressed by simple inclusion of this variable in our primary IVM analyses. However upon stratifying our analyses by whether kidneys were pumped, our findings persisted in all models with the exception of the 5-year outcomes among those with pumped kidneys; this non-significant finding with 5-year mortality outcomes may be due to the exclusion of the majority of our sample in these models.

Overall, this study used a novel technique for analyzing the relationship between DGF and long-term outcomes. Using IVM analyses, we found highly suggestive evidence of a causal effect of DGF on both graft loss and mortality at 1 and 5 years. In addition to the clinical implications of our results on patient prognosis, the results of this study open up

new avenues for research using DGF as a surrogate outcome and improving long-term outcomes by testing therapies to prevent progressive loss in graft function among recipients with DGF.

Chapter 2. The Effect of Organ Procurement Organization Social Network Centrality on Kidney Discard and Transplant Outcomes

Introduction

Kidney transplantation is widely recognized as the treatment of choice for many patients with end-stage renal disease (1). However, the kidney recipient waiting list is growing at a rate that far outstrips the growth in kidney supply (47), which affects the ability of many to receive this life-saving treatment. Furthermore, the discard rate of deceased donor kidneys has increased steadily over the past decade (47), indicating that deceased donor kidney acceptance has become an increasingly important problem. In an effort to address systems-level problems that may be exacerbating the dearth of available organs for transplant, in June of 2013, the United Network of Organ Sharing Board made substantial changes to the kidney allocation policy to be implemented in 2014, which will require sharing of many kidneys on a wider tiered geographic basis (48). On the eve of this revolutionary change in kidney allocation, it becomes important to describe the sharing behavior of OPOs and examine the effect of kidney sharing across geographic areas on allocation and transplant outcomes in order to prepare for the potential effects of this new policy.

Kidney sharing occurs within the organ transplant network. Since the opening of the first regional organ procurement program in 1969, this network developed piecemeal over time until the creation of the unified OPTN in 1984. This network facilitates the transplantation of tens of thousands of organs each year (49), with substantial

geographic variation in practices (50). The evolution of this network has resulted in a complex sharing behavior guided by national and regional allocation policies, behavior of individual OPOs, their relationships with transplant centers and individual patient-surgeon preference (47).

The burgeoning field of network science offers valuable tools to analyze kidney sharing across this complex kidney transplant network. Network analysis tools have proven useful in the development of insight in a variety of fields within medicine, ranging from infectious diseases to obesity (51-53), and in health services research in particular (54-57). However, there has been little work applying these powerful tools to the kidney transplant network in the United States. Although one study has described a static social structure of the transplantation network for different organs (58), to our knowledge there have been no studies describing the dynamics of the organ transplant network structure or relating these transplant network characteristics to outcomes.

Statement of Purpose

This study examined how network centrality characteristics, such as out-degree and in-degree, influence outcomes in kidney transplantation. We hypothesized that kidney discard will be lower when OPOs form sharing relationships that can lead to regular exchange of organs with a greater number of different OPOs and transplant centers. However, we also speculated that broader relationships could come at a cost of increasing CIT due to further geographic sharing, which could lead to poor recipient outcomes. We analyzed interconnectedness among OPOs based on sharing of kidneys

for transplant and changes in network characteristics over time. We then examined whether such OPO network properties had an effect on likelihood of kidney discard and patient outcomes. The results of such analysis can better characterize the social network properties of organ sharing and generate scientific and operational insights into ways to improve the organ transplant network, which can ultimately inform both OPO sharing behavior and national policy in order to improve patient outcomes.

Methods

Participants

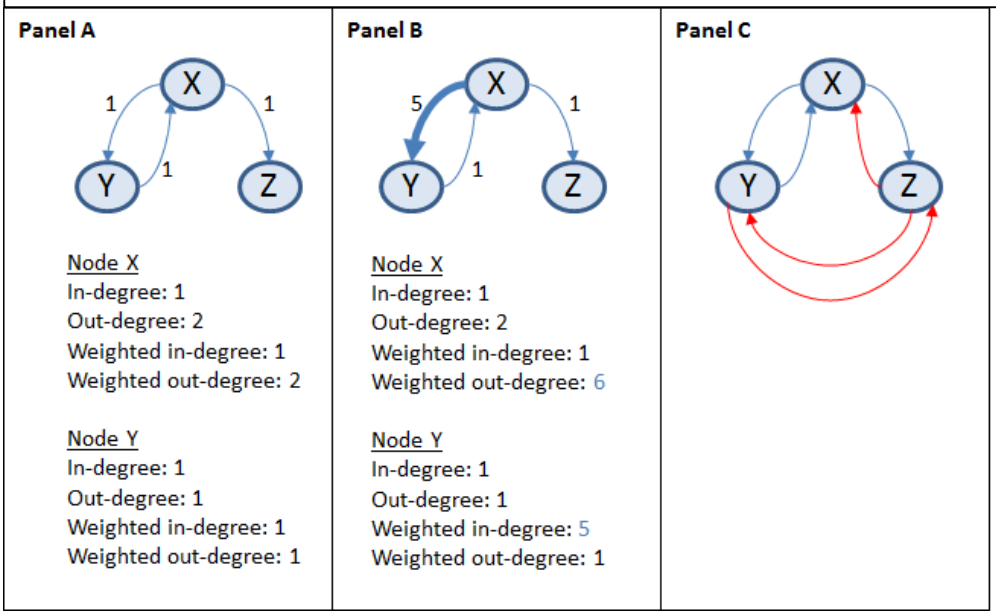
This study used data from the SRTR. We included all 134,747 kidneys recovered for transplant from deceased donors in the United States in the SRTR between January 1, 2000 and December 31, 2010. We sequentially excluded the 9,643 kidneys used in kidney-pancreas transplants, the 14,552 kidneys used in transplants with 0 HLA mismatches, the 4,392 kidneys given to recipients under the age of 18, and the 9,796 kidneys given to recipients with previous transplant, given the systematically altered transplantation allocation practices of such kidneys. Our final sample included 96,364 observations.

Constructing the kidney transplant network

We constructed the kidney transplant network for each year between 2000 and 2010 by limiting our sample to the 14,038 kidneys transplanted during this period that had a different donor and recipient OPO, indicating they were shared across OPOs. Each OPO represented a node in our network in a particular year. We attributed activities of

transplant centers within each OPO's designated service area (such as receipt of kidneys) to that OPO's node, given that OPOs often facilitate this process. Each kidney that was shared across OPOs in a particular year represented a directed connection between 2 OPO nodes. We calculated for each year the network density, a summary statistic across all OPOs defined as the number of different connections present divided by the number of possible different connections between nodes. We additionally calculated out-degree centrality and in-degree centrality for each node. Out-degree is defined as the number of different OPOs to which a particular OPO has given a kidney. In-degree is defined as the number of different OPOs from which a particular OPO has received a kidney. Figure 2 diagrams the concepts underlying these network metrics.

***Figure 2*. Concepts underlying network metrics**
Panel A shows a network with 3 nodes (X, Y, and Z) and 3 kidneys shared among those nodes, along with network centrality metrics for nodes X and Y.
Panel B shows the same network with 4 additional kidneys given from X to Y. There is no change in in-degree or out-degree, but weighted in-degree increases for node Y and weighted out-degree increases for node X.
Panel C shows how network density is calculated. The 3 blue arrows represent connections in the original network. The 3 red arrows describe other possible connections. The density of this network is calculated as the number of connections present (3 blue) divided by the total possible connections (3 blue + 3 red), and is thus 0.5, or 50%.



Variables

The primary outcome in our study was a binary variable indicating whether a kidney was discarded. We additionally looked at transplant recipient outcomes such as CIT in hours, DGF, and death-censored graft loss. DGF was defined as receipt of dialysis in the first week post-transplant. Dichotomous graft loss at 1 year from the transplant date was calculated from time to recorded graft failure or time to start of a regular course of the start of chronic maintenance dialysis in the SRTR database, whichever was shorter. Patients who died with functioning grafts were not included in the graft loss outcome.

The primary exposures examined in this study were 2 measures of social network centrality, out-degree and in-degree, for the procuring OPO in the transplant network in the year of procurement. Although it is possible to weight measures using number of kidneys shared along connections, we chose un-weighted measures of centrality because we were interested in the social network effects of the number of different OPOs to which a particular OPO was connected, as opposed to simply the volume of kidneys shared non-locally, which has been examined briefly elsewhere (59).

We also included as covariates individual kidney KDRI (31) and the mean time spent on the waiting list among transplant recipients in an OPO in a particular year as well as an array of dummy variables indicating procurement year and an array of dummy variables indicating OPO region, defined by the United Network of Organ Sharing.

Statistical analysis

Networks were visualized using the Fruchterman-Reingold algorithm (60). We summarized network characteristics quantitatively and graphically over time.

We estimated pooled cross-sectional logistic regression models with each individual kidney as an observation. We included either out-degree or in-degree as the independent variable and whether a kidney was discarded as the dependent variable, while controlling for an array of dummy variables indicating year and region. We additionally controlled for KDRI and mean waiting time in adjusted models.

We then used separate ordinary least squares regression models with out-degree or in-degree as the independent variable and CIT as the dependent variable. Finally, we estimated pooled cross-sectional logistic regression models with out-degree or in-degree as the independent variable and each of the binary transplant recipient outcomes of interest outlined above as the dependent variable. All such models included KDRI, mean waiting time, and dummy variables indicating year and region as outlined above.

Since we hypothesized that increased connections among OPOs would lead to decreased discard rates, we limited our analysis to observations from the OPOs that were in the upper half of discard rates over the study period in order to increase the number of events used for modeling. Because of a very strong association between likelihood of kidney discard and number of kidneys procured, we stratified analyses by whether a kidney came from an OPO with a kidney procurement volume in the top 50% of OPOs included in our analysis. As a robustness check, we lagged our network metrics

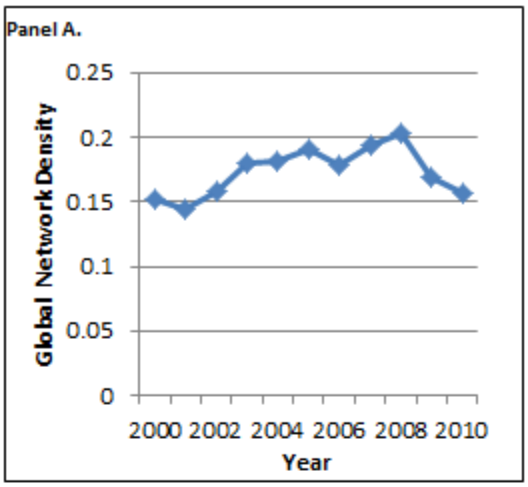
by one year and repeated our analysis for kidneys procured between years 2001 and 2010 in order to test the effect of pre-established relationships on our outcomes of interest and to minimize possibility of endogeneity with whether a kidney was discarded. Additionally, we repeated our analyses of DGF as our dependent variable while including CIT as a covariate to understand the independent effect of social network connections on DGF. All standard errors were clustered around donor OPO in a particular year. All analyses were conducted by Neel Butala using Gephi (Gephi Consortium, Paris, France) and STATA 11.0 IC (StataCorp, College Station, TX).

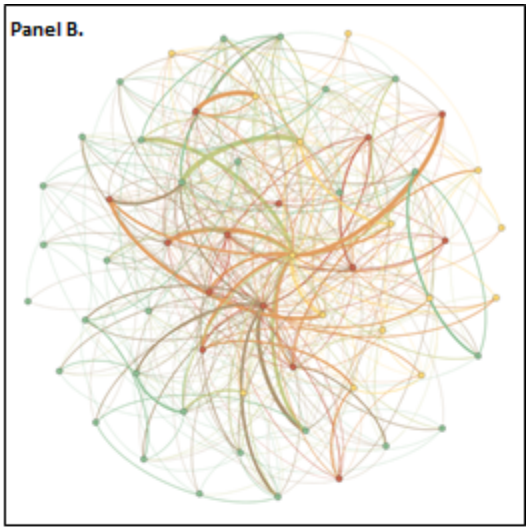
Results

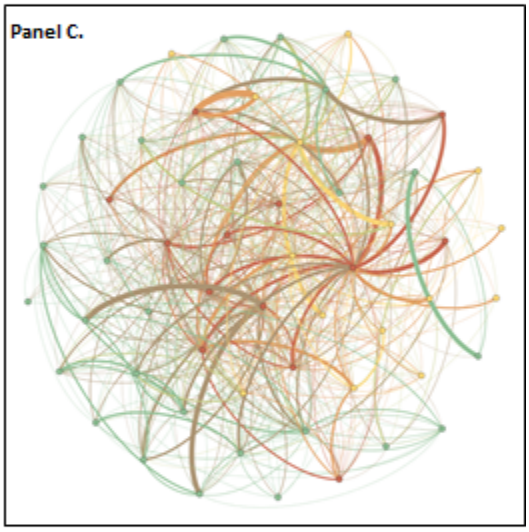
Our sample of kidneys came from 58 OPOs over 11 years resulting in a total of 638 unique OPO-year values. The median discard rate among the 58 OPOs throughout the study period was 22.3%. Thus, we limited our analysis to kidneys from the 29 OPOs with a discard rate greater than 22.3%. Among the remaining OPOs, the median total kidney volume between 2000 and 2010 was 1509 kidneys. We subsequently stratified our analysis into kidneys from the 15 OPOs (and resulting 165 OPO-year values) with a total kidney volume less than or equal to 1509 and kidneys from the 14 OPOs (and resulting 154 OPO-year values) with a total kidney volume greater than 1509.

Transplant network

The OPO network and density over various years in our study period is detailed in Figure 3. The global network density was 0.152 in 2000, indicating that 15.2% of the 3306 possible connections in our network (58 OPOs times 57 possible other OPOs) were







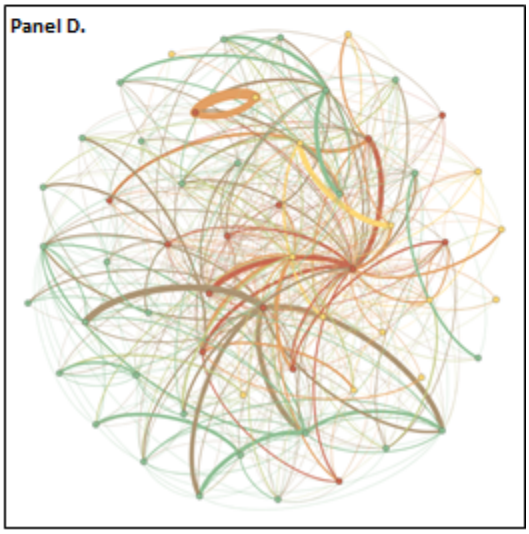


***Figure 3*. OPO network and density from 2000 to 2010**

Panel A. Transplant network density by year
Density = number of distinct connections between nodes/number of possible connections between nodes

Panel B. Transplant network in 2000

Panel C. Transplant network in 2008

Panel D. Transplant network in 2010

Panels B-D.
Edge thickness is proportional to number of kidneys shared.

Node position is based on 2000 network connections.

Node color:
Green = discard rate lower than median discard rate
Yellow = discard rate greater than median discard rate AND kidney volume less than 1509
Red = discard rate greater than median discard rate AND kidney volume greater than 1509

present in our sample in 2000. This decreased to 0.145 in 2001 and then increased steadily to 0.204 in 2008, though fell off precipitously to 0.157 in 2010 (Panel A). The combined global network density for all 11 years was 0.63, indicating that 63% of the 3306 possible connections in our network were present if we consider all 11 years at once. This increased to 0.789 if directionality was ignored (i.e. OPO A sending a kidney to OPO B is the same as OPO B sending a kidney to OPO A). In the OPO network diagram in 2000 (Panel B), most of the centers with a higher discard rate were clustered near the center. In comparing the OPO network in 2000 and in 2008 (Panel C), there were more lines connecting OPOs in the network, indicating that density increased significantly. In comparing the OPO network in 2008 and in 2010 (Panel D), density decreased but lines in the network diagram were thicker, indicating there was greater volume of sharing along certain pre-established relationships.

Baseline characteristics

The baseline characteristics of OPOs and transplant recipients are detailed in Table A4. Among all OPOs in a particular year, the mean out-degree and mean in-degree were 9.90 (equal mathematically), though out-degree ranged from 0 to 34 while in-degree ranged from 0 to 50. Among OPOs with a high mean overall discard rate, the half with higher kidney volume had a greater mean out-degree (14.3) than mean in-degree (14.1) whereas the half with lower kidney volume had a smaller mean out-degree (8.28) than mean in-degree (9.16).

Among all OPOs, the mean yearly discard rate was 22.2%, ranging from 0% to 53.3%. Among OPOs with a high mean overall discard rate during our study period, the mean yearly discard rate was 27% for both high kidney volume and low kidney volume OPOs. Among all transplant recipients, the mean CIT was 17.95 hours, and among OPOs with a high mean overall discard rate, the mean CIT was 18.3 hours for OPOs with both high kidney volume and low kidney volume. Among all transplant recipients, the incidence of DGF was 25.6%, with an incidence of 23.3% among recipients from OPOs with a high mean overall discard rate and lower kidney volume and an incidence of 26.6% among recipients from OPOs with a high mean overall discard rate and higher kidney volume. Among all transplant recipients, the cumulative incidence of 1-year graft loss was 6.39%, with an incidence of 6.63% among recipients from OPOs with a high mean overall discard rate and lower kidney volume and an incidence of 6.98% among recipients from OPOs with a high mean overall discard rate and higher kidney volume.

Network centrality and discard

Our regression analysis of the effect of network characteristics on discard is presented in Table 2. Among OPOs with higher kidney volume, an increase in out-degree was significantly associated with a decrease in likelihood of kidney discard (OR: 0.987, 95% CI: 0.976, 0.998). This association persisted after controlling for individual kidney KDRI and mean recipient waiting time (OR: 0.982, CI: 0.97, 0.995). Thus, in our adjusted model, an increase in one standard deviation in out-degree (i.e. giving kidneys to 6 additional OPOs) by a procuring OPO in the year of procurement was significantly associated with a 10% lower likelihood of discard for a given kidney. In contrast, among

OPOs with lower kidney volume, there was no association between out-degree and likelihood of kidney discard in the unadjusted (OR: 1.006, CI: 0.99, 1.022) or adjusted (OR: 0.988, CI: 0.97, 1.006) models.

Table 2. **Effect of OPO network centrality characteristics on kidney discard likelihood**

Dependent variable	**Kidney discard (binary)**			
Sample	*High kidney volume*		*Low Kidney volume*	
KDRI and mean OPO-year wait time included?	*No*	*Yes*	*No*	*Yes*
Independent variable	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Out-degree	0.987 (0.976 , 0.998)	0.982[A] (0.97 , 0.995)	1.006 (0.99 , 1.022)	0.988 (0.97 , 1.006)
In-degree	1.002 (0.992 , 1.012)	0.99 (0.978 , 1.003)	1.005 (0.995 , 1.016)	1.007 (0.993 , 1.021)
n	38510	38431	13192	13168

[A] *This OR indicates that an increase in one unit of out-degree (i.e. one additional OPO to which a kidney was given) by a procuring OPO is significantly associated with a 1.8% lower likelihood of discard for a given kidney. Similarly, an increase in one standard deviation in out-degree (i.e. giving kidneys to 5.69 additional OPOs) by a procuring OPO in the year of procurement is significantly associated with a 9.8% lower likelihood of discard for a given kidney.*

The effects of out-degree and in-degree on discard were estimated in separate regression models.

All models control for an array of year dummies and an array of region dummies.

OR = odds ratio, KDRI = kidney donor risk index, OPO = organ procurement organization

In models with in-degree as the independent variable (Table 2), there was no association with likelihood of kidney discard among OPOs with higher kidney volume in unadjusted (OR: 1.002, CI: 0.992, 1.012) or adjusted models (OR: 0.99, CI: 0.978, 1.003)

or among OPOs with lower kidney volume in unadjusted (OR: 1.005, CI: 0.995, 1.016) or adjusted models (OR: 1.007, CI: 0.993, 1.021).

Network centrality and recipient outcomes

Our regression analysis of network characteristics and kidney transplant outcomes among OPOs with higher kidney volume is presented in Table 3a. An increase in out-degree was associated with a significantly shorter CIT (B: -0.098, CI: -0.192, -0.004) and a higher incidence of DGF (OR: 1.037, CI: 1.023, 1.051), but there was no significant association with 1-year graft loss (OR: 0.996, CI: 0.987, 1.005). An increase in in-degree had no association with CIT (B: -0.037, CI: -0.122, 0.048) and a higher incidence of DGF (OR: 1.014, CI: 1.006, 1.022), but there was still no significant association with 1-year graft loss (OR: 1.004, CI: 0.996, 1.012).

***Table 3a*. Effect of OPO network centrality characteristics on transplant recipient outcomes from higher volume OPOs**

Dependent variable	**CIT**	**DGF**	**1-year graft loss**
Model	*OLS*	*Logistic*	*Logistic*
Independent variable	*B* (95% CI)	OR (95% CI)	OR (95% CI)
Outdegree	-0.098 (-0.192 , -0.004)	1.037 (1.023 , 1.051)	0.996 (0.987 , 1.005)
Indegree	-0.037 (-0.122 , 0.048)	1.014 (1.006 , 1.022)	1.004 (0.996 , 1.012)
n	25916	28100	26812
The effects of out-degree and in-degree on discard were estimated in separate regression models.			
All models control for kidney donor risk index, mean time spent on waiting list prior to transplant in a particular organ procurement organization in a particular year, an array of year dummies, and an array of region dummies.			
CIT = cold ischemia time in hours, DGF = delayed graft function, OLS = ordinary least squares, OR = odds ratio			

Our regression analysis of network characteristics and kidney transplant outcomes among OPOs with lower kidney volume is presented in Table 3b. An increase in out-degree was associated with a significantly longer CIT (B: 0.239, CI: 0.128, 0.351) and a higher incidence of DGF (OR: 1.049, CI: 1.024, 1.074), but there was no significant association with1-year graft loss (OR: 0.983, CI: 0.96, 1.006). An increase in in-degree was associated with a significantly shorter CIT (B: -0.148, CI: -0.235, -0.062) and a higher incidence of DGF (OR: 1.03, CI: 1.014, 1.046), but there was still no significant association with one year graft loss (OR: 0.991, CI: 0.975, 1.007).

***Table 3b*. Effect of OPO network centrality characteristics on transplant recipient outcomes from lower volume OPOs**

Dependent variable	**CIT**	**DGF**	**1-year graft loss**
Model	*OLS*	*Logistic*	*Logistic*
Independent variable	*B* (95% CI)	OR (95% CI)	OR (95% CI)
Outdegree	0.239 (0.128 , 0.351)	1.049 (1.024 , 1.074)	0.983 (0.96 , 1.006)
Indegree	-0.148 (-0.235 , -0.062)	1.03 (1.014 , 1.046)	0.991 (0.975 , 1.007)
n	8901	9547	9136
The effects of out-degree and in-degree on discard were estimated in separate regression models.			
All models control for kidney donor risk index, mean time spent on waiting list prior to transplant in a particular organ procurement organization in a particular year, an array of year dummies, and an array of region dummies.			
CIT = cold ischemia time in hours, DGF = delayed graft function, OLS = ordinary least squares, OR = odds ratio			

Supplementary results

As a supplementary analysis, we repeated our analyses on out-degree and kidney discard among OPOs with high volume using lagged out-degree as the independent

variable to eliminate any potential endogeneity. We found that our results were robust to use of a lagged out-degree measure instead of out-degree in the unadjusted model ($p=0.009$), though the adjusted effect attenuated slightly ($p=0.058$). Additionally, inclusion of CIT as a covariate in any model with DGF as the dependent variable did not attenuate the effect of out-degree ($p<0.001$) or in-degree ($p=0.002$) in high-volume OPOs or the effect of out-degree ($p<0.001$) or in-degree ($p<0.001$) in low-volume OPOs

Discussion

Our study describes the trends in the organ transplant network over time and examines the effects of social network centrality of OPOs on likelihood of kidney discard and kidney transplant outcomes. This is the first comprehensive analysis of organ transplant network trends. We demonstrated that sharing kidneys with a greater number of different OPOs was associated with a significantly lower likelihood of kidney discard among OPOs with high discard rates and kidney volumes. An increase in 6 additional OPOs to which a kidney was given in a year by a procuring OPO was significantly associated with a 10% lower likelihood of discard for a given kidney. Additionally, we find that CIT, which could be considered a cost of social interaction, was lower with both broader sharing of kidneys among high-volume OPOs, indicating scale-dependency in social connections, and receiving kidneys from a broader network of OPOs among low-volume OPOs, providing evidence suggesting inter-organizational social learning effects.

Transplant network

Our construction of the kidney network adds to the literature on applying network science to organ transplant. One study constructed a kidney transplant network using U.S. states as nodes and found a combined density of 0.87 in looking at all living and deceased-donor transplants between 1987 and 2010 while ignoring directionality (i.e. differences in whether kidneys were received or sent) (58). Similarly, while our study found much lower densities for each year, if we combined all years we found a density of 0.630 in a directed network, which increased to 0.789 if we ignored directionality.

Our study also looked at trends in density by year, finding a linear increase in density over our study period, aside from decreases in 2001, in 2006, and in the years post-2008. Some of this linear increase could stem from changes in kidney allocation policy, such as the allocation algorithm for ECD kidneys in 2002, which caused a reduction in non-local sharing (61). Of note, the two major declines in density coincided with major economic crises in the United States such as the technology bubble in 2001 and the mortgage-backed security crisis in 2008. One explanation for this is decreased procurement during these times, as observed in Europe following the most recent recession (62, 63), though we did not find evidence of decreased procurement over time in the United States in our data. We instead hypothesize that a decrease in organ sharing may stem from a reduction in capital required for OPOs to operate inter-OPO relationships or through financial difficulties troubling capital-intensive transplant center operations reducing sharing, though this remains a rich area for further inquiry as more years of follow-up during economic recovery become available.

Network centrality and discard

Our finding that, among higher volume OPOs, greater social network out-degree centrality, or sharing among a larger network of OPOs, was associated with lower likelihood of kidney discard without affecting graft loss adds to the literature on the effects of broader sharing on discard rates and outcomes. In Europe, a center-oriented rescue algorithm encourages broader sharing after 5 organ refusals (64), and rescued kidneys do not have worse outcomes (65). In the United States, the implementation of DonorNet in 2007 in attempt to expedite organ procurement by permitting simultaneous offers on a national scale resulted in an increase in non-local sharing of kidneys and a reduction in discard rates for kidneys hardest to place (66), though an increase in overall discard rate (67). However, DonorNet required systematic offers in concert with the national match run list, and the effect of broader social ties found in our study applies largely to cases when OPOs went outside of the approved algorithm.

The observed effect of greater social network centrality on reducing likelihood of kidney discard in high volume OPOs can stem from several causes. One study found that discard rates among extended-criteria donor kidneys were often influenced by factors not otherwise associated with graft performance, such as machine perfusion and biopsy results, and much of the local variation in discard rates could not be explained by observable kidney characteristics (68). In fact, some have proposed that kidney acceptance is a function of a center-level aggressiveness phenotype, which is determined in part by waiting times and geographic region (69). Our results extend this work and demonstrate that sharing among a larger network of OPOs can allow an OPO

to potentially take advantage of its social knowledge of variation in kidney preferences and aggressiveness in order to increase likelihood of kidney acceptance. Additionally, another study found that many centers used acceptance criteria listed in DonorNet improperly, resulting in many surplus offers, which can lead to offer overload and network-wide inefficiency (70). In this context, having a broader network of transplant centers with which an OPO is familiar can allow OPOs to target more aggressive centers that may be more likely to accept a higher risk kidney more quickly.

Network centrality and CIT

Our findings on the impact of social network centrality on CIT add to the literature on CIT and broader sharing and provide evidence for scale-dependency in social connections and inter-organizational learning effects. One international study found improvements in CIT with broader sharing, though this was largely due to capacity constraints on number of surgeons available to transplant two recovered kidneys at one center (71). Several studies have found that the implementation of DonorNet had no effect on CIT locally or regionally, but resulted in a slightly higher CIT among all kidneys shared nationally (59, 66, 67). Our study combined regionally and nationally-shared kidneys and found evidence supporting 2 distinct network effects. First, we found that broader sharing of kidneys was associated with a lower CIT among high-volume OPOs and a higher CIT among low-volume OPOs, suggesting increasing efficiency in dealing with transporting kidneys to diverse locations as transplant volume increases. Second, we found that, among low-volume OPOs, receiving kidneys from a broader set of OPOs is associated with a lower CIT, suggesting a social learning effect. Relatively

inexperienced OPOs with centers receiving kidneys from a more diverse set of OPOs may also receive knowledge on techniques for transport of kidneys that can then be used to lower CIT among kidneys transported from that OPO in the future.

Network centrality and DGF

Our finding that greater OPO in-degree or out-degree centrality was associated with increased risk of DGF in kidneys, irrespective of network effects on CIT, is consonant with the literature on kidney sharing and DGF. A recent study found that donor and recipient factors were more likely than CIT to lead to DGF for kidneys that were shared outside of the local OPO (59). Increased levels of DGF in our study among OPOs that share more broadly may be mediated through non-CIT mechanisms, such as recipient characteristics or warm ischemia time, which have also been found as risk factors for DGF (72). In fact, inclusion of CIT in all of our models in supplementary analyses did not attenuate the effect of broader kidney sharing on DGF. Thus, the increased risk of DGF in our study likely stems from unaccounted-for characteristics of donors or recipients as opposed to direct effects of broader kidney sharing. These non-CIT mechanisms are independent of the causal pathway identified in the first chapter of this thesis, and are thus consonant with the findings in Chapter 1, despite elevated DGF and no impact on recipient outcomes found in results from this chapter.

Implications

Our findings have important implications for both OPO behavior and allocation policy to reduce discard rates. We find that among high-volume OPOs, having broader

connections is associated with a lower likelihood of kidney discard but not a higher rate of 1-year graft loss, suggesting that broader connections should be encouraged through policy to improve organ utilization. Some have called for an improved allocation system to share locally-rejected organs in a more timely manner (59), highlighting that the current tiered allocation system creates room for inefficiencies (73). The changes in allocation policy slated for implementation in 2014 make progress in certain respects, such as better matching of donor and recipient characteristics, but fall short in others, such as creating even more tiers of local, regional, and national offers (48), which can lead to greater inefficiency. An evaluation of the equity and efficiency of DonorNet 2007 found that efficiency of hard to match kidneys worsened after implementation and suggested a quicker heuristic may be necessary (67). The existence of an effect on discard in our study suggests that heuristics on likelihood of acceptance may already exist in the social knowledge gathered by the most connected OPOs. Future policy should encourage OPOs to seek out and take advantage of that knowledge to utilize their difficult-to-place kidneys, perhaps through education programs targeted to OPOs with fewer connections, public reporting of OPO and center acceptance rates, or even implementation of a rescue algorithm similar to Europe.

Limitations

Our findings should be interpreted in light of our limitations. First, we cannot control for volume of kidneys due to multicollinearity with likelihood of kidney discard. However, we are able to stratify by volume of kidneys to understand the modifying effect of this variable. Additionally, our findings may not generalize to the entire population of

procured kidneys, as we only look at kidneys from OPOs with a high discard rate. However, one can argue that methods to improve utilization of kidneys are most necessary in the high-discard-rate OPOs that our study examined. Finally, there may be some endogeneity inherent to the relationship between out-degree and likelihood of kidney discard, given that constructing the out-degree variable necessitates considering only kidneys that were not discarded. However, this is low because only a 14.6% of kidneys are shared beyond OPO borders. Additionally, if we lag our out-degree measure by 1 year, we find that the effect of out-degree on reducing likelihood of kidney discard among high-volume centers still persists in unadjusted models, though this effect is slightly attenuated in adjusted models.

Overall, this study introduced concepts of network science to understand transplant outcomes and discard rates. We found that, among a subset of OPOs, greater social network centrality was associated with lower likelihood of kidney discard without sacrificing patient outcomes. These findings have implications for amending allocation policy to encourage broader OPO connections to aid in kidney placement. Additionally, we found evidence of scale-dependency in network effects and inter-organizational social learning. Future research should examine the application of other network science concepts, such as modularity, hierarchy, or diffusion, to kidney transplant and the investigation of the effects of social network effects in other organ transplant networks.

Conclusion

This thesis examines kidney transplant outcomes in novel ways, leveraging interdisciplinary methodologies. Not only do we present findings that can inform development of therapies to improve organ survival, organ allocation decisions, and reduction in organ discard rates, but we also introduce novel methodologies to the transplant literature to spur future research.

The implications of our findings are significant in the context of kidney transplantation. In chapter 1, we found that DGF was causally related to long-term outcomes at 1 and 5 years. In addition to the prognostic implications of our results for patients and physicians, our results open up new avenues for research using DGF as a surrogate outcome and improving long-term outcomes by testing therapies to prevent progressive loss in graft function among recipients with DGF. In chapter 2, we found that sharing kidneys with a broader network of OPOs was a method to reduce kidney discard without sacrificing patient outcomes. This has implications for modifying OPO behavior as well as national allocation policy to encourage broader OPO connections to improve acceptance of donor kidneys.

Our findings also introduce novel methods to the transplantation literature. In chapter 1, we introduced CIT as a valid instrumental variable for DGF for the first time. This novel instrument can be used to examine casual relationships between DGF and other factors or to analyze causality in broader systems issues. In chapter 2, we constructed for the first time the OPO social network and found evidence suggestive of inter-

organizational social learning in looking at network centrality. This OPO social network concept can be used to study the impact of other network characteristics on kidney transplantation and in other organ transplant networks. Overall, this thesis demonstrates the value of orthogonal interdisciplinary approaches to advance the field of kidney transplantation.

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Appendix

Table A1. Recipient and donor characteristics (categorical variables), stratified by median cold ischemia time

Variable	n (% of total)	n CIT<17.55 hrs (%)	n CIT>=17.55 hrs (%)
Total sample	73714 (100%)	36854 (50%)	36860 (50%)
Recipient characteristics			
Gender			
Female	27942 (38%)	13951 (50%)	13991 (50%)
Male	45772 (62%)	22903 (50%)	22869 (50%)
Education			
None	504 (1%)	267 (53%)	237 (47%)
Grade school (0-8)	4628 (6%)	2335 (50%)	2293 (50%)
High school (9-12) or GED	29829 (40%)	15177 (51%)	14652 (49%)
Attended college/technical school	14124 (19%)	7312 (52%)	6812 (48%)
Associate/bachelor degree	7981 (11%)	4117 (52%)	3864 (48%)
Post-college graduate degree	3082 (4%)	1579 (51%)	1503 (49%)
Unknown	12337 (17%)	5629 (46%)	6708 (54%)
Missing	1229 (2%)	438 (36%)	791 (64%)
Race			
Other	1486 (2%)	864 (58%)	622 (42%)
White	31583 (43%)	16065 (51%)	15518 (49%)
Black	26289 (36%)	12734 (48%)	13555 (52%)
Asian	4489 (6%)	2466 (55%)	2023 (45%)
Hispanic	9867 (13%)	4725 (48%)	5142 (52%)
Insurance			
Other	566 (1%)	223 (39%)	343 (61%)
Private	19179 (26%)	9742 (51%)	9437 (49%)
Public	53969 (73%)	26889 (50%)	27080 (50%)
Diabetes Type			
No	47930 (65%)	24114 (50%)	23816 (50%)
Type I	1485 (2%)	827 (56%)	658 (44%)
Type II	8650 (12%)	4683 (54%)	3967 (46%)
Other Type	106 (0%)	58 (55%)	48 (45%)
Unknown Type	13743 (19%)	6491 (47%)	7252 (53%)
Unknown	665 (1%)	281 (42%)	384 (58%)
Missing	1135 (2%)	400 (35%)	735 (65%)
Donor characteristics			
Gender			
Female	30233 (41%)	15053 (50%)	15180 (50%)

Male	43481 (59%)	21801 (50%)	21680 (50%)
Race			
Other	725 (1%)	365 (50%)	360 (50%)
White	51888 (70%)	26254 (51%)	25634 (49%)
Black	9927 (13%)	4776 (48%)	5151 (52%)
Asian	1728 (2%)	921 (53%)	807 (47%)
Hispanic	9446 (13%)	4538 (48%)	4908 (52%)
History of Hypertension			
None	53549 (73%)	27217 (51%)	26332 (49%)
Yes, 0-5 years	9439 (13%)	4682 (50%)	4757 (50%)
Yes, 6-10 years	3227 (4%)	1530 (47%)	1697 (53%)
Yes, >10 years	3587 (5%)	1629 (45%)	1958 (55%)
Yes, Unknown duration	3189 (4%)	1459 (46%)	1730 (54%)
Unknown	643 (1%)	308 (48%)	335 (52%)
Missing	80 (0%)	29 (36%)	51 (64%)
History of Diabetes			
None	68822 (93%)	34548 (50%)	34274 (50%)
Yes, 0-5 years	2304 (3%)	1136 (49%)	1168 (51%)
Yes, 6-10 years	776 (1%)	330 (43%)	446 (57%)
Yes, >10 years	804 (1%)	373 (46%)	431 (54%)
Yes, Unknown duration	556 (1%)	269 (48%)	287 (52%)
Unknown	368 (0%)	168 (46%)	200 (54%)
Missing	84 (0%)	30 (36%)	54 (64%)
Kidney pumped			
Not pumped	57111 (77%)	29709 (52%)	27402 (48%)
Pumped	16333 (22%)	7024 (43%)	9309 (57%)
Missing	270 (0%)	121 (45%)	149 (55%)
Cause of Death			
Anoxia	11330 (15%)	5718 (50%)	5612 (50%)
Stroke	30358 (41%)	14999 (49%)	15359 (51%)
Head trauma	29691 (40%)	15075 (51%)	14616 (49%)
CNS tumor	541 (1%)	264 (49%)	277 (51%)
Other	1730 (2%)	776 (45%)	954 (55%)
Missing	64 (0%)	22 (34%)	42 (66%)
Non-Heart Beating Donor			
Missing	106 (0%)	34 (32%)	72 (68%)
No	67702 (92%)	34070 (50%)	33632 (50%)
Yes	5906 (8%)	2750 (47%)	3156 (53%)
CIT = cold ischemia time			

***Table A2*. Recipient and donor characteristics (continuous variables), stratified by median cold ischemia time**

Variable	Mean (SD)	Mean if CIT <17.55 hrs (SD)	Mean if CIT >=17.55 hrs (SD)
Recipient age	51.21 (12.99)	51.06 (13.16)	51.36 (12.84)
Days on waiting list	818.78 (651.89)	829.31 (652.77)	808.26 (650.86)
Peak PRA[A]	2 (15)	2 (15)	2 (15)
HLA mismatches	4.22 (1.21)	4.27 (1.19)	4.18 (1.23)
Donor age	39.32 (16.69)	38.93 (16.35)	39.71 (17.02)
Donor serum creatinine	1.15 (1.11)	1.10 (1.03)	1.20 (1.18)
SD = standard deviation; CIT = cold ischemia time; PRA = panel reactive antibody			
[A] Peak PRA reported as median (IQR)			

***Table A3*. Exposure and outcome variables, stratified by median cold ischemia time**

Variable	n (% of total)	n CIT <=17.5 hrs (%)	n CIT >17.5 hrs (%)
DGF			
No	53423 (73%)	28508 (53%)	24915 (47%)
Yes	20185 (27%)	8293 (41%)	11892 (59%)
One year graft loss			
Graft functional	66329 (94%)	33562 (51%)	32767 (49%)
Graft lost	4382 (6%)	1893 (43%)	2489 (57%)
Five year graft loss			
Graft functional	32461 (78%)	15733 (48%)	16728 (52%)
Graft lost	9252 (22%)	4098 (44%)	5154 (56%)
One year mortality			
Alive	69861 (95%)	35093 (50%)	34768 (50%)
Deceased	3853 (5%)	1761 (46%)	2092 (54%)
Five year mortality			
Alive	38837 (80%)	18604 (48%)	20233 (52%)
Deceased	9444 (20%)	4234 (45%)	5210 (55%)
CIT = cold ischemia time			

***Table A4*. Characteristics of OPOs and transplant recipients**

	Total (all high and low discard, high and low volume)				High discard, low volume (n<1509 kidneys)				High discard, high volume (n>1509 kidneys)			
	n	**Mean**	**SD**	**Range**	**n**	**Mean**	**SD**	**Range**	**n**	**Mean**	**SD**	**Range**
OPO-year characteristics												
Network measures												
Out-degree	638	9.90	5.69	0-34	165	8.28	4.77	1-25	154	14.3	5.88	2-34
In-degree	638	9.90	7.26	0-50	165	9.16	8.24	0-39	154	14.1	8.52	4-50
Operational measures												
Discard rate (%)	638	22.2	8.6	0-5.3	165	26.5	8.1	6.4-50.0	154	26.8	7.84	7.8-53.3
Mean KDRI	638	1.047	0.087	0.829-1.29	165	1.062	0.091	0.853-1.29	154	1.084	0.0865	0.829-1.24
Mean days on waiting list	638	773	254	242-1788	165	741	222	323-1612	154	855	277	380-1788
Individual kidney/recipient characteristics												
Likelihood of discard (%)	96384	23.2			14701	27.0			38510	26.9		
CIT (hours)	67079	18.0	9.36	0.01-99	10025	18.3	9.48	0.02-99	25966	18.3	8.76	0.08-99
Likelihood of DGF (%)	74013	25.6			10730	23.3			28155	26.6		
Likelihood of 1-year graft loss (%)	70805	6.39			10264	6.63			37219	6.98		

OPO = organ procurement organization, SD = standard deviation, KDRI = kidney donor risk index, CIT = cold ischemia time, DGF = delayed graft function