Kidney Transplant Outcomes for Prolonged Cold Ischemic Times in the Context of Kidney Paired Donation

by

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Thesis Submitted in Partial Fulfillment of the
Requirements for the Degree of
Master of Public Health

in the
Master of Public Health Program
Faculty of Health Sciences

SIMON FRASER UNIVERSITY

Summer 2017

Approval

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Degree: **Masters of Public Health**

Title: ***Kidney Transplant Outcomes for Prolonged Cold Ischemic Times in the Context of Kidney Paired Donation***

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Ethics Statement

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Abstract

The need for kidneys outweighs the current organ supply. This study examines the impact of longer cold ischemic time (CIT) on graft outcomes to help expand living donor transplantation in kidney paired donation (KPD). In a retrospective cohort study of 48,498 living donor (LD) recipients in the United States between 2005-15, multivariate survival analyses reveal no association between CIT <16 hours for all-cause graft loss, or death-censored graft loss (hazard ratios for CIT 8.0-16.0 hours (0.97; 95% CI 0.74-1.26) and (1.09; 95% CI 0.81-1.48) respectively, compared to CIT 0.1-2.0 hours). These results were robust in LD >50 years and in KPD and non-KPD transplants.

While there was a higher incidence of delayed graft function (DGF) in groups with longer CIT, the overall incidence of DGF was low. Multivariate regression analyses show increased odds of DGF only in CIT 8.1-16 hours compared to 0.1-2.0 hours (odds ratio: 1.47; 95% CI 1.05-2.05).

Keywords: Living donor kidney transplantation; kidney paired donation; cold ischemia time; delayed graft function; survival

Acknowledgements

This thesis would not have been possible without all the guidance, support, and generosity from my thesis committee. I would like to extend my gratitude to Malcolm Steinberg, my senior supervisor who invested so much time in answering my questions, reviewing my thesis, providing constructive feedback, and travelling off campus for meetings.

I would also like to express my sincerest gratitude towards Jagbir Gill and Caren Rose. Jagbir Gill provided considerable guidance and expertise for my thesis topic, and has been exceedingly generous with his time invested in this thesis. Caren Rose has been one of the biggest contributors to my thesis completion. She mentored me and gave me the opportunity to work with her. She gave me that last push to finish my thesis, consistently encouraged me, and provided expertise on epidemiologic methodology.

Finally, I would like to thank my dearest partner, Sophie Sherlock, for her infinite patience, continuous emotional support, and grounding me when I needed it the most.

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List of Acronyms

Term	
ACGL	All-Cause Graft Loss
ANZDATA	Australia New Zealand Dialysis and Transplantation
CIT	Cold Ischemic Time
CKD	Chronic Kidney Disease
DCGL	Death Censored Graft Lost
DGF	Delayed Graft Failure
ESRD	End Stage Renal Disease
KPD	Kidney Paired Donation
PRA	Panel Reactive Antibody
SRTR	Scientific Registry of Transplant Recipients

Glossary

Term	
All-Cause Graft Loss	the loss of a graft due to either death or allograft failure
Australia New Zealand Dialysis and Transplantation	an international registry for dialysis and transplantation data in Australia and New Zealand
Cold Ischemic Time	time graft is in an anoxic state of preservation, also known as cold storage (Irish et al., 2003)
Chronic Kidney Disease	defined as either kidney damage or a decreased glomerular filtration rate of less than 60 mL/min/1.73m^2 for at least 3 months (NKF, n.d.)
Death Censored Graft Lost	the loss of graft function due to the death of a recipient
Delayed Graft Failure	when dialysis is required within a week of graft transplantation
End Stage Renal Disease	when the kidneys' filtration rate drops to less than 15mL/min/1.73m^2 and kidney transplantation or dialysis are needed to survive (NKF, n.d.)
Kidney Paired Donation	program which pools other incompatible pairs all across Canada and reallocates donors to compatible candidates through a mathematical matching algorithm (Canadian Blood Services (CBS), n.d.)
Panel Reactive Antibody	an immunological test of the proportion of native antibodies rejecting foreign antibodies
Scientific Registry of Transplant Recipients	a registry of data on all U.S. donors, wait-listed candidates, and transplant recipients. These data are provided by the Organ Procurement and Transplantation Network (OPTN), which is made up of all American transplant centres and overlooked by the Health Resources and Services Administration (HSRA) and the U.S. Department of Health and Human Services

Chapter 1.

Background

Chronic Kidney Disease

Kidneys serve many essential functions in our bodies without which we could not survive. They filter our blood to excrete waste products and excess fluid from our bodies in the form of urine. In addition, they help maintain cardiovascular and skeletal health through the production of hormones, which regulate blood pressure, red blood cell, and calcium production (National Kidney Foundation (NKF), n.d.). When kidney function starts to decline, the kidney's abilities to filter blood and produce hormones are compromised leading to what is called chronic kidney disease (CKD), historically referred to as chronic renal failure. CKD is defined as either kidney damage or a decreased glomerular filtration rate of less than 60 mL/min/1.73m^2 for at least 3 months. As kidney disease progresses, inadequate glomerular filtration and hormone production may lead to health complications such as anemia, skeletal and cardiovascular disease, elevated potassium and phosphorus, as well as fluid build up in the body (NKF, n.d.). When the kidneys' filtration rate drops to less than 15mL/min/1.73m^2, this is the last stage of CKD and is known as end-stage renal disease (ESRD). At this point, the kidneys' functions have declined to the extent where, in order to survive, one would need either dialysis or a kidney transplant.

While chronic kidney disease cannot be cured, it can be prevented or managed. Primary prevention involves reducing the incidence of kidney disease. Kidney disease can be prevented through education and awareness of risk factors and of the disease itself; proper diet and exercise; and reducing risky behaviours

such as smoking (Australia Institute of Health and Welfare (AIHW), 2005). Secondary prevention consists of early detection of kidney disease. Early detection of kidney damage is essential in implementing interventions that aim to prevent or delay chronic kidney disease. Secondary prevention can include screening of high-risk populations (e.g. with risk factors such as vascular disease, high blood pressure, diabetes, Aboriginal populations, or a family history of renal disease) (AIHW, 2005). Finally, tertiary prevention aims at preventing or reducing the progression of chronic kidney disease, and in doing so, reducing the incidence of ESRD and related comorbidities. This consists of proper management of high blood pressure and diabetes through a well-controlled diet and exercise plan, supplemented by drug therapies (e.g. angiotensin-converting enzyme, blood pressure, and blood glucose drug therapies) (AIHW, 2005).

This thesis will focus on the last stage of CKD, end-stage renal disease, when patients require treatment.

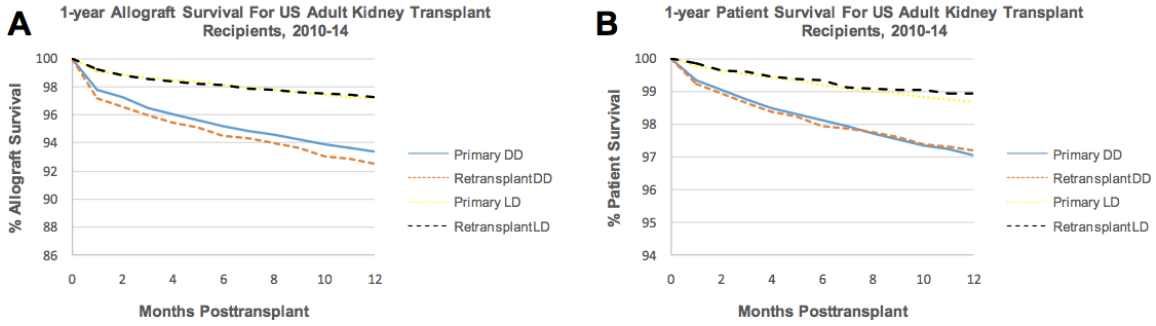
Treatments for End-Stage Renal Disease

There are currently two forms of treatment for patients suffering from end-stage renal disease (ESRD): dialysis and transplantation.

Dialysis is a method used to filter blood and extract metabolic by-products and excess fluids that would otherwise be excreted by the kidneys. However, given that filtering blood is only one of the many functions of the kidneys, persons dialyzed may still experience health-related complications such as cardiovascular or skeletal diseases (NKF, n.d.). Persons on dialysis can survive many years, but patients' quality of life decreases sharply over the years, and the mortality rate is high (Tonelli et al., 2011). In addition, dialysis is a costly method, requiring resources and time both on the part of the patient and health care system (Canadian Organ Replacement Register (CORR), 2015, Statistics Canada, 2017).

Kidney transplantation is the preferred treatment for ESRD since it offers better survival and quality of life compared to dialysis. Kidney transplantation involves taking a kidney from a donor and implanting it into a blood and tissue compatible candidate. There are two types of transplantation: living donor and deceased donor transplantation. Deceased donor kidney transplantation has significantly shorter graft survival rates as compared with living donor kidney transplantation (Nemati, Einollahi, Pezeshki, Porfarziani, & Fattahi, 2014) (see Figure 1.1). A systematic literature review of studies exploring the associations between dialysis and kidney transplantation with mortality and quality of life found that overall, patients having had a kidney transplantation experienced lower rates or mortality and cardiovascular events compared to those on dialysis (Tonelli et al., 2011). In addition, in spite of an aging and sicker ESRD population, the benefits of transplantation, including improved quality of life, increase significantly over time compared to dialysis (Tonelli et al., 2011).

Figure 1.1 A comparison of deceased and living kidney donor allograft and patient survival



Wang, Skeans & Israni, 2016

As such, living donor kidney transplantation is the best treatment for ESRD compared to both deceased kidney transplantation and dialysis. However, due to a shortage of kidneys, the most common treatment for ESRD is dialysis. The average cost of dialysis per one patient year is $70,000 (CORR, 2015, Statistics Canada, 2017). While the average cost of kidney transplantation in the first year after transplantation is $100,000, this cost decreases to an average of $20,000 for each subsequent year (CORR, 2015, Statistics Canada, 2017). In addition to the substantial health and quality of life benefits inferred by kidney transplantation, the cost of transplantation after five years is on average $250,000 less than dialysis (CORR, 2015, Statistics Canada, 2017).

Kidney Transplantation Outcomes

For patients with ESRD who are transplanted, there are three major post-transplant renal outcomes that are used for evaluating the success of the kidney transplant: delayed graft function (DGF), all-cause graft loss (ACGL), and death (Mikhalski et al., 2008; Schwartz, Nankivell & Alexander, 2010).

DGF, defined by the need for dialysis within a week post-transplantation, is more common among deceased than living donor transplants, with an

incidence between 20-50% and 4-10% respectively (Wu, Famure, Li & Kim, 2015). DGF is thought to occur due to damage from ischemia (anoxic state of preservation, also known as cold storage) and reperfusion (reoxygenation) of the organ at the time of transplantation, but its etiology is not well documented (Irish et al., 2003). DGF results in prolonged hospital time and the patient's need for increased medical attention (e.g. dialysis, diagnostic tests, supervision of immunosuppressive therapy) incurring substantial health care expenses compared with immediately functioning grafts (Irish et al., 2003; Mikhalski et al., 2008). DGF is also associated with an increase in acute graft rejections and allograft failure (Simpkins et al., 2007). However, the association between DGF and allograft failure has not been consistently established (Wu et al., 2015). Important risk factors for DGF among deceased kidney transplants include increasing donor age, prolonged cold ischemic time (CIT), and human leukocyte antigen (HLA) crossmatch positive. Risk factors for DGF among living donations are less well understood: kidneys from deceased donors can be damaged from death-related events such as brain death or cardiac injuries and as such, prior associations for risk factors that have been well-established among deceased donor transplants cannot necessarily be generalized to living donors transplants (Krishnan et al., 2016; Simpkins et al., 2007).

ACGL is another major post-transplant outcome for kidneys (Mikhalski et al., 2008; Schwartz et al., 2010). The most common cause of ACGL is the death of the recipient while the graft is still functioning (death with functioning graft) in patients > 40 years (El-Zoghby et al., 2009, Morales et al., 2012). Risk factors for ACGL include acute rejection episodes, high panel reactive antibody (PRA), human leukocyte antigen (HLA) mismatches, infections, older donor age, hypertension, diabetes, use of certain immunosuppressants, non-adherence to immunosuppression regimens, re-transplantation, and DGF (NKF, n.d.; McCaughan, Patterson, Maxwell & Courtney, 2014).

Epidemiology of Kidney Disease in Canada

End-stage renal disease (ESRD) is increasingly prevalent in Canada, and in 2012, was the 10th leading cause of death (CORR, 2015, Statistics Canada, 2017). In 2014 alone, there were 5,269 new cases, and from 1995 to 2014, ESRD has more than tripled, reaching a high of 41,931 cases (CORR, 2015). Of these 41,931 cases, 58.5% are treated with dialysis, and the remainder have received a kidney transplant. The leading causes for kidney failure are diabetes (responsible for 36% of cases) and renal vascular disease (responsible for 13% of cases). (CORR, 2015). Other causes include glomerular nephritis, inherited and congenital childhood diseases, and acute kidney injuries (CORR, 2015).

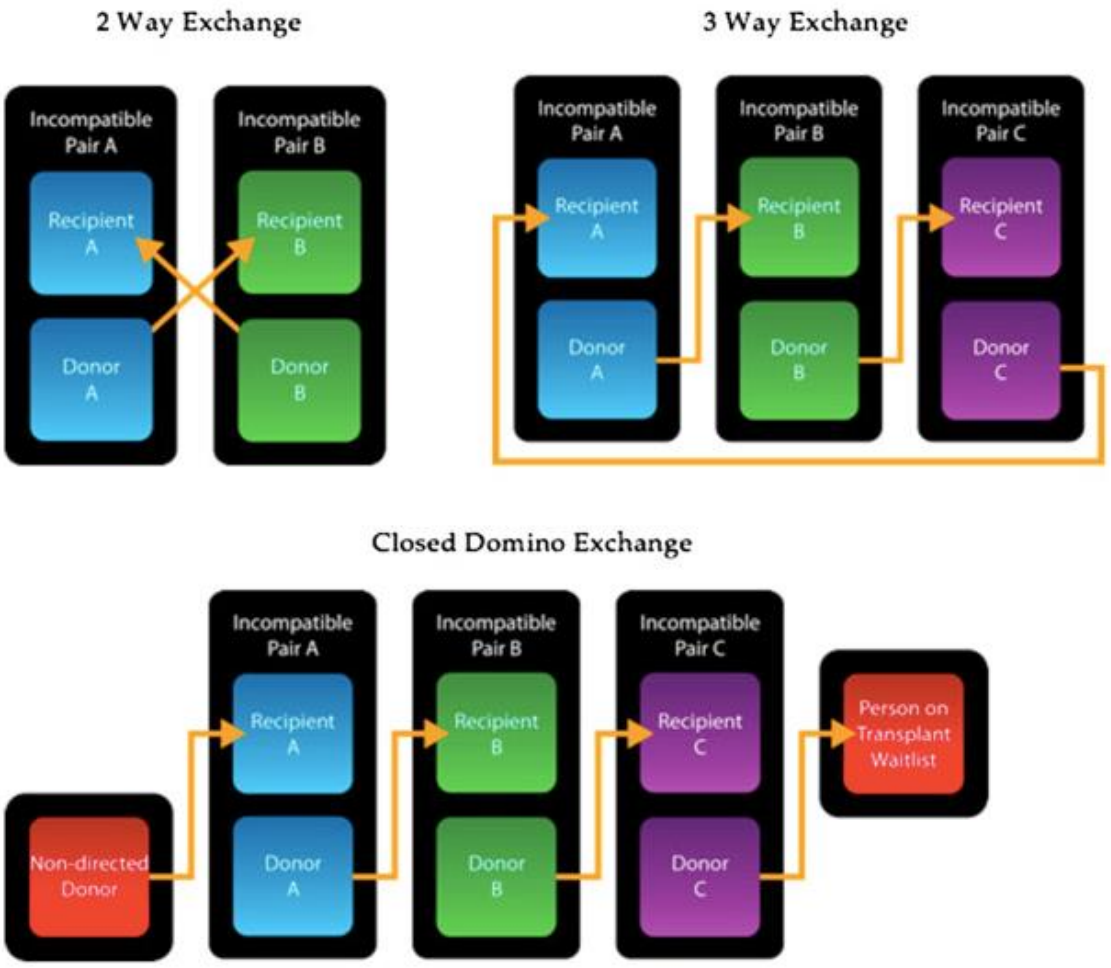
In 2014, 4,433 patients were on an organ waiting list, of which 75% were waiting for kidneys (CORR, 2015, Statistics Canada, 2017). The median wait time across Canada for a deceased donor kidney is 4 years, varying from 2.5 years in Nova Scotia to 5.4 years in Saskatchewan (CORR, 2015). This is especially troubling given that less than 50% of dialysis patients survive more than 5 years on dialysis (CORR, 2015). Meanwhile, living donor kidney transplants only make up 32% of kidney transplants (CORR, 2015).

Kidney transplantation is far preferred over dialysis for its health, quality of life, increased life expectancy, and cost saving benefits (Tonelli et al., 2011). However, the supply of kidneys is insufficient (Tonelli et al., 2011). With the increasing demand for kidney transplantation, coupled with the limited supply of deceased donor kidneys, the aging and sickening population of dialyzed patients, the high mortality rate of dialyzed patients, and the increasing wait list times for deceased donor kidneys, new methods must be developed to expand living donor transplantation (Tonelli et al., 2011).

Kidney Paired Donation

The need for kidneys outweighs the current organ supply and deceased kidney donation rates have not shown any increase since 2006 (KFC, n.d.). One new strategy that has been implemented in Canada to optimize the use of living donor kidneys is kidney paired donation (KPD). For transplant candidates who have incompatible living donors, the donor and candidate can enter the national kidney paired donation program which pools other incompatible pairs all across Canada and reallocates donors to compatible candidates through a mathematical matching algorithm (Figure 1.2) (Canadian Blood Services (CBS), n.d.). While a large number of the matches made within the KPD program are within-city matches, 53% of matches made between 2009-2013 have required either the donor or the candidate to travel (CBS, n.d.).

Figure 1.2 A graphical representation donation exchange in the KPD program



Malik & Cole, 2014

Having the donor travel as a result of an inter-city match in the KPD program can incur significant costs and may delay the transplant. In addition, 25% of matches between 2009-2013 have declined their match pair for non-medical reasons, which may partly be due to an unwillingness or inability to travel on the part of the donor or the candidate (CBS, n.d.). Delays in kidney transplantation carry risks to the patient. While the association between longer dialysis duration and living donor kidney transplant outcomes are less well understood, longer dialysis duration among patients having received a deceased

donor kidney has been associated with poorer graft and patients outcomes (Resende et al., 2009).

To reduce in-person travel-related barriers to kidney paired donation, some programs in the United States ship living donor kidneys to candidate cities. However, shipping kidneys, as opposed to the donor or candidate travelling to undergo surgery in the same location, involves the cold storage of the kidney, which may impact graft outcomes. Studies have shown that among deceased donors, kidneys with longer cold storage times, also described as cold ischemic times, have poorer graft outcomes relative to kidneys with shorter cold ischemic times; however, this association is less well understood for living donor kidneys (Simpkins et al., 2007). The current standard of care in Canada is for the donor to travel to the candidate as opposed to shipping the donor kidney. This is an effort to minimize cold ischemic time (CIT) and its impact on patient and graft outcomes. Further, the transportation of kidneys poses logistical and structural challenges for the transplant program. However, given the large proportion of matched pairs requiring travel that are declined in the KPD program and logistical delays caused by the need to travel, the benefit of limiting delays in kidney transplantation through shipping of the kidney may outweigh risks potentially associated between longer CIT and graft outcomes. As such, given the critical need to expand kidney donation, and in particular, living donor kidney donation, it is urgent to better understand the risks associated with longer CIT in living donor kidney graft and patient outcomes.

Should Kidneys be Shipped? - Literature Review

In the context of shipping living donor kidneys through KPD programs, two studies have examined the impacts of longer cold ischemic times on graft outcomes. Simpkins et al. (2007) found an increased risk of delayed graft function (defined as the need for dialysis within the first week of transplantation) among recipients in the U.S. between 1990-2005 with kidneys having 4-6 hours

of cold ischemic time versus 0-2 hours. However, no association with all-cause graft loss (ACGL), or death-censored graft loss was reported for CIT <8 hours.

Krishnan et al. (2016) published a study using the Australia and New Zealand Dialysis & Transplant Registry (ANZDATA). They found that living donor kidney transplant recipients between 1997-2012 had 28% increased odds of delayed graft function (DGF) with additional hour of CIT. This effect was larger for donors > 50 years. Further, Krishnan et al. (2016) also found an increased risk for ACGL with CIT 4-8 hours compared with CIT 1-2 hours for donors > 50 years.

While both of these studies agree on the impact of longer CIT with DGF, CIT has only been explored up to 8 hours. Further, these studies found contradictory relationships with longer CIT and ACGL. As such, there is a need to explore the relationship with graft outcomes for CIT > 8 hours.

In addition, Simpkins et al.'s (2007) cohort precedes the proliferation of the KPD program in the U.S. in recent years. Krishnan et al. (2016) examine more recent years; however their sample size for recipients participating in the KPD program is too small to draw meaningful insights. It is important to explore the relationship between KPD recipients versus directed living donor recipients because longer CIT in KPD is likely due to shipping times rather than surgical complications.

Research Questions

In this thesis, I will evaluate the impact of kidney transplantation outcomes for living donor kidneys undergoing longer CIT (≤ 16 hours). In accordance with previous literature, I hypothesize that my results will show a dose response relationship of elevated risk of DGF with longer CITs. Further, I believe I will discover a significant relationship between longer CIT and ACGL and DCGL, and

that this relationship will be exaggerated in donors > 50 years. Canada does not yet ship living donor kidneys. Therefore, data from the United States will be used to assess the potential benefits that shipping kidneys could add to Canada's national KPD program.

Dependent variable: Cold ischemic time (CIT)

Stratifications:

1) Donor age > 50 years

2) Being enrolled in the KPD program

Outcomes:

1) Delayed graft function (DGF)

2) All-cause graft loss (ACGL)

3) Death-censored graft loss (DCGL)

Chapter 2.

Methods

DATA SOURCE AND STUDY POPULATION

Data from the U.S. Scientific Registry of Transplant Recipients (SRTR) was used to define the study cohort. The SRTR is a registry of data on all U.S. donors, wait-listed candidates, and transplant recipients, with follow-up data available until December 2, 2015. These data are provided by the Organ Procurement and Transplantation Network (OPTN), which is made up of all American transplant centres and overlooked by the Health Resources and Services Administration (HSRA) and the U.S. Department of Health and Human Services. In 2014, there were a total 98,956 adult kidney transplant candidates on the U.S. waiting list, of which 16,676 were transplanted. Of those, 11,594 were deceased donor transplants, and 5082 were living donor transplants (SRTR, 2014).

Inclusion Criteria:

All blood type compatible, first, living donor, kidney-only transplant recipients from the United States between January 1, 2005 – October 31, 2015 with available cold ischemic time (CIT) were included. October 31, 2015 was chosen as the end of follow up date over December 2, 2015 as it allows for delayed data entry of kidney transplant outcomes. To assess external validity, I compared the characteristics of transplants with and without CIT recorded, using medians and quartiles for continuous variables, and frequencies and proportions for categorical variables. Group differences were compared using the Kruskal-

Wallis or chi-square test as appropriate. N=12,333 of recipients were missing CIT. There were no differences in donor and recipient characteristics between groups, and no difference in the proportion of post-transplant outcomes.

Exclusion Criteria:

All recipients (1.6%) with CIT > 16 hours were excluded from this study as CIT > 16 hours is rare in living donor kidney transplantation, and long CITs may be related to transplant complications during transplant not representative of the study population.

DESCRIPTIVE STATISTICS

The distribution of CIT in the cohort is shown among KPD transplants and non-KPD transplants. Consistent with previous research and an exploratory analysis of its distribution, CIT was stratified into the following categories: 0-2.0 hours, 2.1-4.0 hours, 4.1-8.0 hours, and 8.1-16.0 hours (Krishnan et al., 2016; Simpkins et al., 2007).

Recipient, deceased donor, transplant/surgical, and immunosuppression at discharge characteristics were described across CIT groups using the median and quartiles for continuous variables or frequencies and proportions for categorical variables; group differences were compared using the Kruskal-Wallis or chi-square test as appropriate and were considered significant at alpha=0.05.

Subgroup Analyses

CIT was compared among subgroups of donor age and kidney paired donation (KPD). Donor age was stratified into all donors, and donors > 50; KPD was stratified in those receiving kidney transplants as part of the KPD program and those not (i.e. directed donation).

ANALYTICAL STATISTICS

Outcomes:

Association of Cold Ischemic Time with Delayed Graft Function:

For each CIT stratum, the incidence of delayed graft function (DGF) was calculated. The association of CIT and DGF was explored using a multivariable logistic regression model. DGF was defined as the requirement for dialysis within one week of transplantation. Recipients receiving kidneys before ever being dialyzed (i.e. preemptive transplantation) may retain some of their original kidney function and be misclassified as not having DGF. Therefore, this analysis excluded these patients as they may bias the relationship between CIT and the requirement for dialysis after transplantation.

Association of Cold Ischemic Time with Allograft Loss:

Allograft loss was examined both by all-cause graft loss (ACGL) including death and death-censored graft loss (DCGL). ACGL was determined from the date of living donor kidney transplantation until death, transplant failure (defined by repeat transplant, or return to chronic dialysis), or until end of follow-up December 2, 2015. DCGL was determined similarly with censoring at death. Kaplan Meier curves were used to examine the unadjusted association between CIT and ACGL and DCGL. The log-rank test was used to compare group differences. Multivariable Cox proportional hazards regression was used to determine the adjusted hazard ratios for ACGL and DCGL, where each CIT category was compared to CIT 0-2.0 hours. The proportional hazards assumption was tested for variables in the models using visual inspection of log(-log S(t)) versus log t plots.

Association of Shipping with Delayed Graft Function and Allograft Loss among Kidney Paired Donation Recipients:

To determine whether shipping kidneys confounds the relationship between CIT and post-transplant outcomes, the association between shipped kidneys in the KPD program and DGF, ACGL, and DCGL was examined. In the KPD program, cold ischemic times can be longer due to shipping as opposed to medical complications from either recipient or donor factors. The incidence of DGF among kidneys shipped as part of the KPD program and those not shipped was calculated and a logistic regression was used to compare the adjusted odds of DGF in both groups. Kaplan Meier curves were used to examine the unadjusted association between ACGL and DCGL with shipping and the log-rank test was used to calculate group differences. Multivariable Cox proportional hazards regression was used to determine the adjusted hazard ratios for ACGL and DCGL, where shipped kidneys were compared with non-shipped kidneys. The proportional hazards assumption was tested for variables in the models using visual inspection of log(-log S(t)) versus log t plots.

The following covariates were included in each multivariable model: recipient factors (age, sex, race, ABO blood group, diabetic end stage renal disease, pre-transplant dialysis exposure, and KPD); deceased donor factors (age, sex, race, blood group, body mass index (BMI)); transplant/surgical factors (year, number of HLA mismatches, length of transplant hospitalization, warm ischemic time), and immunosuppression at discharge (induction, calcineurin inhibitors, use of antimetabolites, use of corticosteroids). Missing data were included in all multivariable models as missing. A three-way interaction term between CIT, donor age > 50 years, and KPD was tested in each model to determine whether the association of CIT with DGF, all-cause allograft loss, and death censored graft loss varied by donor age and KPD status. This study was conducted with the approval of the Providence Health Care and Simon Fraser University research ethics boards. All analyses were performed using SAS software, Version 9.4,of the SAS System for [Unix]. Copyright © 2013 SAS

Chapter 3.

Results

Among the n=49,288 living donor kidney-only transplant recipients followed between January 1, 2005 – October 31, 2015 with available cold ischemic time (CIT), 790 were excluded for having a CIT > 16 hours. Of the remaining n=48,498, the median follow-up time was 4.53 years (q1=2.20, q3=7.14).

Cold Ischemic Time:

The median CIT for the study population was 1.0 hour (q1=0.70, q3=2.0). CIT was higher in recipients with the following characteristics: blood type B and AB, peak panel reactive antibody level (PRA) > 30%, pre-transplant dialysis exposure > 1 year, having been transplanted in more recent years, higher human leukocyte antibody (HLA) mismatches, and use of depleting induction therapy (Table 3.1). The median CIT was double in kidney paired donation (KPD) transplant recipients (n=2,839) (2.0 hours, q1=1.0, q3=6.6) versus non-KPD transplant recipients (n=45,659) (1.0 hours, q1=0.70, q3=2.0) ($p<0.0001$) (Figure 3.1). Donors with blood type B and AB and older donors also had higher CITs. The median length of hospitalization stay was 4.0 days (q1=4.0, q3=6.0), and did not differ clinically between CIT groups.

Association of Cold Ischemia Time with Delayed Graft Function:

The overall incidence of delayed graft function (DGF) was low (4.6%), and increased significantly with longer CIT: 0-2.0 hours (3.3%); 2.1-4.0 hours (3.9%);

4.1-8.0 hours (4.3%); and 8.1-16.0 hours (5.5%) (p=<0.001). Longer CIT (8.1-16 hours) was significantly associated with DGF after adjustment for potential confounders; while this association was not significant in shorter CITs (0.1-8 hours), there was a trend of increasing odds ratios as CITs got longer (Table 3.2). After stratification by donor age and KPD, no significant associations were found with CIT. In addition, a three way interaction term between donor age and KPD with CIT was tested in the entire cohort model and was not found to be significant, indicating that the association of CIT with DGF was not modified by KPD status or donor age (p=0.24).

Association of Cold Ischemic Time with Allograft Survival:

Unadjusted Kaplan-Meier curves for all-cause graft loss (ACGL) show no significant differences between CIT categories (Figure 3.2). This was also the case when stratifying by subgroups of KPD recipients, KPD recipient older than 50 years, non-KPD recipients, and non-KPD recipients older than 50 years. Similar results were found when comparing the time to death-censored graft loss (DCGL) among different CIT categories and subgroups (results not shown).

Multivariable cox regression analyses showed no association between ACGL and CIT (Table 3.3). In addition, interaction terms with CIT and donor age (p=0.76) or CIT and KPD (p=0.32) were not found to be significant with ACGL as the outcome.

For DCGL, multivariable Cox regression analyses also revealed no significant association between CIT and time to DCGL: (HR (95%CI) =1.09 (0.81, 1.48)) for CIT 2.1-4.0 hours; 1.17 (0.97, 1.40) for CIT 4.1-8.0 hours; and 1.01 (0.92, 1.10) for CIT 8.1-16.0 hours compared to the reference group of patients with CIT 0-2.0 hours). The interaction terms of CIT and donor age (p=0.71), and CIT and KPD (p=0.31) were not found to be significant in this model.

Association of Shipping with Delayed Graft Function and Allograft Loss among Kidney Paired Donation Recipients:

Among KPD recipients, Table 3.4 shows similar characteristics between recipients whose kidneys were shipped and recipients whose kidneys were not shipped. A slightly higher proportion of recipients whose kidneys were not shipped compared to recipients whose kidneys were shipped were younger, male, had diabetes as the cause of ESRD, had a higher peak PRA, type O blood group, were transplanted in earlier years, had more HLA mismatches, longer CIT, and had more preemptive transplants. However, the incidence of DGF was not significantly higher among recipients whose kidneys were shipped (4.5%) compared to recipients whose kidneys were not shipped (3.3%) (p=0.14). Further, a multivariable logistic regression model of patients whose kidneys were shipped versus those who were not shows no significant difference in the odds of DGF (OR (95% CI): 1.4 (0.88, 2.4)). In addition, multivariable Cox regression analyses revealed no significant association between DCGL HR (95% CI): 0.70 (0.46, 1.08)) or ACGL (HR (95% CI): 0.89 (0.62, 1.3)) with shipping.

Table 3.1 Recipient, donor and transplant characteristics by cold ischemia time				
	Cold Ischemic Time (hours (h))			
	0.1-2.0 h N=38,999	2.1-4.0 h N=6,937	4.1-8.0 h N=1,586	8.1-16.0 h N=976
Recipient Characteristics				
KPD transplant	3.73	6.27	25.25	56.94
Mean Age[1], years (SD)	46.25 (16.0)	45.65 (16.5)	44.91 (17.0)	49.22 (14.2)
<18 year	4.71	6.65	7.38	1.64
18-39	27.40	25.88	26.73	23.77
40-59	45.20	45.34	44.14	48.16
≥60	22.69	22.14	21.75	26.43
Male Sex[1]	61.69	62.16	59.65	50.51
Race[1]				
White	66.08	7.16	57.12	64.14
Black	14.62	11.89	13.75	16.50
Other	19.29	20.95	29.13	19.36
Blood Group[1]				
A	39.04	39.51	36.76	35.86
B	13.07	13.03	16.27	19.57
AB	4.00	3.76	5.11	5.33
O	43.89	43.69	41.87	39.24
Diabetic ESRD	19.96	20.48	19.10	17.83
Peak PRA[1,2]				
0	58.38	59.53	47.65	36.47
1-30	26.88	24.34	26.65	22.09
31-79	9.87	10.83	14.70	21.96

≤80	4.88	5.30	11.01	19.48
Pre-transplant dialysis exposure years[1]				
preemptive	34.51	30.63	27.62	25.51
0.1-1	27.51	27.33	22.26	18.85
1.1-3	26.34	29.29	32.98	31.86
>3	11.63	12.74	17.15	23.77
Donor Characteristics				
Mean Age[1], years (SD)	41.44 (11.6)	41.13 (11.6)	41.54 (11.8)	43.43 (11.6)
Age ≤50	76.11	76.60	75.60	70.49
Age >50	23.89	23.40	24.40	29.51
Male sex	38.79	38.79	36.95	38.52
Race[1]				
White	69.10	69.90	63.24	75.31
Black	12.65	9.77	10.47	11.07
Other	18.25	20.33	26.29	13.63
Blood Group[1]				
A	25.81	26.97	28.69	33.91
B	7.48	7.84	11.66	17.52
AB	0.79	0.76	1.64	3.38
O	65.93	64.42	58.01	45.18
Body Mass Index[1]				
<30	77.85	76.47	77.62	79.71
≥30	22.15	23.53	22.38	20.29
Transplant Characteristics				
Year[1]				
2005-2008	34.85	35.76	23.90	7.17
2009-2012	39.09	36.86	37.39	32.89
2013-2015	26.06	27.37	38.71	59.94

HLA mismatch[1,2]				
0	7.59	7.85	5.50	1.88
1-3	48.52	48.50	41.79	27.20
4-6	43.89	43.64	52.72	70.92
Warm Ischemic Time, mins[1,2]				
0-23.9	24.67	18.18	22.40	22.92
24-31.9	26.45	22.78	18.20	28.28
32-41.9	23.83	31.08	28.27	22.92
≥42	25.05	27.95	31.12	25.88
Immunosuppressive medications at time of hospital discharge				
Induction[1,2]				
Depleting	53.72	60.27	58.09	64.13
Non-depleting	30.83	25.86	26.68	24.76
None	15.45	13.88	15.23	11.11
Calcineurin inhibitor[1,2]				
Tacrolimus	75.83	63.24	67.18	68.15
Cyclosporine	20.78	32.25	29.37	28.68
None	3.39	4.51	3.45	3.17
Antimetabolite[1,2]				
Azathioprine	0.38	0.25	0.38	0.42
Mycophenolic Acid	83.49	71.30	76.01	83.28
None	16.13	28.45	23.61	16.30
Corticosteroids[1,2]	94.48	93.38	94.05	96.19

[1] indicates p value <0.05

[2] Missing: PRA (11.44%); HLA mismatch (1.02%); Warm Ischemic Time (27.97%); Induction (1.81%); Calcineurin inhibitor (1.81%); Antimetabolite (1.81%); Corticosteroids (1.81%).

All values are % unless otherwise stated.

Table 3.2 Multivariate adjusted association of cold ischemia time (CIT) with delayed graft function

	Cold Ischemic Time			
	0-2.0 hours	2.1-4.0 hours	4.1-8.0 hours	8.1-16.0 hours
DGF[1] (Entire cohort[2]) (OR, 95%CI)	1.00	1.11 (0.96, 1.29)	1.27 (0.97, 1.66)	1.47 (1.05, 2.05)
DGF[1] (Only donors > 50yrs[2]) (OR, 95%CI)	1.00	1.08 (0.80, 1.44)	1.15 (0.69, 1.94)	1.14 (0.62, 2.12)

[1] Logistic multivariable regression models

Both models were adjusted for the following variables: Recipient factors (age, sex, race, ABO blood group, PRA, diabetes as cause of ESRD, dialysis duration prior to kidney transplant, KPD); donor factors (age, sex, race, ABO blood group); transplant and immunologic factors (year of transplant, HLA mismatches, warm ischemic time, induction, type of calcineurin inhibitor and antimetabolite, use of corticosteroids).

[2]Preemptive transplant recipients excluded from these analyses to minimize misclassification of DGF.

Interaction for CIT and donor age (>50 years vs ≤50 years): p=0.31

Interaction for CIT and KPD: p=0.76

Table 3.3 Multivariate adjusted association of cold ischemia time (CIT) with all cause graft loss (ACGL)	
Outcome: All cause graft loss[1,3]	**Hazard Ratio (95% CI)**
Cold Ischemic Time (hours)	
0-2.0	1.00
2.1-4.0	1.01 (0.94, 1.09)
4.1-8.0	1.13 (0.97, 1.31)
8.1-16.0	0.97 (0.74, 1.26)
Recipient Characteristics	
Mean Age (years)	
<18 year	1.00
18-39	0.90 (0.80, 1.02)
40-59[2]	0.68 (0.60, 0.77)
≥60	0.99 (0.87, 1.12)
Sex	
Female	1.03 (0.98, 1.09)
Male	1.00
Race	
White	1.00
Black[2]	1.27 (1.12, 1.44)
Other[2]	0.82 (0.73, 0.92)
Blood Group	
A	1.00
B	0.97 (0.87, 1.09)
AB	0.89 (0.76, 1.05)
O	0.93 (0.86, 1.00)
Diabetic ESRD[2]	1.28 (1.20, 1.36)
Peak PRA	
0	1.00
1-30	0.99 (0.93, 1.05)

31-79 ≥80[2]	0.98 (0.90, 1.08) 1.46 (1.32, 1.63)
Pre-transplant dialysis exposure (years) Preemptive 0.1-1.0 [2] 1.1-3.0[2] >3.0[2]	 1.00 1.33 (1.24, 1.43) 1.62 (1.51, 1.74) 1.72 (1.58, 1.88)
Donor Characteristics	
Age ≤50 Age >50[2]	1.00 1.19 (1.12, 1.26)
Sex Female[2] Male	 1.16 (1.10 1.22) 1.00
Race White Back Other	 1.00 1.10 (0.96, 1.26) 0.95 (0.85, 1.06)
Blood Group A B AB O	 1.00 1.05 (0.91, 1.22) 1.06 (0.75, 1.50) 1.06 (0.98, 1.15)
Body Mass Index <30 ≥30	
Transplant Characteristics	
Year 2005-2008[2] 2009-2012[2] 2013-2015	 2.70 (2.36, 3.09) 1.72 (1.50, 1.96) 1.00

HLA mismatch	
0	1.00
1-3[2]	1.66 (1.47, 1.87)
4-6[2]	1.80 (1.59, 2.03)
Warm Ischemic Time (mins)	
0-23.9	1.00
24-31.9	1.03 (0.95, 1.12)
32-41.9	1.04 (0.95, 1.13)
≥42[2]	1.20 (1.11, 1.30)
KPD	0.90 (0.78, 1.04)
Immunosuppressive medications at time of hospital discharge	
Induction	
Depleting	1.02 (0.95, 1.10)
Non-depleting	1.00 (0.93, 1.08)
None	1.00
Calcineurin inhibitor	
Tacrolimus[2]	0.54 (0.48, 0.60)
Cyclosporine[2]	0.60 (0.53, 0.68)
None	1.00
Antimetabolite	
Azathioprine	1.25 (0.86, 1.83)
Mycophenolic Acid[2]	0.88 (0.81, 0.96)
None	1.00
Corticosteroids	1.12 (1.00, 1.25)
None	1.00

[1] Cox multivariate regression model

Model was adjusted for the following variables: Recipient factors (age, sex, race, ABO blood group, PRA, diabetes as cause of ESRD, dialysis duration prior to kidney transplant, KPD); donor factors (age, sex, race, ABO blood group, BMI); transplant and immunologic factors (year of transplant, HLA mismatches, warm ischemic time, induction, calcineurin inhibitors, antimetabolites, corticosteroids).

[2] Indicates p value <0.05

[3]ACGL: Interaction for CIT and donor age (>50 years vs ≤50 years): p=0.76; Interaction for CIT and KPD: p=0.32

Table 3.4 Among KPD, recipient, donor and transplant characteristics by kidney shipping status

	Shipping Status	
	Not Shipped n=1651	Shipped n=772
Recipient Characteristics		
Mean Age[1], years (SD)	49(14)	49(15)
<18 year	23	21
18-39	52	49
40-59	1	3
≥60	24	27
Male Sex	54	51
Race[1]		
White	62	65
Black	16	17
Other	22	18
Blood Group		
A	36	35
B	17	21
AB	6	6
O	41	38
Diabetic ESRD[1]	21	16
Peak PRA[1,2]		
0	38	30
1-30	27	25
31-79	20	21
≤80	15	24
Pre-transplant dialysis exposure years[1]		
preemptive	27	22
0.1-1	20	19
1.1-3	30	34
>3	23	25
Donor Characteristics		
Mean Age, years	44(12)	44(11)

(SD) Age ≤50 Age >50	 69 31	 68 32
Male sex	37	34
Race[1] White Black Other	 73 10 17	 72 13 15
Blood Group[1] A B AB O	 30 14 3 53	 35 19 4 42
Transplant Characteristics		
Year[1] 2005-2008 2009-2012 2013-2015	 10 58 32	 2 45 53
HLA mismatch[1,2] 0 1-3 4-6	 1 20 79	 1 25 74
Cold Ischemic Time, hours[1] 0.1-2 2.1-4 4.1-8 8.1-16	 70 17 8 5	 11 10 28 51
Warm Ischemic Time, mins[1,2] 0-23.9 24-31.9 32-41.9 ≥42	 16 26 26 32	 30 27 23 20
Immunosuppressive medications at time of hospital discharge		
Induction[2] Depleting Non-depleting None	 76 16 8	 71 19 10
Calcineurin inhibitor[2] Tacrolimus Cyclosporine None	 94 3 3	 93 3 4

Antimetabolite[2] Azathioprine Mycophenolic Acid None	 0 95 5	 0 96 4
Corticosteroids[2]	95	96
[1] indicates p value <0.05 [2] Missing: PRA (7%); HLA mismatch (2%); Warm Ischemic Time (23%); Induction (4%); Calcineurin inhibitor (4%); Antimetabolite (4%); Corticosteroids (4%). All values are % unless otherwise stated.		

Figure 3.1 Distribution of cold ischemic time in KPD and non-KPD living donor kidney transplants between 2005-2015

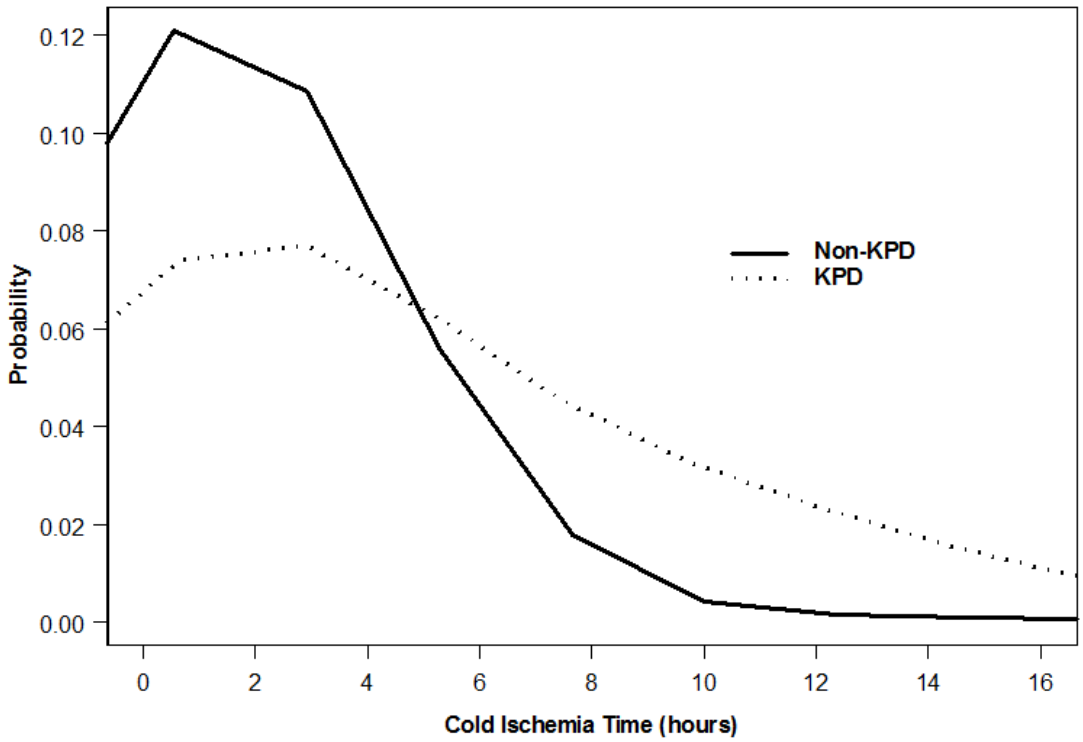
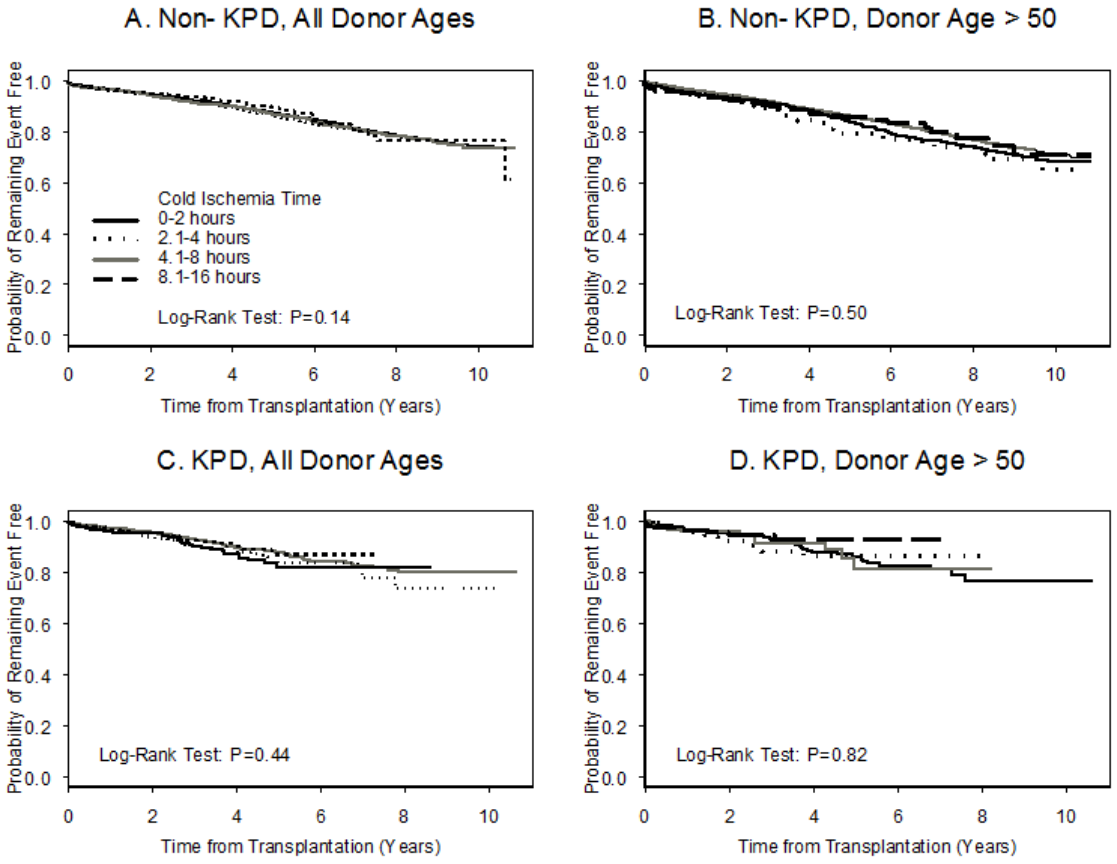


Figure 3.2 Kaplan-Meier survival curves for all cause graft survival, by cold ischemia time, in KPD and non-KPD transplant recipients and by living donor age



Kaplan-Meier curves showing relationship between cold ischemia time and recipient all cause graft survival.

Subgroups: Panel A- All directed living donors (non-KPD). Panel B- Directed (non-KPD) living donors aged more than 50 years. Panel C- All living donors participating in kidney paired donation (KPD). Panel D- Living donors aged more than 50 years participating in KPD

Chapter 4.

Discussion

In light of the growing gap between the supply and demand of kidneys, this analysis uses current data to inform the expansion of Canada's kidney paired donation (KPD) program to include shipping kidneys. The purpose of this analysis was to examine the association between prolonged cold ischemic time (CIT) that may occur due to transportation, and post-transplant outcomes. Currently in Canada, CITs are short for living donor kidneys; however, if shipping of kidneys in the paired exchange program is introduced, CITs will likely increase similar to increasing CITs in the US since the introduction of KPD.

This analysis shows a significant association of longer CIT (8.1-16 vs 0.1-2 hours) with increased odds of delayed graft function (DGF), but no significant associations with all-cause graft failure (ACGL) or death-censored graft loss (DCGL). These findings carry important implications for expanding the living donation program in Canada.

Association of Delayed Graft Function with Cold Ischemic Time

In previous research, Simpkins et al. (2007) found increased odds of DGF among kidney transplant recipients in the U.S. between 1990-2005 with kidneys having 4-6 hours of CIT versus 0-2 hours. Given that national shipping times may well exceed 8 hours of CIT and that the majority of my study cohort who received KPD kidneys had >8 hours of CIT, this analysis expands on Simpkins el al.'s research to a contemporary era when shipping in KPD is more common. While these results show the same dose-response trend in longer CITs, only CIT 8.1-

16 hours was significantly different from CIT 0.1-2 hours. This difference may be explained by my larger cohort size and the considerably smaller incidence of DGF (5.5%) in even the highest risk group (8.1-16 hours) in my study cohort compared to the incidence of DGF (5.8%) in Simpkins el al.'s lowest risk group (2-4 hours). This may be due to cohort size differences and changes over time, including better patient care and post-transplant outcomes for kidneys with longer CITs.

Associations of All-Cause Graft Loss and Death-Censored Graft Loss with Cold Ischemic Time

Consistent with this analysis, Simpkins et al. (2007) report no significant association between all-cause graft loss (ACGL) or death-censored graft loss (DCGL) with CIT ≤ 8 hours. In addition, this analysis reports no association between ACGL and DCGL with CIT ≤ 16 hours. In a stratified analysis, a study of New-Zealand and Australian living donor kidney transplant data shows significant associations between ACGL and DCGL with CIT 4.1-8 hours compared to CIT 1.0-2.0 hours among recipients of living donor kidneys > 50 years of age (Krishnan et al., 2016). These findings were inconsistent with the results of this analysis as no significant associations between ACGL and DCGL were found with CIT among recipients of living donor kidneys > 50 years of age. However, this difference may be due to several factors: this analysis consisted of a much larger cohort with longer CITs and a larger proportion of KPD transplants. The larger number of KPD transplants may be indicative of more experience with KPD transplants in the U.S., which may lead to different patient care management practices (e.g. use and type of immunosuppression therapy) and post-transplant outcomes. In addition, the demographic characteristics of the New Zealand/Australian cohort and life expectancies in both New Zealand and Australia differ from the U.S. cohort and the U.S. life expectancy, which may also lead to different post-transplant outcomes.

Further, previous studies (Chang, 2012; Gill J.S. et al., 2006; Gill J. et al., 2008) have shown that living donor age ≤ 65 years has little impact on post-transplant outcomes in the U.S. This could explain international variations in age as an effect modifier for the associations of ACGL and DCGL with CIT that should be studied when considering shipping living donor kidneys in the Canadian context.

Association of Shipping with Longer Cold Ischemic Times

The selected study cohort included living donor kidney recipients with long CITs who were not part of the KPD program. Longer CITs outside the KPD program could be due to a variety of reasons, including factors related to transplant complications or worse living donor kidney quality that could impact post-transplant outcomes. In contrast, living donor kidneys part of the KPD program could have longer CITs due to shipping. Stratified multivariable analyses were run to verify whether the association of post-transplant outcomes CIT for living donor kidney within the KPD program differed from those not in the KPD program and found that being part of a KPD program did not act as an effect modifier for the associations of DGF, ACGL, or DCGL with CIT.

Strengths and Limitations

This analysis highlights several important strengths. The study cohort was the largest studied in this context and was obtained from a national U.S. data registry that has been long established. This analysis included a contemporary cohort with living donor kidneys with significantly longer CITs (8.0-16.0 hours) than previous studies (Simpkins et al., 2007; Krishnan et al., 2016). Further, the consistency of these results was established across KPD and non-KPD groups, which carries an important significance for the expansion of the KPD program in the Canadian context where shipping of kidneys has not yet been established as a practice. The associations between post-transplant outcomes and CIT were

also found to be consistent between younger (≤50 years) and older donors (>50 years).

There are several limitations to this study. It is important to iterate the limitations in the interpretation of results in studies using observational data: causality cannot be inferred, and the data were not collected for study purposes and therefore potentially introduced non-random missingness. While many clinically relevant covariates were adjusted for, residual confounding remains a limitation in observational studies. Although the definition of DGF used in this study has been previously established (Irish et al., 2010), it does not consider intermediate cases where allograft function was not immediate but did not require dialysis, nor does it account for variations in the severity of DGF. Finally, given that this study was based on a U.S. cohort, international differences in population demographics and clinical practices may affect the generalizability of my results to the Canadian context.

Conclusion & Future Recommendations

No significant associations were found between ACGL and DCGL with CIT up to 16 hours, and between DGF and CIT up to 8 hours for living donor kidneys. These results were consistent across age groups and KPD status of living donors. These findings may encourage the expansion of the KPD program in Canada where shipping of kidneys is not standard practice. This may allow for more, and potentially better matched kidneys at the national level, which could lead to improvements in post-transplant outcomes over time. More effective use of living donor kidneys in Canada is essential to address the widening gap between the limited supply of kidneys and the ever-growing waitlist. Further studies should attempt to address the limitations of this study listed above in order to ensure the meaningfulness and generalizability of these results in the Canadian context.

In particular, future studies should further explore the relationship between prolonged CIT and DGF and the impact that DGF has on ACGL and DCGL in the context of living kidney donation. Very little is understood about the relationship between DGF and ACGL and DCGL, and few studies have examined this relationship in living donor kidneys, where results have been inconsistent. Some of these inconsistencies may be related to the lack of standardization in the measurement of DGF, as well as the lack of sufficient granularity in this variable to accurately understand and describe etiological processes affecting graft outcomes. Future studies should consider studying continuous variables measuring post-transplant graft function such as estimated glomerular filtration rates, peak serum creatinine, and urine output in conjunction with DGF, to better measure and understand the relationship between prolonged CIT and graft outcomes in living donor kidneys.

To advance living donor kidney transplantation in Canada, key policies need to be implemented to create a national database for the collection of accurate, standardized, and granular data on kidney transplantation. Currently, granular data on kidney transplantation is only collected at the provincial level and therefore research on kidney outcomes across Canada is underdeveloped. In addition, data collection on relevant covariates is inconsistent in both accuracy and scope across provinces, making it difficult to pool provincial data into a larger, national database. Future steps should be made to standardize and evaluate data collection across Canada, as well as create a national data collection agency. This will allow for further studies on kidney transplantation outcomes in Canada at a national level, and provide important baseline data for the generalizability of the findings in this thesis, as well as other crucial international findings, for the expansion of kidney donation in Canada.

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