Inter-centre variation in the management of kidney transplant recipients and its impact on clinical outcomes

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ABSTRACT

Introduction: There is an increasing number of Canadians living with end stage renal disease (ESRD). Kidney transplantation is currently the best treatment for ESRD but long-term outcomes remain suboptimal. Identifying factors associated with better outcomes may lead to interventions or practice change that could improve patient survival or quality of life. The objectives of this thesis were to: i) systematically review the literature to examine centre variation in kidney transplantation outcomes and identify centre and provider level factors that may contribute to variation in outcomes; ii) describe differences that may exist at the patient, centre and provider level at the time of kidney transplantation across the six transplant centres in Ontario, Canada; iii) examine variation in graft and patient survival rates across transplant centres in Ontario; and iv) examine whether patient, centre and provider level characteristics contribute to variation in graft and survival rates across transplant centres.

Methods: The first objective of this thesis was met by conducting a systematic review of the literature according to a predefined protocol. The last three objectives of the thesis were met by conducting a population based retrospective cohort study using administrative data from Ontario. Differences at the patient, centre and provider level were described at the time of kidney transplantation. Outcomes of interest included total graft loss; graft loss with follow-up censored at death; death with graft function; and total mortality. All outcomes were assessed at one year post transplantation and at the end of study follow up. Cox proportional hazards regression was used to obtain hazard ratios (HR) for each centre relative to the average across

all centres. The independent effect of centre volume and provider characteristics on outcomes was also examined.

Results: The systematic review identified 24 eligible studies. Outcomes included graft survival (n=24) and patient survival (n=9). The main characteristics evaluated were centre volume (n=17) and provider volume (n=2). Centre variation in graft survival was described in 80% (12/15) of studies, while less than half of studies (8/17) found a significant association between volume and graft survival. The population based retrospective cohort included 5092 adults (≥18 years) who received a primary solitary kidney transplant across 6 transplant centres in Ontario between January 1st 2000 and December 31st 2013. Variation in patient, centre and provider level factors existed across centres at the time of transplantation. At the end of study follow-up, case-mix adjusted HRs for total graft loss ranged from 0.84 (95% CI 0.53-1.33) to 1.16 (95% CI 1.00-1.34) across centres (p-value for between centre variation 0.46). After adjusting for centre and provider factors, differences across centres persisted. Centre volume, provider experience and provider type were not independently associated with either short or long-term outcomes (all p>0.05) with the exception of graft loss with follow-up censored at death.

Discussion: This thesis suggests that there is variation in clinical outcomes across transplant centres in Ontario which is not explained by patient factors, centre volume or provider characteristics at the time of transplantation. Additionally centre volume, provider type and experience were not independently associated with outcomes. Future prospective studies with a larger sample size of transplant centres that examine follow-up care after discharge from hospital (e.g. frequency of visits) are required to better understand this phenomenon.

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GLOSSARY

BMI	Body mass index
CCP	Canadian Classification of Diagnostic Therapeutic and Surgical Procedures
CCI	Canadian Classification of Interventions
CI	Confidence interval
CIHI	Canadian Institute for Health Information
CKD	Chronic kidney disease
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CORR	Canadian Organ replacement registry
DAD	Ontario discharge abstract database
DSA	Donor specific antibodies
ECD	Expanded Criteria Donors
ESRD	End stage renal disease
GN	Glomerulonephritis
ICES	Institute for Clinical Evaluative Sciences
HLA	Human leukocyte antigen mismatch
HR	Hazard ratio
ICU	Intensive care unit
IKN	ICES key number
IPDB	ICES physician database
IQR	Interquartile Range
OHIP	Ontario Health Insurance Plan
OPTN	Organ Procurement and Transplantation Network
PRA	Panel reactive antibody
RPDB	Ontario Registered Persons Database

RVD	Renal vascular disease
SD	Standard deviation
SRTR	Scientific Registry of Transplant Recipients
SR	Standardized ratio
TIA	Thrombotic ischemic stroke
UNOS	United Network for Organ Sharing
USRDS	United States Renal Data Sharing

CHAPTER 1: BACKGROUND

1.1 End Stage Renal Disease in Canada

Chronic Kidney Disease (CKD) is defined as either kidney damage or reduced kidney function lasting for a duration of more than three months.[1] The diagnosis of CKD is typically established through a combination of bloodwork, imaging and biopsy findings or urinary abnormalities.[1] When renal function declines such that the kidneys are permanently impaired, CKD progresses to kidney failure, referred to as end stage renal disease (ESRD). The prevalence and incidence of ESRD has increased over the last two decades.[2-4] In 2014, there were 35,281 Canadians living with ESRD [1,291.0 rate per million (rpm)], up from 25,600 patients in 2005 (1,039.7 rpm), a 38% increase. Furthermore, there were 5,200 new incident diagnoses of ESRD occurring in 2014 (192.8 rpm) compared to 4,200 in 2005 (172.0 rpm).[5]

Recent international reports have demonstrated the overall age of patients with ESRD has also increased worldwide. Concepcion et al.[6] reviewed data from the United States Renal Data System (USRDS), and found that more than 40% of patients with ESRD in the United States were over the age of 65 in 2014. In Canada, according to the most recent report from the Canadian Organ Replacement Registry (CORR), the percentage of patients with ESRD who are ≥65 years of age has steadily increased from 28% in 1995 to 42.6% in 2014. Moreover, the percentage of patients receiving a kidney transplant that were over the age of 60 increased from 29.5% in 2005 to 44.8% in 2014.[7,8]

Patients with ESRD transplanted beyond the year 2000 have an increased number of comorbid conditions compared to prior[9-11], specifically; there is an increased prevalence of diabetes and

cardiovascular disease in patients with ESRD.[12] Grosso et al.[9] reported in their study of 223 patients transplanted between January 2002 and December 2007 that 50% had ≥1 associated condition pretransplant, of which; diabetes (42.2%), coronary disease (9.9%) and peripheral artery disease (8.5%) were the most common. According to CORR's most recent report,[8] the prevalence of patients starting hemodialysis in Canada who have diabetes had increased to 53.4% in 2013 from 45% in 2004. In addition, a recent study by Lam et al.[13] which analyzed data from CORR, found the proportion of kidney transplant recipients in Ontario with pretransplant coronary artery disease increased from 22% (1994-1997) to 37% in 2006 to 2009.

1.2 Renal Replacement therapy in Canada

Renal replacement therapy which is essential for survival of patients with ESRD includes either kidney transplantation or dialysis. It is estimated that 1.2% of the total health care costs in Canada are directed to the care of patients with ESRD.[14] The annual cost per patient with ESRD in Canada has been estimated to be approximately $55,446,[14,15] and this figure exceeds the average amount spent on any other health care condition in Canada. While the number of kidney transplants being performed may have increased, the number of patients waiting for a kidney transplant is 2.5 times higher than the number of kidney transplants performed.[16] As such, the median wait time for a deceased donor kidney transplant has increased in North America and currently ranges between 3 and 7 years.[17] In Canada, the median wait time for a deceased donor kidney is 3.9 years, with the longest median wait time in the province of Manitoba (5.0 years) and shortest in the province of Saskatchewan (2.2 years).[18]

Kidney transplantation is the preferred and more effective therapy for patients with ESRD resulting in: improved quality of life, lower risk of cardiovascular events and lower risk of death compared to patients who remain on dialysis.[19] A systematic review performed by Tonelli et al.[22] including 110 studies determined that the benefits of kidney transplantation over dialysis were pervasive across different types of dialysis, as well as, differing types of donors (living and deceased). In addition, the survival benefit which occurred from transplantation compared to dialysis was increasing with calendar year. For example, the unadjusted relative risk of mortality associated with transplantation compared to dialysis was 0.44 in 1985 compared to 0.17 in 2005. The authors hypothesize this finding may be attributable to newer immunosuppressive medications, better management of their comorbid conditions or a more carefully selected type of transplant patient.[19]

In Canada, both 1 and 5 year graft survival rates have improved with time.[20] One-year unadjusted graft survival rates in patients receiving deceased donor kidneys increased to 96.6% in 2013 from 92.3% in 2005 and 5 year graft survival rates increased to 81.4% in 2009 from 79.9% in 2005. For patients receiving a living donor transplant, 1 year graft survival rates increased to 97.7% in 2013 from 95.7% in 2005 and 5 year graft survival rates rose to 90.8% in 2009 from 88.9% in 2005.[21] Patient survival for those waiting on dialysis have remained relatively unchanged over the last ten years with 1 year unadjusted survival rates of 83.2% in 2006 and 82.3% in 2014 and 5 year unadjusted patient survival rates of 41.1% in 2006 and 44.8% in 2010.[5]

1.3 Graft loss and associated factors

Early graft loss (defined as loss occurring within the first 6 months post transplantation) is typically secondary to acute rejection (an immune reaction to the transplanted kidney), a non-viable kidney or technical issues related to the surgery.[22] Graft loss that occurs after the first year of transplant is often due to other causes such as patient death (occurring with a functioning graft), glomerular pathology (including recurrent disease, transplant glomerulopathy or *de novo* glomerular disease) and interstitial fibrosis/atrophy secondary to polyoma nephropathy or immunologic processes.[23]

Patient and transplant specific characteristics known to impact graft survival have been well documented.[24-26] Some of the recipient and donor factors that have been found to be associated with worse transplant outcomes include: recipient age (worse outcomes with older age[24,26-30]), race (with Africans having the worst outcomes[29,31]), cause of ESRD (in particular having diabetes worsens outcome[26]), time spent on dialysis pretransplant (longer time having worse outcomes[32]), donor type (improved outcomes with living donor[24,25,29,33]), and donor age (greater donor age confers a worse outcome[24,26]). In 2006, the majority of Canadian organ procurement organizations began accepting kidneys from expanded criteria donors (ECD), a term which is defined as a donor over the age of 60 or between 50-59 with a two or more of either a history of hypertension, elevated creatinine (>133 umol/L) or where death was from stroke.[34] Patients receiving an ECD kidney have been known to have worse outcomes compared to those receiving non-ECD kidneys.[35] In a recent Canadian study of 1400 patients who were transplanted with deceased donor kidneys (23% from ECD), the adjusted relative risk of death censored graft loss was 1.80 (95% CI 1.19-2.71) for ECD compared to non-ECD.[36] Other transplant specific factors associated with worse patient outcomes include: presence of donor

specific antibodies (DSA)[37], higher panel reactive antibody level (PRA)[24,38], human leukocyte antigen mismatch (HLA)[38,39] and cold ischemia time.[30]

1.4 Patient mortality post kidney transplantation

While patient survival post kidney transplantation has improved[40], the leading causes of death among deceased donor transplant patients remain cardiovascular disease, infection and malignancy.[41,42] Patient survival rates have been found to be influenced by recipient age, comorbidities, and the type of donor (living compared to deceased).[42] Recipients of living donor kidneys have higher survival rates compared to those who have received deceased donor kidneys.[43] In the United States, 1 and 5 year patient survival rates among those patients who received a living donor graft were 98.7 and 93.1 compared to 97.0 and 86.1 among deceased donor recipients.[4] A study by Kim et al.[44] compared post-transplant mortality between Canadian and American kidney transplant recipients between January 1st 1991-December 31st 1998 using data from the USRDS and CORR. The study showed while the mortality risk in the US and Canada was similar the first year post transplant, following the first year of transplantation, the risk of mortality was much higher in the US (covariate adjusted hazard 35%) compared to Canada. One plausible explanation suggested by the authors was the much higher proportion of recipients of African American descent because this patient population has a much higher risk of death compared to other ethnicities. Wang et al.[43] also demonstrated that the US has worse long term outcomes compared to Australia, New Zealand and Europe. Similar to the study by Kim et al.[44], Wang[43] and colleagues demonstrated that while one year patient survival rates were similar across countries, longer term (defined as 5 years after transplantation) varied

across countries with the US having a lower 5 year patient survival rate compared to Europe, Australia and New Zealand.

1.5 *Centre variation in Kidney transplantation*

Centre variation has been defined as "*the differences in clinical outcomes which exist between centres after taking into account the between centre variability in risk factors known to impact outcomes which implies the centre itself impacts the patient outcome*".[45] Centre variation in kidney transplantation outcomes was first studied in 1975. Opelz et al.[46] compared one year graft survival rates of primary kidney transplants (deceased and living related) performed between January 1969 - 1973 across 179 centres (n=4547 transplants). While this study found variability in the graft survival rates across centres, its data did not support a significant volume-outcome association. Since then, several American database studies [47-53] have found up to 25-30% variability in post-transplant outcomes between centres. For example, Cho et al.[47] reported up to 30% variation in patient adjusted (17 recipient, donor and transplant related factors) graft survival rates among 115 centres performing deceased donor transplants between October 1987 to November 1992. Despite the fact that these earlier studies included patients transplanted prior to more recent advances in immunosuppressive regimes, did not always adjust for patient factors and, used a variety of methodologies to assess for variation, the finding of 30% variation in outcomes across centres remains compatible with more recent studies evaluating the phenomenon of centre effect. Zenios et al.[54] observed that 29% of graft failures and 33% of deaths in transplant patients could be attributed to differences across centres. Their results were obtained by using data from 150, 000 patients who had been

transplanted between 1996 and 2009. A limitation of their study is that the reasons for the observed differences in survival rates were not examined.

1.6 Factors contributing to centre variation

In the study by Gjertson et al.[55] the following patient factors were found to contribute to centre variation in outcomes from living donors: recipient race, age, sex, cause of ESRD, obesity status, time on dialysis, donor relationship, donor age, sex, and race. In addition to patient characteristics, the calendar year of transplantation has also been shown to impact variability in graft survival rates. Additionally Gjertson et al.[56] found that variation in survival rates attributable to the centre decreased with later calendar year.[57-59] That is, in 1989 variation attributable to centre effects was 32% whereas in 1990 it was 27%.

Certain behaviours such as smoking and alcohol use may also impact transplant outcomes.[57-59] Schold et al.[60] created a community risk score based on the following community indicators: potential life years lost, birthweight, physical health, mental health, smoking status, income, inactivity rate, preventable hospitalization, obesity rate, and poor health care. The study found the prevalence of community risk factors varied by individual transplant centre. The community risk score was significantly associated with post-transplant mortality independent of known patient risk factors and its overall contribution to the variation in mortality rates seen across centres was moderate.

Specific centre-level factors that could potentially affect transplant outcomes include: surgical volume at the centre, type of transplant centre (pediatric compared to adult), type and number of providers caring for patients in-hospital, model of care at the centre (shared care compared

to individual provider level care) and, location and frequency of follow-up visits after transplantation. While the centre volume outcome relationship has been studied[29,61-65] it remains unclear whether a significant association exists between centre volume and graft and patient survival. Furthermore, it remains uncertain whether centre volume contributes to variations in patient outcome. For example, Gjertson et al.[65] found the type of centre (defined by pediatric volume) did not contribute to variation in survival rates.

The provider-level factors which could potentially affect outcomes include: years of experience, provider specialty (e.g. general surgeon compared to urologist), country of medical school graduation, location of practice (e.g. urban or rural) and patient caseload. None of these variables have been well studied in association with centre variation.

1.7 Designs and methods for evaluating centre variation

The use of administrative databases and registries to study patient outcomes in kidney transplantation has many advantages compared to conducting prospective cohort studies or retrospective single-institution analyses.[66] Firstly, they are inexpensive as the data has already been collected. Secondly, they allow for a larger sample size of patients by pooling outcomes from many centres and therefore increase the study power to potentially improve detection of significant associations and confidently exclude lack of association between variables. Lastly they are faster to complete. In the US, the vast majority of transplant studies assessing centre performance have used from data collected through the Organ Procurement and Transplantation Network (OPTN). In Canada, CORR is the national registry for organ failure. CORR is a longitudinal database which collects data on patients with ESRD from the time they

start dialysis or are transplanted until organ failure or death.[20] Data is voluntarily submitted to the Canadian Institute for Health Information (CIHI) by a particular transplant centre twice per year.[18] Documentation of the transplant procedure in CORR has been found to have 98.5% agreement with the Ontario discharge abstract database (DAD).[67]

Specific analytical methods to measure and compare centre outcomes post kidney transplantation have been previously applied.[68,69] Descriptive methods include the use of the Kaplan-Meier method to compute unadjusted survival curves as cumulative success rates, as well as the actuarial method which uses estimates of death rates to compute a survival rate over a time interval. These methods do not consider differences in patient case mix.[68] Conversely, adjusted methods allow for the comparison of patient subgroups across centres while controlling for patient characteristics.[70] Indirect standardization is one approach whereby results from subgroups from a standard population are used to calculate an expected number of events per subgroup.[71-73] A ratio of the observed to the expected count of events is then created and compared across centres. Cox proportional hazards modeling is a commonly used approach for survival analysis which describes the relationship between incidence of events and a set of covariates. The outcome is expressed as a hazard function (number of events per interval time) determined by a set of covariates (recipient, and donor risk factors) which are weighted in a risk-adjustment process.[68] The Cox model allows one to calculate the effect of each covariate on an outcome and taken together can calculate an expected outcome for a patient. A centre effect is then added as an additional variable. When the sample size of centres is small a model with a fixed centre effect is chosen; however if there is a larger sample of centres being compared then a random effects model is preferred.[74]

1.8 Proposed thesis and rationale

The primary objective of this thesis project was to examine variation in graft and patient survival rates across transplant centres in Ontario. This thesis project is the first Canadian transplant study which explores variation in practice patterns among Ontario kidney transplant centres. Understanding discrepancies that occur at the centre and provider level and which centre or provider factors may impact post-transplant outcomes is important in order to improve transplant care.

The thesis consists of the following projects: i) a systematic review of the literature to understand which factors, beyond patient related variables, may explain centre variability; and ii) the creation of a study cohort consisting of primary solitary kidney transplant recipients who were transplanted in Ontario using linked administrative databases.

A systematic search of published articles was performed. Studies which included kidney transplant recipients (all ages), with a time to event outcome of either graft survival or patient survival, or assessed quality of life or functional status, and compared any type of centre or provider differences post-kidney transplantation were reviewed. We then summarized centre variation in graft and patient survival rates among the studies and identified potential factors which may be associated with outcomes. (Chapter 2-Manuscript 1).

The study cohort used data from administrative datasets at the Institute for Clinical Evaluative Sciences (ICES). All renal transplant recipients were identified using CORR. Patient comorbidities and outcomes were obtained from the Ontario Discharge Abstract Database (DAD), the Ontario Registered Persons Database (RPDB) and the Ontario Health Insurance Plan

(OHIP). Information on the responsible care provider was obtained through the ICES Physician Database. We used descriptive statistics to summarize characteristics of patients at the time of transplant by centre. (Chapter 3 - Manuscript 2). The one, five and ten year survival distributions were described per centre using the Kaplan-Meier method and statistical significance of differences across centres were assessed using the log rank test. To account for differences in patient case mix across transplant centres, we used fixed effects multivariable Cox proportional hazards regression. Adjusted hazard ratios (HR) with 95% confidence intervals were calculated for each transplant centre, relative to the average across all centres. Centres having HRs with both upper and lower confidence limits below 1 imply that the centre has a survival rate significantly better than average after accounting for patient case mix, while HRs for centres with both limits above 1 imply that the centre is performing significantly worse than average. We then also used fixed effects multivariable Cox proportional hazards regression to examine the independent effects of centre volume, provider experience and provider type. Our modelling allowed for a comparison of the centres to one another and a better understanding of which patient, centre and provider factors affected variation across outcomes. (Chapter 4 - Manuscript 3 and Chapter 5 – Manuscript 4).

This work contributes to the literature in several ways. To our knowledge, it is the first Canadian population based cohort to study differences at the centre and provider level among transplant centres in Ontario. The results of our study have important clinical implications as they confirm that Ontario transplant centres vary substantially in the type of patients deemed acceptable for transplantation and that patient characteristics such as greater BMI, co-morbidities and older donor age are associated with patient outcomes. Furthermore our study showed variation in

post kidney transplantation outcomes, specifically, variation in graft and patient survival rates which was not explained by patient characteristics, centre volume or provider characteristics alone.

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Chapter 2 – [Manuscript 1] – **Centre Variation and the Effect of Centre and Provider Characteristics on Clinical Outcomes in Kidney Transplantation: A Systematic Review of the Evidence**

2.1 Preface to manuscript 1 –

The first manuscript systematically reviews the literature on centre effect in kidney transplantation published from inception until June 2016. In this manuscript we included 24 observational studies, 15 of which assessed centre variation in graft survival and 7 of which assessed centre variation in patient survival. Seventeen of the included studies assessed for a volume-outcome association. Tables with detailed description of the study characteristics, findings and risk of bias are provided. Meta-analysis of the included studies was not possible due to their heterogeneity.

This manuscript has been accepted for publication at the *Canadian Journal of Kidney Health and Disease.*

Centre Variation and the Effect of Centre and Provider Characteristics on Clinical Outcomes in Kidney Transplantation: A Systematic Review of the Evidence

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ABSTRACT

Background: Kidney transplantation is the best treatment option for patients with end-stage renal disease. While patient level factors affecting survival are established, the presence of variation in the management of transplant recipients remains unknown.

Objective: To examine centre variation in kidney transplantation and identify centre and provider characteristics that may be associated with clinical outcomes.

Design: Systematic review.

Data sources: Ovid Medline, Embase and Cochrane library from inception to June 2016 were used.

Study eligibility: Any study examining the association between centre or provider characteristics and graft or patient survival, quality of life or functional status were included.

Results: We identified 6327 records and 24 studies met eligibility. Most studies used data registries. Characteristics evaluated include centre volume (n=17), provider volume (n=2), provider experience (n=1), centre type (n=2) and location of follow-up (n=1). Outcomes assessed included graft survival (n=24) and patient survival (n=9). Significant centre variation was described in 12/15 and 5/7 studies for graft and patient survival. There was a significant and positive association between centre volume and graft and patient survival in 8 and 2 studies respectively. Provider experience and volume was significantly associated with less allograft loss and provider volume with lower risk of death. There was no association between graft survival and location of follow-up or centre type.

Limitations: There was substantial heterogeneity in the variables assessed and methodology used to analyze associations.

Conclusion: This systematic review found centre variation in kidney transplantation. Future studies in the current era are necessary to better evaluate this important topic.

Running Title: Centre Variation Post Kidney Transplant

Keywords: Kidney transplantation, centre variation, allograft survival, quality of life.

What was known before: Prior earlier studies have described centre variation in graft and patient survival rates post kidney transplantation. However, it has yet to be established which centre and provider factors may contribute to this variation.

What this study adds: This review highlights the heterogeneity of studies published on centre variation and provides a comprehensive summary on centre and provider factors that have been examined in association with centre variation. The literature suggests there is centre variation in graft survival rates, however it remains unclear which centre and provider factors contribute to this.

INTRODUCTION

Kidney transplantation is the optimal treatment for end stage renal disease as it is associated with increased survival, improved quality of life and reduced cost compared to chronic dialysis [1]. With improved immunosuppression regimens, one-year graft and patient survival rates are now greater than 90% [2]. Despite these improvements, medium and long term graft survival remains unchanged with 20% suffering from transplant failure within the first 5 years [3] and up to 50% by ten years [4].

Traditional recipient and donor risk factors for graft and patient survival have been established and include such variables as recipient age, race, gender, body mass index, time on dialysis, medical comorbidities etc [5, 6]. While these patient-level factors, amongst others, have been associated with graft and patient survival, they do not fully explain differences in survival across transplant centres. The "centre effect", defined as the variability in graft outcomes at different centres that cannot be accounted for by case mix or chance alone [7, 8], was first described by Opelz in 1975 [9]. Since then, several studies have attempted to better understand this phenomenon [6, 10-13]. A study by Zenios et al[14] reported that 29% of graft failures and 33% of deaths could be attributed to differences across centres. That is, if every centre included in their study matched the top centre for outcomes, 33% of deaths and 29% of graft losses would be avoided over the three years. However, reasons for the observed differences were not determined [14].

Specific centre-level factors that could potentially affect transplant outcomes include: surgical volume at the centre, type of transplant centre (pediatric compared to adult), type and number of providers caring for patients in-hospital, model of care at the centre (shared care compared to individual provider level care), location and frequency of follow-up visits after transplantation. The provider-level factors which could potentially affect outcomes include: years of experience, provider specialty (e.g. general surgeon compared to urologist), country of medical school graduation, location of practice (e.g. urban or rural) and caseload. These centre and provider level factors may differ further depending on the type of patient population, pediatric compared to the adult population. Neither centre nor provider level factors have been analyzed in a systematic fashion to determine to what extent they explain centre variation in important clinical outcomes. The purpose of this systematic review is to describe the magnitude of centre variation in kidney transplantation and to identify and summarize centre- and provider-level variables associated with patient-important outcomes (allograft and patient survival, quality of life and functional status) following kidney transplantation in randomized and observational studies. We hypothesized centre variation would not be explained by case-mix alone.

METHODS

Search strategy

This study was conducted and prepared using the Meta-analysis Of Observational Studies in Epidemiology statement [15]. We conducted systematic electronic searches using Ovid Medline (1946 to 2016 June) and Embase (1947 to 2016 June) and Cochrane Central (2016 January)

databases without language restriction. The search strategy was designed and implemented by an information specialist. Full details are in Appendix A. Bibliographies from recent reviews and published studies were searched as well. A protocol for this review has not been registered.

Study selection

An initial screen of identified titles and abstracts was performed by two investigators (AB, NF) and clearly irrelevant records removed at this stage. Full-text versions of potentially eligible studies were obtained and independently screened by two of three investigators (AT, AB, NF) to determine their eligibility based on the selection criteria. Any disagreements during the screening process were resolved through discussion amongst the authors in accordance with the selection criteria. We included studies that met the following criteria: 1) randomized controlled trial, prospective non-randomized interventional study, prospective or retrospective cohort or case control study involving kidney transplant recipients (all ages) with a time to event outcome; 2) compared any type of centre or provider differences post-kidney transplantation; 3) reported either graft survival, patient survival, quality of life or functional status. We excluded: 1) manuscripts not available in English; 2) studies that lacked more than one comparison group; 3) animal studies; 4) abstracts without a full-text publication and 4) case reports, reviews, commentaries and unpublished studies; 5) cross sectional studies or other studies that lacked follow up post-transplantation. Reason for study exclusion was noted.

Data abstraction

Data were abstracted independently by two of three investigators (AT, AB, NF) using a standardized data abstraction form. Any disagreements were resolved by discussion or a third reviewer. Reviewers were not blinded to the authors or journal articles. Our primary outcomes were allograft failure and patient death. Allograft failure was defined as a permanent return to dialysis, re-transplantation or death. Patient death was defined as death at any time post-transplant. Secondary outcomes included quality of life and functional status. We collected information on the following characteristics: primary author, publication year, country, number of centres, number of participants, study design, data registry, calendar years the transplants were conducted, length of follow up, inclusion/exclusion criteria for selecting participants, method of analysis and outcome assessed. Data collected on the exposure(s) included type of exposure (for example, centre volume, provider experience), how the exposure was measured (categorical, continuous), statistical modelling used, and methods and variables considered if adjusted for case-mix. When data was only available in figures, the GNU image manipulation program (GIMP 2.8; http://www.gimp.org/) was used to extract data. Contact with authors was not made as half (n=12) of the manuscripts were published prior to the year 2000, 10 of which were registry based further complicating the ability to obtain missing information. Abstracted studies which did not have an appropriate exposure (e.g. socioeconomic status) or included only a subgroup of transplant recipients (e.g recipients with only a certain diagnosis) were excluded from the review.

Risk of bias assessment

Study quality was independently assessed by two of three investigators (AT, AB, NF) who were not blinded. All studies were assessed using a modified version of the Ottawa Newcastle scale [16, 17] (See Appendix B for scale applied). We considered >20% missing in follow up to have high risk of bias [18].

Data analysis

Survival rates, unadjusted or adjusted for case-mix, were described at variable time points post-transplant using tables and a figure. Outcome data adjusted for case-mix was summarized based on the analytical method used in the study, which included odds ratios, hazard ratios, and risk ratios. We were unable to pool the data as studies were too heterogeneous in both exposures, approaches to analysis and type of reported effect size. We were unable to use any statistical indices to quantify heterogeneity in the study.

RESULTS

Study Selection

The electronic search revealed 6,327 independent records. After exclusions, we reviewed the full text version of 236 citations and 215 were excluded (Figure 1). We found additional references from reviewing bibliographies of included articles. Twenty-four independent studies met all eligibility criteria.

Description of Included Studies

The characteristics of each study are presented in Table 1. Studies were published between 1975 and 2014. Most of the studies (n=23) were retrospective observational studies with the exception of one prospective observational study [19]. Twelve studies originated from the USA [7, 12, 20-29], six from Europe [10, 19, 30-33], two from Taiwan [34, 35], one each from Canada [6], North America [9], Australia [11] and South Africa [36]. Eight studies included adult patients (≥18 years) [6, 7, 10, 11, 20, 30, 32, 35], eight studies included patients of all ages [12, 21, 24, 25, 27-29, 34] and two studies were restricted to pediatric patients (<21 years)[22, 23]. Six studies did not report the selected age range included [9, 19, 26, 31, 33, 36]. All 24 studies assessed graft survival as an outcome, however only one study censored for death[30], thirteen included death in their graft survival outcome [6, 10-12, 19-21, 25, 27, 29, 32-34] while the rest of the studies did not specify. Nine studies also assessed patient survival. The mean (SD) of the number of centres assessed was 99 (98) ranging from 1 to 258. One study did not report the number of centres included [26]. We did not identify any studies assessing centre differences associated with quality of life or functional status.

Risk of Bias

The quality of the included studies is presented in Table 2. There was a range in the quality of the studies, with most having some risk of bias or were unclear due to insufficient reporting. Just over half of the studies had high risk of bias with regards to the representativeness of the study cohort as they only included a specific subset of the transplant population, for example living donor only. The greatest source of bias in the included studies related to the differing methodologies and the diverse analytical approaches used within individual studies to assess

for centre variation. For example, ten studies [7, 9, 19, 23, 24, 26, 31, 33, 35, 37] did not appropriately adjust for differences in patient case mix across centres that may have confounded the estimates of centre effect. With regards to follow up, the vast majority of studies were not clear in their reporting or had high risk of bias as they either did not report the percentage that was missing in follow up or more than 20% of their study population missing by study end.

Centre Variation

Graft Survival

Fifteen studies assessed the extent of centre variation in graft survival (Table 3). All of these studies with the exception of 2 [7, 19] adjusted for patient case-mix , 11 adjusted for calendar year or era [6, 10-12, 21, 22, 26, 27, 30, 32] and 1 study adjusted for centre volume [6]. Nine studies provided the spread in 1-year graft survival across centres (Figure 2a) while only 2 studies provided the spread across centres in 3 and 5-year graft survival. Twelve studies [6, 7, 12, 19, 21, 22, 25-27, 30, 32, 33] reported significant variation across centres in graft survival, (2 of these studies did not adjust for case-mix) and 3 studies found no significant variation across centres [10, 11, 29]. Five studies used fixed effects Cox proportional modelling of which three studies [6, 10, 30] provided hazard ratios for graft failure/survival, 1 study provided relative risk for graft failure [29] and 1 study did not describe their findings [32]. Five studies used random effects Poisson regression modelling and described centre variation using intraclass correlation coefficients [12, 21, 22, 25, 27]. Two studies used random effects logistic regression modelling,

both reporting survival rates [11, 26]. The remaining 3 studies used actuarial life tables and the log rank method [7, 19, 24].

The variation in graft survival between centres in some studies was quite small, while in others it was substantial. For example, in Briganti et al[11] the 1-year graft survival ranged between 89.2% and 92.2% across 16 different sites, while in Gjertson et al[27], the 1-year graft survival ranged between 62% and 100% at 223 different sites, despite adjustment for case-mix in both of these studies. We stratified studies warranting further analysis by using the risk of bias tool. When including only those studies with the lowest risk of bias (defined as "3 or more +"), 6 out of the 24 studies remained, all of which were published after 2000 [10-12, 20, 30, 34]. Of the 4 studies which assessed centre variation and graft survival rates, two [12, 30] of the four found statistically significant variation while the others did not [10, 11].

Patient Survival

Seven studies reported on centre variation in patient survival [6, 10, 11, 19, 29, 30, 33] (Table 3). Five studies adjusted for case mix [6, 10, 11, 29, 30], 4 adjusted for time era [6, 10, 11, 30] and 1 study adjusted for centre volume [6]. Six studies provided the spread in 1-year patient survival across centres (Figure 2b) while 3 studies provided the spread across centres in 3 and 5-year graft survival. Four studies used fixed effects modelling [6, 10, 29, 30] to test for variation with 2 studies reporting hazard ratios [6, 30] , 1 reporting mortality rates[10] and 1 reporting relative risk [29]. Briganti et al[11] used random effects logistic regression modelling. The remaining two studies used actuarial life tables and log rank tests of survival rates [19, 33].

Five studies found statistically significant variation in patient survival across centres [6, 10, 19, 29, 30], 1 study reported no significant variation[33] and in one study their conclusions were not clear [11]. Again, between-centre differences was highly variable across studies. For example, Elinder et al[10] reported 1-year patient survival that varied only minimally from 97.9% to 98.6% across 3 centres, while Kim et al[6] reported a range from 89.9% to 97.7% across 20 centres. When considering only those studies with the lowest level of bias [10, 11, 30], of the 3 studies which assessed centre variation and patient survival rates, two [10, 30] of three found statistically significant variation while the other was inconclusive [11].

Effect of Volume on Clinical Outcomes

Graft Survival

Seventeen studies examined the relationship between centre volume and graft survival/graft loss (Table 4); 11 studies categorized volume data [6, 7, 11, 20, 21, 23, 24, 26, 28, 34, 35], 4 presented volume as a continuous measure [9, 12, 22, 27] and 2 studies described a volume relationship without providing any supporting numbers [29, 32]. We were unable to present pooled results due to heterogeneity in number of categories and thresholds described, methodology used and reporting of outcomes. For example, some studies reported a binary outcome while others used time to event outcomes. Overall, 8 studies documented improved graft survival with higher centre volume [6, 20-23, 28, 34, 35] however one study did not provide effect measures, p values or confidence intervals [21]. Gjertson et al[22] and Schurman et al[23] were the only two studies which included pediatric patients exclusively. In both studies, there was a significant association between centre volume and 5 year graft survival

rates. Five studies did not observe an association between volume and graft survival/failure [7, 9, 26, 29, 32] and 4 studies were inconclusive and did not give any estimates with regards to the nature of the relationship (direction or significance) [11, 12, 24, 27]. When including only low risk of bias studies which assessed volume and graft survival, two studies reported a positive and significant association with graft survival [20, 34] while the other two were inconclusive [11, 12].

Patient Survival

Four studies examined the relationship between centre volume and patient survival [6, 28, 29, 35]; 2 categorized volume data [6, 35], 1 treated volume as a continuous variable [29] and 1 study described the relationship between volume and patient survival without providing any data [28]. Two of the 4 studies reported a significant association [6, 35] and 2 studies did not observe an association between volume and patient survival [28, 29].

Provider Volume

Two of the above included studies also examined the association between provider volume and graft survival. Weng et al[34] found that graft failure (including death) within 1 year was 3.1 times greater (95% CI 1.80 – 5.33) for lower volume surgeons (≤ 33), defined as total patient volume over the study period, compared to higher volume surgeons. And 10 year survival rates were significantly lower in the lower volume physician groups ($p<0.001$). Evans et al[28] examined average surgeon volume and observed no-significant association with graft survival ($p=0.69$). However, they did show that high surgeon volume (>500 procedures) was associated with a significant reduction in patient death (odds ratio 0.79; $p=0.016$).

Additional Factors Assessed

Additional factors assessed in association with transplant outcomes included: provider experience [28], type of centre defined as for-profit or teaching hospitals in one study [28] and defined by percentage of pediatric cases performed in the other [22], location of post-transplantation follow-up after being discharged from one transplant centre [36] and cross-match policy (i.e. use of historical compared to only using current sera) [31]. (Supplementary table 1)

DISCUSSION

Our systematic review synthesized data from 24 studies to assess the magnitude of variation and impact of centre characteristics in kidney transplant patient outcomes. Of the variables investigated, centre volume was most commonly studied with inconsistent results. Overall, the data were inconclusive and challenging to analyze as studies used different methodology and did not always report the statistical significance of their findings. However, most of the studies reported variation amongst centres in graft survival rates and just over half described centre variation in patient survival rates. None of the studies investigated quality of life or functional status.

To our knowledge, this is the first systematic review to assess the presence of centre variation in kidney transplantation. Understanding differences in transplant centre performance and improving quality of care has become a priority in the US with program specific reports now

widely available to the public [38, 39]. These reports provide survival data and compare each centre to national standards. They do not, however, explore which centre or provider factors (including which potentially modifiable factors) may be responsible for variability across centres. We identified two studies that assessed provider experience (using provider volume and years in practice) in association with graft survival and patient survival [28] and only one study that examined location of follow up care (centre compared to rural), in association with graft survival [36]. This study did not find a significant difference in outcomes between location of follow up however the study was retrospective and the sample size was small. We identified one study by Israni et al[40] that characterized the frequency of follow up visits post-transplantation in the United States. They found that the frequency of visits at various time intervals post-transplantation differed by region as did the number of visits to the transplant centre. Centres with "medium" volumes were more likely to follow their patients than centres with lower or greater volumes. This study was not included in our review as it failed to link follow up pattern with an outcome, however it does highlight the variation in patterns of care which may impact on patient outcome. Future, larger prospective studies comparing frequency and location of follow up care post-transplant are needed to help determine if they may improve graft and patient survival as well as quality of life.

The volume-outcome association has been well studied and summarized in other surgical areas especially cardiac surgery where a definite association between volume and mortality is clear and defining a volume threshold may be possible [41, 42]. For example, the review by Pettit et al[42] suggested that centres conducting less than 10 to 12 heart transplants per year may

correspond with higher mortality rates. Within the field of nephrology, the volume-outcome relationship was recently reviewed in dialysis [43]. For peritoneal dialysis, all included studies showed higher volume facilities significantly favored technique survival however there was no significant association found for greater volume and patient survival. There was only one study looking at hemodialysis patients which found a positive and significant association between volume and patient survival.

The volume-outcome association has not been studied for kidney transplant outcomes. In our review, less than half of the studies assessing centre volume and graft survival found that greater centre volume had a higher survival rate. Two of these studies included only pediatric patients [22, 23] and both reported a significant association between graft survival and centre volume. These results suggest that the effects of centre volume and other provider level factors may differ between adult and pediatric populations. The remaining studies found no association or were inconclusive in both the direction and significance, although 90% (8/9) of these studies did not report an effect size or P value. None of the studies in our review used the same threshold to define volume categories and five studies included volume as a continuous variable. When we analyzed the four studies with lower risk of bias separately, the findings were similar with only 50% showing a positive and significant association. Overall, it remains unclear whether a volume-outcome association is present in kidney transplantation. Future large observational studies using appropriate statistical methodology adjusting for case mix and assessing transplant volume as a continuous variable are required to assess this relationship.

Based on our findings it appears that there is variation in graft survival rates across centres which is not explained by patient factors only. One hypothesis is that it may be partially explained by the calendar year in which the transplants were conducted as several studies [6, 10, 11, 22, 25, 27, 30, 32] found a significant improvement in graft survival with later calendar year. Furthermore, the study by Gjertson et al[25], reported variation in 1 year graft survival rates attributable to the transplant centre decreased with calendar year. For example, in 1989 intraclass correlation coefficient was 32%, in 1990 it was 27% and by 1996 it was 17%. The type of statistical model used may also impact the findings with respect to the presence of variability across centres. For example, when Briganti et al[11] used multivariate hierarchical modelling compared to unadjusted models and fixed effects models, there was no longer a discrepancy in graft survival rates across centres included. This highlights the importance of choosing an appropriate statistical model and adjusting for relevant factors.

Quality of life and functional status are an often overlooked but very important patient outcomes. Health related quality of life has been reported as being more important to patients with end stage renal disease (ESRD) as it may reflect how the patient feels compared to other measures [44]. Greater physical health related quality of life is associated with decreased mortality and improved graft survival even after adjusting for clinical variables in kidney transplant recipients [45, 46]. We did not identify any studies which compared centre or provider differences in association with quality of life or functional status.

Strengths and Limitations

The strengths of our review include its comprehensiveness and the variety of studies assessed. There was a wide range of countries represented, and data registries were not only US based but also included Canada, Europe, South Africa and Asia. The studies we included spanned over four decades of time (1975 – 2014). Of the one third of studies (8/24) that included patients transplanted during or after the year 2000, all eight also included patients transplanted prior to 2000. This precluded the ability to comment on centre variation in the era of newer immunosuppressive regimens. While this certainly limited our analysis, it points towards the need for more updated studies evaluating centre effect in patients exclusively transplanted after the year 2000.

Unfortunately we were unable to pool data across studies due to significant clinical, methodological, and analytical heterogeneity. Explanatory variables differed in their definition across studies and not all studies adjusted for case mix or adjusted for different patient and recipient factors. Furthermore, the length of follow up time and outcome endpoints varied across studies and we were unable to assess centre variation in longer term graft and patient survival rates. We recognize this to be an additional limitation of our review. The vast majority of the studies included in our systematic review relied upon registry databases which may not have contained information on important factors such as socioeconomic status, medical insurance, or transportation which have been shown to impact graft survival in kidney transplantation [47, 48]. Eight of the included studies used the united network for organ sharing (UNOS) registry and some of these studies overlapped in their time frame and thus the same patients may have contributed to more than one study. Lastly, we were unable to assess

for publication bias. It is possible that by excluding unpublished studies and published abstracts we missed additional factors influencing centre variation.

CONCLUSION

In summary, our systematic review identified centre variation in kidney transplantation in some of the included studies however due to the substantial heterogeneity in the analytical methodology used and specific centre and provider factors identified there was no conclusive evidence that any specific variable, such as centre volume, was associated with outcomes. Our results are important as they demonstrate inconsistencies within studies investigating centre effect and kidney transplant outcomes and the need for future prospective studies with more detailed clinical information. Moreover, there is a paucity of literature assessing other potentially influential centre characteristics as well as important outcomes such as quality of life. Further research, with appropriate statistical methodology (hierarchical modelling) adjusting for all known confounders and longer follow-up time, is needed to better characterize factors contributing to centre variation in patient-important outcomes such as graft survival and quality of life.

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Abbreviations: USA; United States of America, SD; standard deviation, PRA; panel reactive antibody, ESRD; end stage renal disease, UNOS; united network for organ sharing

Competing interests: The authors declare they have no competing interests.

Author contributions: AT was responsible for the conception and design of the study, analysis and interpretation of data, drafted and finalized the manuscript. GK was responsible for conception and design, analysis and interpreting the data, drafting and approval of final manuscript. NF was responsible for data abstraction and interpretation, drafting and final approval of the manuscript. AB was responsible for data abstraction and interpretation, drafting and final approval of the manuscript. MT was responsible for conception, design, analysis and interpreting the data, drafting and approval of final manuscript. DF was responsible in the conception and design of the work, analysis and interpretation of data, drafting and final approval of the manuscript.

FIGURE LEGENDS

Figure 1. Flow diagram demonstrating electronic search results.

Figure 2a. The range in one year graft survival rates across centres (n) reported by each study. Studies are organized by year they were conducted as well as whether they adjusted for case-mix. The * symbol implies the study adjusted the rate for case-mix and the ǂ symbol implies the study adjusted the rates for centre volume.

Figure 2b. The range in one year patient survival rates across centres (n) reported by each study. Studies are organized by year they were conducted as well as whether they adjusted for case-mix. The * implies the study adjusted the rate for case-mix and the ǂ implies the study adjusted the rates for centre volume.

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Table 1. Characteristics of Included Studies

Study	Country	Year of Transplant	Outcome	Time points	Data registry	Study population	Number of centres	Number of patients
Weng[34] 2014	Taiwan	1999-2007	Composite of graft failure or death	1yr 10yr	Taiwan National health insurance research database	All ages	35	1,779
Medcalf[30] 2011	UK	1992-2003	Graft failure (censored at death) Patient mortality	Over 14 yrs	Clinical computer system Electronic records at the NHS blood and transplant	Age ≥18 yrs First kidney transplant	5	2,650
Tsao[35] 2011	Taiwan	1996-2003	Graft failure* Patient mortality	1yr 2yr 3yr	National health insurance claims database	Age ≥18 yrs First kidney transplant	29	1,060
Elinder[10] 2009	Sweden	Whole cohort - 1964-2007 Refined cohort- 1991-2007	Composite of graft failure or death Patient mortality	Over 10 yrs for refined cohort	Swedish renal replacement registry	Whole cohort: none Refined cohort: Age ≥19 yrs First kidney transplants Combined kidney-pancreas transplants	3	5,393 2,956
Gjertson[12] 2005	USA	1995-2005	Composite of graft failure or death	1yr	OPTN/UNOS	All ages Excluded multi-organ	246	141,406
Kim[6] 2004	Canada	1988-1997	Composite of graft failure or death Patient mortality	1yr 3yr 5yr	CORR	Age >20 yrs First kidneytransplant Excluded centres grafting <50	20	5,082
Axelrod[20] 2004	USA	1996-2000	Composite of graft failure or death	1yr	SRTR	Age ≥18 yrs	258	60,778

Doxiadis[31] 2003	Europe	1982-2000	Graft failure*	2yr	Eurotransplant database	Age range NR First deceased donor kidney transplant only Centres grafting >60 per/year included	24	29,245
Briganti[11] 2002	Australia	1993-1998	Composite of graft failure or death Patient mortality	1yr	ANZDATA	Age >18 yrs First kidney transplant	16	1,986
Gjertson[21] 2001	USA	1996-2001	Composite of graft failure or death	1yr 5yr	UNOS	Age range NR Living donor kidney transplant only	234	21,830
Gjertson[22] 2001	USA	1987-1998	Graft failure*	1yr 5yr	UNOS	Age <21 yrs Centres grafting >10 included	144	8,422
Pontin[36] 2000	South Africa	1982-1989	Graft failure*	1yr 3yr 5yr	Chart review of records from Groote Schuur Hospital in Cape Town	Age range NR	1	480
Schurman[23] 1999	USA	1987-1995	Graft failure*	3mo 5yr	NAPTRCS	Age <18 yrs	104	4,715
Terasaki[24] 1999	USA	1987-1999	Graft failure*	3yr 10yr	UNOS	All ages	254	120,262
Morris[32] 1999	United Kingdom	1986-1993	Composite of graft failure or death	1yr 5yr	UK transplant support service authority	Age ≥ 18 yrs Deceased donor kidney transplant only	23	6,363
Gjertson[25] 1996	USA	1987-1996	Composite of graft failure or death	1yr 5yr	UNOS	All ages Centres grafting >10 included	244	83,867
Hunsicker[26] 1993	USA	1987-1989	Graft failure*	1yr	UNOS	NR	NR	NR

Gjertson[27] 1992	USA	1988-1991	Composite of graft failure or death	3mo 1yr 2yr	UNOS	Age range NR Centres grafting > 10 included	223	35,625
Evans [28] 1991	USA	1986-1987	Graft failure* Patient mortality	Over 2 yrs	Program Management and Medical Information System	All ages Deceased donor kidney transplant only	145	9,853
Ogura[7] 1991	USA	1987-1991	Graft failure*	1yr	UNOS	Ages 16-55 yrs. First deceased donor kidney transplant Centres performed >50 included.	118	19,095
Terasaki[33] 1988	Italy	1983-1988	Composite of graft failure or death Patient mortality	1yr 2yr	Northern Italian transplant program	Age range NR Deceased door kidney transplant only All treated with cyclosporine	7	1,004
Sanfilippo[29] 1986	USA	1977-1982	Composite of graft failure or death Graft failure secondary to rejection Patient mortality	Over 7 yrs	Southeastern organ procurement foundation	All ages Deceased donor kidney transplant only Excluded those on Cyclosporine.	42	3,811
Taylor[19] 1985	UK Ireland	1977-1981	Composite of graft failure or death Patient mortality	1yr 2yr	NR	Age range NR First deceased donor kidney transplant	8	399
Opelz[9] 1975	USA Canada	1969-1973	Graft failure*	1yr	NR	Age range NR First kidney transplants	95 deceased donor 84 living	4,547 total

OPTN, Organ procurement and transplantation network; UNOS, United network for organ sharing; CORR, Canadian Organ Replacement Register; SRTR, Scientific registry of transplant recipients; ANZDATA, Australia and New Zealand Dialysis and transplant registry; NAPRTCS, North American Pediatric Renal Trials and Collaborative Studies; NHS, National Health services; NR, not reported *unclear if graft failure includes death

Table 2. Risk of Bias and Methodological Quality Assessment of Observational Studies

Study	Representativeness	Comparability	Outcome Assessment	% loss to follow-up	Total (+)
Weng[34]	+	+	+	?	3
Medcalf[30]	+	+	+	+	4
Tsao[35]	+	?	-	?	1
Elinder[10]	+	+	+	?	3
Gjertson[12]	+	+	+	?	3
Kim[6]	-	+	+	?	2
Axelrod[20]	+	+	+	?	3
Doxiadis[31]	-	?	-	?	0
Briganti[11]	+	+	+	+	4
Gjertson[21]	-	+	+	?	2
Gjertson[22]	-	+	-	-	1
Pontin[36]	-	?	-	?	0
Schurman[23]	+	-	-	?	1
Terasaki[24]	?	?	-	?	0
Morris[32]	-	+	+	+	3
Gjertson[25]	-	+	+	?	2
Hunsicker[26]	?	-	-	+	1
Gjertson[27]	-	+	+	?	2
Evans[28]	-	+	-	?	1
Ogura[7]	-	-	-	?	0
Terasaki[33]	-	-	+	?	1
Sanfillipo[29]	-	+	+	?	2
Taylor[19]	-	-	+	?	1
Opelz[9]	+	-	-	?	1

+ low risk of bias, - high risk of bias, ? unclear

Table 3. Studies which Assessed Centre Variation in Graft and Patient Survival

Study Author Year	Number of Centres	Patients	Methodology Used	Variables Adjusted for	Effect Size		
Graft Survival					**ICC (% variation between clusters)**	**Survival/Failure (Range across centres)**	**HR/RR (95% CI)[a]**
Medcalf[30] 2011	5	2,650	Fixed effects Cox Proportional hazard	Recipient age, sex, ethnic group, diabetes as cause of ESRD, time on dialysis, donor type, age, sex, genetic mismatch, transplant year cohort			0.8 (0.56,1.15) p=0.22 0.65 (0.45,0.93) p=0.02 0.7 (0.49,0.99) p=0.04 0.71 (0.51,0.99) p=0.04[a]
Elinder[10] 2009	3	2,956	Fixed effects Cox Proportional hazard	Recipient gender, age at first transplantation, primary kidney disease, time on dialysis, donor type, time on waiting list, presence of type I or II diabetes, time period of transplantation.			Refined cohort: 0.73 [0.47-1.13] p=0.16 0.85 [0.58-1.26] p=0.42[a]
Gjertson[12] 2005	246	141,406	Kaplan Meier survival curves and Random effects Poisson regression modelling	Recipient race and sex, donor race and sex and transplant calendar year	1 year: 10%	1 year: 72 to 99%	
Kim[6] 2004	20	5,082	Fixed effects Cox Proportional Hazard And survival curves	Recipient age, sex, race, donor source, primary renal disease, calendar period, time on dialysis, comorbidity,		1 year: 81 to 93%, 3 year: 70 to 89% 5 year: 59 to 84%	Range across centres: 0.51 to 1.77 (20 separate models)

				Hazard ratios adjusted for centre volume and transplant time period but not survival rates			
Briganti[11] 2002	16	1,986	Fixed effects multivariable Cox Proportional Hazard regression modelling and hierarchical logistic regression modelling	Recipient age, sex, race, primary kidney disease, time on dialysis, peak PRA, presence of diabetes or vascular disease Donor: age, sex, organ source, cause of death, cold ischemia time, HLA mismatch, calendar period		Fixed effects model 1 year: 82.1 (95% CI 71.4,89) to 97% (95% CI 82.2,99.5) Random effects model 1 year: 89.2 (95% CI 83,91.8) to 92.2% (95% CI 90.3, 94.5)	
Gjertson[21] 2001	234	21,830	Random effects Poisson regression modelling	Recipient re-graft, sex, race, obese, age, original disease, pretransplant time on dialysis, peak PRA, pretransplant transfusions, working status, pretransplant pregnancies Donor: relationship, sex, race, age, Transplant: year of transplant, CMV status, HLA mismatch, induction therapy, maintenance drugs at discharge , delayed graft function	1 year: 57.5% 5 year: 26.5%		

Gjertson[22] 2001	144	8,422	Kaplan-Meier curves Imputed survival rates Empirical Bayes approach	Recipient prior transplant, age, gender, race, BMI, pretransplant medical status, original disease, number of pretransplant transfusion, Peak PRA , time on dialysis pre transplant Donor: relationship, age, gender, CMV status, cause of donor death, cold ischemia time, HLA-AB mismatch, HLA-DR mismatch, ancillary positive crossmatch, induction therapy, maintenance immunosuppressive, calendar year Type of pediatric centre	1 year: 5.07% 5 year/1 year: 25.2%		
Morris[32] 1999	23	6,363	Fixed effects Cox proportional hazard	Donor: age, sex, blood group, cause of death, side of kidney Recipient: age, sex, blood group, primary kidney disease, kidney exchange, waiting time, HLA mismatch, time period			

Gjertson[25] 1996	244	83,867	Random effects Poisson regression modelling	Recipient age, sex, race, BMI, number of prior transplants, original disease, pretransplant medical status, pre transplant pregnancies, pretransplant transfusions, peak PRA, Donor relationship, age, sex, race, pump preservation, cold ischemia time, warm ischemia time, organ disposition, cause of donor death Transplant: year of transplant, CMV status, ABO compatibility, HLA mismatches, ancillary positive crossmatch	1 year: 1989: 32.4% 1990: 27.3% 1996: 16.9% >1 year:= 15.8%		
Hunsicker[26] 1993	NR	NR	Random effects Logistic regression	Transplant number, donor source, age of recipient, race of recipient, date of transplant	Not reported	1 year: 63 to 96%	
Gjertson[27] 1992	223	35,625	Random effects Poisson regression modelling	Recipient sex, race, age, BMI, number of prior transplants, number of prior transfusions, health status, highest PRA, original disease, Donor: sex, age, race, left or right side, year of transplant	3 month 28.1% 1 year 45.4% 2 year 26.6%		
Ogura[7] 1991	118	19,095	Actuarial method	Not Adjusted.		1 year: 60 to 93%.	
Terasaki[33] 1988	7	1,004	Actuarial method and log rank	Graft number, number of pretransplant transfusions, highest PRA, HLA mismatches, cold ischemia time		1 year: 78.4 to 87.1% 2 year: 70 to 86.7% p=0.025	

Sanfilippo[29] 1986	42	3,811	Actuarial life table and Fixed effects Cox regression model	HLA mismatch, delayed graft function, pretransplant transfusion, recipient race, sex, prior transplant, antilymphocyte treatment post-transplant, PRA, pretransplant bilateral nephrectomy, insulin dependent diabetes, donor source, recipient splenectomy, history of pregnancy, blood group, time on dialysis, donor race, method of organ preservation, length of preservation, cross match sensitivity, year of transplant, transplant volume			Range across centres: 0.62 to 1.46 p=0.058
Taylor[19] 1985	8	399	Log rank method	Not reported		1 year: 54 to 82% 2 year: 50 to 82%	
Patient Survival					**ICC (% variation between clusters)**	**Survival/Failure (Range across centres)**	**HR/RR (95% CI)**
Medcalf[30] 2011	5	2,650	Fixed effects Cox Proportional hazard and survival curves	Recipient age, sex, ethnic group, diabetes as cause of ESRD, time on dialysis, donor type, age, sex, genetic mismatch, transplant year cohort			2.13(1.67,2.78) 1.96 (1.52,2.56) 2.0 (1.56,2.63) 1.85 (1.49,2.33) All p<0.0001[a]
Elinder[10] 2009	3	2,956	Fixed effects Cox Proportional hazard and survival curves	Recipient gender, age at first transplantation, primary kidney disease, time on dialysis, donor type, time on waiting list, presence of type I		Refined cohort: 1 year: 92 to 95%, 3 year: 84 to 91% 5 year: 78 to 88%	Refined cohort: 1.13(0.92,1.38) p=0.23 1.55(1.29,1.87) p<0.0001[a]

				or II diabetes, time period of transplantation.			
Kim[6] 2004	20	5,082	Fixed effects Cox Proportional Hazard And survival curves	Recipient age, sex, race, donor source, primary kidney disease, calendar period, time on dialysis, comorbidity, Hazard ratios adjusted for centre volume but not survival rates		1 year: 89.9 to 97.7 3 year: 81.1 to 95.1 5 year: 70.9 to 92.9%	Range across centres: 0.44 to 1.84
Briganti[11] 2002	16	1,986	Not reported	Not adjusted		1 year: 91.2 to 100%	
Terasaki[33] 1988	7	1,004	Actuarial method and log rank test	Not adjusted		1 year: 92.4 to 98.1% 2 year: 89.2 to 97.1% p=0.44	
Sanfilippo[29] 1986	42	3,811	Actuarial life table and Fixed effects Cox regression model	HLA mismatch, delayed graft function, pretransplant transfusion, recipient race, sex, prior transplant			Range across centres: 0.42 to 1.558 p=0.004
Taylor[19] 1985	8	399	Log rank method	Not Reported		1 year: 84 to 98% 2 year: 82 to 98%	

ICC, Intraclass correlation coefficient; HR, hazard ratio; RR, relative risk; ESRD, end-stage renal disease; PRA, panel reactive antibody; HLA, human leukocyte antigen; CMV, cytomegalovirus; BMI, body mass index; NR, not reported [a] relative to a reference site

Table 4. Studies which Assessed Centre Volume in Association with Graft and Patient Survival

Study	Number Centres	Patients	Patient Volume definition	Patient Volume Categories	Time point Reported	Average Survival Rate	Effect Measure
Graft Survival							
Weng[34]	35	1,779	Categorical*	≤95 vs >95 (reference) ≤95 vs >95 (reference)	1 year 10 year	NR NR	OR: [a] 3.17, 95% CI 1.85-5.46 Log rank p<0.0001
Tsao[35]	29	1,060	Categorical Volume is over study period	≤72 vs >72 ≤72 vs >72 ≤72 vs >72	1 year 2 year 3 year	85.8 vs 89.5 74.6 vs 81 73.3 vs 80.5	Log rank p=0.132 Log rank p=0.036 Log rank p=0.019
Gjertson[12]	246	14,406	Continuous Volume is over study period	N/A	NR	N/A	NR
Kim[6]	20	5,082	Categorical Volume is over study period	0-199 200-399 >400 (reference)	NR	NR	HR: 1.28, 95% CI: 1.12-1.47 HR: 1.07, 95% CI: 0.94-1.22 HR: 1.0 (reference)
Axelrod[20]	258	60,778	Categorical Volume is per year	1-45, 46-75, 76-124, 125-278 (reference)	1 year	90.4 90.1 90.3 91.4	OR: [a]1.22, 95% CI 1.01-1.48 OR: 1.22, 95% CI: 1.01-1.48 OR: 1.21, 95% CI: 0.99-1.49 OR: 1.0 (reference) Chi-square, p=0.0014
Briganti[11]	16	1,986	Categorical Volume is over study period	1-99 , 100-199, 200	NR	NR NR NR	NR
Gjertson[21]	234	21,830	Categorical*	≤100 , 101-400, >400	NR	NR NR NR	NR
Gjertson [22]	144	8,422	Continuous Volume is over the study period	N/A	NR	Data not extractable from figure	Log rank p<0.0001
Schurman[23]	104	4,715	Categorical	≤ 50 51-100	[a]3 months	88.4(0.9)[b] 90.2(0.7)	NR

			Volume is over study period	>100 ≤ 50 51-100 >100	 5 year	90.4(0.8) 65.5(1.8) 69.4(1.5) 68.4(1.6)	
Terasaki[24]	254	120,262	Categorical*	>1000 other	NR	NR	NR
Morris[32]	23	6,363	Not reported	NR	NR	NR	NR
Hunsicker[26]	NR	NR	Categorical Volume is over study period	<25 25-50, 51-80, 81-150 (reference) >150	1 year	NR NR NR NR NR	OR: [a]1.0 OR: 1.1 OR: 1.1 p <0.05 OR: 1.0 (reference) OR: 1.0
Gjertson[27]	223	35,625	Continuous Volume is over the study period	N/A	NR	N/A	NR
Evans[28]	145	9,853	Categorical Volume is per year	<35	NR	NR	NR
Ogura[7]	118	19,095	Categorical Volume is over study period	50-100, 100-150, >150	NR	NR	NR
Sanfilippo[29]	42	3,811	Continuous Average transplant number per centre per year	N/A	NR	N/A	NR
Opelz[9]	179	4,547	Continuous Volume is over study period				
Study	**Number Centres Patients**		**Volume definition**	**Volume Categories**	**Time point**	**Average Survival Rate**	**Effect Measure**

Patient survival							
Tsao[35]	29	1,060	Categorical Volume is over study period	<72 vs >72 <72 vs >72 <72 vs >72	1 year 2 year 3 year	91.2 vs 96.3 87.1 vs 94.1 85.4 vs 93.5	Log rank p= 0.002 Log rank p= 0.001 Log rank p= 0.002
Kim[6]	20	5,082	Categorical Volume is over study period	0-199 200-399 >400 (reference)	NR		HR: 1.33, 95% CI: 1.1-1.61 HR: 0.96, 95% CI: 0.79-1.16 HR: 1.0 (reference)
Evans[28]	145	9,853	Volume is over the study period	NR	NR	NR	NR
Sanfilippo[29]	42	3,811	Continuous Average transplant number per centre per year	N/A	NR	N/A	NR

HR, Hazard ratio; OR,Odds ratio; CI, confidence interval; NR, not reported; N/A, not applicable

* Study does not report time period of volume. [a] Adjusted analyses. [b]reports standard error

Figure 1. Flow diagram demonstrating electronic search results.

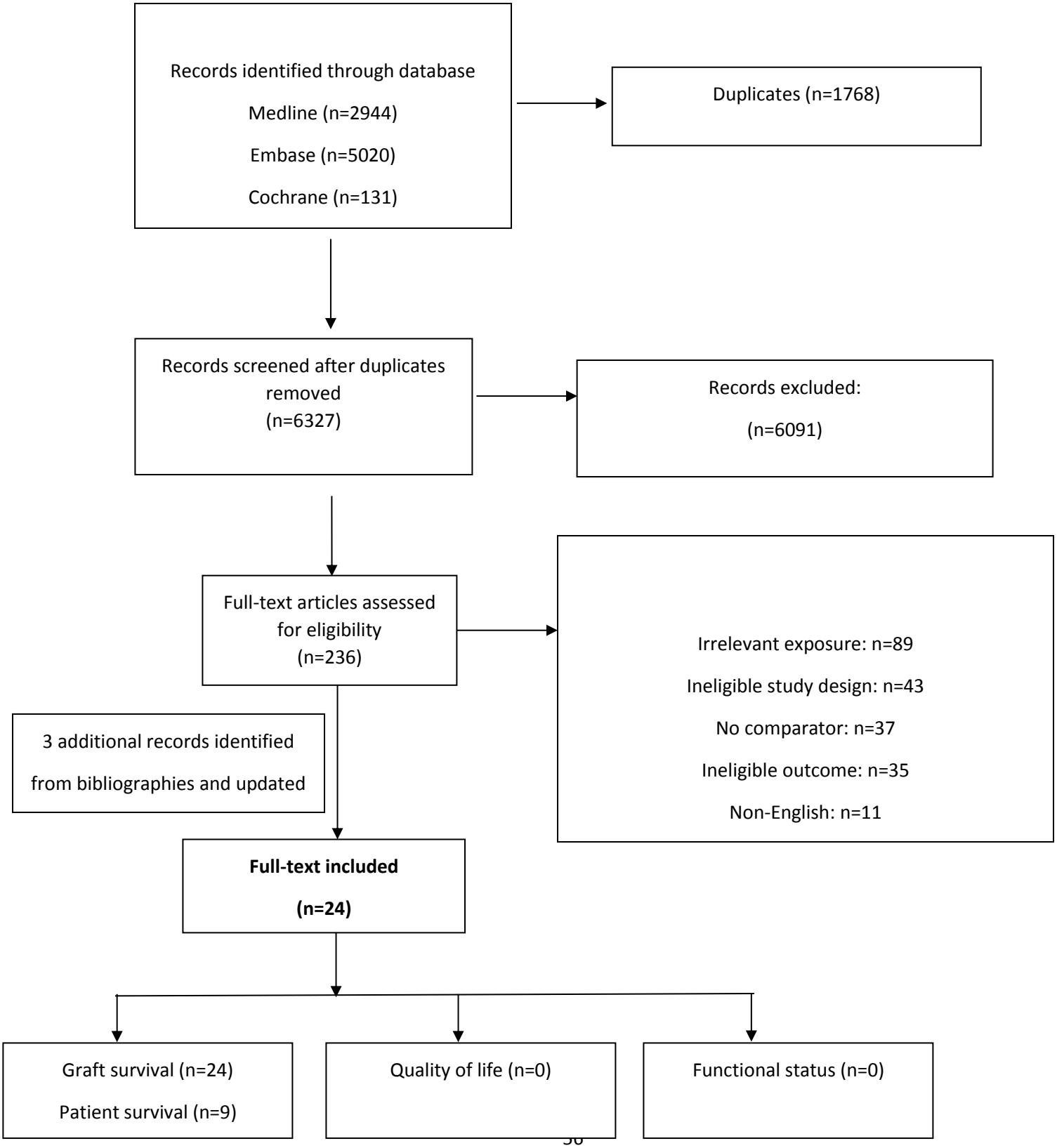
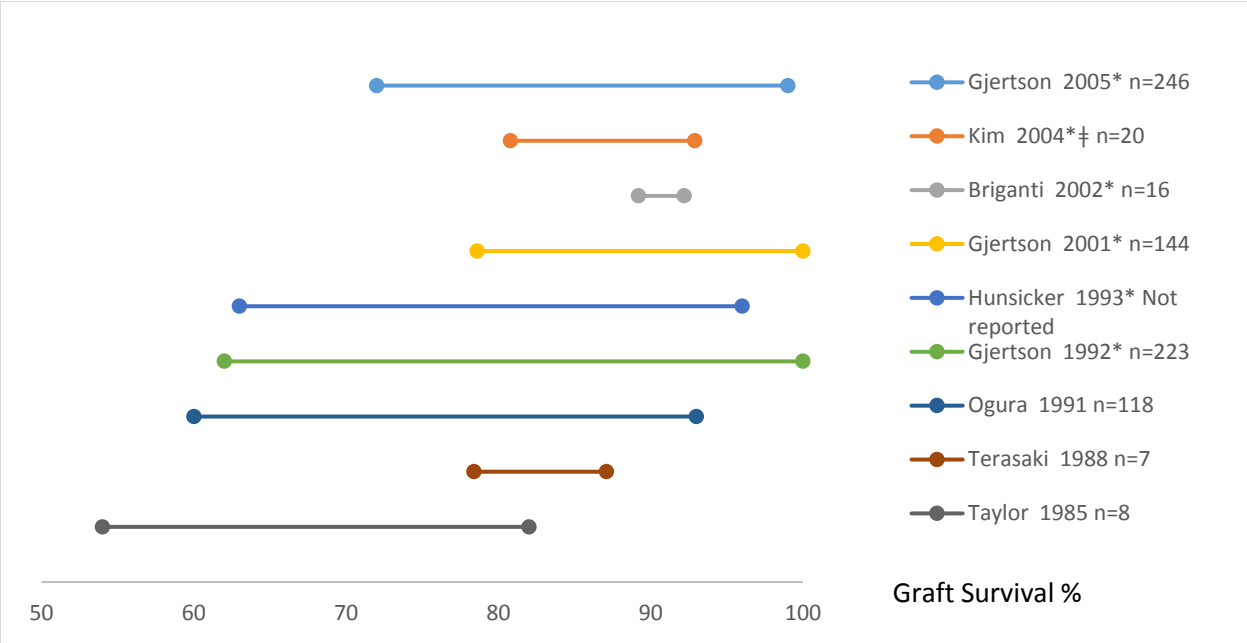


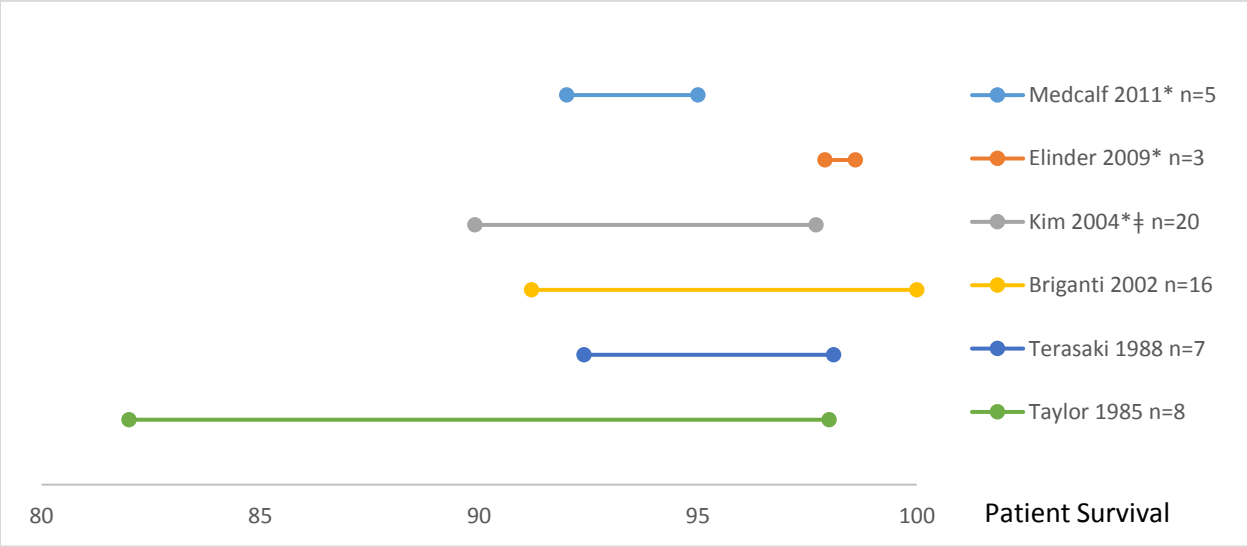
Figure 2a-b The range in one year graft and patient survival rates across centres (n) reported by each study.

Figure 2a. Variability in 1 year graft survival rates among centres.



*adjusted for case-mix ‡ adjusted for center volume

Figure 2b. Variability in 1 year patient survival rates among centres.



*adjusted for case-mix ‡ adjusted for center volume

Supplementary Table 1 – Additional factors assessed in association with Graft and Patient survival.

Study	Number Centres	Factor assessed and patient sample size	Outcome	Study Findings:
Doxiadis[31]	24	Type of cross match policy: Historical and current sera Current sera only Not defined or patient specific Historical and current sera Current sera only Not defined or patient specific	Graft survival unsensitised (PRA <10%): Graft survival sensitised (PRA >50%):	Survival rate 73.9% 78.9% 78.5% 71.7% 67.2% 70.3%
Gjertson[22]	144	Type of centre (percentage of pediatric cases): Dedicated pediatric vs volume >10% vs other (occasional)	Graft survival 1 year 5 year	Survival rate: 89.7 vs 89.7 vs 88.4% p=0.66 78.9 vs 76.4 vs 77.3% p=0.55
Pontin[36]	1*	Location of follow up post transplant Transplant centre (n=299) vs rural centre with general practitioner (n=181)	Graft survival deceased donor: 1 year 3 year 5 year Graft survival living donor: 1 year 3 year 5 year	Survival rate: 61 vs 61% 49 vs 50% 40 vs 41% Survival rate: 90 vs 90% 84 vs 79% 72 vs 72%
Evans[28]	145	Type of centre: For profit hospital Teaching hospital Type of centre: For profit hospital Teaching hospital Transplant physician experience: > 15 years experience	Graft survival Patient survival Graft survival Patient survival	Odd's ratio: 1.16 p=0.4 Odd's ratio: 0.97 p=0.61 Odd's ratio: 1.06 p=0.82 Odd's ratio: 0.83 p=0.03 Odd's ratio: 0.81 p=0.002 Odd's ratio: 0.85 p=0.09

*All patients were transplanted at the same centre however follow up post transplantation occurred at 2 different centres.
Abbreviation: PRA – panel reactive antibody

APPENDIX

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy: June 16, 2014

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1 Kidney Transplantation/ (78977)

2 ((kidney or renal) adj transplant$).tw. (57786)

3 1 or 2 (88629)

4 Comorbidity/ (68258)

5 "Quality of Health Care"/ (57103)

6 Health Services Accessibility/ (51009)

7 exp Socioeconomic Factors/ (339794)

8 Health Status Indicators/ (19969)

9 (comorbid$ or community health indicator$).tw. (69730)

10 ((transplant$ or organ) adj1 (cent$ or hospital$)).tw. (4622)

11 "quality of life"/ (117784)

12 Mental Health/ (21733)

13 Depression/ (76188)

14 Depressive Disorder/ (58287)

15 (cent$ adj2 variation$).tw. (827)

16 Quality Assurance, Health Care/ (48945)

17 or/4-16 (822665)

18 3 and 17 (4625)

19 exp Host vs Graft Reaction/ (79644)

20 Mortality/ (34276)

21 mortality.tw. (466895)

22 (graft survival or graft failure or graft loss).tw. (23799)

23 exp Renal Insufficiency/ (124554)

24 ((kidney or renal) adj failure).tw. (77752)

25 or/19-24 (698857)

26 18 and 25 (2944)

Database: Embase Classic+Embase <1947 to 2014 June 16>

Search Strategy:

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1 kidney transplantation/ or kidney allograft/ or kidney graft/ (113325)

2 ((kidney or renal) adj transplant$).tw. (78990)

3 1 or 2 (120592)

4 comorbidity/ (124598)

5 health care quality/ (183996)

6 health care delivery/ (129044)

7 exp socioeconomics/ (177887)

8 health status indicator/ (757)

9 (comorbid$ or community health indicator$).tw. (104448)

10 ((transplant$ or organ) adj1 (cent$ or hospital$)).tw. (7638)

11 "quality of life"/ (251461)

12 mental health/ (78645)

13 depression/ (249379)

14 (cent$ adj2 variation$).tw. (1008)

15 or/4-14 (1106098)

16 3 and 15 (8134)

17 graft rejection/ (59505)

18 (graft survival or graft failure or graft loss).tw. (34371)

19 mortality/ (549341)

20 mortality.tw. (648953)

21 exp kidney failure/ (244261)

22 ((kidney or renal) adj failure).tw. (105116)

23 or/17-22 (1150585)

24 16 and 23 (5020)

*Updated search

Database: Embase Classic+Embase <1947 to 2016 June 24> , Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

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1 Kidney Transplantation/ (193900)

2 ((kidney or renal) adj transplant$).tw. (157844)

3 1 or 2 (228242)

4 Comorbidity/ (240728)

5 "Quality of Health Care"/ (224399)

6 Health Services Accessibility/ (179236)

7 exp Socioeconomic Factors/ (589638)

8 Health Status Indicators/ (22571)

9 (comorbid$ or community health indicator$).tw. (247134)

10 ((transplant$ or organ) adj1 (cent$ or hospital$)).tw. (15712)

11 "quality of life"/ (461222)

12 Mental Health/ (124518)

13 Depression/ (377529)

14 Depressive Disorder/ (135497)

15 (cent$ adj2 variation$).tw. (2208)

16 Quality Assurance, Health Care/ (201833)

17 or/4-16 (2226240)

18 3 and 17 (15207)

19 exp Host vs Graft Reaction/ (185921)

20 Mortality/ (707720)

21 mortality.tw. (1368657)

22 (graft survival or graft failure or graft loss).tw. (69819)

23 exp Renal Insufficiency/ (423663)

24 ((kidney or renal) adj failure).tw. (201846)

25 or/19-24 (2211384)

26 18 and 25 (9846)

27 ("20140617" or "20140618" or "20140619" or 2014062* or 2014063* or 2015* or 2016*).dc. (1954720)

28 26 and 27 (305)

29 28 use ppez (305)

30 kidney transplantation/ or kidney allograft/ or kidney graft/ (214382)

31 ((kidney or renal) adj transplant$).tw. (157844)

32 30 or 31 (234806)

33 comorbidity/ (240728)

34 health care quality/ (268775)

35 health care delivery/ (217526)

36 exp socioeconomics/ (209558)

37 health status indicator/ (23492)

38 (comorbid$ or community health indicator$).tw. (247134)

39 ((transplant$ or organ) adj1 (cent$ or hospital$)).tw. (15712)

40 "quality of life"/ (461222)

41 mental health/ (124518)

42 depression/ (377529)

43 (cent$ adj2 variation$).tw. (2208)

44 or/33-43 (1865337)

45 32 and 44 (14869)

46 graft rejection/ (117300)

47 (graft survival or graft failure or graft loss).tw. (69819)

48 mortality/ (707720)

49 mortality.tw. (1368657)

50 exp kidney failure/ (423663)

51 ((kidney or renal) adj failure).tw. (201846)

52 or/46-51 (2167641)

53 45 and 52 (9122)

54 ("20140617" or "20140618" or "20140619" or 2014062* or 2014063* or 2015* or 2016*).dd. (3046621)

55 53 and 54 (896)

56 55 use emczd (896)

57 29 or 56 (1201)

58 remove duplicates from 57 (1019)

59 58 use ppez (287) Medline

60 58 use emczd (732) Embase

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <January 2016>

Search Strategy:

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1 Kidney Transplantation/ (3141)
2 ((kidney or renal) adj transplant$).tw,hw. (6108)
3 1 or 2 (6108)
4 Comorbidity/ (2752)
5 "Quality of Health Care"/ (661)
6 Health Services Accessibility/ (452)
7 exp Socioeconomic Factors/ (7089)

8 Health Status Indicators/ (915)
9 (comorbid$ or community health indicator$).tw,hw. (7783)
10 ((transplant$ or organ) adj1 (cent$ or hospital$)).tw,hw. (301)
11 "quality of life"/ (15226)
12 Mental Health/ (736)
13 Depression/ (5753)
14 Depressive Disorder/ (4362)
15 (cent$ adj2 variation$).tw,hw. (88)
16 Quality Assurance, Health Care/ (556)
17 or/4-16 (39277)
18 3 and 17 (209)
19 exp Host vs Graft Reaction/ (2678)
20 Mortality/ (331)
21 mortality.tw,hw. (30219)
22 (graft survival or graft failure or graft loss).tw,hw. (2875)
23 exp Renal Insufficiency/ (4872)
24 ((kidney or renal) adj failure).tw,hw. (7826)
25 or/19-24 (40928)
26 18 and 25 (131)

APPENDIX B - Modified Version of the Ottawa-Newcastle Quality Assessment Scale for Cohort Studies

A study was awarded a (+) if it was found to have low risk of bias for an item, (-) for high risk of bias and (?) if it was unclear or not reported in the study.

SELECTION

1) Representativeness of the study cohort.
   The representativeness of the transplant cohort was rated as follows:
   - Low risk if cohort did not have strict exclusion criteria and included all primary renal transplant recipients, as well there was no minimum graft number required per centre.
   - High risk if study had exclusions and included a subset of patients such as cadaveric transplants only or living only, included re-transplants or multi-organ transplants or only included centres grafting a minimum number.
   - Unclear if study did not mention any inclusion/exclusion criteria in their Methods

COMPARABILITY

1) Comparability of cohorts.
   The comparability of participants in the different volume categories or at different centres was coded as:
   - Low risk if the study adjusted for either sex or age in their analytical model.
   - High risk if the study did not adjust for any covariates at all or adjusted for covariates other than sex or age (for example comorbidities) in their analytical model.
   - Unclear if the study did not report whether they adjusted in their model.

OUTCOME

1) Assessment of outcome.
   The assessment of outcome confirmation was coded as:
   - Low risk if the study clearly defined what the outcome was, for example graft survival censoring for death or graft survival excluding death.
   - High risk if the study reported the outcome but was not clear in its definition, for example graft survival but did not specific whether it included or excluded death.
   - Unclear if study did not report how the outcome was confirmed.

2) Adequacy of follow up.
   Attrition was coded as follows:
   - Low risk if all patients were accounted for or there was less than 20% missing at the end of study period.
   - High risk if there was more than 20% missing at the end of the study period or a study excluded those with missing follow up from the study.
   - Unclear if there is no statement on follow up

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4
2	Hypothesis statement	5
3	Description of study outcome(s)	5
4	Type of exposure or intervention used	5
5	Type of study designs used	5
6	Study population	5
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	5
8	Search strategy, including time period included in the synthesis and key words	5
9	Effort to include all available studies, including contact with authors	6
10	Databases and registries searched	5
11	Search software used, name and version, including special features used (eg, explosion)	5
12	Use of hand searching (eg, reference lists of obtained articles)	5
13	List of citations located and those excluded, including justification	Fig1
14	Method of addressing articles published in languages other than English	6
15	Method of handling abstracts and unpublished studies	6
16	Description of any contact with authors	6
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	6/7
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	6
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	6
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	6
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	7
22	Assessment of heterogeneity	7
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	NA
24	Provision of appropriate tables and graphics	Tables1,2 Figure 1

Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figure 2a,2b
Item No	**Recommendation**	**Reported on Page No**
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	Table 2, 9, 17
30	Justification for exclusion (eg, exclusion of non-English language citations)	
31	Assessment of quality of included studies	9 Table 2
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	17
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	17
34	Guidelines for future research	16, 17
35	Disclosure of funding source	Title page (1)

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

Transcribed from the original paper within the NEUROSURGERY® Editorial Office, Atlanta, GA, United Sates. August 2012.

Chapter 3 – [Manuscript 2] – **Case-mix, patterns of care and in-patient outcomes among Ontario kidney transplant centres: a population-based study**

3.1 Preface to manuscript 2 –

In this manuscript, we describe the creation of a study cohort of over 5000 kidney transplant recipients transplanted across 5 Ontario centres between January 1st 2000 to December 31st 2013. This study describes differences across centres at the patient level and at the centre and provider levels. Three of the four patient outcomes assessed: length of initial transplant admission, proportion of patients requiring in-hospital dialysis and proportion of patients' requiring intensive care unit admission during their initial post-transplant period varied significantly across the centres. Furthermore, after adjusting for patient case mix as well as centre and provider factors, the hazard ratios for length of stay censored at the time of death varied significantly across centres which implies that additional unmeasured factors may be involved.

The Editor and reviewers for the *Canadian Journal of Kidney Health and Disease* requested that one of the six Ontario transplant centres be excluded for the following reasons: *Centre E is an extreme outlier compared to the other centres performing 55/5092 (~1%) of the transplants included. Due to their low numbers, many of their characteristics/outcomes are suppressed. Furthermore for many Canadian physicians, Centre E is easily identifiable/distinguished from the other centres. While the individual recipients are unlikely to be identifiable through this data, the physicians at this centre who are caring for these patients are more likely to be identifiable*". Therefore this final manuscript includes 5 transplant centres and a cohort of 5037 patients.

This manuscript has been accepted for publication at the *Canadian Journal of Kidney Health and Disease.*

Case-mix, patterns of care and in-patient outcomes among Ontario kidney transplant centres: a population-based study.

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4. Department of Epidemiology and Biostatistics, Western University.
5. Institute for Clinical Evaluative Sciences; London Ontario Canada.
6. Department of Medicine (Critical Care), University of Ottawa
7. Department of Family Medicine, University of Ottawa
8. Department of Medicine, University of Ottawa
9. Institute for Evaluative Sciences, Toronto, Ontario, Canada
10. School of Epidemiology, Public Health and Preventive Medicine, University of Ottawa

ABSTRACT

Background: Significant variation in both patient case-mix and the structure of care in kidney transplantation has been previously described in the United States.

Objective: The objective of our study was to characterize patient case-mix, patterns of care, and in-patient outcomes across 5 kidney transplant centres in the province of Ontario, Canada.

Design: This was a retrospective population-based cohort study using health care administrative databases.

Setting: The setting is Ontario, Canada.

Patients: We included adult (≥ 18 years) transplant recipients who received a primary, solitary kidney between January 1st 2000 to December 31st 2013 (n=5037).

Methods: Using linked administrative healthcare databases we characterized kidney transplant recipient and donor factors, centre characteristics, provider characteristics and in-patient outcomes across transplant centres in Ontario. To compare case-mix adjusted differences in length of stay across centres, multivariable Cox proportional hazards regression was used to obtain hazard ratios (HR) for each centre relative to the average across all centres. Centre volume and provider characteristics were added to the models to examine whether these factors explain differences in length of stay across centres.

Results: We saw significant differences across transplant centres in patient race, cause of end stage renal disease, body mass index, comorbidities, time on dialysis and donor type. Mean annual transplant-centre volumes during the study period ranged between 51.5 (9.3) to 101.7 (23.9) transplants/year across centres (p<0.0001). Physician specialty most responsible for in-hospital transplant care varied significantly across centres with the most common combination being nephrologist and urologist. Less than 31 deaths occurred in hospital during the index transplant admission but mortality risk did not differ significantly between centres. Overall, 25.1% of recipients required dialysis in hospital post-transplantation (range across centres 18.3-33.5%, p<0.0001) and 24.7% of recipients spent time in the intensive care unit (ICU) (range across centres 5.7-58.0%, p<0.0001). The proportion of participants requiring dialysis did not

change with time (p=0.12) whereas the proportion staying in the ICU increased steadily over time (p<0.0001). The median length of stay in hospital after transplantation ranged from 7 to 9 days across centres (p<0.0001) and decreased significantly over time. After adjusting for patient case mix as well as centre and provider factors, HRs for length of stay censored at the time of death ranged between 0.75 (95% CI 0.69-0.82) and 1.29 (95% CI 1.20-1.38) across centres. Centre volume and provider experience were not independently associated with length of hospital stay.

Limitations: Data was missing (0.8 to 16.7%) for certain covariates of interest.

Conclusions: This study found significant heterogeneity across kidney transplant centres in case mix, practice patterns and in-patient outcomes. Future studies are needed to examine the influence of length of stay and practice patterns on long-term outcomes such as patient/graft survival and quality of life.

Keywords: Kidney transplantation, centre variation, health services delivery, in-hospital outcomes,

Running Title: Centre Variation in Ontario

What was known before: Studies from the United States have characterized differences in kidney transplant recipients across transplant centres. Variation in patterns of care and provider characteristics among Ontario kidney transplant centres has not been described.

What does this study add: This large population based study is the first to characterize differences in centre and provider level care during kidney transplantation in Ontario. We found significant differences in patient factors, practice patterns and provider characteristics.

INTRODUCTION

There is an increasing number of Canadians living with end stage renal disease (ESRD)(1-3). In 2014, there were 35,281 Canadians with ESRD, which increased by 38% from 2005. Kidney transplantation is associated with improved survival, better quality of life and decreased long term healthcare costs compared to dialysis(4, 5). Little is known regarding the structure of inpatient care after kidney transplantation and its impact on patient outcomes. In an American survey,(6) significant variation in the structure and processes of care (including provider type) at kidney transplant centres was demonstrated.

Length of hospital stay post kidney transplantation is important, as it has been shown to be associated with: increased hospital expenses(7, 8), increased risk of re-admission after discharge(9), decreased graft survival(10) and increased patient mortality(10, 11). The following risk factors have been found to be associated with an increased length of stay in hospital after kidney transplantation including: African American race, obesity, deceased donor type, time on dialysis before transplantation and, higher Charlson comorbidity index, as well as, the presence of comorbid conditions such as cardiac disease, respiratory disease, cancer(8, 12). To our knowledge, length of hospital stay after kidney transplantation has not been evaluated in Canada and while centre volume has been studied in association with length of hospital stay in two preliminary studies(13, 14), provider level factors such as provider type and experience have not been.

The objectives of the present study are therefore to: 1) describe baseline patient-level characteristics (donor and recipient) at five adult kidney transplant centres in Ontario; 2)

characterize the type of provider caring for recipients at the time of transplant; 3) compare provider characteristics (age, years in practice, gender, country of medical training) between the sites; 4) describe in-hospital outcomes during the transplant admission including duration of stay, mortality, post-transplant dialysis and need for intensive care admission (ICU) and 5) determine whether patient characteristics, centre volume and/or provider characteristics such as type of provider and provider experience are associated with length of stay and contribute to its variation across centres.

METHODS

Study Design and Setting

This was a population-based retrospective cohort study using health care databases at the Institute for Clinical Evaluative Sciences (ICES) in Ontario, Canada. Ontario has a population of approximately 13.6 million residents who have universal access to health care services. This study was approved by the institutional review board at Sunnybrook Health Sciences Centre (Toronto, Canada). The reporting of this study followed guidelines described for observational studies.(15, 16) The full data set creation plan is available from the authors upon request.

Data sources

We used several linked datasets to create the cohort, and to obtain patient, centre and provider characteristics and outcome data. These datasets were linked using unique encrypted patient-specific identifiers and analyzed at ICES. Kidney transplant recipients were identified using the Canadian Organ Replacement Register (CORR). CORR captures information on all

kidney transplant recipients in Ontario. Its sensitivity to correctly identify kidney transplant recipients is 96% and positive predictive value is 98%(17). Demographic and vital status was ascertained from the Ontario Registered Persons database (RPDB). RPDB provides basic demographic information on anyone with a valid Ontario health card number. Renal recipient comorbidities were captured using the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) and Ontario Health Insurance Plan (OHIP) Claims Database. CIHI-DAD captures information on all hospitalizations and same day surgeries in Ontario and OHIP provided information on Ontario physician billing claims for approximately 95% of physician services conducted in Ontario. We used similar codes to those used in prior kidney transplant studies from ICES(17-19). We obtained provider information using the ICES Physician Database (IPDB). IPDB contains information on physician demographics, training and practice setting from the Corporate Provider Database, the Ontario Physician Human Resource Data Centre database and the OHIP database of physician billings.

Study Cohort

We included all adults (≥18 years) who received a first-time solitary kidney transplant in Ontario, Canada between January 1st 2000 and December 31st 2013 using CORR. We excluded individuals with an invalid ICES key number [(IKN) a confidential ICES patient number] (n=353), who received a multi-organ transplant as this is a rare event (n=313), were not from Ontario, had a death date prior to transplant date and therefore were invalid, had unknown age or sex (n=14), were younger than age 18 or transplanted at a children's hospital (n=223), and whose OHIP transplant billing or hospitalization dates did not align with transplant date (n=117). We

also excluded patients who were transplanted at one centre given the small volume of transplants performed during this time period (n=55).

Identification of patient, centre and provider characteristics

Transplant recipients were classified by the centre at which their transplant occurred using the CORR facility code number. Information on the transplant centre was obtained using CORR, OHIP and IPDB. We identified physicians that provided care to transplant recipients during their admission by linking the patient IKN with an encrypted physician number using the OHIP database. We identified the most responsible surgeon and most responsible physician by using the following OHIP transplant related billing codes: S435 (surgical transplant fee) and G412 (nephrology component of renal transplant) which is specific for the day of the transplant. The surgical transplant fee code has been validated for identifying kidney transplant recipients(17). Provider characteristics including specialty type, age, years since graduation, sex and country of graduation were obtained from IPDB.

Outcomes

Outcomes of interest, defined at the individual recipient level, included: length of transplant hospital admission, admission to the ICU and step-down unit during the transplant hospital admission using CIHI-DAD billing codes limited to those transplanted after March 30th 2002, death during the initial transplant admission, and need for dialysis in hospital post-transplant (dialysis start at least 2 days post-transplant).

Statistical Analysis

All statistical analyses were performed using SAS (Statistical Analysis Software) version 9.4 (SAS Institute, Cary NC). We used descriptive statistics to summarize characteristics of patients at the time of transplant by centre. Continuous variables were described using mean and standard deviation (SD) when the data followed a normal distribution or median and interquartile range [IQR] if not normally distributed. Frequencies and percentages were used for categorical data. The statistical significance of differences across transplant centres were examined using analysis of variance (ANOVA) or Kruskal-Wallis tests for continuous variables and Chi-squared tests or Fisher's exact for categorical variables. Centre volume was calculated as average annual volume (the total number of primary solitary kidney transplants performed at a given centre over the number of years performing transplants during this study period) as well as total number of transplants per year for each centre. We categorized the study period into three time periods: January 1st 2000 - December 31st 2004, January 1st 2005 – June 30th 2009, July 1st 2009 – December 31st 2013. For each centre, we calculated the proportion of transplant patients seen by each type of provider. This was calculated as the number of patients who saw the provider type divided by the total number of transplants at that centre with a transplant billing code. For each type of provider, the provider mean age and years since graduation were calculated. We also calculated the proportions of encounters with Canadian trained providers and with male providers. For each type of provider, we calculated the years of experience as years since graduation. For each patient we calculated the average provider experience of the care team as the average years since graduation of the providers linked to a given patient.

We assessed change in length of stay over time using the Kruskal-Wallis test and the Chi-square trend test for proportion of patients requiring dialysis and requiring the ICU. We were unable to analyze and report the change in number of deaths with time due to the small number of events. We did not present variables that were missing more than 20% data including: distance from hospital, class 2 panel reactive antibody (PRA) peak, PRA method and cold ischemia time.

To account for differences in patient case mix across transplant centres, we used fixed effects multivariable Cox proportional hazards regression with the event of interest defined as hospital discharge censored at the time of in-hospital death. Adjusted hazard ratios (HR) with 95% confidence intervals were calculated for each transplant centre, relative to the average across all centres. Our models adjusted for the following patient characteristics: recipient age, sex, race, cause of ESRD, BMI, Charlson comorbidity index, pretransplant dialysis modality (none vs hemodialysis or peritoneal dialysis), time on dialysis before transplantation, time era of transplant (as defined above), donor source and donor age. A centre with a HR and both limits of its 95% confidence interval below 1 implies that the centre has a significantly longer length of stay than the average after accounting for patient case mix, while a centre with a HR and both limits of its 95% confidence interval above 1 implies that the centre has a significantly shorter length of stay compared to the average. On the other hand, a centre with a confidence interval including 1 implies the length of stay is not significantly different than the average after accounting for patient case mix, centre volume and provider characteristics.

Data were missing for the following variables; recipient race (10.0%), cause of ESRD (7.9%), Charlson comorbidity index (5.5%), BMI (16.9%), donor type (0.75%) and donor age (0.79%).

Prior to performing our analyses, we performed multiple imputation using the fully conditional specification (FCS) method which does not assume a joint distribution but instead applies a separate conditional distribution for each of the imputed variables(20). For categorical values we used the discriminant method and for continuous variables, linear regression was applied. We conducted ten imputations using 100 burn in iterations. Multivariable analyses were conducted for each imputation dataset and combined across datasets using Rubin's rules(21).

RESULTS

Patient case mix

The final cohort included 5037 kidney transplant recipients (Figure 1). The mean (SD) age of the overall cohort was 50.9 (13.5) years, 63.1% were male and 63.4% were Caucasian. The most common cause of ESRD was glomerulonephritis (33.4%). Just under half (42.0%) received a living donor kidney. Variation in recipient and donor characteristics across centres is described in Table 1. The majority of recipient and donor factors varied significantly across the centres including important known prognostic variables such as race, cause of ESRD, time on dialysis and presence of diabetes. The proportion of missing data in recipient and donor variables ranged between 0.75% and 18.4% with panel reactive antibody (PRA) having the most missing values.

Practice patterns

Average annual kidney transplant volume ranged between 51.5 (9.3) and 101.7 (23.9) across the five centres ($p<0.0001$). There was significant variation in transplant volume by centre.

(Figure 2). The proportion of patients seen by a provider type varied significantly across centres. (Table 2). The majority of patients (85.3%) saw a nephrologist and this proportion ranged between 82.5 to 94.7% across centres ($p<0.0001$). The type of surgeon also varied across centres. Urologists performed all transplant in 3 centres, while in the other 2 there was a mixture of urologists and general surgeons. The proportion of patients who had a urologist perform their transplant ranged between 43.5 to 94.8% and the proportion who had a general surgeon ranged between 0 to 51.3% across centres (both $p<0.0001$). A total 63.5% of patients had a combination of nephrologist and urologist as their care providers; this proportion ranged between 37.5 and 78.5% and varied significantly across centres ($p<0.0001$). Nephrologist and urologist was the most common combination of care providers (Table 2).

Provider Characteristics

There were 185 physicians across 5 centres providing the initial care during the transplant admissions from 2000 to 2013. This included nephrologists (n=66), surgeons (n=67) (urologists and general surgeons) and fellows [specialist undertaking further training (n=32)], internists and family physicians (n=20). The characteristics of these physicians are summarized in Table 3. Overall the majority of encounters were with male providers and this varied between 71.8 to 100% depending on the specialty. The proportion of encounters with male providers varied significantly by centre for nephrologists, urologists and fellows. Overall the proportion of encounters with providers who were Canadian graduates ranged between 61.0 and 97.8% depending on the specialty and varied significantly by centre for nephrologists, urologists,

general surgeons and fellows. There were significant differences across centres in the provider age and years since graduation for all provider types (all p<0.0001).

Patient Outcomes

Table 4 describes between-centre variation in patient outcomes that occurred during the initial transplant hospitalization. The overall median [IQR] length of the initial transplant admission was 8 [7, 12] days and the median time varied significantly across centres from 7 to 9 (p<0.0001). The overall length of stay decreased significantly with time; 9 [7,14] in 2000-2004, 8 [7,11] in 2005-2009 and 7 [6,10] in 2009-2013 (p<0.0001). There were less than 31 in-hospital deaths and the proportion of deaths did not vary significantly across centres (p=0.3). There were 25.1% of recipients who required post-transplant dialysis in hospital; the percentage ranged significantly between centres from 18.3 to 34.5% (p<0.0001). The majority of patients who required dialysis were those who had received a deceased donor graft (71.8% [909/1266]). The proportion of patients requiring dialysis in hospital fluctuated with time; 26.0% in 2000-2004, 25.9% in 2005-2009 and 23.8% in 2009-2013 (p=0.12). Overall 24.6% of recipients transplanted after March 30th 2002 required admission to intensive care including the step-down unit; this percentage ranged between 5.7 and 58.0 across centres (p<0.0001). The proportion requiring admission to the ICU increased significantly with time; 8.4 % in 2002-2004, 25.3% in 2005-2009 and 30.6% in 2009-2013 (p<0.0001).

Adjusted Hazard Ratios – Length of stay censoring at time of death

Centre-specific hazard ratios for length of stay censored at the time of death obtained from Cox proportional hazards regression models revealed statistically significant differences across centres, after accounting for patient case mix only ($p<0.0001$), adding centre volume ($p<0.0001$) and provider characteristics ($p<0.0001$). Centre specific hazard ratios ranged between 0.75 (95% CI 0.69-0.82) and 1.29 (95% CI 1.20-1.38) in the full models. Patient characteristics found to be statistically significantly associated with this outcome included recipient sex, age, BMI, Charlson comorbidity index, time on dialysis, donor type and donor age and time era. Centre volume, provider experience and all provider types were not significantly associated with the outcome with the exception of fellow. (Table 5).

DISCUSSION

To our knowledge, this is the first Canadian study to assess variation in in-patient outcomes, practice patterns and provider characteristics in kidney transplantation. In this population-based retrospective cohort study, we found substantial heterogeneity in not only patient factors, but also in patterns of care defined by provider characteristics in a single Canadian province. Furthermore, the length of hospital admission post kidney transplantation varied significantly across Ontario transplant centres and this variation was not explained by patient factors, centre volume or provider experience.

Our study found significant between-centre differences in patient-level factors. For example, the prevalence of medical co-morbidities, such as: diabetes, hypertension and peripheral vascular disease varied substantially across centres, as did average Charlson

comorbidity index. Our findings are similar to an earlier Canadian study by Kim et al in which the range in the proportion of transplant recipients over the age of 65 varied across centres (between 1.1 to 13.8%), as did the proportion of recipients with diabetes mellitus as the primary cause of ESRD (between 5.5 to 23.9%) and those receiving a graft from a living donor (between 1.3 to 32.2%) (22). It is well known that kidney transplant recipients commonly have at least one, if not multiple comorbid conditions at the time of transplant and that these comorbidities are associated with an increased length in hospital stay post transplantation(8, 12). In our study, the HR for Charlson comorbidity index was 0.92 (95% CI 0.90,0.94) implying that each 1 unit increase in the score was associated with a 9% decreased risk of being discharged from the hospital and therefore increased length of stay.

Our study observed substantial variation in kidney transplant volume and the type of physician providing care during the post-transplant admission at the centre level. Centre volume was not independently associated with length of stay post kidney transplantation. This is similar to what has been found in prior studies. Weng et al did not find a significant association between centre volume (using a categorical threshold of 95 patients) and length of hospital stay(14). Neither did the study by Tsao et al which used a categorical threshold of 72 transplants(13). In contrast to our study, which used multivariable modelling, neither of these studies adjusted for patient factors when testing for significance.

The majority of the studies published to date, within the field of kidney transplantation, assessing centre level variables have included centre volume (generally defined as the number of transplants over a given time period or a categorical threshold) and proportion of recipient

and donor types transplanted at a centre(9, 22, 23). For example, the USA based study by Orandi et al which aimed to determine centre-level variables associated with the incidence of delayed graft function (DGF), found significant heterogeneity even after adjusting for patient and centre level characteristics(23). Centre level variables found to impact DGF incidence included: a centre's proportion of donation after cardiac death, of imported kidneys, of pre-emptive transplants and kidneys with cold ischemia time greater than 30 hours. Interestingly, centre volume was not associated with DGF incidence. The hypothesis by Orandi et al was that differences in these variables reflect a centre's experience managing the kidney transplant population; however, these variables may simply represent differences in case mix and do not necessarily reflect differences in patient care(23).

To our knowledge, only one study has evaluated differences in provider types across kidney transplant centres. Israni et al studied the structure and delivery of care in 208 adult kidney transplant centres in the USA using surveys(6). Similar to our study, they found significant variation in the type of provider caring for kidney transplant recipients in hospital immediately after transplantation. For example, most of the centres surveyed in their study had nephrology subspecialty trainees (60.3%) and general surgery trainees (71.8%) providing inpatient care, whereas, only 24.4% of centres had urology trainees. In their study, 60.2% of the nephrologists and 48.1% of the transplant surgeons surveyed had worked at the transplant centre for more than 10 years. Provider experience and characteristics across the centres was not studied. Little is known about differences in provider experience (years in practice) and provider volume (physician caseload) in kidney transplantation in association with length of hospital stay. In our study, we found that both the type of surgeon (urologist vs general

surgeon) a patient had for their transplant and provider years of experience (defined as years since graduation) varied significantly across centres. Interestingly, the average provider experience was not associated with length of stay. Only one prior study assessed for a similar association. Weng et al found greater provider volume (defined as more than 33 transplants) was associated with a shorter length of hospital stay, this analysis did not adjust for patient case mix(14).

Our study is the first Canadian study to characterize differences in centre and provider level care during kidney transplantation. The strengths of our study include the large sample size of transplant patients obtained from a validated kidney transplant registry(17) and our ability to describe provider characteristics across transplant centres in a large Canadian province with a universal health care system. There are several limitations to this study, the majority of which relate to the provider information. First, we did not incorporate all inpatient transplant related provider encounters as we elected to include only the billing codes that were used on the day of transplant. The provider information was captured by using transplant specific OHIP billings linked to IPDB which has not yet been validated in the transplant setting. Although a prior study (24) which aimed to identify the number of new nephrology consultations using administrative databases, also found the number of new and active nephrologists in Ontario was similar when defined using OHIP billings compared with IPDB listing thus supporting the use of IPDB for identifying providers. Secondly, we were unable to identify the type of specialty a fellow was part of and therefore do not have information on who is intimately involved in the day to day care. However the overall objective was to provide a brief overview and not specific details which we admit is not possible with administrative

data. Thirdly, we included data from only one province and therefore cannot generalize our results to the rest of the country; however, Ontario has the greatest number of transplant centres and performs the highest volume in the country. For example, between 2005 and 2014 there were 5000 kidney transplants performed in Ontario alone representing 42% of Canada's kidney transplant volume(3). Lastly, as we relied on the use of administrative data, and we were limited to the detail provided within the registry, there was missing data for some of the variables of interest including cold ischemia time, HLA mismatch and ABO-incompatible status which precluded our ability to compare these factors. Furthermore clinical information on immunosuppressive medications and biopsy results used a given centre are not available within this administrative dataset.

In summary, this study found significant variation in important patient outcomes such as length of hospital stay, following kidney transplantation. We also showed that there were differences at the patient, centre and provider-level among Ontario kidney transplant centres. The variation seen across centres in the length of stay was not explained by patient case mix, centre volume or provider characteristics alone which implies that additional unmeasured factors may be involved. The results of our study have important clinical implications as they confirm that Ontario transplant centres vary substantially in the type of patient deemed acceptable for transplantation and certain patient characteristics such as greater BMI, co-morbidities and older donor age are associated with an increased length of hospital stay. Future studies are needed to examine the influence of length of stay and practice patterns on long-term outcomes such as patient/graft survival and quality of life.

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Abbreviations: ESRD; end stage renal disease, ICU; intensive care unit, ICES; Institute for Clinical Evaluative Sciences, CORR; Canadian Organ Replacement Register, ORPB; Ontario Registered Persons database, CIHI-DAD; Canadian Institute for Health Information Discharge Abstract Database, OHIP; Ontario Health insurance plan, IPDB; ICES Physician Database, SD; standard deviation, IQR; interquartile range.

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Authors' contributions: AT helped conceive the idea and design of the study, performed all statistical analyses, interpreted the results and drafted the manuscript. SD participated in the

study design, data cleaning, statistical analyses and interpretation of results. MT participated in the design of the study, in the statistical analyses and interpretation of results and drafting of the manuscript. CVW participated in the statistical analysis and interpretation of results. SE and DM participated in the study design and interpretation of results. GK and DF helped conceive the idea and design of the study, interpret the results and helped to draft the manuscript. All authors read and approved the final manuscript.

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FIGURE LEGEND

Figure 1. Study cohort creation

Figure 2. Kidney transplant volume performed per year over the study period at each individual transplant centre.

Table 1 Characteristics of kidney transplant recipients and donors across centres at the time of transplant

	Overall Cohort	Centre A	Centre B	Centre C	Centre D	Centre F	P-value[a]
Patient Characteristics	**N=5037**	**N=720**	**N=909**	**N=1206**	**N=1395**	**N=807**	
Age years, Mean, (SD)	50.9, (13.5)	51.2, (13.6)	51.5, (13.1)	50.7, (13.6)	50.5, (13.6)	51.0, (14.0)	0.44
Age n (%)							
18-34	690 (13.7)	90 (12.5)	119 (13.1)	164 (13.6)	197 (14.1)	120 (14.9)	
35-49	1473 (29.2)	229 (31.8)	249 (27.4)	365 (30.2)	405 (29)	225 (27.9)	
50-59	1348 (26.8)	181 (25.1)	244 (26.8)	318 (26.4)	393 (28.2)	212 (26.3)	
60-69	1183 (23.5)	156 (21.6)	229 (25.2)	292 (24.2)	317 (22.7)	189 (23.4)	
≥70	343 (6.8)	64 (8.9)	68 (7.5)	67 (5.6)	83 (5.9)	61 (7.6)	
Male n (%)	3177 (63.1)	467 (64.9)	592 (65.1)	725 (60.1)	865 (62.0)	528 (65.4)	0.04
Race n (%)							
Caucasian	3194 (63.4)	525 (72.9)	659 (72.5)	577 (47.8)	792 (56.8)	641 (79.4)	
African	361 (7.2)	39 (5.4)	22 (12.4)	133(11.0)	155 (11.1)	12 (1.3)	
Asian	345 (6.8)	37 (5.1)	27 (3.0)	158 (13.1)	103 (7.4)	20 (2.5)	
Other	634 (12.6)	48 (6.7)	50 (5.5)	228 (18.9)	239 (17.1)	69 (8.5)	
Unknown	503 (10.0)	71 (9.9)	151 (16.6)	110 (9.1)	106 (7.6)	65 (8.1)	<0.0001
Cause of ESRD n (%)							
Glomerulonephritis	1684 (33.4)	225 (31.3)	280 (30.8)	435 (36.1)	479 (34.3)	265 (32.8)	
Diabetes	990 (19.7)	180 (25.0)	181 (19.9)	190 (15.8)	280 (20.1)	159 (19.7)	
Cystic Kidney disease	680 (13.5)	109 (15.1)	127 (14.0)	153 (12.7)	201 (14.4)	90 (11.2)	
Renal Vascular	553 (11.0)	58 (8.1)	65 (7.2)	146 (12.1)	171 (12.3)	113 (14.0)	
Other	733 (14.6)	102 (14.1)	134 (14.7)	150 (12.4)	202 (14.5)	145 (18.0)	
Unknown	397 (7.9)	46 (6.4)	122 (13.4)	132 (10.9)	62 (4.4)	35 (4.3)	<0.0001
BMI Mean, (SD)	26.6, (5.7)	27.1, (6.1)	27.6, (6.1)	25.5, (5.3)	26.4, (5.6)	26.8, (5.4)	<0.0001
Missing n (%)	850 (16.9)						
Charlson Comorbidity Index Mean, (SD)	2.7, (1.3)	2.8, (1.3)	2.9, (1.3)	2.6, (1.3)	2.7, (1.4)	2.8, (1.3)	<0.0001
Missing n (%)	275 (5.5)						
Pre-transplant dialysis modality n (%)							
Pre-emptive	515 (10.2)	95 (13.2)	94 (10.3)	135 (11.2)	162 (11.6)	29 (3.6)	

Hemodialysis	3379 (67.1)	443 (61.5)	664 (73.1)	809 67.1)	917 (65.7)	546 (67.7)	
Peritoneal Dialysis	1143 (22.7)	182 (25.3)	151 (16.6)	262 (21.7)	316 (22.7)	232 (28.8)	<0.0001
Time on dialysis prior to transplant (years)*							
Median [IQR]	2.7 [1.1,5.1]	2.4 [0.8, 4.1]	2.8 [1.3,5.0]	4.2 [1.3,6.6]	3.2 [1.2, 5.5]	1.8 [1.1,3.0]	<0.0001
Comorbidity Prevalence n (%)							
Diabetes	1406 (27.9)	226 (31.4)	264 (29)	302 (25)	392 (28.1)	222 (27.5)	0.04
Hypertension	3807 (75.6)	499 (69.3)	702 (77.2	917 (76)	1054 (75.6)	635 (78.7)	0.0003
Congestive heart Failure	961 (19.1)	144 (20.0)	184 (20.2)	222(18.4)	271 (19.4)	140 (17.4)	0.5
Coronary artery disease	2049 (40.7)	186 (25.8)	717 (78.9)	394 (32.7)	532 (38.1)	220 (27.3)	<0.0001
COPD	NR	≤5	19 (2.1)	19 (1.6)	8 (0.6)	25 (3.1)	0.0001
PVD	720 (14.3)	62 (8.6)	193 (21.2)	175 (14.5)	207 (14.8)	83 (10.3)	<0.0001
Chronic liver disease	595 (11.8)	76 (10.6)	77 (8.5)	126 (10.5)	210 (15.1)	106 (13.1)	<0.0001
Cancer	1326 (26.3)	184 (25.6)	222 (24.4)	306 (25.4)	379 (27.2)	235 (29.1)	0.18
Stroke	46 (0.9)	12 (1.7)	15 (1.7)	10 (0.8)	9 (0.7)	9 (1.1)	0.08
TIA	25 (0.5)	7 (0.9)	7 (0.7)	NR	6 (0.4)	NR	0.1
Live Rural n (%)[b]	559 (11.1)	135 (18.7)	70 (7.7)	53 (4.4)	114 (8.2)	187 (23.2)	<0.0001
Donor type n (%)							
Deceased/Missing**	2922 (58.0)	392 (54.4)	511 (56.2)	701 (58.1)	694 (49.7)	624 (77.3)	
Living	2115 (42.0)	328 (45.6)	398 (43.8)	505 (41.9)	701 (50.3)	183 (22.7)	<0.0001
Living only							
Age mean, (SD)	44.5, (13.3)	46.6, (13.5)	45.8, (14.5)	42.8, (12.2)	43.4, (12.4)	46.9, (15.3)	<0.0001
Male n (%)	845	137 (41.8)	158 (39.7)	175 (34.7)	299 (42.7)	76 (41.5)	0.22
Deceased only							
Age mean, (SD)	45.5, (15.9)	43.8, (15.9)	43.6, (14..7)	46.3, (16.3)	48.8, (16.2)	43.4, (15.9)	<0.0001
Male n (%)	1680	203 (53)	293 (57.6)	405 (48.6)	399 (58.3)	380 (61.7)	0.29
Most common causes of donor death n (%)							
Central nervous system[c]	1461 (50.0)	200 (52.1)	246 (48.3)	355 (51.3)	385 (56.1)	275 (44.6)	
Trauma[d]	708 (14.1)	100 (26.0)	128 (25.2)	158 (22.8)	124 (18.1)	198 (32.1)	
Anoxia/hypoxia	417 (8.3)	51 (13.3)	84 (16.5)	104 (15.0)	90 (13.1)	88 (14.3)	<0.0001

Class 1 PRA peak (%) Median [IQR] Missing n (%)	 0 [0,11] 925 (18.4)	 4[1,12]	 0[0,0]	 0[0,15]	 0[0,20]	 0[0,7]	 <0.0001

[a]Chi-square test for categorical variables, ANOVA for normally distributed continuous variables (age, BMI, Charlson comorbidity index, deceased and living age) and Kruskal-Wallis for non-normal (time on dialysis and PRA).

[b]Rural is defined as living in an area with <10,000 people.

[c]Central nervous system (CNS) related includes cerebrovascular, CNS tumor, ruptured cerebral aneurysm, spontaneous intracranial hemorrhage, intracranial event, CNS infection, cerebral oedema.

[d]Trauma includes trauma from motor vehicle accidents, gunshots and additional non motor vehicle related traumas.

*This time includes those who did not spend time on dialysis as well.

**The total under deceased also includes those with missing status.

≤5 implies n is smaller than or equal to 5 and thus cannot be reported due to privacy concerns.

NR: not reported to prevent unblinding of small cell numbers in other columns.

Abbreviations: SD, standard deviation; ESRD, End stage renal disease; BMI, body mass index; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease; TIA, transient ischemic attack; PRA, panel reactive antibody; NA; not applicable, NR; not reportable

Table 2. Percentage of patients overall and across each centre who saw the listed provider type.

Provider type	Overall cohort N= 5016	Centre A N=717	Centre B N=905	Centre C N=1200	Centre D N=1387	Centre F N=807	P-value[a]
Nephrologist n (%)	4277 (85.3)	569 (79.4)	756 (83.5)	990 (82.5)	1198 (86.4)	764 (94.7)	<0.0001
Fellow* n (%)	567 (11.3)	7 (0.98)	24 (2.7)	282 (23.5)	19 (1.4)	235 (29.1)	<0.0001
Internist n (%)	222 (4.4)	72 (10.0)	26 (2.9)	62 (5.2)	38 (2.8)	24 (3.0)	<0.0001
Urologist n (%)	3746 (74.7)	502 (70.0)	858 (94.8)	1138 (94.8)	603 (43.5)	645 (79.9)	<0.0001
General surgeon n (%)	1125 (22.4)	251 (35.0)	0	0	711 (51.3)	163(20.2)	<0.0001
Combination							
Nephrologist + Urologist n (%)	3186 (63.5)	410 (57.2)	710 (78.5)	933 (77.8)	520 (37.5)	613 (76.0)	<0.0001
Nephrologist + General Surgeon n (%)	932 (18.6)	176 (24.5)	0	0	601(43.3)	155 (19.2)	<0.0001
Internist + Urologist n (%)	161 (3.2)	46 (6.4)	26 (2.9)	60 (5.0)	11 (0.8)	18 (2.2)	<0.0001
Internist + General Surgeon n (%)	NR	32 (4.5)	0	0	27 (1.9)	≤5	<0.0001
Fellow + Urologist n (%)	485 (9.7)	7 (1.0)	23 (2.5)	269 (22.4)	9 (0.6)	177 (21.9)	<0.0001
Fellow + General Surgeon n (%)	47 (0.9)	≤5	0	0	<10	37 (4.6)	<0.0001

The sample size in this table includes those participants who had at least one physician (medical or surgical) billing code associated with their admission.

The proportions for surgical providers do not sum up to 100 at a given centre as more than one provider may have billed.

[a]P-value was calculated using Chi-square or Fisher's exact

*Fellows which means qualified specialist undertaking further training

≤5 implies n is smaller than or equal to 5 and thus cannot be reported due to privacy concerns.

NR – Not reported to prevent unblinding of small cell numbers in other columns.

Table 3. Characteristics of physicians providing care to the included renal transplant recipients across centres.

	Overall Cohort	Centre A	Centre B	Centre C	Centre D	Centre F	P value[a]
Physician Characteristics							
Nephrologists **Encounters**	N=66 N=4328	18 570	19 776	12 1009	6 1208	11 765	
Male n (%)	3798 (87.7)	396 (69.5)	555 (71.5)	945 (93.7)	1137 (94.1)	765 (100)	<0.0001
Canadian Graduate n (%)	3509 (80.9)	536 (94.0)	546 (70.4)	711 (70.5)	1208 (100)	508 (66.4)	<0.0001
Age mean, (SD)	47.0, (10.2)	41.8, (7.0)	46.7, (8.9)	43.2, (6.6)	51.6, (12.6)	49.2, (9.3)	<0.0001
Years since graduation mean, (SD)	21.3, (10.3)	16.6, (7.2)	19.1, (9.2)	18.5, (6.2)	26.2, (12.7)	23.0, (9.9)	<0.0001
Urologist[b] **Encounters**	N=42 N=4401	<10 524	8 975	13 1503	7 616	<10 783	
Male n (%)	4175 (98.2)	524 (100)	975 (100)	1345 (94.7)	614 (100)	717 (100)	<0.0001
Canadian Graduate n (%)	3378 (79.5)	515 (98.3)	946 (97.0)	989 (69.6)	611 (99.5)	717 (100)	<0.0001
Age mean, (SD)	46.7, (11.6)	41.6, (6.9)	45.9,(6.5)	46.5, (12.9)	62.8, (5.3)	38.0, (6.0)	<0.0001
Years since graduation mean, (SD)	20.9, (11.6)	15.7, (6.0)	20.2, (6.8)	20.5, (12.3)	37.8, (5.5)	12.4, (6.7)	<0.0001
General Surgeon[b] **Encounters**	N=25 N=1189	<10 252	0 0	0 0	14 757	<10 180	
Male n (%)	1167 (99.8)	252 (100)	NA	NA	738 (99.7)	175 (100)	0.4
Canadian Graduate n (%)	713 (61.0)	0	NA	NA	669 (90.4)	41 (23.4)	<0.0001
Age mean, (SD)	50.4, (10.6)	65.6, (3.0)	NA	NA	46.1, (7.7)	46.3,(7.8)	<0.0001
Years since graduation mean, (SD)	25.6, (11.0)	41.6, (3.0)	NA	NA	20.7, (7.5)	22.9, (8.5)	<0.0001
Fellows* Encounters	N=32 N=582	≤5 7	≤5 24	8 286	11 20	8 244	
Male n (%)	471 (71.8)	7 (100)	24 (100)	179 (62.6)	17 (85)	244 (100)	<0.0001
Canadian Graduate n (%)	568 (97.8)	≤5	24 (100)	285 (99.7)	15 (75)	241 (98.8)	<0.0001
Age mean, (SD)	32.9, (2.3)	34.6, (2.1)	39.1, (2.5)	32.4, (1.6)	37.3, (5.3)	32.6, (1.1)	<0.0001
Years since graduation mean, (SD)	6.2, (1.8)	9.7, (3.2)	7.5, (1.0)	5.9, (0.8)	10.7, (6.8)	6.1, (1.1)	<0.0001

[a]Chi-square test or Fisher's exact test for categorical variables and ANOVA for continuous variables (age and years since graduation).

[b]For some provider types, the physician characteristic was missing and therefore the denominator used is different than total encounters. For example the denominator used for urologists, was 4250 as this was the sample size who had information.

*Fellows which means qualified specialist undertaking further training

NA –not applicable as there are no providers of that type at the given centre.

≤5 implies n is smaller than or equal to 5 and thus cannot be reported due to privacy concerns.

Table 4. Description of in-hospital patient outcomes among renal transplant recipients during their transplant admission (2000-2013) across centres.

In-hospital outcome	Overall Cohort N= 5037	Centre A N=720	Centre B N=909	Centre C N=1206	Centre D N=1395	Centre F N=807	P-value[a]
Length of transplant admission (days) Median [IQR]	8 [7,12]	8 [7,12]	7 [6,10]	7 [6,9]	9 [7,13]	9 [7,13]	<0.0001
Proportion requiring dialysis posttransplant n (%)	1266 (25.1)	133 (18.5)	166 (18.3)	296 (24.5)	468 (33.5)	203 (25.2)	<0.0001
Time to dialysis (days) Median [IQR]	4 [2,5]	3 [2,5]	5 [3,6]	4 [3,5]	3 [2,5]	4 [2,5]	<0.0001
Number of deaths during admission n (%)	<31	≤5	≤5	12 (0.9)	7 (0.5)	≤5	0.3
Number transplanted after March 2002	N=4405	N=634	N=809	N=1061	N=1230	N=671	
Admission to ICU[b] n (%)	1088 (24.7)	36 (5.7)	147 (18.2)	112 (10.6)	714 (58.0)	79 (11.8)	<0.0001

[a]Chi-square test for categorical variables and Kruskal-Wallis for continuous variables (length of admission, length of stay in ICU, time to dialysis, time to death).

[b]This was determined based on billing codes and only among those transplanted after April 1st 2002 (n=4405) and includes the step-down unit. (See Appendix).

≤5 implies n is smaller than or equal to 5 and thus cannot be reported due to privacy concerns.

Table 5.Centre-specific hazard ratios from multivariable Cox Proportional hazards regression analysis of hospital discharge, censoring for death (total number of events=5007)

	Adjusting for patient case mix only (n=5037)	Adjusting for patient case mix and centre volume (n=5037)	Adjusting for patient case mix, centre volume and provider characteristics (n=5037)
Covariate	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Age, (per 5 year increase)	0.95 (0.94,0.97)	0.95 (0.94,0.97)	0.95 (0.94,0.97)
Sex ; Female	0.91 (0.86,0.96)	0.91 (0.85,0.96)	0.90 (0.85,0.96)
Male	Reference	Reference	Reference
Race; Caucasian	0.96 (0.88,1.05)	0.96 (0.88,1.05)	0.96 (0.88,1.05)
African	0.93 (0.82,1.06)	0.93 (0.82,1.06)	0.93 (0.81,1.05)
Asian	0.97 (0.85,1.11)	0.97 (0.85,1.11)	0.96 (0.84,1.09)
Other[1]	Reference	Reference	Reference
Cause of ESRD; GN	1.02 (0.93,1.11)	1.02 (0.93,1.11)	1.01 (0.93,1.11)
Diabetes	1.00 (0.90,1.12)	1.00 (0.90,1.12)	1.01 (0.90,1.12)
Cystic	1.09 (0.98,1.22)	1.09 (0.98,1.22)	1.09 (0.98,1.22)
RVD	1.03 (0.92,1.16)	1.03 (0.92,1.16)	1.04 (0.92,1.16)
Other	Reference	Reference	Reference
BMI (per 1 unit)	0.99 (0.98,0.99)	0.99 (0.98,0.99)	0.99 (0.98,0.99)
Charlson comorbidity Index (1 unit)	0.92 (0.90,0.95)	0.92 (0.90,0.95)	0.92 (0.90,0.94)
Preemptive transplant	1.01 (0.91,1.12)	1.01 (0.90,1.12)	1.02 (0.91,1.12)
Pretransplant dialysis[2]	Reference	Reference	Reference
Time on dialysis pretransplant (per 1 year increase)	0.94 (0.93,0.95)	0.94 (0.93,0.95)	0.94 (0.93,0.95)
Donor type; Living	1.27 (1.18,1.37)	1.27 (1.18,1.36)	1.25 (1.15,1.34)
Deceased	Reference	Reference	Reference
Donor age (per 5 year increase)	0.98 (0.97,0.99)	0.98 (0.97,0.99)	0.97 (0.96,0.98)
Time era of transplant: 2000-2004	Reference	Reference	Reference
2005-2009	1.33 (1.24,1.44)	1.30 (1.21,1.41)	1.33 (1.22,1.44)
2009-2013	1.84 (1.71, 1.98)	1.75 (1.58, 1.94)	1.80 (1.62,2.01)
Centre[3] A	0.93 (0.87,0.99)	0.95 (0.88,1.03)	0.95 (0.87,1.03)
B	1.31 (1.24,1.40)	1.33 (1.25,1.41)	1.28 (1.20,1.37)
C	1.32 (1.25,1.40)	1.29 (1.21,1.38)	1.29 (1.20,1.38)

D F	0.76 (0.72, 0.80) 0.81 (0.76,0.87)	0.73 (0.67,0.79) 0.83 (0.77,0.90)	0.75 (0.69,0.82) 0.85 (0.79,0.92)
Centre Volume (per 25 patients)		1.04 (0.98,1.10)	1.03 (0.98,1.09)
Average provider experience (per 5 years experience)			0.99 (0.97,1.01)
Provider Type: Urologist General Surgeon Fellow Nephrologist Internist			 1.00 (0.91,1.11) 0.91 (0.83,1.03) 0.86 (0.78,0.96) 0.99 (0.90,1.09) 1.08 (0.92,1.27)

Other[1] includes Aboriginal, Indian subcontinent, Pacific Islander,Multiracial.

Pretransplant dialysis[2] includes both peritoneal dialysis and hemodialysis.

Centre[3] -the reference is the average across all centres.

Abbreviations: ESRD, end stage renal disease; GN, glomerulonephritis; RVD, renal vascular disease; BMI, body mass index

Figure 1. Cohort Creation

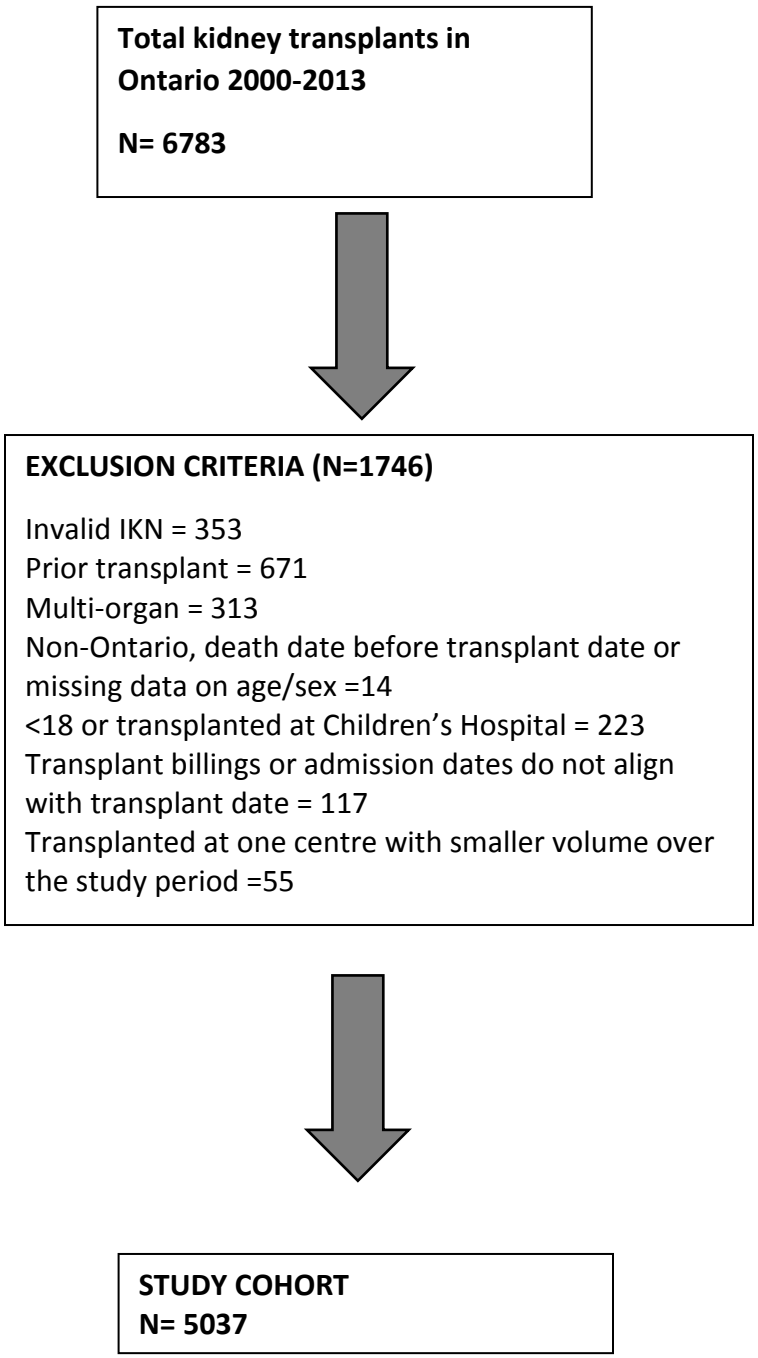
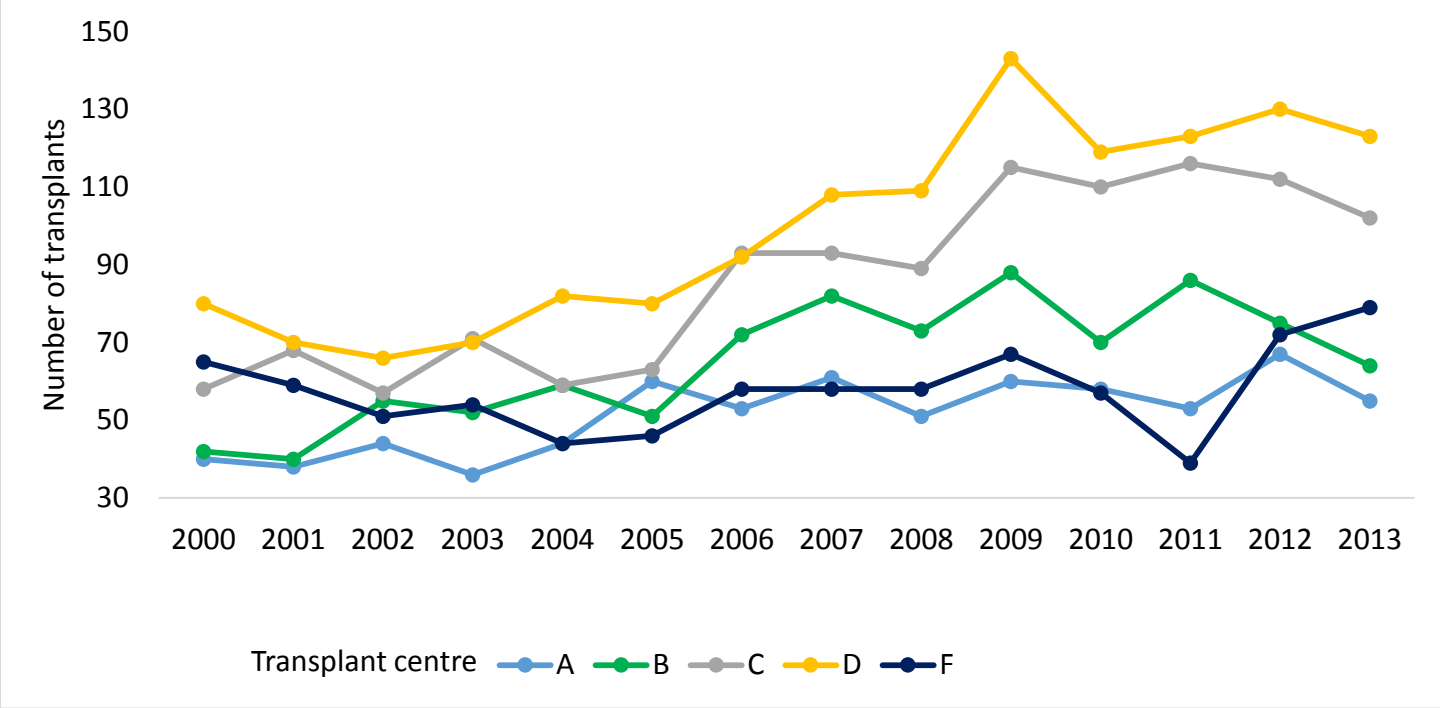


Figure 2. Kidney transplant volume per year across Ontario renal transplant centres



APPENDIX

Table 1. STROBE CHECKLIST

	Item No	Recommendation	Reported on Page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Title/Abstract
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction
Methods			
Study design	4	Present key elements of study design early in the paper	Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods-Figure 1
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Supplemental table
Bias	9	Describe any efforts to address potential sources of bias	Methods
Study size	10	Explain how the study size was arrived at	Methods, Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	NA
		(b) Describe any methods used to examine subgroups and interactions	Methods
		(c) Explain how missing data were addressed	Methods

		(d) If applicable, explain how loss to follow-up was addressed	Not applicable
		(e) Describe any sensitivity analyses	NA
Results			
Participants	13	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 1
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	Table 1,
		(b) Indicate number of participants with missing data for each variable of interest	Table 1/Results
		(c) Summarise follow-up time (e.g. average and total amount)	Results/Table 4
Outcome data	15	Report numbers of outcome events or summary measures over time	Results, Table 4
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(b) Report category boundaries when continuous variables were categorized	Table 1
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	Figure 2, Results
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	After discussion

Table 2. Coding definitions for recipient demographic and comorbid conditions

Characteristic	Database	Codes Used
Baseline Characteristic of Transplant Recipients and Donors		
Age, Sex, Rural	RPDB	
Renal Transplant	CORR	Treatment_Code: 171 Transplanted_Organ_Type_Code[1-3]: 10, 11, 12, 18, 19
Date of transplant,	CORR	Treatment_date
Cause of primary renal disease	CORR	Glomerulonephritis/Auto-immune disease: 05, 06, 07, 08, 09, 10, 11, 12, 13, 14, 15, 16, 17, 19, 73, 74, 84, 85, 86, 88 Diabetes: 80, 81 Cystic kidney disease: 40, 41, 42, 43, 49 Renal vascular disease: 70, 71, 72, 79 Other: 20, 21, 22, 23, 24, 25, 29, 30, 31, 32, 33, 39, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 66, 78, 82, 83, 87, 89, 90, 91, 92, 93, 94, 95, 96, 97, 99 Unknown: 00, 98
Race	CORR	Caucasian: 01; Asian: 02; African-American: 03; Indian: 05 Other: 08, 09, 10, 11, 99 Unknown: 98
Body Mass Index	CORR	Initial_Height Initial_Weight
Dialysis modality	CORR	Hemodialysis: 111, 112, 113, 121, 122, 123, 131, 132, 133, 211, 221, 231, 311, 312, 313, 321, 322, 323, 331, 332, 333, 413, 423, 433, Peritoneal Dialysis:141, 151, 152, 241, 242, 251, 252, 443, 453 Other – 060
Time on dialysis	CORR	TRANSPLANT ([Treatment_Date] & [Treatment_Code]) – DIALYSIS ([Treatment Date] & [Treatment_Code])
Pre-emptive	CORR	
Donor source	CORR	Living: 02, 03, 04, 05, 06, 07, 10, 12, 15 Deceased: 01 Unknown/Out-of-country transplant: 98
Donor age	CORR	Donor Age_Units
Donor sex	CORR	
Cause of donor death	CORR	CNS related: 01,02,06,07,08,10,11,13 Motor vehicle/trauma: 03,04,09 Poison: 05,12 Unknown: 98 Other: 99

Diabetes	CIHI-DAD/OHIP	ICD9: 250 ICD10: E10,E11,E13,E14 OHIP diagnosis: 250 OHIP fee: Q040,K029,K030
Hypertension	CIHI-DAD/OHIP	ICD9: 401,402,403,404,405 ICD10: I10,I11,I12,I13,I15 OHIP diagnosis: 401,402,403
Congestive Heart Failure	CIHI-DAD/OHIP	ICD9: 425,5184,428,514 ICD10: I500,I501,I509,I255,J81 CCP: 4961,4962,4963,4964 CCI: 1HP53,1HP55,1HZ53GRFR,1HZ53LAFR,1HZ53SYFR OHIP fee: R701,R702,Z429 OHIP diagnosis: 428
Coronary Artery Disease without angina	CIHI-DAD/OHIP	ICD-9: 410, 411, 412 ICD-10: I21, I22, T82.2, Z95.5 CCP: 48.01, 48.02, 48.03, 48.04, 48.05, 48.1, 48.2, 48.3 CCI: 1IJ50, 1IJ76 OHIP diagnosis code: 410, 412 OHIP fee code: E646, E651, E652, E654, E655, G298, R741, R742, R743, Z434, Z448
Peripheral vascular disease	CIHI-DAD/OHIP	ICD9: 4402,4408,4409,5571,4439,444 ICD10: I700,I702,I708,I709,I731,I738,I739,K551 CCP: 5125,5129,5014,5016,5018,5028,5038, CCI: 1KA76,1KA50,1KE76,1KG26,1KG50,1KG57,1KG76MI,1KG87 OHIP:R787,R780,R797,R804,R809,R875,R815,R936,R783,R784,R785,E626,R814,R786,R937,R860,R861,R855,R856,R933,R934,R791,E672,R794,E672,R794,E672,R813,R867,E649
Chronic obstructive lung disease	CIHI-DAD	ICD9: 491,492,496 ICD10: J41,J43,J44
Chronic liver disease	CIHI-DAD/OHIP	ICD9:4561,4562,070,5722,5723,5724,5728,573,7824,V026,2750,2751,7891, 7895, 571 ICD10:B16,B17,B18,B19,I85,R17,R18,R160,R162,B942,Z225,E831,E830,K70,K713,K714,K715,K717,K721,K729,K73,K74,K753,K754,K758,K759,K76,K77 OHIP diagnosis code: 571,573,070 OHIP fee code: Z551,Z554
Cancer		**ICD9**: V10, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 170, 171, 172, 173, 174, 175, 176, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 230, 231, 232, 233, 234

		ICD10: 80003, 80006, 80013, 80023, 80033, 80043, 80102, 80103, 80106, 80113, 80123, 802, 803, 80413, 80423, 80433, 80443, 80453, 80502, 80503, 80513, 80523, 807, 808, 80903, 80913, 80923, 80933, 80943, 80953, 81103, 81202, 81203, 81213, 81223, 81233, 81243, 81303, 81402, 81403, 81406, 81413, 81423, 81433, 81443, 81453, 81473, 81503, 81513, 81523, 81533, 81543, 81553, 81603, 81613, 81623, 81703, 81713, 81803, 81903, 82003, 82013, 82102, 82103, 82113, "82203", 82213, 823, 82403, 82413, 82433, 82443, 82453, 82463, 82473, 82503, 82513, 82603, 82612, 82613, 82623, 82632, 82633, 82703, 82803, 82813, 82903, 83003, 83103, 83123, 83143, 83153, 83203, 83223, 83233, 83303, 83313, 83323, 83403, 83503, 83703, 83803, 83813, 83903, 84003, 84013, 84103, 84203, 84303, 84403, 84413, 84423, 84503, 84513, 84603, 84613, 84623, 84703, 84713, 84723, 84733, 84803, 84806, 84813, 849, 85002, 85003, 85012, 85013, 85023, 85032, 85033, 85042, 85043, 851, 852, 85303, 854, 85503, 85603, 85623, 857, 85803, 86003, 86203, 86303, 86403, 86503, 86803, 86933, 87003, 87103, 87202, 87203, 87213, 87223, 87233, 87303, 87403, 87412, 87413, 87422, 87423, 87433, 87443, 87453, 87613, 87703, 87713, 87723, 87733, 87743, 87803, 88003, 88006, 88013, 88023, 88033, 88043, 88103, 88113, 88123, 88133, 88143, 88303, 88323, 88333, 88403, 88503, 88513, 88523, 88533, 88543, 88553, 88583, 88903, 88913, 88943, 88953, 88963, 89003, 89013, 89023, 89103, 89203, 89303, 89333, 89403, 89413, 895, 89603, 89633, 89643, 897, 89803, 89813, 89903, 89913, 90003, 90203, 90403, 90413, 90423, 90433, 90443, 90503, 90513, 90523, 90533, 906, 90703, 90713, 90723, 90803, 90813, 90823, 90833, 90843, 90853, 90903, 91003, 91013, 91023, 91103, 91203, 91243, 91303, 91333", 91403, 91503, 91703, 91803, 91813, 91823, 91833, 91843, 91853, 91903, 92203, 92213, 92303, 92313, 92403, 92503, 92513, 92603, 92613, 92703, 92903, 93103, 93303, 93623, 93643, 93703, 93803, 93813, 93823, 93903, 93913, 93923, 940, 941, 942, 94303, 944, 945, 94603, 947, 948, 94903,95003,95013, 95023, 95033, 95043, 951, 952, 95303, 95393, 95403, 95603, 95613, 95803, 95813, 959, 965, 966, 967, 968, 969, 970, 971, 972, 973, 97403, 97413, 97603, 97613, 97623, 97633, 97643, 980, 982, 98303, 984, 98503, 986, 98703, 98803, 989, 99003, 99103, 993, 994, C00, C01, C02, C03, C04, C05, C06, C07, C08, C09, C10, C11, C12, C13, C14, C15, C16, C17, C18, C19, C20, C21, C22, C23, C24, C25, C26, C30, C31, C32, C33, C34, C37, C38, C39, C40, C41, C43, C44, C45, C46, C47, C48, C49, C50, C51, C52, C53, C54, C55, C56,

		C57, C58, C60, C61, C62, C63, C64, C65, C66, C67, C68, C69, C70, C71, C72, C73, C74, C75, C76, C77, C78, C79, C80, C81, C82, C83, C84, C85, C86, C88, C90, C91, C92, C93, C94, C95, C96, C97, D00, D01, D02, D03, D04, D05, D06, D07, D09, Z85 **OHIP Diagnosis code**: 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164,165, 170, 171, 172, 173, 174, 175, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 230, 231, 232, 233, 234
Stroke/TIA	CIHI-DAD	ICD9: 434,435,436, ICD1: H341,I630,I631,I632,I633,I634,I635,I638,I639,I64, H340,G450,G451,G452,G453,G458,G459
Charlson Comorbidity Index	CIHI-DAD	Charlson Macro
Peak Panel Reactive Antibody	CORR	PRA_1_PEAK_RESULT CORR
Transplant Centre	CORR	TREATMENT_FACILITY_NUM
Baseline Characteristic of Physicians		
Provider Type	IPDB	MAINSPEC*
Sex	IPDB	Sex
Provider age	IPDB	BIRTHYR
Provider years since graduation	IPDB	GRADYR
Country of graduation	IPDB	CMG, IMG, USMG

Coding Definitions for Renal Recipient Outcomes

OUTCOMES	**Database**	**Codes Used**
Death	RPDB	
Length of stay	CIHI-DAD	DCSDATE- ADMDATE
Intensive care unit	CIHI-DAD*	SCU: 10,20,30,40,45,60,90,93,95,99
Dialysis post transplant	CIHI-DAD/OHIP	CCP: 5195, 6698 CCI: 1PZ21 OHIP fee: R849, G323, G325, G326, G860, G863, G866, G330, G331, G332, G861, G082, G083, G085, G090, G091, G092, G093, G094, G095, G096, G294, G295

*Prior to March 30th 2002, special care unit codes were hospital-specific and varied across institutions and cannot be relied upon. Therefore our analyses for that variable are limited to those recipients who were transplanted after March 30th 2002.

All comorbidities had a 5 year look back window with the exception of Diabetes.

Abbreviations: RPDB: Registered Person's database, CORR: Canadian Organ Reporting Register, CIHI: Canadian Institute for Health information, DAD: Discharge abstract database, CCP; Canadian Classification of Diagnostic Therapeutic and Surgical Procedures, CCI; Canadian Classification of Interventions, IPDB: ICES physician database, TIA: thrombotic ischemic stroke.

Chapter 4 – [Manuscript 3] – **Graft and Patient Survival Rates Across Kidney Transplant Programs in Ontario, Canada accounting for Patient Case mix**

4.1 Preface to manuscript 3 –

In this manuscript, we analyzed data from 5097 patients to examine variation in observed survival rates and case-mix adjusted centre specific hazard ratios across the 6 kidney transplant centres in Ontario. We examined 4 outcomes: total graft loss, time to graft loss censored at the time of death, death with graft function and total mortality. Cox proportional hazards regression was used to obtain hazard ratios (HR) for each centre relative to the average across all centres. Prior to analysis, we performed multiple imputation using the fully conditional specification method to generate 10 imputations. Multivariable analyses were conducted for each imputation dataset and combined across datasets. To assess sensitivity to the imputation procedure, all analyses were also conducted using only complete cases. We also performed subgroup analyses by donor type (living and deceased) for all four outcomes.

This manuscript is in preparation for publication.

Graft and Patient Survival Rates Across Kidney Transplant Programs in Ontario, Canada accounting for Patient Case mix

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ABSTRACT

Background: Graft and patient survival rates vary significantly across kidney transplant programs in the United States. The objective of this study was to examine variation in survival rates across six kidney transplant centres in Ontario, Canada.

Methods: We conducted a population based cohort study using administrative data. The primary outcome of interest was time to total graft loss. Additional outcomes included: time to graft loss censored at the time of death, death with graft function, total mortality and graft loss treating death as a competing risk. One, five, and ten-year survival distributions were described using the Kaplan-Meier method and compared across centres using log-rank tests. Cumulative incidence functions for graft loss treating death as a competing risk were calculated. To compare differences across centres adjusting for patient case mix, Cox proportional hazards regression was used to obtain ratios (HR) for each centre relative to the average across all centres.

Results: The study cohort included 5092 adult (≥ 18 years) transplant recipients who received a primary, solitary kidney between January 1st 2000 to December 31st 2013 (n=5092). There were 1502 composite events of graft loss and death over the study period, median follow-up time was 5.3 (Interquartile range 2.7, 8.6) years. Differences across transplant centres in patient race, cause of end stage renal disease, body mass index, Charlson comorbidity index, time on dialysis, donor type and age were observed. Observed one, five and ten-year survival rates for all outcomes varied significantly across centres (all $p<0.05$ using log-rank tests). The cumulative incidence for graft loss varied significantly across centres ($p=0.0001$). After adjusting for patient

case mix, HRs for total graft loss ranged across centres from 0.85 (95% confidence interval (CI) 0.54-1.35) to 1.10 (95% CI 0.98-1.24), for graft loss from 0.77 (95% CI 0.62-0.95) to 1.15 (95% CI 0.96-1.38), for death with graft function from 0.51 (95% CI 0.19-1.32) to 1.24 (95% CI 0.97-1.60) and for total mortality from 0.74 (95% CI 0.38-1.45) to 1.18 (95% CI 0.97-1.43).

Conclusions: We found significant centre variation in observed survival rates for all outcomes, which was no longer statistically significant after accounting for differences in patient risk factors. There were notable differences in centre specific hazard ratios with up to a 20% difference from average. Our study was limited by the small number of centres which may have restricted our ability to detect any significant difference across centres.

INTRODUCTION

"Centre effect" is a term used to describe differences in patient outcomes that are not accounted for by known risk factors and implies the centre itself independently influences the patient outcome.[1] Variation in graft and patient survival rates across centres have been described in studies from the United States (US) [2-4], Canada [5] and Europe.[6-8] Specific methods to measure and compare centre outcomes in kidney transplantation that have been applied include descriptive analyses such as Kaplan-Meier survival curves or cumulative incidence as well as comparative analyses including standardization and regression modelling.[9,10]

In the United States program specific report cards for each transplant centre are published every six months by the Scientific Registry of Transplant recipients.[11] This registry reports both unadjusted survival rates as well as an adjusted standardized ratio of observed to expected events (graft losses and deaths) for each centre compared to the national average.[12-15] The standardized ratios use Cox regression modelling to incorporate the effect of different important patient covariates on the outcome as well as to calculate the expected number of events.[16,17] This method ensures that a transplant centre is not unnecessarily penalized due to the type of patient population it serves. In Canada, an annual report is published by the Canadian Organ replacement registry (CORR) which communicates unadjusted graft survival rates across provinces.[18] This report however does not compare centre outcomes within a province nor does it account for patient case mix.

The objectives of the present study are to: i) compare unadjusted survival rates for all outcomes across transplant centres in Ontario, ii) determine which patient factors are

associated with poor patient outcomes and iii) assess whether significant variation in graft and patient survival rates persists after adjusting for important patient characteristics. We hypothesized that centre variation post-kidney transplant will not be fully explained by differences in patient case mix only.

METHODS

Study Design and Setting

We conducted a population-based retrospective observational cohort study using health care databases at the Institute for Clinical Evaluative Sciences (ICES) in Ontario, Canada. Ontario has a population of approximately 13.6 million residents who have universal access to health care services. This study was approved by the institutional review board at Sunnybrook Health Sciences Centre (Toronto, Canada). The reporting of this study followed the STROBE and RECORD reporting guidelines for observational studies (supplemental file).[19,20] The full data set creation plan is available from the authors upon request.

Data sources

We used 4 linked datasets to create the cohort, and to obtain patient, centre and outcome data as previously described.[21] These datasets were linked using unique encrypted patient-specific identifiers and analyzed at ICES. We used the Canadian Organ Replacement Register (CORR) to identify kidney transplant recipients. CORRs sensitivity to correctly identify kidney transplant recipients is 96% and positive predictive value is 98%.[22] Demographic and vital status of renal transplant recipients was obtained using Ontario Registered Persons database (ORPD). The

Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) and Ontario Health insurance plan (OHIP) were used to obtain information on recipient comorbidities and outcomes. We used similar codes to those used in prior kidney transplant studies.[22-24] (Supplemental Table)

Study Cohort

The creation of this study cohort has been previously described.[21] In brief, we included all adults (≥18 years) who received a first-time solitary kidney transplant in Ontario Canada between January 1st 2000 and December 31st 2013. We excluded those with an invalid IKN (a confidential ICES patient number), were not from Ontario, died prior to transplant date, had unknown age or sex and whose OHIP transplant billing or hospitalization dates did not align with transplant date. (Supplemental Figure 1).

Outcomes

Patients were followed from the date of transplant until March 31st 2015. The primary outcome was a composite of total graft failure, defined as graft loss (return to chronic dialysis or retransplant) or death after kidney transplant, whichever occurred first. Secondary outcomes of interest included: graft failure censored at the time of death, death with graft function (death after primary kidney transplant but prior to graft loss), total mortality, and graft failure treating death as a competing event.

Statistical Analysis

We used descriptive statistics to summarize characteristics of patients at the time of transplant by centre. Continuous variables were described using mean and standard deviation (SD) when

the data followed a normal distribution or median and interquartile range [IQR] if not normally distributed. Frequencies and percentages were used for categorical data.

We categorized the study period into four equal time periods with their duration set at 3 ½ years: January 1st 2000 - June 30th 2003, July 1st 2003 – December 31st 2006, January 1st 2007 – June 30th 2010 and July 1st 2010 – December 31st 2013. Differences in patient case mix across transplant centres were examined using analysis of variance (ANOVA) or Kruskal-Wallis tests for continuous variables and Chi-squared tests or Fisher exact for categorical variables.

Incidence rates (per 1000 person-years of follow-up) were calculated for all outcomes, together with 95% confidence intervals. The one, five and ten year survival distributions were described overall and per centre using the Kaplan-Meier method and statistical significance of differences across centres were assessed using the log rank test. The cumulative incidence function (CIF) for graft loss with competing risk of death at 1-,5- and 10 years post-transplant was calculated using a non-parametric method and compared across centres using Gray's test for equality. CIF is the cumulative probability of failure from a specific cause over time. Its use is recommended when there are competing events as outcomes such as graft loss and death.[25,26]

To account for differences in patient case mix across transplant centres, we used fixed effects multivariable Cox proportional hazards regression. Adjusted hazard ratios (HR) with 95% confidence intervals were calculated for each transplant centre, relative to the average across all centres. Our models adjusted for the following patient characteristics: recipient age, sex, race, cause of ESRD, BMI, Charlson comorbidity index, pretransplant dialysis modality (none vs hemodialysis or peritoneal dialysis), time on dialysis before transplantation, time era of

transplant (as defined above), donor source and donor age. A centre with a HR and both limits of its 95% confidence interval below 1 implies that the centre has a survival rate significantly better than average after accounting for patient case mix, while a centre with a HR and both limits of its 95% confidence interval above 1 implies that the centre is performing significantly worse than average. On the other hand, a centre with a confidence interval including 1 implies a survival rate that is not significantly different than the average after accounting for patient case mix.

Data were missing (0.77 to 16.7%) for the following variables; recipient race (9.9%), cause of ESRD (7.9%), Charlson index (5.4%), BMI (16.7%), donor type (0.77%) and donor age (0.79%). Prior to performing our analyses, we performed multiple imputation using the fully conditional specification (FCS) method which does not assume a joint distribution but instead applies a separate conditional distribution for each of the imputed variables.[27] For categorical values we used the discriminant method and for continuous variables, linear regression was applied. We conducted ten imputations using 100 burn in iterations. Multivariable analyses were conducted for each imputation dataset and combined across datasets using Rubin's rules.[28] To assess sensitivity to the imputation procedure, all analyses were also conducted using only complete cases. We also performed subgroup analyses by donor type (living and deceased) for all four outcomes. All statistical analyses were performed using SAS (Statistical Analysis Software) version 9.4 (SAS Institute, Cary NC). A two-sided p value <0.05 was considered statistically significant.

RESULTS

Patient characteristics at the time of transplant

The study included 5092 primary kidney transplant recipients from six transplant centres in Ontario. The mean (SD) age of the overall cohort was 50.9 (13.5) years, 63.1% were male and 63.7% were Caucasian. The characteristics of the transplant population across centres has previously been reported[21] and are summarised in Table 1. Most patient factors varied significantly across centres including recipient race, cause of ESRD, BMI, Charlson index, pretransplant dialysis modality, time on dialysis, donor type and donor age. Over the entire study period, a total of 921 (18%) patients died and 817 (16%) patients experienced graft loss. The median follow-up time was 5.3 [IQR 2.7, 8.6] years, total person-years of observation was 29,951. Seventy-three (1.4%) participants were loss to follow up.

Unadjusted survival rates

Primary Outcome – Total Graft failure

There were 1502 composite events [685 (13.5%) deaths and 817 (16.0%) patients had graft loss over the study period; incidence rate of 50.1 events per 1000 person-years, (95% CI 47.7-52.7). The 1-, 5- and 10 year graft survival rates for the entire cohort were 91.2, 79.2 and 61.5% respectively and varied significantly across centres (log-rank p=0.04). The incidence rates and observed graft survival rates by centre are presented in Table 2 and illustrated in Figure 1a.

Additional Outcomes

The incidence rates by centre for each outcome are described in table 2. The overall observed graft survival rates, censored at the time of death, were 97.4 at 1-year, 88.8 at 5-year and

75.6% at 10 years and differed significantly across centres (log-rank p=0.003) (Figure 1b, table 2). The overall observed survival rates for the outcome death with graft function were 97.7 at 1-year, 91.0 at 5 year and 78.5% at 10 years and varied significantly across centres (log-rank p<0.0001). (Figure 1c, Table 2). The observed patient survival rates at 1-,5- and 10 years varied significantly across centres (log-rank p=0.0001). (Figure 1d and Table 2). The cumulative incidence of graft loss accounting for the competing risk of death varied significantly across centres (Gray's p=0.001). (Table 2).

Adjusted Hazard Ratios

Primary Outcome - Total Graft loss

Centre-specific hazard ratios for the primary outcome of total graft failure obtained from Cox proportional hazards regression models (Figure 2a) revealed no statistically significant differences across centres, after accounting for patient case mix (p=0.5). Hazard ratios ranged from 0.85 (95% CI 0.54-1.35) at the best performing centre to 1.16 (95% CI 1.00-1.33) at the worst. Patient case mix factors found to be significantly associated with total graft loss included: recipient age, Charlson index, years on dialysis, donor type and donor age. A later time era of transplantation was associated with a significantly lower HR. Compared to the referent group (transplanted between 2000-2003) the following hazard ratios were found: transplanted between 2007-2010 HR 0.83 (95% CI 0.71-0.96) and transplanted between 2010-2013 HR 0.73 (95% CI 0.60-0.87). (Table 3).

Additional Outcomes

Centre-specific hazard ratios for graft loss, with follow-up times censored at the time of death, ranged across centres from 0.77 (95% CI 0.62-0.95) to 1.15 (95% CI 0.96-1.38), with no statistically significant differences (p=0.7) (Figure 2b). Factors significantly associated with this outcome include: recipient age, BMI, Charlson index, years on dialysis pretransplant, donor type and donor age. (Table 3). Recipients transplanted between 2010-2013 had a significantly lower HR 0.76 (95% CI 0.60-0.97) compared to those transplanted between 2000-2003. The adjusted HR's for the outcome death with graft function ranged between 0.51 (95% CI 0.19-1.32) and 1.24 (95% CI 0.97-1.60) p=0.16 (Figure 2c). Factors found to be significantly associated with death with graft function include: recipient sex, age, Charlson index, years on dialysis pretransplant and donor age. Compared to those transplanted between 2000-2003 the following hazard ratios were found: transplanted between 2007-2010 HR 0.69 (0.55-0.87) and transplanted between 2010-2013 HR 0.70 (0.52-0.93). (Table 3). The adjusted HR's for total mortality ranged between 0.74 (95% CI 0.38-1.45) to 1.18 (95% CI 0.97-1.43) p=0.38 (Figure 2d). Factors associated with this outcome include: recipient sex, age, Charlson index, time on dialysis pretransplant and donor age. Compared to those transplanted between 2000-2003, the following hazard ratios were found: transplanted between 2007-2010 HR 0.77 (0.63-0.93) and transplanted between 2010-2013 HR 0.69 (0.54-0.91). (Table 3).

Sensitivity Analysis

When complete case analysis was performed (n=3759) without imputation, results were similar. That is, there was no statistically significant variation in performance across transplant

centres for any of the outcomes, after accounting for patient case mix and centre rankings were similar.

Additional analysis

When examining outcomes by donor type, deceased and living separately, we found no significant variation across centres for any of the outcomes (Supplemental tables 2 and 3).

DISCUSSION

While our study did not find any statistically significant variation in either graft or patient survival outcomes across Ontario kidney transplant centres compared to the average across all centres after adjusting for case-mix, there were notable differences in the centre specific hazard ratios with up to a 20% difference from the average. Our study did however find significant variation in observed survival rates for all outcomes across kidney transplant centres in Ontario. Our results suggest that differences in graft and patient survival rates seen across transplant centres in Ontario likely relate to the variation in patient risk factors as well as the year of transplant.

These results are different than what was previously found in a Canadian study by Kim et al.[5] that included 5082 participants transplanted across 20 Canadian centres between 1988 and 1997. Their study found significant variation in facility specific covariate adjusted hazard ratios for both total graft survival as well as total mortality. Our methodology was different in several key aspects, including our use of multiple imputation rather than exclusion of patients with missing covariate information, the inclusion of all centres rather than exclusion of centres

performing <50 transplants. Furthermore, their study included transplant centres across Canada while our study focused on centres in Ontario exclusively.

Other studies[6,8,29] which have also compared centre outcomes have found conflicting results. Briganti et al.[29] found significant variation in graft survival rates across 16 transplant centres in Australia when using a fixed effects multivariable Cox proportional hazards regression model; however when hierarchical modelling treating centre as random effects was used there was no longer a significant difference in outcome. Elinder et al.[8] describe non-significant variation in graft survival rates across 3 transplant centres in Sweden and a significant difference for mortality. Medcalf et al.[6] found significant variation for both graft and patient survival rates across 5 transplant centres when comparing to one reference centre. Plausible explanations for the differences in findings include: the time era of transplant, the length of follow up period, the inclusion and exclusion criteria of the cohort studies, the choice of reference centre, and covariates adjusted for.

We found significant differences in patient risk factors across centres; however, some differences may not be clinically relevant. For example the average Charlson index ranged between 2.5 and 2.9, which may not be clinically important. As would be expected, we found differences in which patient covariates were associated with each outcome. For example, recipient sex (being a female), was significantly associated with improved patient survival but not with graft survival whereas donor type, receiving a living donor kidney was associated with improved graft survival but not patient survival. This highlights the importance of assessing each outcome independently. Furthermore, we found a significant association between the

time period of transplant with all outcomes. That is being transplanted in the most recent time era (between 2010-2013) had a 30% lower chance of graft loss or death compared to being transplanted between 2000-2003. This is in keeping with findings from prior studies.[5,6,8,29]

Our study has several strengths. It included a large patient cohort with a long follow-up period which allowed for the calculation of longer-term (10 year) survival rates. This study cohort included patients who were transplanted in a more recent time era, starting in 2000 and on, after the introduction of newer immunosuppressive agents and therefore allowed for more up to date comparison of graft/patient survival rates. Furthermore, we assessed each outcome separately and accounted for the competing risk of death which may allow transplant programs to assess where they are performing better or worse compared to the average and allow for improvement.

There are several limitations to our study. Firstly it was retrospective in nature and relied on administrative data which precluded the ability to explore additional factors of interest; however we were able to include most important patient covariates that have been found to be associated with graft and patient survival. Secondly, we did not have complete information on all patient case mix factors; to address this limitation we used a robust method of multiple imputation under a multivariable model. And lastly, due to the smaller number of kidney transplant centres in Ontario we may have been limited in our ability to detect any statistically significant differences across centres. One centre, in particular, had a much smaller patient population, leading to wider confidence intervals and decreased ability to detect differences due to sampling variability.[30]

In summary, while both longer-term graft and patient survival rates post kidney transplantation varied across centres in Ontario, we were unable to identify any centres that were statistical outliers compared to the average. The clinical significance however, remains important as there were differences in outcomes that were not explained by patient factors alone. Future studies are needed which compare additional centre and provider level factors.

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Figure Legend

Figures 1a-d. Comparison of observed survival rates for each outcome across transplant centres in Ontario. 1a) Total graft loss, 1b) Graft loss censoring for death, 1c) Death with graft function, 1d) Total mortality

Figures 2a-d. Adjusted hazard ratios (HR) with 95% confidence intervals for each outcome by transplant centre. 2a) Total graft loss, 2b) Graft loss censoring for death, 2c) Death with graft function, 2d) Total mortality.

Supporting Information

Table S1. Coding definitions for kidney transplant recipient demographic and comorbid conditions and outcomes.

Table S2. Centre-specific patient case mix hazard ratios from multivariable Cox Proportional hazards regression analysis for each outcome for living donor transplant.

Table S3. Centre-specific patient case mix hazard ratios from multivariable Cox Proportional hazards regression analysis for each outcome for deceased donor transplant.

Figure S1. Flow diagram of study cohort.

Table 1. Participant characteristics across centres at the time of kidney transplant

Characteristic	Aggregate Range	P value
Age, Mean (SD)	50.5, (13.6) - 51.2, (13.6)	0.56
Sex, Male n (%)	60.1 – 67.3%	0.07
Race, n (%)		
Caucasian	47.8 – 85.5%	
African	1.3 - 12.4%	
Asian	2.5 - 13.1%	
Other	5.5 - 18.9%	<0.0001
Cause of ESRD n (%)		
Glomerulonephritis	30.8 – 43.6%	
Diabetes	NR - 25.0%	
Cystic Kidney	10.9 – 15.1%	
Renal Vascular	7.2 – 14.0%	<0.0001
BMI, Mean (SD)	25.5, (5.3) - 27.6, (6.1)	0.0001
Charlson Index, Mean (SD)	2.5, (0.9) - 2.9, (1.3)	<0.0001
Pretransplant dialysis modality n (%)		
Premptive		
Dialysis Pretransplant	0 -13.2%	
	86.8 - 100%	<0.0001
Years on dialysis* Median [IQR]	1.8 [1.1,3.0] - 4.2 [1.3,6.6]	<0.0001
Donor Type n (%)		
Living	0 – 50.1%	
Deceased**	49.9 – 100%	<0.0001
Donor Age, Mean (SD)		
Living	42.8, (12.2) - 46.9, (15.3)	<0.0001
Deceased	43.4, (15.9) - 48.8, (16.2)	<0.0001
Time era of transplant, n (%)		
2000-2003	0 – 25.3%	
2003-2007	20.5 – 40.0%	
2007-2010	26.8 – 31.0%	
2010-2013	26.5 – 32.4%	<0.0001

Chi-square test for categorical variables, ANOVA for normally distributed continuous variables (age, BMI, Charlson comorbidity index, deceased and living age) and Kruskal-Wallis for non-normal (years on dialysis).

*Includes those who did not receive dialysis and have a time 0.

**Total number for deceased also includes those with missing donor type

Other[1] includes Aboriginal, Indian subcontinent, Pacific Islander,Other/Multiracial.

Pretransplant dialysis[2] includes both peritoneal dialysis and hemodialysis.

Each time period is 3 ½ years in length.

≤5 implies n is smaller than or equal to 5 and thus cannot be reported due to privacy concerns.

Abbreviations: SD, standard deviation; ESRD, End stage renal disease; BMI, body mass index; IQR, interquartile range; NA; not applicable, NR; not reportable due to privacy reasons

Table 2. Event incidence rates (per 1000 patient years) and observed survival rates (%) for each outcome of interest by transplant centres.

Centres	1	2	3	4	5	6
Total Graft loss - Incidence rate (95% CI) / 1000 patient years						
	42.8 (24.8,73.7)	46.7 (42.2,51.6)	47.6 (41.5,54.6)	60.1(53.5,67.4)	48.5 (43.6,53.9)	51.6 (45.8,57.9)
Total Graft loss[A] (death or graft loss) - Observed survival rates ± standard error						
1 year	92.7 ± 0.04	91.4 ± 0.008	93.2 ± 0.009	89.9 ± 0.01	89.7 ± 0.009	92.6 ± 0.009
5 year	86.7 ± 0.05	80.1 ± 0.01	80.4 ± 0.02	75.2 ± 0.02	79.9 ± 0.01	78.7 ± 0.01
9 year	65.5 ± 0.09	69.0 ± 0.02	64.9 ± 0.02	60.8 ± 0.02	65.9 ± 0.02	63.6 ± 0.02
Graft loss censoring for death - Incidence rate (95% CI) /1000 patient year						
	32.9 (17.7,61.2)	28.8 (25.4,32.7)	20.2 (16.3,24.9)	32.9 (28.2,38.5)	28.8 (25.1,33.0)	23.3 (19.5,27.7)
Graft loss censoring for death[A] - Observed survival rates ± standard error						
1 year	92.7 ± 0.04	92.9 ± 0.007	95.5 ± 0.008	92.6 ± 0.009	92.1 ± 0.008	94.9 ± 0.007
5 year	88.4 ± 0.05	86.3 ± 0.01	90.4 ± 0.01	83.3 ± 0.01	86.7 ± 0.01	88.6 ± 0.01
9 year	73.4 ± 0.08	79.9 ± 0.02	85.8 ± 0.02	78.4 ± 0.02	79.1 ± 0.02	81.9 ± 0.02
Death with graft function - Incidence rate (95% CI) /1000 patient year						
	9.9 (3.2 – 30.6)	17.7 (15.1-20.9)	27.4 (22.9-32.9)	27.1 (22.8 – 32.2)	19.7 (16.6-23.2)	28.3 (24.1-33.2)
Death with graft function[C] – Observed survival rates ± standard error						
1 year	100	98.4 ± 0.003	97.6 ± 0.006	97.0 ± 0.006	97.4 ± 0.005	97.6 ± 0.005
5 year	98.0 ± 0.02	92.8 ± 0.008	88.9 ± 0.01	90.3 ± 0.01	92.0 ± 0.008	88.8 ± 0.01
9 year	89.3* ± 0.06	86.2 ± 0.02	75.6 ± 0.02	77.5 ± 0.02	83.5 ± 0.02	77.5 ± 0.02
Total Mortality - Incidence rate (95% CI) /person-1000 year /1000 patient-year						
	19.7 (8.9,43.9)	26.0 (22.7,29.7)	34.7 (29.5,40.8)	37.2 (32.1,43.1)	26.1 (22.6,30.2)	35.9 (31.2,41.4)
Total Mortality[B] – Observed survival rates ± standard error						
1 year	100	98.1 ± 0.004	97.2 ± 0.006	96.6 ± 0.007	97.4 ± 0.005	97.3 ± 0.005
5 year	96.2 ± 0.03	90.6 ± 0.009	86.4 ± 0.02	87.7 ± 0.01	90.3 ± 0.008	86.8 ± 0.01
9 year	81.2* ± 0.07	80.4 ± 0.02	71.9 ± 0.02	70.9 ± 0.02	78.4 ± 0.02	71.8 ± 0.02
Graft loss with competing risk of death[A] – Cumulative incidence fraction (95%CI)						
1 year	7.0 (2.3,16.2)	7.0 (5.8,8.5)	4.0 (3.0, 6.0)	7.0 (5.7,9.2)	7.8 (6.4,9.4)	5.0 (4.0,7.0)
5 year	11.5 (4.6,21.9)	13.4 (11.5,15.3)	9.0 (7.0,12.0)	16.0 (13.5,18.8)	12.8 (10.1,14.8	10.9 (8.9,13.1)
10 year	No events	20.7 (17.9,23.5)	14.0 (11.0,18.0)	22.3(18.9,25.8)	21.9 (18.9,25.0)	18.0 (15.1,21.6)

P values for log-rank test across centres include; NS (not significant), A<0.05,B<0.001, C<0.0001. *Only 9 years of follow-up

Table 3.Centre-specific patient case mix hazard ratios from multivariable Cox Proportional hazards regression analysis for each outcome

Outcome of interest (Number of events)	**Total graft loss N=1502**	**Graft loss censoring for death N=817**	**Death with graft function N=685**	**Total Mortality N=921**
Covariate	**Hazard ratio, (95% CI)**	**Hazard ratio, (95% CI)**	**Hazard ratio, (95% CI)**	**Hazard ratio, (95% CI)**
Age, (per 5 year increase)	1.07 (1.04-1.09)	0.92 (0.89-0.95)	1.34 (1.29-1.39)	1.28 (1.24-1.32)
Sex ; Female	0.95 (0.85-1.06)	1.07 (0.93-1.24)	0.83 (0.70-0.98)	0.85 (0.74-0.98)
Male	Reference	Reference	Reference	Reference
Race; Caucasian	1.37 (1.14-1.65)	1.14 (0.90-1.44)	1.80 (1.33-2.42)	1.57 (1.22-2.01)
African	1.22 (0.94-1.57)	1.35 (0.99-1.83)	0.94 (0.58-1.50)	0.99 (0.68-1.44)
Asian	1.27 (0.98-1.65)	1.21 (0.87-1.70)	1.47 (0.95-2.25)	1.40 (0.99-1.99)
Other[1]	Reference	Reference	Reference	Reference
Cause of ESRD: GN	0.86 (0.73-1.00)	0.93 (0.76-1.14)	0.76 (0.59-0.98)	0.73 (0.59-0.91)
Diabetes	1.10 (0.91-1.32)	0.87 (0.66-1.14)	1.44 (1.09-1.89)	1.32 (1.05-1.66)
Cystic	0.66 (0.54-0.81)	0.71 (0.54-0.94)	0.69 (0.50-0.94)	0.65 (0.49-0.85)
RVD	1.03 (0.85-1.25)	1.03 (0.77-1.33)	1.04 (0.77-1.40)	0.98 (0.76-1.27)
Other	Reference	Reference	Reference	Reference
BMI	1.01 (1.00-1.02)	1.02 (1.00-1.03)	1.01 (0.99-1.02)	1.01 (1.00-1.03)
Charlson Index	1.14 (1.09-1.20)	1.13 (1.06-1.21)	1.17 (1.09-1.25) p<0.0001	1.19 (1.12-1.27)
Preemptive transplant	0.83 (0.65-1.05)	0.77 (0.56-1.06)	0.91 (0.62-1.32)	0.82 (0.58-1.15)
Pretransplant dialysis[2]	Reference	Reference	Reference	Reference
Time on dialysis pretransplant* (per 1 yr increase)	1.05 (1.03-1.07)	1.03 (1.00-1.06)	1.07 (1.05-1.10)	1.07 (1.05-1.10)
Donor type; Living	0.79 (0.69-0.90)	0.74 (0.61-0.88)	0.86 (0.71-1.04)	0.85 (0.72-1.01)
Deceased	Reference	Reference	Reference	Reference
Donor age (per 5 year increase)	1.05 (1.03-1.06)	1.06 (1.04-1.09)	1.03 (1.01-1.06)	1.04 (1.02-1.07)
Time era of transplant:				
2000-2003	Reference	Reference	Reference	Reference
2003-2007	0.88 (0.77-1.02)	0.91 (0.75-1.10)	0.86 (0.70-1.05)	0.86 (0.76-1.02)
2007-2010	0.83 (0.71-0.96)	0.95 (0.78-1.16)	0.69 (0.55-0.87)	0.77 (0.63-0.93)
2010-2013	0.73 (0.60-0.87)	0.76 (0.60-0.97)	0.70 (0.52-0.93)	0.69 (0.54-0.91)
Centre : 1	0.85 (0.54-1.35)	1.11 (0.65-1.88)	0.51 (0.20-1.33)	0.74 (0.38-1.45)

2	0.98 (0.85-1.11)	1.07 (0.91-1.27)	0.91 (0.71-1.15)	0.91 (0.75-1.09)
3	0.96 (0.83-1.12)	0.77 (0.62-0.95	1.24 (0.97-1.60)	1.12 (0.92-1.37)
4	1.16 (1.00-1.33)	1.15 (0.96-1.38)	1.24 (0.96-1.59)	1.18 (0.97-1.43)
5	1.06 (0.92-1.22)	1.08 (0.91-1.29)	1.12 (0.88-1.44)	1.00 (0.83-1.22)
6	1.02 (0.88-1.17)	0.88 (0.73-1.06)	1.24 (0.98-1.58)	1.12 (0.93-1.35)

Other[1] includes Aboriginal, Indian subcontinent, Pacific Islander,other/Multiracial.

Pretransplant dialysis[2] includes both peritoneal dialysis and hemodialysis. Each time period is 3 ½ years in length.

Centre[3] -the reference is the average across all centres.

*Time on dialysis includes a 0 for those who did not have any pretransplant dialysis.

Abbreviations: ESRD, end stage renal disease; GN, glomerulonephritis; RVD, renal vascular disease; BMI, body mass index

Figure 1. Centre specific Kaplan-Meier survival curves for each outcome

Figure 1a. Total graft loss (p=0.04).

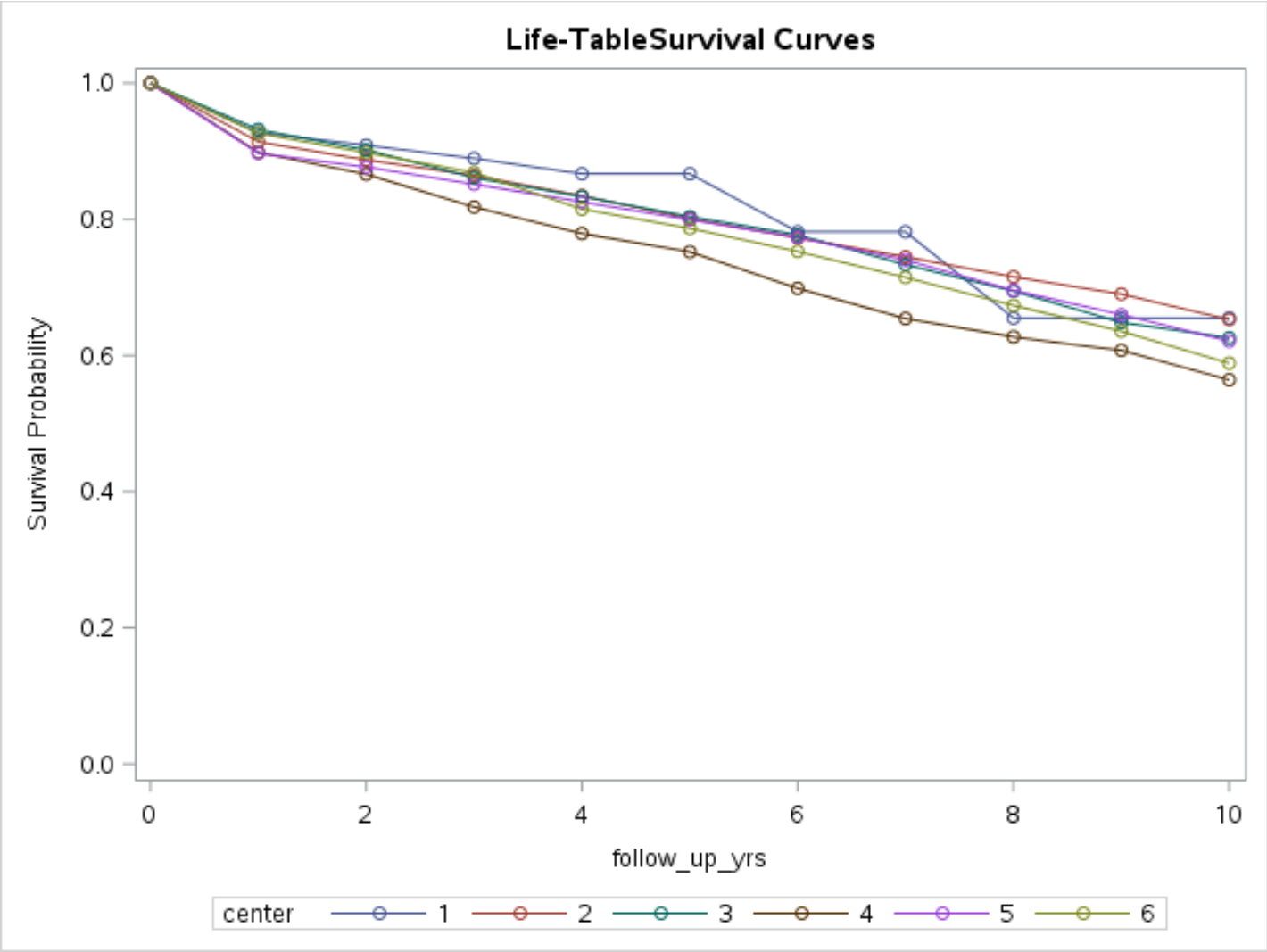


Figure 1b. Graft loss censored at the time of death (p=0.003).

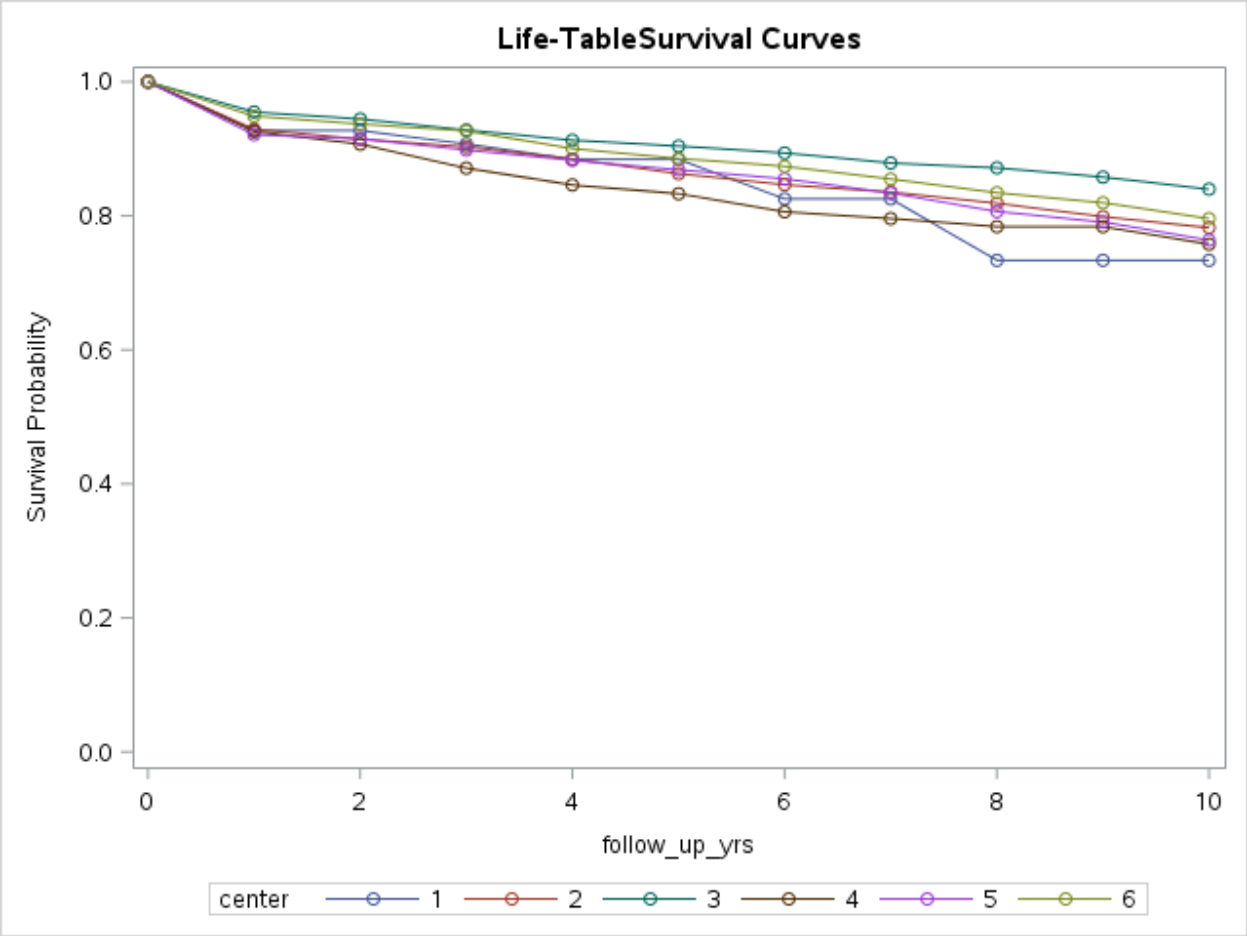


Figure 1c. Death with graft function (p<0.0001).

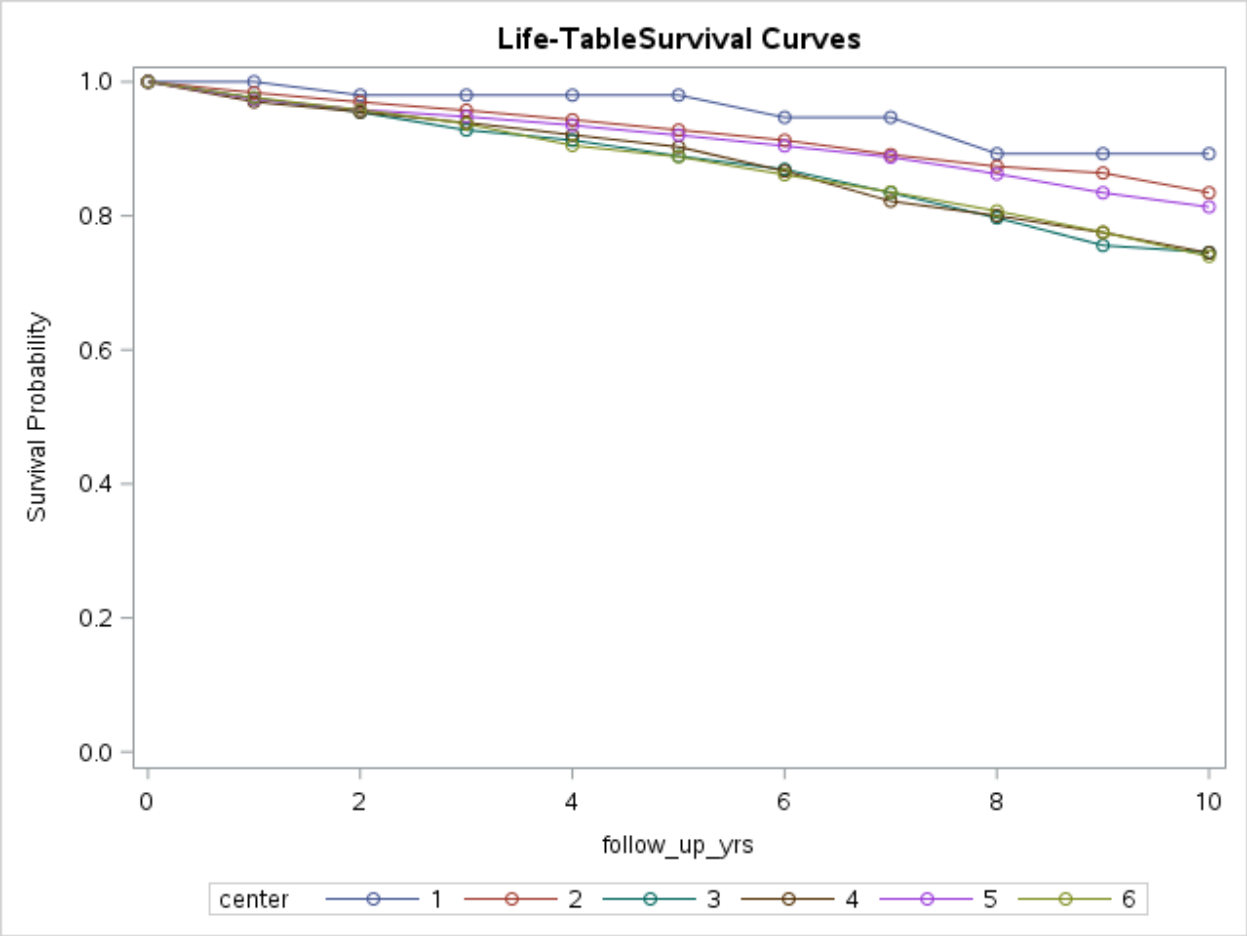


Figure 1d. Total mortality (p=0.0001).

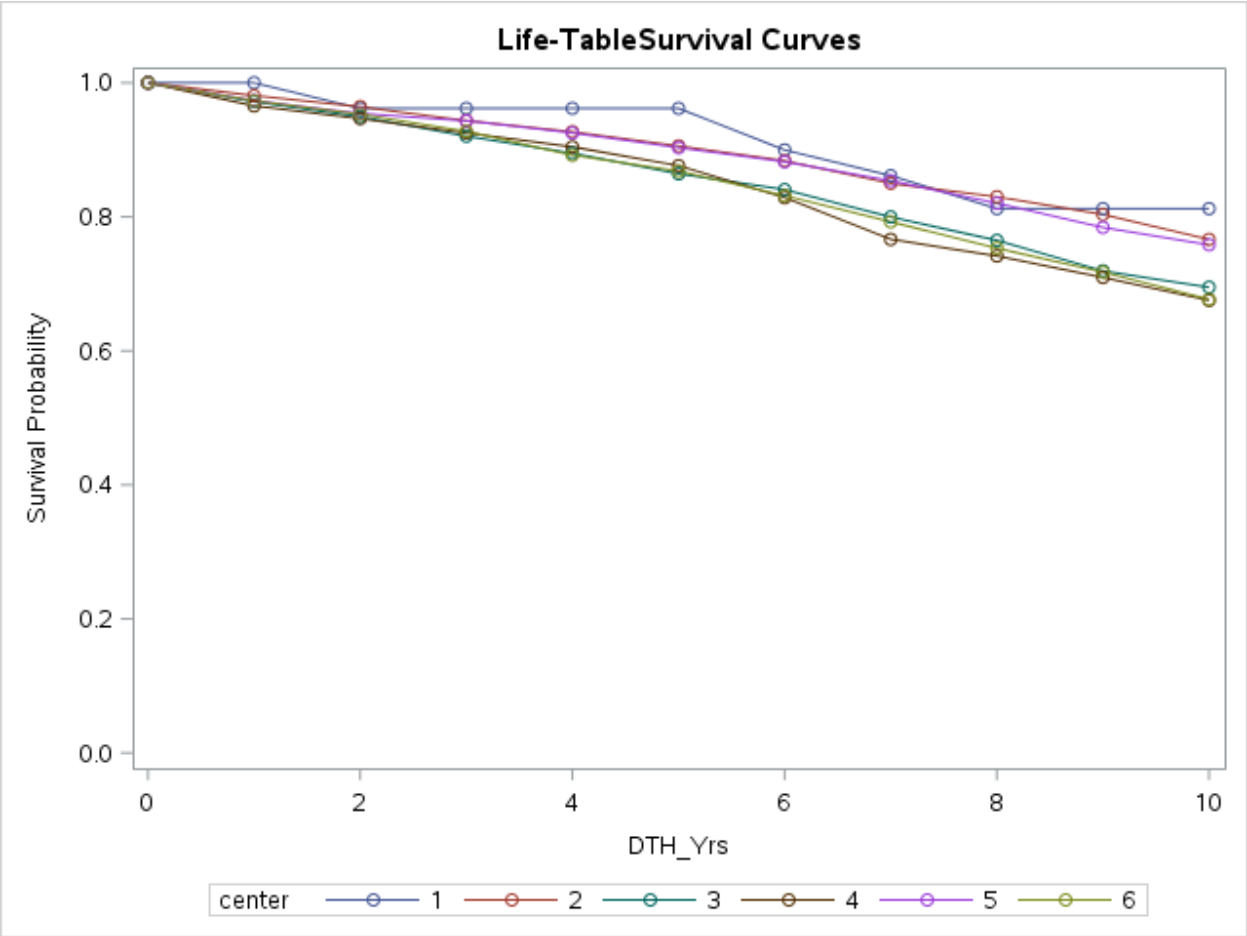
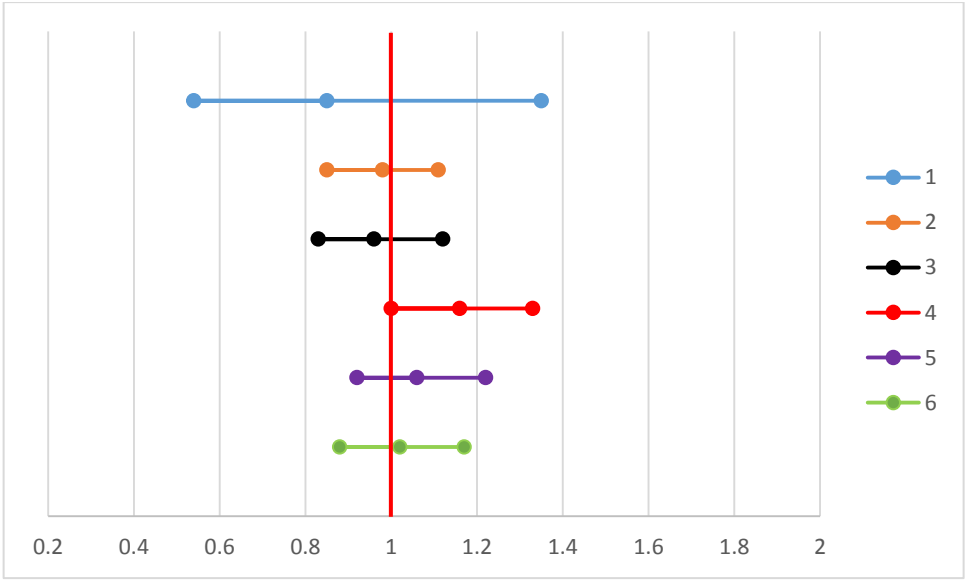
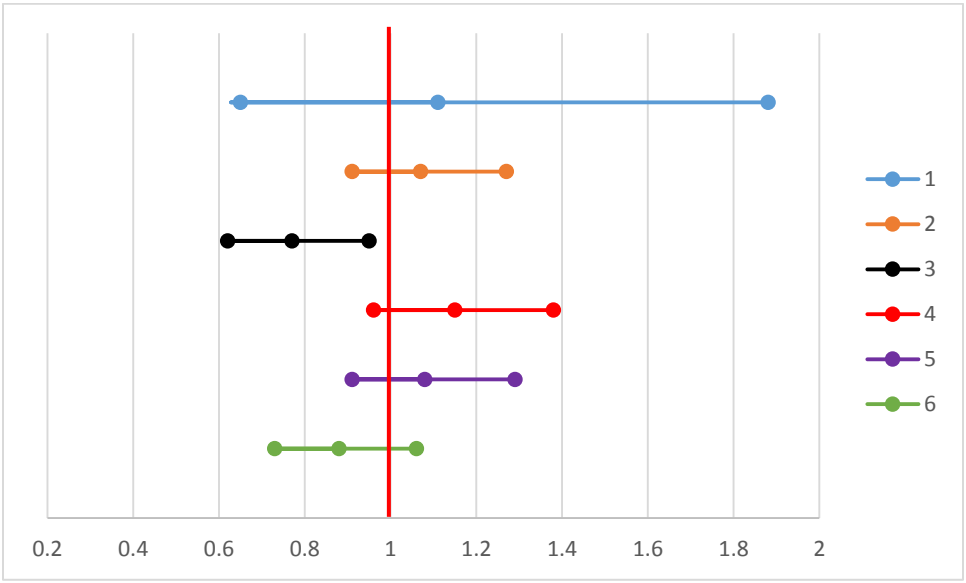


Figure 2. Adjusted hazard ratios (HR) with 95% confidence intervals for each transplant centre.

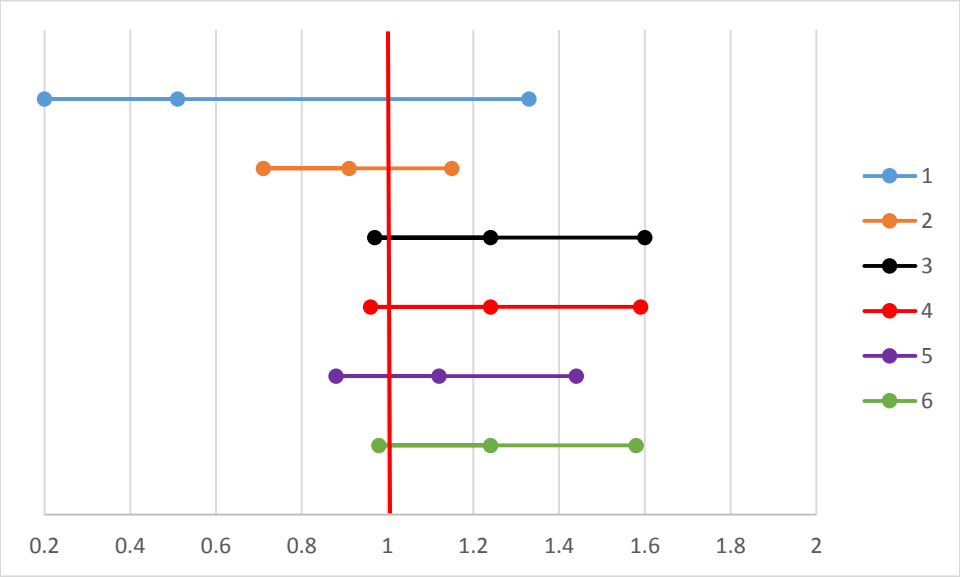
2a. Total Graft Loss



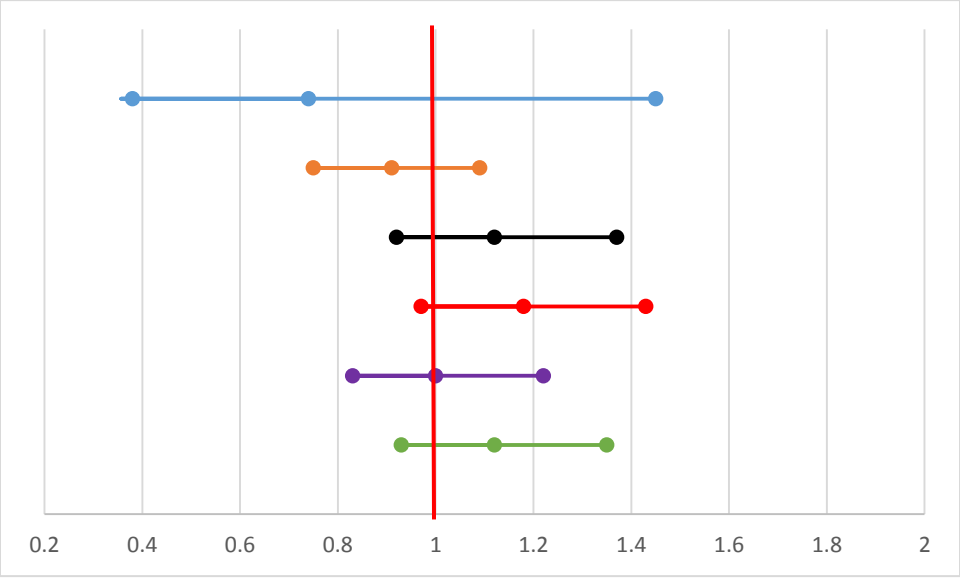
2b. Graft loss censored at the time of death



2c. Death with Graft Function



2d. Total Mortality



All ratios are adjusted for recipient sex, race, age, BMI, cause of ESRD, Charlson index, dialysis required and vintage, donor type and donor age and time period of transplant. The number corresponding to the transplant centre in one figure corresponds with a matching number in other figures. The reference line at 1 implies a program's performing the same as the centre average. The outer dots represent 95% confidence intervals.

SUPPLEMENTAL TABLES

Table S1. Coding definitions for kidney transplant recipient demographic and comorbid conditions

Characteristic	Database	Codes Used
Baseline Characteristic of Transplant Recipients and Donors		
Age, Sex, Rural	RPDB	
Renal Transplant	CORR	Treatment_Code: 171 Transplanted_Organ_Type_Code[1-3]: 10, 11, 12, 18, 19
Date of transplant,	CORR	Treatment_date
Cause of primary renal disease	CORR	Glomerulonephritis/Auto-immune disease: 05, 06, 07, 08, 09, 10, 11, 12, 13, 14, 15, 16, 17, 19, 73, 74, 84, 85, 86, 88 Diabetes: 80, 81 Cystic kidney disease: 40, 41, 42, 43, 49 Renal vascular disease: 70, 71, 72, 79 Other: 20, 21, 22, 23, 24, 25, 29, 30, 31, 32, 33, 39, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 66, 78, 82, 83, 87, 89, 90, 91, 92, 93, 94, 95, 96, 97, 99 Unknown: 00, 98
Race	CORR	Caucasian: 01; Asian: 02; African-American: 03; Indian: 05 Other: 08, 09, 10, 11, 99 Unknown: 98
Body Mass Index	CORR	Initial_Height Initial_Weight
Dialysis modality	CORR	Hemodialysis: 111, 112, 113, 121, 122, 123, 131, 132, 133, 211, 221, 231, 311, 312, 313, 321, 322, 323, 331, 332, 333, 413, 423, 433, Peritoneal Dialysis:141, 151, 152, 241, 242, 251, 252, 443, 453 Other – 060
Preemptive	CORR	
Time on dialysis	CORR	TRANSPLANT ([Treatment_Date] & [Treatment_Code]) – DIALYSIS ([Treatment Date] & [Treatment_Code])
Donor source	CORR	Living: 02, 03, 04, 05, 06, 07, 10, 12, 15 Deceased: 01 Unknown/Out-of-country transplant: 98
Charlson Comorbidity Index	CIHI-DAD	Charlson Macro
Peak Panel Reactive Antibody	CORR	PRA_1_PEAK_RESULT CORR

Transplant Centre	CORR	TREATMENT_FACILITY_NUM
Baseline Characteristic of Physicians		
Provider Type	IPDB	MAINSPEC*
Provider age	IPDB	BIRTHYR
Provider years since graduation	IPDB	GRADYR

Coding Definitions for Renal Recipient Outcomes

OUTCOMES	**Database**	**Codes Used**
Death	RPDB	
Dialysis post transplant	CIHI-DAD/OHIP CORR CHRONIC	CCP: 5195, 6698 CCI: 1PZ21 OHIP fee: R849, G323, G325, G326, G860, G863, G866, G330, G331, G332, G861, G082, G083, G085, G090, G091, G092, G093, G094, G095, G096, G294, G295 111,112,113,121,122,123,131,132,133,211,221,231, 311,312,313,321,
Repeat kidney transplant	CORR CHRONIC	Treatment_Code: 171 Transplanted_Organ_Type_Code[1-3]: 10, 11, 12, 18, 19

Abbreviations: RPDB: Registered Person's database, CORR: Canadian Organ Reporting Register, CIHI: Canadian Institute for Health information, DAD: Discharge abstract database, CCP; Canadian Classification of Diagnostic Therapeutic and Surgical Procedures, CCI; Canadian Classification of Interventions, IPDB: ICES physician database, TIA: thrombotic ischemic stroke.

Table S2. Centre-specific patient case mix hazard ratios from multivariable Cox Proportional hazards regression analysis for each outcome for living donor transplant.

Outcome of interest (Number of events)	**Total graft loss N=505**	**Graft loss censoring for N=297**	**Death with graft function N=208**	**Total Mortality N=276**
Covariate	**Hazard ratio, (95% CI)**	**Hazard ratio, (95% CI)**	**Hazard ratio, (95% CI)**	**Hazard ratio, (95% CI)**
Age, (per 5 year increase)	1.04 (1.01-1.08)	0.91 (0.87-0.96)	1.31 (1.23-1.39)	1.28 (1.21-1.35)
Sex ; Female	1.08 (0.90-1.30)	1.27 (1.01-1.61)	0.84 (1.19-6.21)	0.87 (0.67-1.12)
Male	Reference	Reference	Reference	Reference
Race; Caucasian	1.34 (0.93-1.92)	1.05 (0.70-1.57)	2.72 (1.33-2.42)	1.75 (0.98-3.14)
African	1.36 (0.80-2.32)	1.27 (0.69-2.34)	1.80 (0.59-5.46)	1.30 (0.54-3.14)
Asian	0.92 (0.51-1.658)	0.79 (0.39-1.58)	1.60 (0.45-5.70)	1.17 (0.45-3.02)
Other[1]	Reference	Reference	Reference	Reference
Cause of ESRD: GN	0.93 (0.71-1.21)	1.10 (0.78-1.54)	0.65 (0.41-1.04)	0.67 (0.45-0.99)
Diabetes	1.17 (0.85-1.61)	0.99 (0.64-1.53)	1.38 (0.85-2.24)	1.22 (0.81-1.85)
Cystic	0.71 (0.50-1.00)	0.77 (0.48-1.23)	0.67 (0.39-1.16)	0.60 (0.37-1.00)
RVD	1.06 (0.73-1.54)	1.37 (0.85-2.21)	0.67 (0.36-1.23)	0.74 (0.45-1.24)
Other	Reference	Reference	Reference	Reference
BMI	1.01 (1.00-1.02)	1.02 (0.99-1.04)	1.00 (0.97-1.04)	1.01 (0.99-1.04)
Charlson Index	1.11 (1.02-1.21)	1.09 (0.97-1.23)	1.12 (0.98-1.29)	1.19 (1.06-1.34)
Preemptive transplant	0.78 (0.60-1.03)	0.73 (0.51-1.03)	0.86 (0.57-1.32)	0.79 (0.54-1.16)
Pretransplant dialysis[2]	Reference	Reference	Reference	Reference
Time on dialysis pretransplant* (per 1 yr increase)	1.05 (1.01-1.09)	1.02 (0.96-1.08)	1.09 (1.03-1.14)	1.08 (1.03-1.13)
Donor age (per 5 year increase)	1.01 (0.98-1.05)	1.00 (0.95-1.06)	1.04 (0.98-1.09)	1.04 (0.99-1.09)
Time era of transplant:				
2000-2003	Reference	Reference	Reference	Reference
2003-2007	0.85 (0.67-1.08)	0.96 (0.70-1.30)	0.70 (0.48-1.00)	0.67 (0.49-0.93)
2007-2010	1.04 (0.81-1.35)	1.06 (0.76-1.49)	1.01 (0.67-1.51)	1.00 (0.70-1.43)
2010-2013	0.81 (0.57-1.15)	0.94 (0.62-1.44)	0.53 (0.27-1.03)	0.53 (0.29-0.97)
Centre : 1	NA	NA	NA	NA
2	1.03 (0.88-1.21)	1.17 (0.95-1.43)	0.85 (0.66-1.10)	0.99 (0.79-1.22)

3	0.86 (0.69-1.07)	0.81 (0.60-1.10)	0.90 (0.65-1.25)	0.98 (0.75-1.30)
4	1.05 (0.82-1.36)	0.98 (0.70-1.36)	1.29 (0.88-1.89)	1.20 (1.00-1.69)
5	0.99 (0.83-1.18)	1.01 (0.80-1.27)	0.95 (0.72-1.24)	0.86 (0.68-1.11)
6	1.08 (0.91-1.29)	1.06 (0.83-1.35)	1.07 (0.83-1.38)	0.99 (0.79-1.26)

Other[1] includes Aboriginal, Indian subcontinent, Pacific Islander,other/Multiracial.

Pretransplant dialysis[2] includes both peritoneal dialysis and hemodialysis. Each time period is 3 ½ years in length.

Centre[3] -the reference is the average across all centres.

*Time on dialysis includes a 0 for those who did not have any pretransplant dialysis.

Abbreviations: ESRD, end stage renal disease; GN, glomerulonephritis; RVD, renal vascular disease; BMI, body mass index

Table S3. Centre-specific patient case mix hazard ratios from multivariable Cox Proportional hazards regression analysis for each outcome for deceased donor transplant.

Outcome of interest (Number of events)	**Total graft loss N=997**	**Graft loss censoring for N=520**	**Death with graft function N=477**	**Total Mortality N=645**
Covariate	**Hazard ratio, (95% CI)**	**Hazard ratio, (95% CI)**	**Hazard ratio, (95% CI)**	**Hazard ratio, (95% CI)**
Age, (per 5 year increase)	1.08 (1.05-1.11)	0.92 (0.88-0.95)	1.36 (1.30-143)	1.28 (1.23-1.34)
Sex ; Female	0.89 (0.77-1.02)	0.96 (0.80-1.16)	0.80 (0.66-0.99)	0.84 (0.70-0.99)
Male	Reference	Reference	Reference	Reference
Race; Caucasian	1.39 (1.14-1.65)	1.19 (0.90-1.57)	1.66 (1.19-2.31)	1.55 (1.17-2.06)
African	1.22 (1.12-1.72)	1.38 (0.96-1.96)	0.85 (0.51-1.43)	0.97 (0.64-1.47)
Asian	1.38 (1.03-1.85)	1.42 (0.98-2.07)	1.41 (0.88-2.27)	1.42 (0.96-2.11)
Other[1]	Reference	Reference	Reference	Reference
Cause of ESRD: GN	0.84 (0.69-1.03)	0.86 (0.66-1.12)	0.81 (0.59-1.11)	0.76 (0.58-0.99)
Diabetes	1.07 (0.85-1.35)	0.81 (0.58-1.14)	1.45 (1.04-2.01)	1.36 (1.03-1.80)
Cystic	0.66 (0.51-0.86)	0.72 (0.51-1.02)	0.68 (0.46-1.01)	0.67 (0.47-0.94)
RVD	1.4 (0.82-1.32)	0.91 (0.65-1.26)	1.20 (0.85-1.69)	1.10 (0.81-1.47)
Other	Reference	Reference	Reference	Reference
BMI	1.01 (1.00-1.03)	1.02 (1.01-1.04)	1.01 (0.99-1.03)	1.01 (1.00-1.03)
Charlson Index	1.16 (1.09-1.24)	1.14 (1.05-1.25)	1.20 (1.10-1.31)	1.20 (1.12-1.30)
Preemptive transplant	1.55 (0.57-4.22)	1.24 (0.30-5.07)	2.41 (0.58-9.95)	2.74 (0.86-8.78)
Pretransplant dialysis[2]	Reference	Reference	Reference	Reference
Time on dialysis pretransplant* (per 1 yr increase)	1.05 (1.03-1.07)	1.04 (1.01-1.07)	1.07 (1.04-1.10)	1.07 (1.04-1.10)
Donor age (per 5 year increase)	1.07 (1.04-1.09)	1.10 (1.07-1.14)	1.04 (1.00-1.10)	1.05 (1.02-1.08)
Time era of transplant:				
2000-2003	Reference	Reference	Reference	Reference
2003-2007	0.93 (0.78-1.11)	0.90 (0.70-1.16)	0.97 (0.76-1.24)	0.98 (0.79-1.21)
2007-2010	0.73 (0.60-0.88)	0.86 (0.67-1.11)	0.59 (0.44-0.77)	0.68 (0.54-0.86)
2010-2013	0.67 (0.54-0.84)	0.67 ((0.50-0.90)	0.72 (0.52-1.01)	0.72 (0.54-0.98)
Centre : 1	0.85 (0.54-1.34)	1.12 (0.66-1.90)	0.50 (0.20-1.30)	0.71 (0.36-1.40)
2	0.91 (0.78-1.07)	1.01 (0.83-1.23)	0.85 (0.65-1.11)	0.83 (0.67-1.02)

3	1.01 (0.85-1.20)	0.77 (0.60-1.00)	1.32 (1.01-1.73)	1.16 (0.94-1.45)
4	1.18 (1.01-1.38)	1.24 (1.01-1.52)	1.19 (0.91-1.56	1.17 (0.95-1.44)
5	1.10 (0.94-1.29)	1.13 (0.92-1.39)	1.19 (0.90-1.57)	1.08 (0.87-1.34)
6	0.99 (0.84-1.17)	0.81 (0.64-1.03)	1.24 (0.96-1.62)	1.15 (0.93-1.42)

Other[1] includes Aboriginal, Indian subcontinent, Pacific Islander,other/Multiracial.

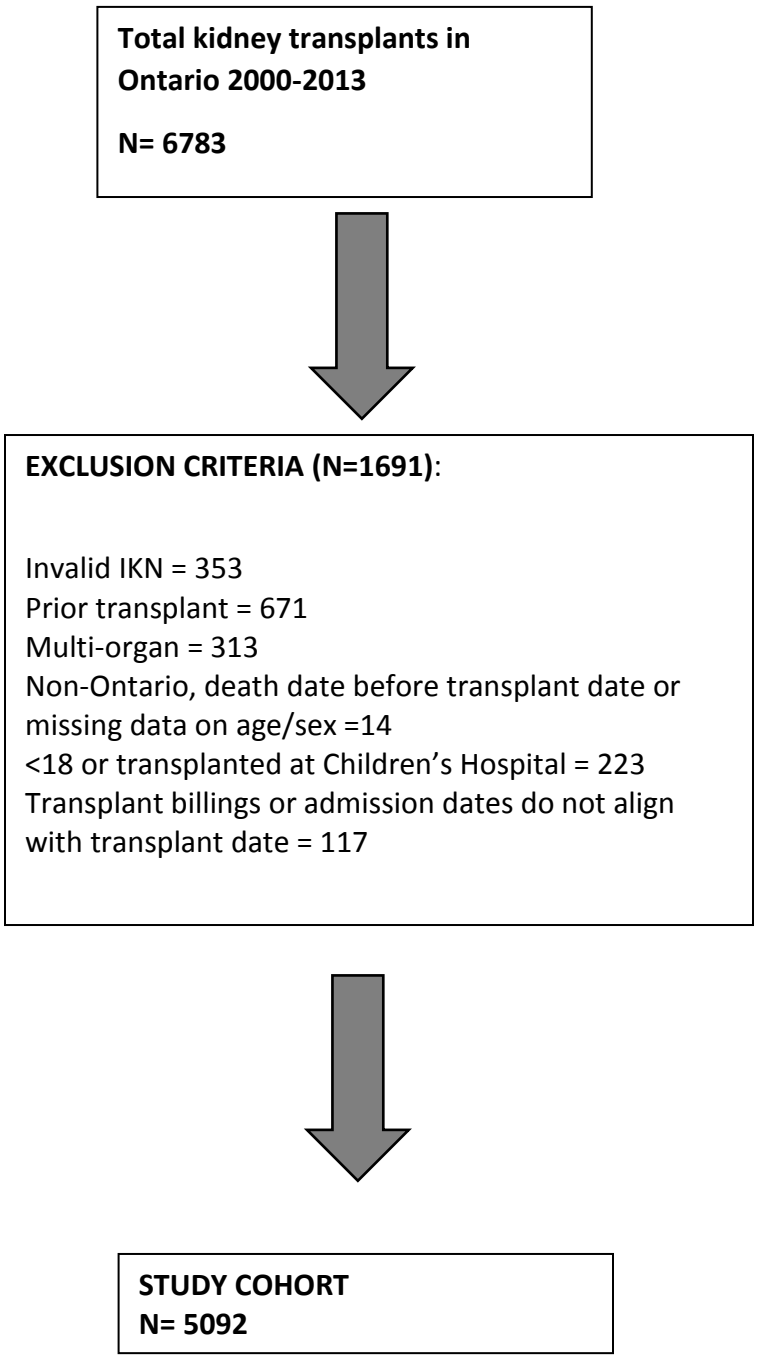
Pretransplant dialysis[2] includes both peritoneal dialysis and hemodialysis. Each time period is 3 ½ years in length.

Centre[3] -the reference is the average across all centres.

*Time on dialysis includes a 0 for those who did not have any pretransplant dialysis.

Abbreviations: ESRD, end stage renal disease; GN, glomerulonephritis; RVD, renal vascular disease; BMI, body mass index

Figure S1. Cohort Creation



Chapter 5 – [Manuscript 4] – **Variation in Post-kidney transplantation outcomes between centres is not due to patient volume or provider characteristics**

5.1 Preface to manuscript 4 –

In this manuscript, we examined centre variation across Ontario transplant centres accounting for patient factors, centre volume and provider characteristics (years of experience and type of provider). The main outcomes were graft loss (with follow-up times censored at the time of death) and all-cause mortality assessed at 1 year post transplantation and at the end of study follow up. We used multivariable Cox proportional hazards regression applied to imputation-completed datasets to obtain hazard ratios (HR) for each centre relative to the average across all centres. Centre volume and provider characteristics were then added to the models to determine whether these factors were independently associated with outcomes and explain differences across centres. We excluded the smallest transplant centre from this manuscript since this centre differed substantially from other centres. This manuscript is in preparation for publication.

Variation in Post-kidney transplantation outcomes between centres is not due to patient volume or provider characteristics

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ABSTRACT

Background: We recently found that differences in outcomes post kidney transplant were not explained by patient factors alone. The objective of this study was to examine whether centre volume and provider characteristics contribute to variation in graft and patient survival rates across five kidney transplant centres in Ontario, Canada.

Methods: We conducted a population-based cohort study using administrative data of all adults (>18 yrs) undergoing primary, solitary kidney transplantation between January 1st 2000 to December 31st 2013 in Ontario, Canada. The main outcome was graft loss (with follow-up times censored at the time of death) and all-cause mortality. To compare case-mix adjusted differences across centres, multivariable Cox proportional hazards regression was used to obtain hazard ratios (HR) for each centre relative to the average across all centres. Centre volume and provider characteristics were then added to the models to determine whether these factors were independently associated with outcomes and explain differences across centres.

Results: The study cohort included 5037 patients. We found significant differences between centres for transplant volume (mean (SD) ranged between 51.5 (9.3) – 101.7 (23.9) transplants per year), average provider experience mean (SD) between 17.2 (6.4) – 27.3 (9.2) years, and provider speciality. At one year follow-up, after adjusting for patient case mix, as well as centre and provider factors, HRs for graft loss censored at the time of death ranged between 0.73 (95% CI 0.51-1.04) and 1.41 (95% CI 1.08-1.83) across centres, and for total mortality between 0.78 (95% CI 0.43-1.42) and 1.43 (0.92-2.21). At the end of total follow up, after adjusting for

patient case mix, as well as centre and provider factors, HRs for graft loss censoring at time of death ranged from 0.72 (95% CI 0.58-0.90) to 1.18 (95% CI 1.00-1.40), and for total mortality from 0.85 (95%CI 0.70-1.04) to 1.14 (95%CI 0.98-1.33). Centre volume and provider type were not independently associated with any outcome.

Conclusions: Our study found clinically important but statistically non-significant variation in graft and patient survival outcomes across kidney transplant centres in Ontario which was not explained by case-mix, centre volume or provider factors alone. Future prospective observational studies detailing type of clinical practice and care are necessary to better understand these differences.

INTRODUCTION

Variation in graft and patient survival rates between centres have been observed in studies from the United States (US)[1-3], Canada [4] and Europe.[5-7] While the role of patient characteristics (both recipient and donor) at the time of transplant have been well-examined[1,2,4,5,7,8], centre and provider level factors which may contribute to variation have not been extensively examined. To date, studies examining centre level factors, including centre volume[3,4,8-12] (mainly measured over the entire study cohort) and centre type[13,14] (eg. for profit or teaching hospital), have found conflicting results. Many of the studies which assessed the centre volume-outcome relationship included patients transplanted prior to2001[1,3,4,8,11,12 10] which may be less relevant given changes in immunosuppressive agents. While associations between provider caseload and patient outcomes have been examined among nephrologists and hemodialysis patients[15,16], very few studies have examined comparable associations among kidney transplant recipients.[9,13]

The objectives of the present study are to: i) compare graft and patient survival outcomes across 5 transplant centres in Ontario and ii) to determine whether centre volume and/or provider characteristics such as type of provider and provider experience are associated with graft and patient outcomes and contribute to centre variation. We hypothesized that higher centre volume and provider experience would be associated with improved graft and patient survival, particularly at one year post-transplant. If better outcomes are associated with greater transplant volumes, it may encourage the centralization of clinical services.

METHODS

Study Design and Setting

We conducted a population-based retrospective observational cohort study using health care databases at the Institute for Clinical Evaluative Sciences (ICES) in Ontario, Canada. Ontario has a population of approximately 13.6 million residents who have universal access to health care services. This study was approved by the institutional review board at Sunnybrook Health Sciences Centre (Toronto, Canada). The reporting of this study followed the STROBE and RECORD reporting guidelines for observational studies.[17,18] The full data set creation plan is available from the authors upon request.

Data sources

We used 5 linked datasets to create the cohort, and to obtain patient, centre, provider, and outcome data as previously described.[19] These datasets were linked using unique encrypted patient-specific identifiers and analyzed at ICES. We used the Canadian Organ Replacement Register (**CORR**) to identify kidney transplant recipients. CORR's sensitivity to correctly identify kidney transplant recipients is 96% and positive predictive value is 98%.[20] Demographic and vital status of renal transplant recipients was obtained using Ontario Registered Persons database (**RPDB**). The Canadian Institute for Health Information Discharge Abstract Database (**CIHI-DAD**) and Ontario Health Insurance Plan (**OHIP**) were used to obtain information on recipient comorbidities and outcomes. These were determined using codes that were similar to those used in prior kidney transplant studies.[20-22] (Supplemental Table 1) Finally,

we obtained provider information using the ICES Physician Database (**IPDB**) which contains information on physician demographics, training and practice setting from the Corporate Provider Database, the Ontario Physician Human Resource Data Centre database and the OHIP database of physician billings.

Study Cohort

The creation of this study cohort has been previously described.[19] In brief, we included all adults (≥18 years) who received a first-time solitary kidney transplant in Ontario Canada between January 1st 2000 and December 31st 2013. We excluded those with an invalid IKN (a confidential ICES patient number), or who were not from Ontario, died prior to transplant date, had unknown age or sex and whose OHIP transplant billing or hospitalization dates did not align with transplant date. (Supplemental Figure 1). For this study, we also excluded patients who were transplanted at one centre given the small volume of transplants performed over the study period (n=55).

Identification of patient, centre and provider characteristics

Transplant recipients were classified by the centre at which their transplant occurred using the CORR facility code number. Information on the transplant centre was obtained using CORR, OHIP and IPDB. We identified physicians who provided care to transplant recipients during their admission by linking the patient IKN with an encrypted physician number using the

OHIP database. We identified the most responsible surgeon and most responsible physician by using the following OHIP transplant related billing codes: S435 (surgical transplant fee) and G412 (nephrology component of renal transplant). The surgical transplant fee code has been validated for identifying kidney transplant recipients.[23] Provider characteristics including specialty type and years since graduation were obtained from IPDB.

Outcomes

Patients were followed from the date of transplant until March 31st 2015. The primary outcome was graft failure with follow-up times censored at the time of death and total mortality. Additional outcomes included total graft failure, defined as graft loss (return to chronic dialysis or re-transplant) or death after kidney transplant, whichever occurred first and death with graft function (death after primary kidney transplant but prior to graft loss). We assessed the above mentioned outcomes at 1 year post transplant as well as over the duration of the study follow up.

Statistical Analysis

We used descriptive statistics to summarize characteristics of patients at the time of transplant: entire cohort and by centre. Continuous variables were described using mean and standard deviation (SD) when the data followed a normal distribution or median and interquartile range [IQR] if skewed. Frequencies and percentages were used for categorical data.

We categorized the study period into three time evenly distributed tertile periods: the first time period was January 1st 2000 - December 31st 2004, and the second and third were January 1st 2005 – June 30th 2009 and July 1st 2009 – December30th 2013 respectively. Centre volume was described as the total volume at a centre over a time period. Distribution of centre volume within each time era was compared across centres using the Chi-squared test. For each centre, we calculated the proportion of transplant patients seen by each provider type. This was calculated as the number of patients who saw the provider type divided by the total number of transplants at that centre. For each type of provider, we calculated the years of experience as years since graduation.

The proportion of events at one year was calculated for each time era and volume tertile. The one, five and ten year observed survival distributions by centre volume tertile and average provider experience tertile were described using the Kaplan-Meier method and statistical significance of differences across centres were assessed using the log-rank test.

To account for differences in patient case mix across transplant centres, we used fixed effects multivariable Cox proportional hazards regression. Fixed effects modelling was used given the small sample size of centres (i.e. <6). Adjusted hazard ratios (HR) with 95% confidence intervals (CI) were calculated for each transplant centre, using effects coding to express differences relative to the average across all centres. Our models adjusted for the following patient characteristics: recipient age, sex, race, cause of end stage renal disease (ESRD), body mass index (BMI), Charlson comorbidity index, pre-transplant dialysis modality (none vs hemodialysis or peritoneal dialysis), years on dialysis before transplantation, era of transplant (as defined

above), donor source (living vs. deceased) and donor age. For total mortality we used stepwise backwards elimination to remove non-significant case mix variables from the model. We also calculated unadjusted centre hazard ratios for the two co-primary outcomes (graft failure with follow-up times censored at the time of death and total mortality) in order to assess the influence of patient characteristics.

Centres having Hazard Ratios with both upper and lower confidence limits below 1 imply that the centre has a survival rate significantly better than average after accounting for patient case mix, while HRs for centres with both limits above 1 imply that the centre is performing significantly worse than average. On the other hand, centres with confidence intervals including 1 have a survival rate that is not significantly different than the average after accounting for patient case mix.

For the purposes of modelling, centre volume was defined as the total number of transplants performed at a given centre in the calendar year *prior* to a patient's transplant. Provider experience of the care team for each patient was modelled as the average number of years since graduation of the providers linked to a given patient. Centre volume and provider experience were specified as continuous variables to avoid losing meaningful information and the statistical power through categorization outcome.[23] To interpret the resulting associations in a clinically relevant manner, hazard ratios for volume were expressed in units of 25 transplants performed, and provider experience in units of 5 years.

Data were missing for the following variables; recipient race (10.0%), cause of ESRD (7.9%), Charlson comorbidity index (5.5%), BMI (16.9%), donor type and donor age (both are 0.75%),

provider years since graduation (0.44%). Prior to analysis, we performed multiple imputation using the fully conditional specification method which does not assume a joint distribution for all variables in the imputation model, but instead applies a separate conditional distribution for each of the variables to be imputed.[24] For categorical variables we used the discriminant method and for continuous variables, linear regression. We conducted 10 imputations using 100 burn-in iterations. Multivariable analyses were conducted for each imputation dataset and combined across datasets using Rubin's rules.[25]

To assess the sensitivity of the results to the imputation procedure, all analyses were also conducted using cases-only with no missing provider variables (n=5015). In additional analyses, we calculated adjusted centre specific HRs using the imputed data as described above, for the additional outcomes total graft loss and death with graft function. Furthermore, we conducted all analyses including the patients transplanted at the smaller centre (study cohort size of 5092 participants).

All statistical analyses were performed using SAS (Statistical Analysis Software) version 9.4 (SAS Institute, Cary NC). A two-sided p value <0.05 was considered statistically significant.

RESULTS

Patient, centre and provider characteristics at the time of transplant

The study included 5037 primary kidney transplant recipients from five transplant centres in Ontario. The mean (SD) age of the overall cohort was 50.9 (13.5) years, 63.1% were male and 63.4% were Caucasian (Table 1). The characteristics of the transplant population across centres has previously been reported.[19] The annual transplant volume varied by

transplant centre and calendar year. The proportion of patients seen by a specific type of provider varied significantly across centres. The most common type of physicians providing care at time of transplant were nephrologists (85.0%) and urologists (74.4%). The mean (SD) years of experience of the providers caring for transplant recipients in-hospital was 21.1 (8.3) and ranged between 17.2 (6.4) and 27.3 (9.2) across centres ($p<0.0001$). (Table 1).

One year Outcomes

At one year post transplant, there were 442 composite events of graft loss and death, 329 patients with graft loss with follow-up times censored at the time of death, and 128 deaths. The proportion of events varied with each time era and volume category (Figure 1, Table 2). The observed 1 year survival rates for graft loss censoring at time of death did not vary significantly by time era: 93.4% for those transplanted between 2000-2004, 93.7% between 2005-2009 and 93.8% transplanted after 2009 (log rank $p=0.74$). The observed 1 year survival rates for total mortality were: 97.1% for those transplanted between 2000-2004, 96.8% transplanted between 2005-2009 and 97.6% transplanted after 2009 (log rank $p=0.24$).

Unadjusted and Adjusted Hazard Ratios – Primary outcomes graft loss censoring at time of death and total mortality

Unadjusted centre-specific hazard ratios for the primary outcome of graft failure with follow-up times censored at the time of death obtained from Cox proportional hazards regression models revealed statistically significant differences across centres ($p=0.008$) however, there were no statistically significant differences across centres, after accounting for patient case mix only ($p=0.08$), or after adding centre volume ($p=0.38$) and provider characteristics ($p=0.94$). Centre

hazard ratios ranged between 0.73 (95% CI 0.51-1.04) and 1.41 (95% CI 1.08-1.83) in the full models. (Figure 2a,2b) Covariates found to be statistically significantly associated with this outcome included preemptive transplant, donor type and donor age. Centre volume, provider experience and provider type were not significantly associated with this outcome. (Table 3). Centre-specific hazard ratios for the primary outcome total mortality obtained from Cox proportional hazards regression models revealed no statistically significant differences across centres, in unadjusted models (p=0.8), after accounting for patient case mix (p=0.11), centre volume (p=0.12) and provider characteristics (p=0.42) and ranged between 0.78 (95% CI 0.43-1.42) to 1.43 (0.92-2.21). (Figure 2c,2d) Factors found to be associated with this outcome included recipient age, Charlson index, donor type and donor age. Centre volume, average provider experience and provider type were not significantly associated with this outcome. (Table 4).

Total follow up - Observed survival rates

Primary outcomes – Graft loss censoring with follow-up times censored at the time of death and total mortality

The 1-, 5- and 10 year observed graft survival rates with follow-up times censored at the time of death did not vary significantly by volume category (log-rank p=0.8) nor did they vary with increasing provider experience (log-rank p=0.26). (Supplemental Tables 2 and 3). The observed 1-, 5- and 10 year survival rates for total mortality increased significantly with increasing

volume (log-rank p=0.0008). (Supplemental table 2). They did not vary significantly with average experience of the provider (log-rank p=0.1). (Supplemental table 3).

Total follow up – Unadjusted and Adjusted Hazard Ratios

Primary Outcome - Graft loss censoring for death and total mortality

Centre-specific hazard ratios for the primary outcome graft loss with follow-up times censored at the time of death obtained from Cox proportional hazards regression models varied significantly across centres, in unadjusted models (p=0.001), after accounting for centre volume (p=0.04), but were no longer significant after adjusting for provider characteristics (p=0.21). Hazard Ratios ranged between 0.72 (95% CI 0.58-0.90) and 1.18 (95% CI 1.00-1.40). (Figure 3a,3b) Patient case mix factors found to be significantly associated with this outcome included: recipient age, BMI, Charlson index, pretransplant time on dialysis, donor type and donor age. While centre volume and provider type were not significant, average provider experience was: adjusted HR 1.05 (95%CI 1.00-1.10) per additional 5 years of experience. (Table 5) Centre-specific hazard ratios for total mortality obtained from Cox proportional hazards regression models varied significantly across centres, in unadjusted models (p<0.0001), and even after accounting for patient case mix (p=0.01), centre volume (p=0.04) but not provider characteristics (p=0.11) and ranged between 0.85 (95%CI 0.70-1.04) and 1.14 (95%CI 0.98-1.33). (Figure 3c,3d) Patient case mix factors found to be significantly associated with total mortality included: recipient age and sex, Charlson index, time on dialysis pretransplant, donor age and time era of transplant. Centre volume, provider experience and provider type were not significantly associated with this outcome. (Table 6).

Sensitivity Analysis

Results were similar when we repeated the above analyses excluding those with missing provider information (study cohort size of 5015 participants): there was no statistically significant association between provider experience and outcome other than for graft loss with follow-up times censored at the time of death (adjusted HR 1.05 (95% CI 1.00-1.11) and no significant association between provider type and outcome. When analyses were performed including the patients transplanted at the smaller centre (study cohort size of 5092 participants), we found similar findings for one year primary outcomes, that is there was no statistically significant variation across centres for either primary outcome, however the confidence intervals were much wider. Centre and provider factors were not significantly associated with either outcome. When analyses were performed with the full follow-up including the additional 55 patients, the confidence intervals for adjusted centre specific hazard ratios became wider and the variation seen across centres was no longer statistically significant. Centre and provider covariates were not associated with outcomes, with the exception of average provider experience and graft loss with follow-up times censored at the time of death (HR 1.06 95% CI 1.00-1.11).

Additional analyses

Centre-specific hazard ratios for the outcome total graft loss at one year obtained from Cox proportional hazards regression models revealed no statistically significant differences across centres. (Supplemental table 4). Centre-specific hazard ratios for the outcome total graft loss at the end of follow up obtained from Cox proportional hazards regression models revealed no

statistically significant differences across centres. (Supplemental table 5). Centre-specific hazard ratios for the outcome of death with graft function at the end of follow up obtained from Cox proportional hazards regression models revealed statistically significant differences across centres, even after accounting for patient case mix (p=0.002), centre volume (p=0.008) and provider characteristics (p=0.04) (Supplemental table 6).

DISCUSSION

Our study found statistically significant centre variation in total mortality and death with graft function at long term follow up across five Ontario renal transplant centres. These findings persisted even after accounting for patient factors and centre volume for total mortality, and accounting for patient, centre and provider factors for death with graft function. While we did not detect statistically significant differences across centres in either graft loss with follow-up times censored at the time of death or total graft loss, there were clinically significant differences in the adjusted HRs across centres. For example, the risk of graft loss with follow-up times censored at the time of death, after adjusting for all covariates was close to 30% lower at one centre (HR 0.72 95% CI 0.58-0.90) compared to almost 20% higher at another centre (HR 1.18 95% CI 1.00-1.40). Centre volume and provider type were not independently associated with either graft or patient survival. To our knowledge this is first Canadian study to assess the association between provider characteristics and kidney transplant outcomes.

In our study, which included a cohort of over 5000 patients who underwent primary solitary kidney transplantation in Ontario between 2000-2013, we found that centre variation

in graft and patient outcomes is not explained by centre volume, provider experience or provider type. That is, these factors were not statistically significantly associated with outcomes and when we compared the centre hazard ratios from models which only adjusted for case mix to those which also adjusted for centre and provider factors, differences among centres persisted, implying that the centre and provider factors do not explain variation in longer term outcomes. While we did identify larger fluctuations in a given centre's hazard ratio at one year post transplant when adjusting for patient case-mix only [HR 1.04 (95%CI 0.75-1.45)] compared to those adjusting for centre and provider factors [0.85 (95%CI 0.56-1.31)], we concluded that this was more likely related to the low frequency of events that occurred at one year.

Interestingly, we did not detect any independent association between a centre's transplant volume and either graft survival or patient survival. The literature examining whether an association between kidney transplant centre volume and post transplantation outcomes exists was recently summarized in a systematic review.[26] While just under half of these prior studies found a positive and significant association between greater volume and graft survival[1,4,9-12,14], seven had categorized centre volume using different cut-points and four had included volume as the total transplants over the entire study period rather than on an annual basis and therefore an actual volume threshold for improved outcomes could not be determined. The remainder of prior studies included in this review, either found no association between volume and outcome[3,6,27-29] or were inconclusive.[2,8,30,31] It therefore remains unclear whether greater centre transplant volume is beneficial for graft or patient survival outcomes. While our study found improved observed survival rates with increasing centre volume

categories, these findings were no longer statistically significant when we adjusted for patient characteristics.

To date only one prior study has examined the association between provider experience (defined by years of experience) with graft survival post kidney transplantation.[13] Evans et al found a significant association between provider experience and less allograft loss. This is in contrast with what we observed in our study which found non-significant associations between physician experience and all outcomes with the exception of graft loss with follow-up times censored at the time of death where greater average provider experience was associated with higher risk of graft loss. Our study however combined the experience of all providers caring for the patient in hospital while the study by Evans et al[13] used only the average surgeon's experience.

Provider experience and its association with patient outcomes has also been examined among patients on hemodialysis. Slinin al[16] detected an inverse association between patient mortality among incident in centre hemodialysis patient and years since end of training of caring nephrologists; an increased risk of mortality with increased years since end of training, however this association was no longer significant after adjusting for patient factors. This inverse relationship was also described in a large systematic review which found decreasing performance with increasing years of practice in 50% of the 60 studies included.[32] While the review included studies from all fields of medicine it is consistent with our findings.

The limitations of our study included: 1) The estimate used for provider experience was an average of all the different physicians billing for one patient at the time of transplant as there

was not one specific provider who was most responsible for the patient's care. 2) With regards to provider type, we were limited to the detail available in the administrative database used and therefore ancillary providers which potentially play an important role in hospital care, could not be included in our models. 3) We examined the effects of physician characteristics during the initial transplant hospitalization on longer term outcomes. While we also examined such effects on outcomes at one year post transplantation, the number of events that occurred at one year was much smaller and we may have lacked the statistical power to detect any relationships.

In summary, our study showed clinically significant variation in post kidney transplantation outcomes across Ontario kidney transplant centres. This variation is not explained by patient characteristics, centre volume or provider characteristics alone. Future prospective observational studies which include a larger sample size of transplant centres, and more detailed information about providers and clinical care post transplantation are required in order to better understand what may be contributing to the variation in outcomes seen.

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Figure Legend

Figure 1a-b. Percentage of events at 1 year post transplant by volume category and time era.

Figures 2a-d. Adjusted hazard ratios (HR) with 95% confidence intervals for each transplant centre at one year post transplantation. 1a-Graft loss with follow-up times censored at the time of death adjusted for case-mix, 1b) Graft loss with follow-up times censored at the time of death adjusted for case-mix, centre transplant volume, provider experience and provider type. 1c) Total mortality adjusted for case-mix, 1d) Total mortality adjusted for case-mix, centre transplant volume, provider experience and provider type.

Figures 3a-d. Adjusted hazard ratios (HR) with 95% confidence intervals for each transplant centre at the end of study follow up. 1a-Graft loss with follow-up times censored at the time of death adjusted for case-mix, 1b) Graft loss with follow-up times censored at the time of death adjusted for case-mix, centre transplant volume, provider experience and provider type. 1c) Total mortality adjusted for case-mix, 1d) Total mortality adjusted for case-mix, centre transplant volume, provider experience and provider type.

Supporting Information

Table S1. Coding definitions for kidney transplant recipient demographic and comorbid conditions

Table S2. Observed survival rates (%) for each outcome of interest by volume category.

Table S3. Observed survival rates (%) for each outcome of interest by average provider experience category.

Table S4.Centre-specific patient case mix hazard ratios from multivariable Cox Proportional hazards regression analysis for total graft loss at 1 year post transplant

Table S5.Centre-specific hazard ratios from multivariable Cox Proportional hazards regression analysis of death with graft function

Table S6.Centre-specific patient case mix hazard ratios from multivariable Cox Proportional hazards regression analysis for total graft loss for full follow up

Table S7.Centre-specific patient case mix hazard ratios from multivariable Cox Proportional hazards regression analysis for death with graft function over full follow up

Figure S1. Flow diagram of study cohort.

Table 1. Participant characteristics at the time of kidney transplant (n=5037)

Characteristic	Overall Cohort	Range across centres
Age, Mean (SD)	50.9 (13.5)	50.5 (13.6) – 51.5 (13.1)
Sex, Male n (%)	3177 (63.1)	60.1 – 65.4%
Race, n (%)		
Caucasian	3194 (63.4)	47.8 – 79.4%
African	361 (7.2)	1.3- 11.1%
Asian	345 (6.8)	2.5 - 13.1%
Other	634 (12.6)	5.5 - 18.9%
Cause of ESRD n (%)		
Glomerulonephritis	1684 (33.4)	30.8 - 36.1%
Diabetes	990 (19.7)	15.8 - 25.0%
Cystic Kidney	680 (13.5)	11.2 -15.1%
Renal Vascular	553 (11.0)	7.2 - 14.0%
BMI, Mean (SD)	26.6 (5.7)	25.5 (5.3) – 27.6 (6.1)
Charlson Index. Mean (SD)	2.7 (1.3)	2.6 (1.3) - 2.8 (1.3)
Pretransplant dialysis modality n (%)		
Premptive	515 (10.2)	3.6 -13.2%
Dialysis Pretransplant	4522 (89.8)	86.8 - 96.4%
Years on dialysis, Median [IQR]	2.7 [1.1,5.1]	1.8 [1.1,3.0] - 4.2 [1.3,6.6]
Donor Type n (%)		
Living	2115 (42.0)	22.7 - 50.3%
Deceased*	2922 (58.0)	49.7 - 77.3%
Donor Age, Mean (SD)		
Living	44.5 (13.3)	42.8 (12.2) – 46.9 (15.3)
Deceased	45.5 (15.9)	43.4 (15.9) – 48.8 (16.2)
Time era of transplant,** n (%)		
2000-2004	1404 (27.9)	26.0-33.8%
2005-2009	1659 (32.9)	31.5-34.7%
2009-2013	1974 (39.2)	34.7-42.2%
Annual Mean (SD) volume over the study period	77.6 (27.0)	51.5 (9.3) – 101.7 (23.9)
Proportion seen by provider type N (%)		
Urology	3746 (74.4)	43.5-94.8%
General Surgery	1125 (22.4)	0-51.3%
Nephrology	4277 (85.2)	79.4-94.7%
Fellow	567 (11.3)	0.98-29.1%
Internist	222 (4.4)	2.8-13.5%
Average Provider experience Mean (SD) years	21.1 (8.3)	17.2 (6.4) -27.3(9.2)

*Total number for deceased also includes those with missing donor type.

**First time period is 5 years, second two are 4 ½ years.

Other[1] includes Aboriginal, Indian subcontinent, Pacific Islander, Other/Multiracial. Pretransplant dialysis[2] includes both peritoneal dialysis and hemodialysis. Average provider experience was calculated as the average years since graduation for each provider.

Abbreviations: SD, standard deviation; ESRD, End stage renal disease; BMI, body mass index; IQR, interquartile range;

Table 2. Percentage of events at 1 year post-transplant by volume category and time era

Graft loss censoring for death (number of events=329)	**Low volume** (<60 transplants)	**Mid-volume** (60-87 transplants)	**High-volume** (≥87 transplants)	**Overall volume categories**
2000-2004	6.8 (54/796)	6.3 (38/608)		6.6 (92/1404)
2005-2009	4.9 (29/586)	6.3 (35/560)	9.7 (50/513)	6.9 (114/1659)
2009-2013	5.4 (16/299)	6.3 (33/526)	6.4 (74/1149)	6.2 (123/1974)
Over all time eras	5.9 (99/1681)	6.3 (106/1694)	7.5 (124/1662)	
Total Mortality (number of events=128)	**0 (<60 transplants)**	**1 (60-87 transplants)**	**2 (≥87 transplants)**	
2000-2004	2.8 (22/796)	1.5 (9/608)		2.2 (31/1404)
2005-2009	4.4 (26/586)	1.6 (9/560)	3.2 (16/513)	3.1 (41/1659)
2009-2013	2.3 (7/299)	2.7 (14/526)	2.2 (25/1149)	2.3 (56/1974)
Over all time eras	3.3% (55/1681	1.9% (32/1694)	2.5% (41/1662)	
Total Graft loss (number of events=442)	**0 (<60 transplants)**	**1 (60-87 transplants)**	**2 (≥87 transplants**	
2000-2004	9.4 (75/796)	7.7 (47/608)		8.7 (122/1404)
2005-2009	9.0 (53/586)	7.1 (40/560)	12.5 (64/513)	9.5 (157/1659)
2009-2013	7.0 (21/299)	8.6 (45/526)	8.4 (97/1149)	8.3 (163/1974)
Over all time eras	8.9 (149/1681)	7.8 (132/1694)	9.7 (161/1662)	

*First time era is 5 years and the second two time eras are 4 ½ years each.

Table 3.Centre-specific hazard ratios from multivariable Cox Proportional hazards regression analysis of graft loss, censoring for death, at one year (total number of events=329)

	Unadjusted (n=5037)	Adjusting for patient case mix only (n=5037)	Adjusting for patient case mix and centre volume (n=5037)	Adjusting for patient case mix, centre volume and provider characteristics (n=5037)
Covariate		**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Age, (per 5 year increase)		0.96 (0.92-1.01)	0.96 (0.92-1.01)	0.96 (0.92-1.01)
Sex ; Female		1.09 (0.87-1.37)	1.10 (0.87-1.37)	1.09 (0.87-1.36)
Male		Reference	Reference	Reference
Race; Caucasian		1.31 (0.91-1.88)	1.31 (0.91-1.88)	1.33 (0.92-1.90)
African		1.17 (0.72-1.91)	1.18 (0.72-1.91)	1.19 (0.73-1.94)
Asian		1.11 (0.66-1.85)	1.11 (0.66-1.83)	1.12 (0.67-1.87)
Other[1]		Reference	Reference	Reference
Cause of ESRD; GN		0.94 (0.67-1.32)	0.94 (0.67-1.32)	0.94 (0.67-1.31)
Diabetes		0.67 (0.44-1.02)	0.67 (0.44-1.02)	0.68 (0.45-1.03)
Cystic		0.68 (0.44 -1.05)	0.68 (0.44 -1.05)	0.68 (0.44-1.05)
RVD		0.82 (0.53-1.26)	0.82 (0.53-1.27)	0.82 (0.53-1.26)
Other		Reference	Reference	Reference
BMI		1.02 (1.00-1.04)	1.02 (1.00-1.04)	1.02 (1.00-1.04)
Charlson Index		1.11 (1.00-1.23)	1.11 (1.00-1.23)	1.11 (1.00-1.23)
Preemptive transplant		0.37 (0.18-0.74)	0.37 (0.18-0.74)	0.37 (0.18-0.74)
Pretransplant dialysis[2]		Reference	Reference	Reference
Time on dialysis pretransplant (per 1 year increase)		1.03 (1.00-1.07)	1.03 (1.00-1.08)	1.03 (0.99-1.07)
Donor type; Living		0.72 (0.54-0.95)	0.72 (0.54-0.94)	0.76 (0.57-1.01)
Deceased		Reference	Reference	Reference
Donor age (per 5 year increase)		1.04 (1.01-1.08)	1.04 (1.01-1.08)	1.04 (1.01-1.08)
Time era of transplant: 2000-2004		Reference	Reference	Reference
2005-2009		1.05 (0.69-1.38)	1.02 (0.76-1.39)	1.04 (0.76-1.43)
2009-2013		0.90 (0.68-1.18)	0.85 (0.57-1.28)	0.89 (0.58-1.37)
Centre[3] 1	1.14 (0.94-1.39)	1.20 (0.98-1.46	1.15 (0.84-1.57)	0.99 (0.70-1.38)
2	0.71 (0.53-0.96)	0.74 (0.55-0.99)	0.76 (0.54-1.08)	0.73 (0.51-1.04)

3 4 5	1.19 (0.94-1.49) 0.81 (0.63-1.04) 1.27 (1.05-1.55)	1.09 (0.86-1.39) 0.78 (0.61-1.01) 1.32 (1.07-1.62)	1.11 (0.85-1.46) 0.79 (0.61-1.03) 1.29 (1.01-1.64)	1.17 (0.88-1.55) 0.85 (0.65-1.13) 1.41 (1.08-1.83)
Centre Volume (per 25 patients)			1.04 (0.84-1.28)	1.02 (0.82-1.27)
Average provider experience (per 5 years experience)				1.05 (0.97-1.13)
Provider Type: Urologist General Surgeon Fellow Nephrologist Internist				 0.81 (0.55-1.19) 1.10 (0.72-1.67) 1.07 (0.74-1.54) 0.84 (0.59-1.18) 0.90 (0.49-1.66)

Other[1] includes Aboriginal, Indian subcontinent, Pacific Islander,other/Multiracial.

Pretransplant dialysis[2] includes both peritoneal dialysis and hemodialysis.

Centre[3] -the reference is the average across all centres.

Abbreviations: ESRD, end stage renal disease; GN, glomerulonephritis; RVD, renal vascular disease; BMI, body mass inde

Table 4.Centre-specific hazard ratios from multivariable Cox Proportional hazards regression analysis of total mortality, at one year (total number of events=128)

Outcome of interest (Number of events)	**Unadjusted (n=5037)**	**Adjusting for patient case mix only (n=5037)**	**Adjusting for patient case mix and centre volume (n=5037)**	**Adjusting for patient case mix, centre volume and provider characteristics (n=5037)**
Covariate		**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Age, (per 5 year increase)		1.21 (1.12-1.32)	1.21 (1.12-1.32)	1.21 (1.11-1.32)
Charlson Index		1.37 (1.19-1.57)	1.37 (1.19-1.57)	1.37 (1.19-1.57)
Time on dialysis pretransplant (per 1 yr increase)		1.05 (0.99-1.11)	1.05 (0.99-1.11)	1.05 (0.99-1.11)
Donor type; Living Deceased		0.51 (0.31-0.83) Reference	0.51 (0.31-0.84) Reference	0.45 (0.27-0.76) Reference
Donor age (per 5 year increase)		1.07 (1.00-1.13)	1.07 (1.00-1.13)	1.07 (1.00-1.13)
Time era of transplant: 2000-2004 2005-2009 2009-2013		Reference 1.16 (0.74-1.83) 0.72 (0.45-1.15)	Reference 1.08 (0.66-1.77) 0.62 (0.32-1.18)	Reference 1.08 (0.65-1.71) 0.62 (0.32-1.20)
Centre[1] 1 2 3 4 5	0.72 (0.51-1.02) 1.06 (0.72-1.55) 1.29 (0.92-1.82) 1.00 (0.70-1.43) 1.01 (0.73-1.39)	0.75 (0.53-1.07) 1.10 (0.75-1.62) 1.21 (0.85-1.73) 0.95 (0.67-1.36) 1.04 (0.75-1.45)	0.65 (0.38-1.12) 0.98 (0.68-1.42) 1.31 (0.86-1.99) 0.98 (0.68-1.42) 0.96 (0.64-1.44)	0.78 (0.43-1.42) 0.84 (0.57-1.24) 1.43 (0.92-2.21) 0.84 (0.57-1.24) 0.85 (0.56-1.31)
Centre Volume (per 25 patients)			1.14 (0.79-1.63)	1.17 (0.81-1.67)
Average provider experience (per 5 years experience)				1.02 (0.90-1.16)
Provider type: Urologist General Surgeon Fellow Nephrologist Internist				 1.12 (0.79-1.58) 0.80 (0.56-1.15) 0.86 (0.63-1.17) 0.81 (0.61-1.05) 0.83 (0.93-1.47)

The above models used backwards elimination process to reduce the number of covariates included given the smaller number of events and ability to test for associations. Centre[1] -the reference is the average across all centres.

Table 5 .Centre-specific patient hazard ratios from multivariable Cox Proportional hazards regression analysis for graft loss censoring at time of death over full follow up (total number of events=807)

	Unadjusted (n=5037)	Adjusting for patient case mix only (n=5037)	Adjusting for patient case mix and centre volume (n=5037)	Adjusting for patient case mix, centre volume and provider characteristics
Covariate		**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Age, (per 5 year increase)		0.92 (0.89-0.95)	0.92 (0.89-0.95)	0.92 (0.89-0.95)
Sex ; Female Male		1.08 (0.93-1.24) Reference	1.07 (0.93-1.24) Reference	1.07 (0.92-1.23) Reference
Race; Caucasian African Asian Other[1]		1.13 (0.90-1.44) 1.31 (0.96-1.77) 1.19 (0.86-1.65) Reference	1.13 (0.89-1.43) 1.30 (0.96-1.77) 1.19 (0.86-1.65) Reference	1.14 (0.90-1.45) 1.32 (0.97-1.80) 1.18 (0.85-1.65) Reference
Cause of ESRD: GN Diabetes Cystic RVD Other		0.93 (0.75-1.16) 0.86(0.66-1.13) 0.69 (0.52-0.91) 0.96 (0.72-1.27) Reference	0.93 (0.75-1.16) 0.86(0.66-1.13) 0.69 (0.52-0.91) 0.96 (0.72-1.27) Reference	0.94 (0.76-1.17) 0.87 (0.66-1.14) 0.69 (0.52-0.91) 0.97 (0.73-1.28) Reference
BMI		1.02 (1.00-1.03)	1.02 (1.00-1.03)	1.02 (1.00-1.03)
Charlson Index		1.13 (1.06-1.21)	1.13 (1.06-1.21)	1.13 (1.06-1.21)
Preemptive transplant Pretransplant dialysis[2]		0.77 (0.56-1.05) Reference	0.77 (0.56-1.05) Reference	0.76 (0.56-1.05) Reference
Time on dialysis pretransplant (per 1 yr increase)		1.03 (1.00-1.06)	1.03 (1.00-1.06)	1.03 (1.00-1.06)
Donor type; Living Deceased		0.73 (0.61-0.87)	0.73 (0.61-0.87)	0.72 (0.60-0.86)
Donor age (per 5 year increase)		1.06 (1.04-1.09)	1.06 (1.04-1.09) p<0.0001	1.06 (1.04-1.09)
Time era of transplant: 2000-2004 2005-2009 2009-2013		Reference 1.09 (0.92-1.29) 0.86 (0.69-1.05)	Reference 1.14 (0.95-1.37) 0.98 (0.75-1.29)	Reference 1.12 (0.92-1.35) 0.96 (0.72-1.28)

Centre[3] 1	1.09 (0.97-1.24)	1.10 (0.97-1.25)	1.22 (1.01-1.47)	1.14 (0.93-1.40)
2	0.76 (0.64-0.92)	0.78 (0.65-0.93)	0.72 (0.58-0.89)	0.72 (0.58-0.90)
3	1.24 (1.08-.143)	1.18 (1.01-1.37)	1.13 (0.96-1.33)	1.14 (0.96-1.36)
4	0.88 (0.76-1.03)	0.89 (0.76-1.04)	0.87 (0.74-1.02)	0.90 (0.76-1.07)
5	1.09 (0.96-1.24)	1.11 (0.97-1.28)	1.16 (1.00-1.35)	1.18 (1.00-140)
Centre Volume: (per 25 patients)			0.90 (0.78-1.04)	0.91 (0.79-1.05)
Average provider experience (per 5 years experience)				1.05 (1.00-1.11)
Provider Type:				
Urologist				1.02 (0.79-1.32)
General Surgeon				1.04 (0.79-1.36)
Fellow				1.20 (0.93-1.54)
Nephrologist				0.98 (0.78-1.23)
Internist				0.99 (0.67-1.45)

Other[1] includes Aboriginal, Indian subcontinent, Pacific Islander,other/Multiracial.

Pretransplant dialysis[2] includes both peritoneal dialysis and hemodialysis.

Centre[3] -the reference is the average across all centres.

Abbreviations: ESRD, end stage renal disease; GN, glomerulonephritis; RVD, renal vascular disease; BMI, body mass index

Table 6. Centre-specific hazard ratios from multivariable Cox Proportional hazards regression analysis for total mortality over full follow up (total number of events=915)

	Unadjusted (n=5037)	Adjusting for patient case mix only (n=5037)	Adjusting for patient case mix and centre volume (n=5037)	Adjusting for patient case mix, centre volume and provider characteristics
Covariate		**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Age, (per 5 year increase)		1.28 (1.24-1.32)	1.28 (1.24-1.32)	1.28 (1.24-1.32)
Sex ; Female		0.85 (0.73-0.98)	0.85 (0.73-0.98)	0.85 (0.73-0.98)
Male		Reference	Reference	Reference
Race; Caucasian		1.52 (1.19-1.95)	1.52 (1.19-1.95)	1.51 (1.18-1.94)
African		0.97 (0.66-1.42)	0.97 (0.66-1.42)	0.97 (0.66-1.42)
Asian		1.34 (0.94-1.92)	1.35 (0.94-1.93)	1.34 (0.94-1.92)
Other[1]		Reference	Reference	Reference
Cause of ESRD: GN		0.72 (0.58-0.89)	0.71 (0.58-0.89)	0.71 (0.58-0.89)
Diabetes		1.29 (1.02-1.63)	1.29 (1.02-1.63)	1.29 (1.02-1.63)
Cystic		0.62 (0.47-0.81)	0.62 (0.47-0.81)	0.62 (0.47-0.81)
RVD		0.95 (0.74-1.22)	0.95 (0.74-1.21)	0.95 (0.74-1.22)
Other		Reference	Reference	Reference
BMI		1.01 (0.99-1.03)	1.01 (0.99-1.03)	1.01 (0.99-1.03)
Charlson Index		1.19 (1.12-1.27)	1.19 (1.12-1.27)	1.19 (1.12-1.27)
Preemptive transplant		0.82 (0.58-1.16)	0.82 (0.58-1.16)	0.83 (0.59-1.17)
Pretransplant dialysis[2]		Reference	Reference	Reference
Time on dialysis pretransplant (per 1 yr increase)		1.07 (1.05-1.10)	1.07 (1.05-1.10)	1.07 (1.05-1.10)
Donor type; Living		0.86 (0.72-1.02)	0.86 (0.73-1.02)	0.85 (0.71-1.01)
Deceased		Reference	Reference	Reference
Donor age (per 5 year increase)		1.04 (1.02-1.07)	1.04 (1.02-1.07)	1.04 (1.02-1.07)
Time era of transplant: 2000-2004		Reference	Reference	Reference
2005-2009		0.87 (0.74-1.02)	0.85 (0.71-1.02)	0.84 (0.71-1.01)
2009-2013		0.72 (0.58-0.90)	0.69 (0.52-0.92)	0.68 (0.51-0.90)
Centre[3] 1	0.82 (0.73-0.93)	0.85 (0.75-0.97)	0.82 (0.69-0.99)	0.85 (0.70-1.04)

2	1.11 (0.96-1.27)	1.06 (0.92-1.22)	1.09 (0.91-1.30)	1.12 (0.93-1.35)
3	1.15 (1.01-1.31)	1.11 (0.97-1.29)	1.13 (0.97-1.32)	1.14 (0.98-1.33)
4	1.16 (1.02-1.32)	1.05 (0.92-1.19)	1.06 (0.92-1.21)	1.03 (0.89-1.19)
5	0.83 (0.73-0.94)	0.95 (0.83-1.09)	0.93 (0.80-1.09)	0.90 (0.76-1.05)
Centre Volume: (per 25 patients)			1.04 (0.90-1.20)	1.04 (0.90-1.21)
Average provider experience (per 5 years experience)				0.99 (0.95-1.04)
Provider Type:				
Urologist				0.96 (0.76-1.22)
General Surgeon				0.87 (0.68-1.11)
Fellow				1.04 (0.79-1.35)
Nephrologist				0.89 (0.68-1.11)
Internist				0.95 (0.67-1.35)

Other[1] includes Aboriginal, Indian subcontinent, Pacific Islander,other/Multiracial.

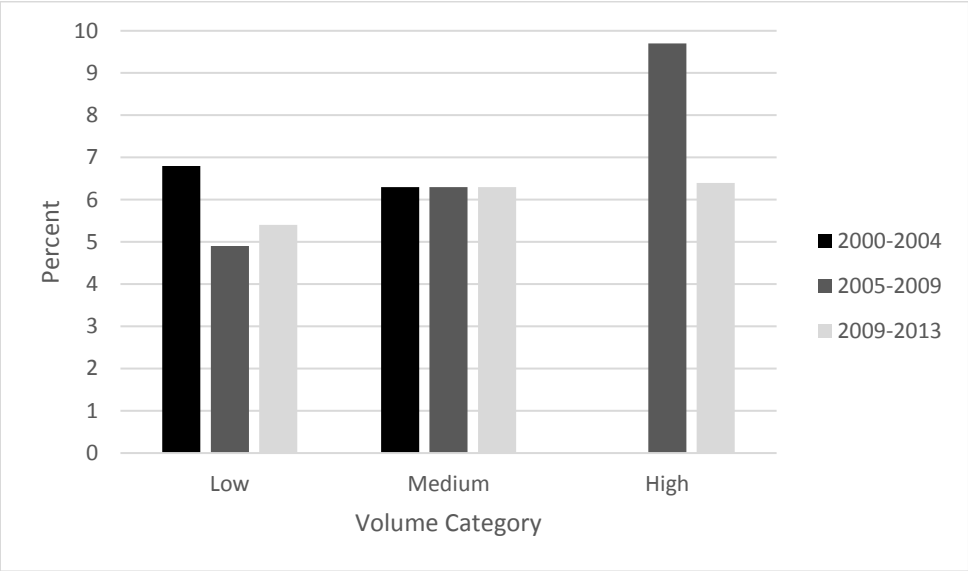
Pretransplant dialysis[2] includes both peritoneal dialysis and hemodialysis.

Centre[3] -the reference is the average across all centres.

Abbreviations: ESRD, end stage renal disease; GN, glomerulonephritis; RVD, renal vascular disease; BMI, body mass index

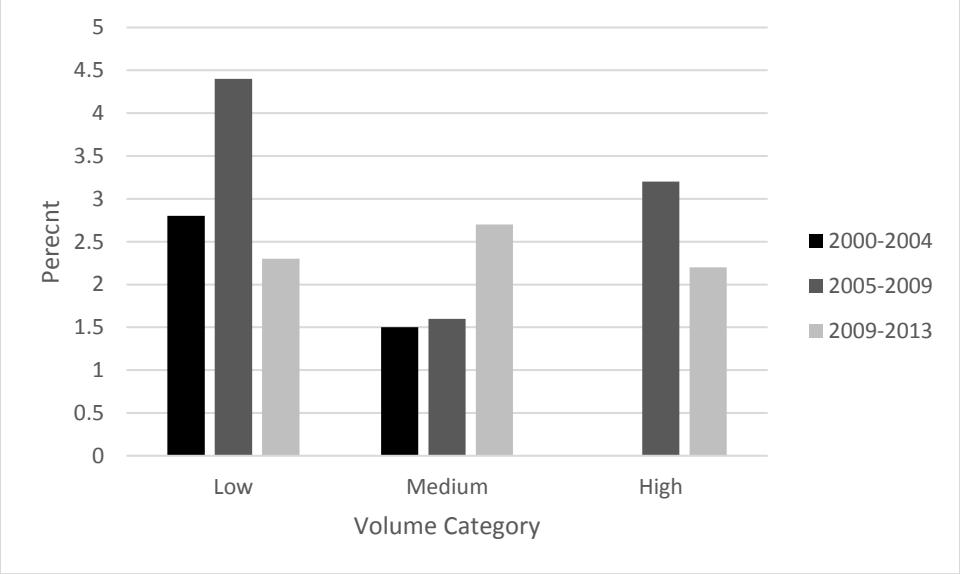
Figure 1. Percentage of events at 1 year post-transplant by volume category and time era

1a Graft loss censoring for death



Low volume <60 transplants per year; Medium Volume 60-87 transplants per year; High Volume ≥87 transplants per year

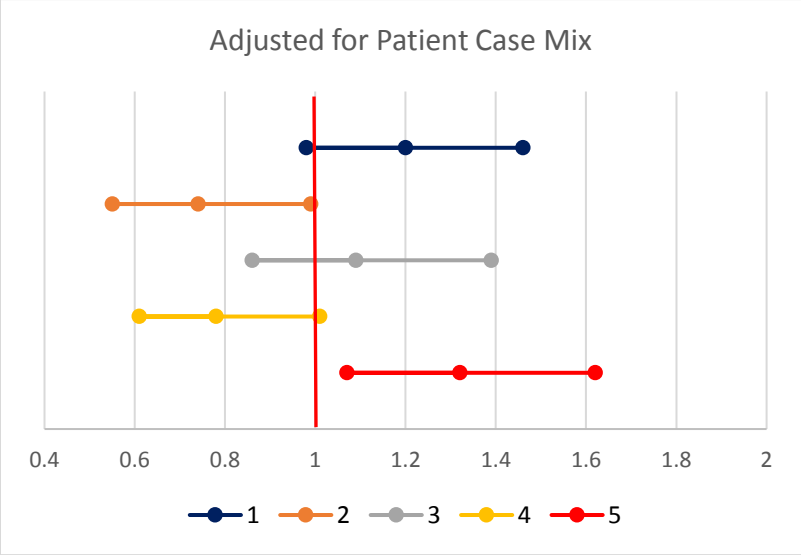
1b Total Mortality



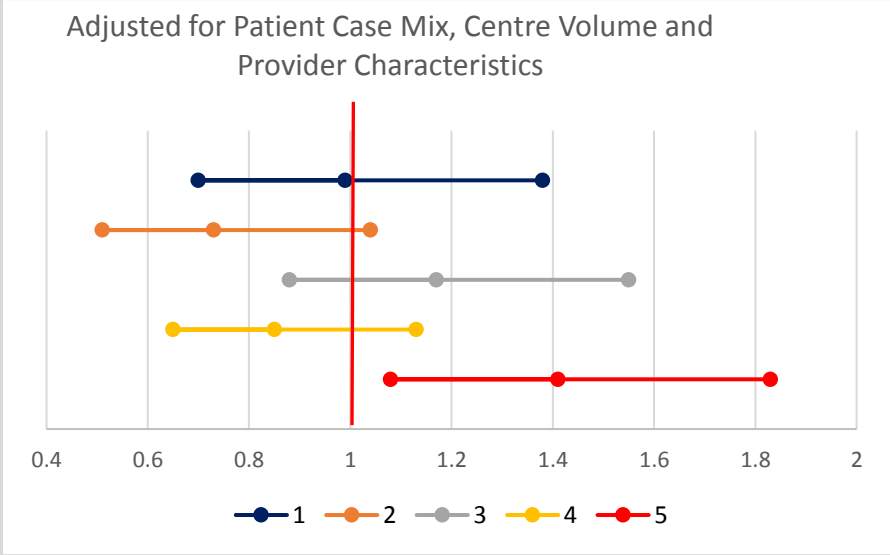
Low volume <60 transplants per year; Medium Volume 60-87 transplants per year; High Volume ≥87 transplants per year

Figures 2a-d. Adjusted hazard ratios (HR) with 95% confidence intervals for each transplant centre at one year post transplantation.

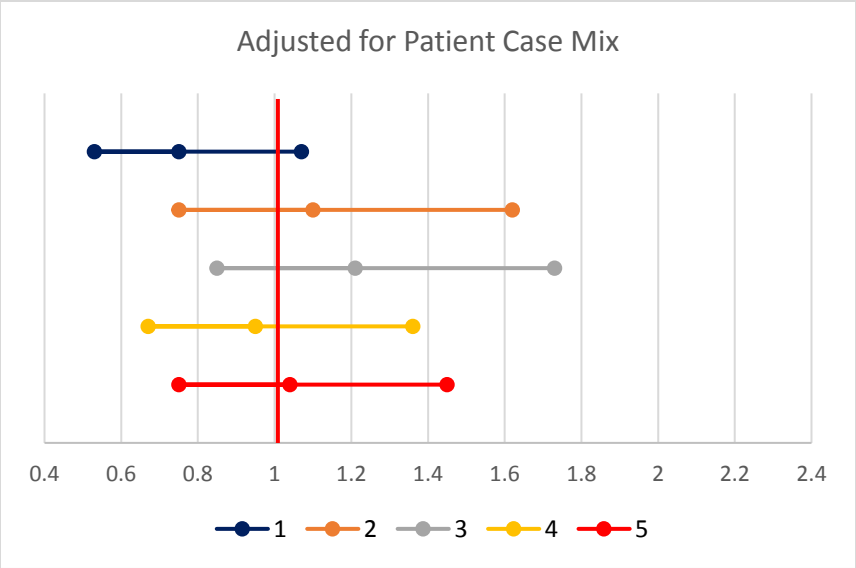
2A) Graft loss with follow-up times censored at the time of death



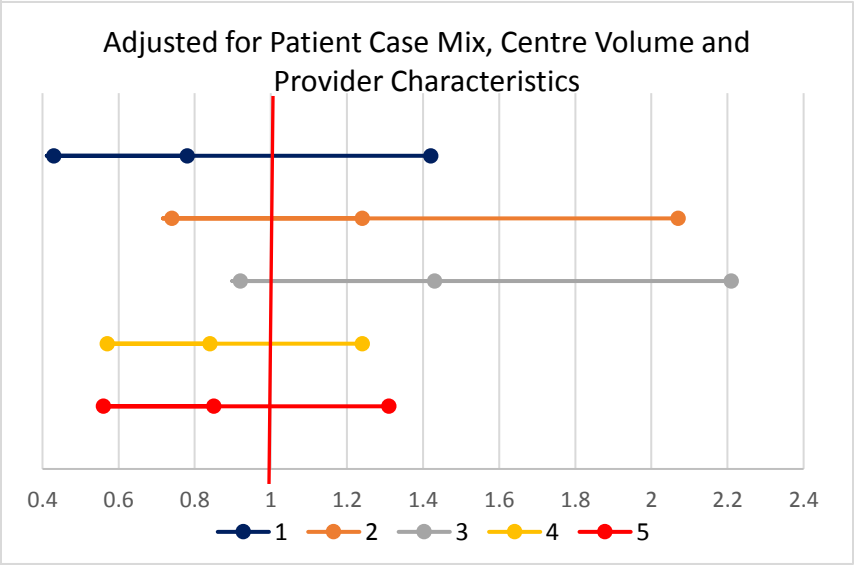
2B) Graft loss with follow-up times censored at the time of death



2C) Total mortality

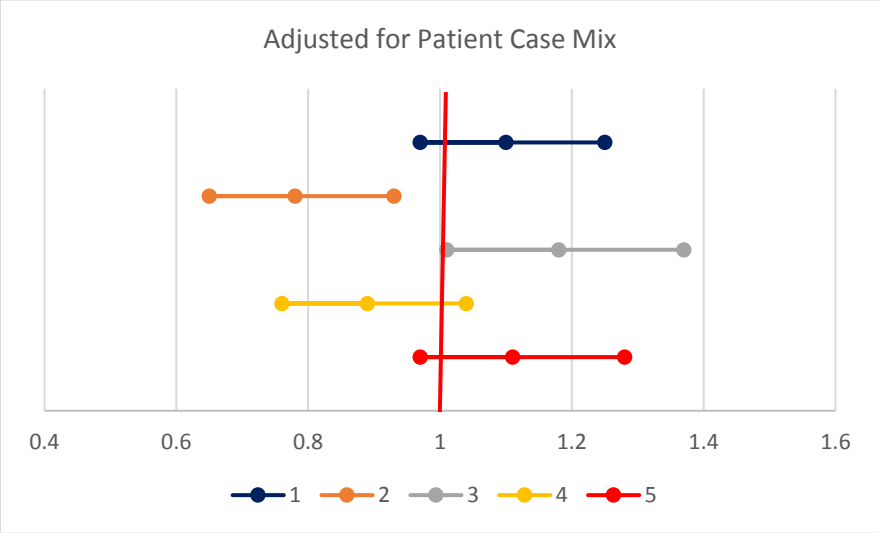


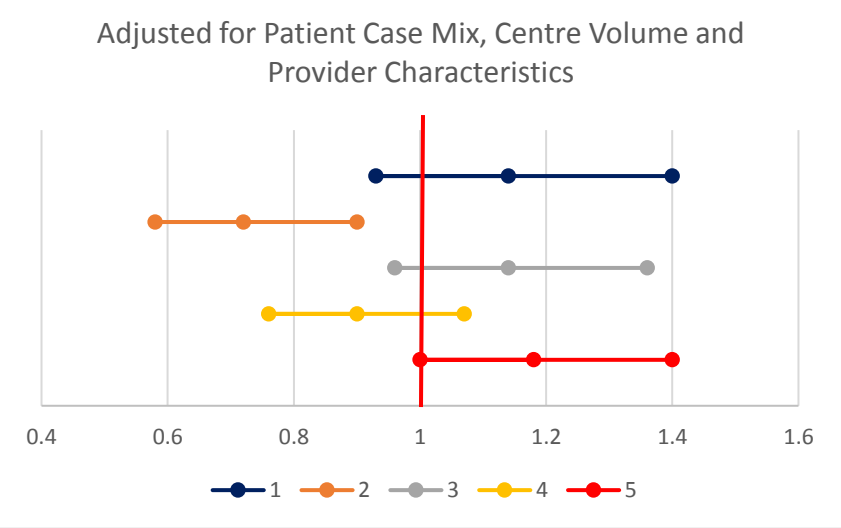
2D) Total mortality



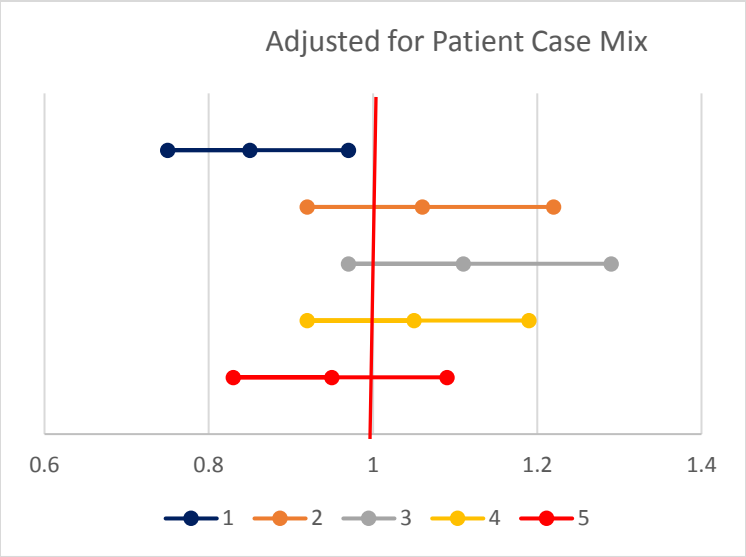
Case mix includes for recipient sex, race, age, body mass index, cause of end stage renal disease, Charlson index, dialysis required and time on dialysis pretransplant, donor type and donor age, and time period of transplant. Centre volume was defined as the total number of transplants performed at a given centre in the calendar year prior to a patient's transplant. Provider characteristics includes average provider experience and provider type. The color corresponding to the transplant centre in one figure corresponds with the matching colors in other figures. The reference line at 1 represents average performance across all centres. The outer dots represent 95% confidence intervals.

Figures 3a-d. Adjusted hazard ratios (HR) with 95% confidence intervals for each transplant centre at the end of study follow up.
3A) Graft loss with follow-up times censored at the time of death 3B) Graft loss with follow-up times censored at the time of death

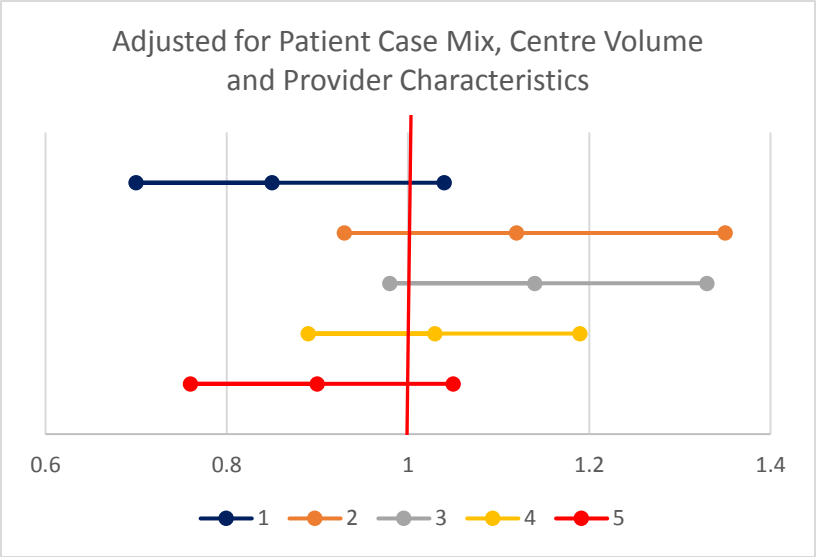




3C) Total mortality



3D) Total mortality



Case mix includes for recipient sex, race, age, body mass index, cause of end stage renal disease, Charlson index, dialysis required and time on dialysis pretransplant, donor type and donor age, and time period of transplant. Centre volume was defined as the total number of transplants performed at a given centre in the calendar year prior to a patient's transplant. Provider characteristics includes average provider experience and provider type. The color corresponding to the transplant centre in one figure corresponds with the matching colors in other figures. The reference line at 1 represents average performance across all centres. The outer dots represent 95% confidence intervals.

SUPPLEMENTAL TABLES

Table S1. Coding definitions for kidney transplant recipient demographic and comorbid conditions

Characteristic	Database	Codes Used
Baseline Characteristic of Transplant Recipients and Donors		
Age, Sex, Rural	RPDB	
Renal Transplant	CORR	Treatment_Code: 171 Transplanted_Organ_Type_Code[1-3]: 10, 11, 12, 18, 19
Date of transplant,	CORR	Treatment_date
Cause of primary renal disease	CORR	Glomerulonephritis/Auto-immune disease: 05, 06, 07, 08, 09, 10, 11, 12, 13, 14, 15, 16, 17, 19, 73, 74, 84, 85, 86, 88 Diabetes: 80, 81 Cystic kidney disease: 40, 41, 42, 43, 49 Renal vascular disease: 70, 71, 72, 79 Other: 20, 21, 22, 23, 24, 25, 29, 30, 31, 32, 33, 39, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 66, 78, 82, 83, 87, 89, 90, 91, 92, 93, 94, 95, 96, 97, 99 Unknown: 00, 98
Race	CORR	Caucasian: 01; Asian: 02; African-American: 03; Indian: 05 Other: 08, 09, 10, 11, 99 Unknown: 98
Body Mass Index	CORR	Initial_Height Initial_Weight
Dialysis modality	CORR	Hemodialysis: 111, 112, 113, 121, 122, 123, 131, 132, 133, 211, 221, 231, 311, 312, 313, 321, 322, 323, 331, 332, 333, 413, 423, 433, Peritoneal Dialysis:141, 151, 152, 241, 242, 251, 252, 443, 453

		Other – 060
Preemptive	CORR	
Time on dialysis	CORR	TRANSPLANT ([Treatment_Date] & [Treatment_Code]) – DIALYSIS ([Treatment Date] & [Treatment_Code])
Donor source	CORR	Living: 02, 03, 04, 05, 06, 07, 10, 12, 15 Deceased: 01 Unknown/Out-of-country transplant: 98
Charlson Comorbidity Index	CIHI-DAD	Charlson Macro
Peak Panel Reactive Antibody	CORR	PRA_1_PEAK_RESULT CORR
Transplant Centre	CORR	TREATMENT_FACILITY_NUM
Baseline Characteristic of Physicians		
Provider Type	IPDB	MAINSPEC*
Provider age	IPDB	BIRTHYR
Provider years since graduation	IPDB	GRADYR

Coding Definitions for Renal Recipient Outcomes

OUTCOMES	**Database**	**Codes Used**
Death	RPDB	
Dialysis post transplant	CIHI-DAD/OHIP	CCP: 5195, 6698 CCI: 1PZ21 OHIP fee: R849, G323, G325, G326, G860, G863, G866, G330, G331, G332, G861, G082, G083, G085, G090, G091, G092, G093, G094, G095, G096, G294, G295
	CORR CHRONIC	111,112,113,121,122,123,131,132,133,211,221,231, 311,312,313,321,

Repeat kidney transplant	CORR CHRONIC	Treatment_Code: 171 Transplanted_Organ_Type_Code[1-3]: 10, 11, 12, 18, 19

Abbreviations: RPDB: Registered Person's database, CORR: Canadian Organ Reporting Register, CIHI: Canadian Institute for Health information, DAD: Discharge abstract database, CCP; Canadian Classification of Diagnostic Therapeutic and Surgical Procedures, CCI; Canadian Classification of Interventions, IPDB: ICES physician database, TIA: thrombotic ischemic stroke.

Table S2. Observed survival rates (%) for each outcome of interest by volume category.

Primary Outcomes:			
Graft loss censoring	1 year	5 year	9 year
Volume tertile			
0 (n=1681)	94.0 ± 0.006	86.2 ± 0.009	80.4 ± 0.01
1 (n=1694)	93.7 ± 0.006	87.8 ± 0.008	81.3 ± 0.01
2 (n=1662)	92.5 ± 0.007	86.9 ± 0.009	81.3 ± 0.02 p=0.8
Total mortality	1 year	5 year	9 year
0	96.7 ± 0.004	87.1 ± 0.009	71.2 ± 0.01
1	98.1 ± 0.003	90.2 ± 0.008	78.7 ± 0.01
2	97.5 ± 0.004	91.5 ± 0.008	80.5 ± 0.02 p=0.0008
Additional Outcomes:			
Total graft loss	1 year	5 year	9 year
0	91.1 ± 0.007	77.2 ± 0.01	62.4 ± 0.01
1	92.2 ± 0.007	80.7 ± 0.01	68.2 ± 0.01
2	90.3 ± 0.007	79.4 ± 0.01	70.1 ± 0.02 p=0.03
Death with graft function	1 year	5 year	9 year
0	96.9 ± 0.004	89.6 ± 0.008	77.6 ± 0.01
1	98.4 ± 0.003	91.9 ± 0.007	83.9 ± 0.01
2	97.7 ± 0.004	91.4 ± 0.008	86.3 ± 0.02 p=0.0003

Volume Tertiles: 0 (n=1663) 12.6± 2.5 (range is 5 -16.3); 1 (n=1670) 19.9 ± 2.1 (range is 16.5 – 23.5); 2 (n=1682) 30.8 ± 5.5 (range is 23.6 – 47.7)

We report 9 year observed survival rates as one volume category only had 9 years of data.

Table S3. Observed survival rates (%) for each outcome of interest by average provider experience category.

Primary Outcomes:			
Graft loss censoring	1 year	5 year	10 year
Average experience tertile			
0 (n=1663)	93.9 ± 0.006	87.2 ± 0.009	77.3 ± 0.02
1 (n=1670)	93.3 ± 0.006	87.1 ± 0.009	80.1 ± 0.01
2 (n=1682)	93.1 ± 0.006	86.7 ± 0.009	78.1 ± 0.01 P=0.56
Total mortality			
0	96.9 ± 0.004	87.7 ± 0.009	69.9 ± 0.02
1	97.3 ± 0.004	88.9 ± 0.009	72.0 ± 0.02
2	98.1 ± 0.003	89.7 ± 0.008	74.4 ± 0.01 P=0.1
Additional Outcomes:			
Total graft loss	1 year	5 year	10 year
0	91.3 ± 0.007	78.6 ± 0.01	58.1 ± 0.02
1	91.0 ± 0.007	79.0 ± 0.01	62.9 ± 0.02
2	91.4 ± 0.007	79.7 ± 0.01	63.3 ± 0.02 P=0.26
Death with graft function	1 year	5 year	10 year
0	97.3 ± 0.004	90.1 ± 0.008	75.1 ± 0.02
1	97.6 ± 0.004	90.7 ± 0.008	78.5 ± 0.02
2	98.2 ± 0.003	91.9 ± 0.007	81.0 ± 0.01 p=0.01

Average experience Tertiles: 0 (n=1663) 12.6± 2.5 (range is 5 -16.3); 1 (n=1670) 19.9 ± 2.1 (range is 16.5 – 23.5); 2 (n=1682) 30.8 ± 5.5 (range is 23.6 – 47.7)

We report 9 year observed survival rates as one volume category only had 9 years of data.

Table S4.Centre-specific patient case mix hazard ratios from multivariable Cox Proportional hazards regression analysis for total graft loss at 1 year post transplant (Number of events =442)

	Adjusting for patient case mix only (n=5037)	Adjusting for patient case mix and centre volume (n=5037)	Adjusting for patient case mix, centre volume and provider characteristics
Covariate			
Age, (per 5 year increase)	1.01 (0.97-1.05)	1.01 (0.97-1.05)	1.01 (0.97-1.05)
Sex ; Female	1.07 (0.88-1.30)	1.07 (0.88-1.30)	1.07 (0.88-1.30)
Male	Reference	Reference	Reference
Race; Caucasian	1.48 (1.06-2.05)	1.48 (1.06-2.05)	1.50 (1.08-2.08)
African	1.18 (0.76-1.84)	1.18 (0.76-1.84)	1.19 (0.77-1.86)
Asian	1.26 (0.80-1.98)	1.26 (0.81-1.98)	1.26 (0.80-1.98)
Other[1]	Reference	Reference	Reference
Cause of ESRD: GN	0.92 (0.69-1.24)	0.92 (0.69-1.24)	0.92 (0.69-1.24)
Diabetes	0.78 (0.55-1.10)	0.78 (0.55-1.10)	0.79 (0.56-1.13)
Cystic	0.65 (0.45-0.96)	0.65 (0.45-0.96)	0.67 (0.46-0.97)
RVD	0.79 (0.54-1.15)	0.79 (0.54-1.15)	0.83 (0.57-1.20)
Other	Reference	Reference	Reference
BMI	1.01 (0.99-1.03)	1.01 (0.99-1.03)	1.01 (0.99-1.03)
Charlson Index	1.16 (1.06-1.27)	1.16 (1.06-1.27)	1.16 (1.06-1.27)
Preemptive transplant	0.52 (0.29-0.91)	0.52 (0.29-0.91)	0.51 (0.29-0.90)
Pretransplant dialysis[2]	Reference	Reference	Reference
Time on dialysis pretransplant (per 1 yr increase)	1.04 (1.00-1.07)	1.04 (1.00-1.07)	1.04 (1.00-1.07)
Donor type; Living	0.65 (0.51-0.83)	0.65 (0.51-0.83)	0.66 (0.50-0.83)
Deceased	Reference	Reference	Reference
Donor age (per 5 year increase)	1.04 (1.01-1.08)	1.05 (1.01-1.08)	1.05 (1.01-1.08)
Time era of transplant: 2000-2004	Reference	Reference	Reference
2005-2009	1.05 (0.83-1.34)	1.03 (0.79-1.33)	1.05 (0.81-1.38)
2009-2013	0.85 (0.66-1.08)	0.80 (0.56-1.13)	0.81 (0.56-1.17)

Centre 1	1.08 (0.91-1.29)	1.03 (0.79-1.35)	0.95 (0.71-1.28)
2	0.81 (0.64-1.03)	0.84 (0.63-1.12)	0.83 (0.61-1.11)
3	1.09 (0.89-1.34)	1.12 (0.89-1.41)	1.18 (0.93-1.51)
4	0.81 (0.65-0.99)	0.82 (0.66-1.02)	0.82 (0.65-1.04)
5	1.29 (1.08-1.55)	1.26 (1.02-1.55)	1.30 (1.03-1.63)
Centre Volume (per 25 patients)		1.05 (0.87-1.26)	1.04 (0.86-1.26)
Average provider experience (per 5 years experience)			1.04 (0.97-1.11)
Provider			
Urologist			0.94 (0.67-1.32)
General Surgeon			1.00 (0.69-1.45)
Fellow			0.97 (0.70-1.33)
Nephrologist			0.78 (0.58-1.05)
Internist			0.83 (0.49-1.40)

Other[1] includes Aboriginal, Indian subcontinent, Pacific Islander,other/Multiracial.

Pretransplant dialysis[2] includes both peritoneal dialysis and hemodialysis.

Centre[3] -the reference is the average across all centres.

Abbreviations: ESRD, end stage renal disease; GN, glomerulonephritis; RVD, renal vascular disease; BMI, body mass index

Table S5.Centre-specific hazard ratios from multivariable Cox Proportional hazards regression analysis of death with graft function (total number of events=113)

Outcome of interest (Number of events)	**Adjusting for patient case mix only (n=5037)**	**Adjusting for patient case mix and centre volume (n=5037)**	**Adjusting for patient case mix, centre volume and provider characteristics (n=5037)**
Covariate	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Age, (per 5 year increase)	1.20 (1.10-1.32)	1.20 (1.10-1.32)	1.21 (1.11-1.32)
Charlson Index	1.39 (1.20-1.61)	1.39 (1.20-1.61)	1.38 (1.19-1.60)
Donor type; Living	0.44 (0.27-0.73)	0.45 (0.27-0.73)	0.39 (0.23-0.65)
Deceased	Reference	Reference	Reference
Donor age (per 5 year increase)	1.05 (0.98-1.12)	1.05 (0.98-1.12)	1.07 (1.00-1.13)
Time era of transplant: 2000-2004	Reference	Reference	Reference
2005-2009	1.06 (0.66-1.70)	1.04 (0.62-1.74)	1.05 (0.61-1.79)
2009-2013	0.66 (0.40-1.07)	0.62 (0.31-1.23)	0.63 (0.31-1.26)
Centre[1] 1	0.76 (0.52-1.10)	0.72 (0.41-1.26)	0.85 (0.40-1.60)
2	1.04 (0.69-1.57)	1.08 (0.64-1.83)	1.11 (0.64-1.90)
3	1.08 (0.75-1.58)	1.12 (0.72-1.73)	1.21 (0.77-1.91)
4	0.95 (0.65-1.39)	0.96 (0.65-1.43)	0.83 (0.55-1.24)
5	1.23 (0.88-1.73)	1.20 (0.80-1.80)	1.06 (0.69-1.64)
Centre Volume (per 25 patients)		1.05 (0.72-1.53)	1.08 (0.74-1.58)
Average provider experience (per 5 years experience)			1.03 (0.90-1.18)
Provider type:			
Urologist			1.54 (0.71-3.30)
General Surgeon			0.76 (0.35-1.64)
Fellow			0.73 (0.37-1.41)
Nephrologist			0.65 (0.37-1.14)
Internist			0.69 (0.25-1.95)

The above models used backwards elimination process to reduce the number of covariates included given the smaller number of events and ability to test for associations.

Centre[1] -the reference is the average across all centres.

Table S6.Centre-specific patient case mix hazard ratios from multivariable Cox Proportional hazards regression analysis for total graft loss for full follow up (number of events =1489)

	Adjusting for patient case mix only (n=5037)	Adjusting for patient case mix and centre volume (n=5037)	Adjusting for patient case mix, centre volume and provider characteristics
Covariate			
Age, (per 5 year increase)	1.07 (1.04-1.09)	1.07 (1.04-1.09)	1.07 (1.04-1.09)
Sex ; Female	0.95 (0.85-1.06)	0.95 (0.85-1.06)	0.95 (0.85-1.06)
Male	Reference	Reference	Reference
Race; Caucasian	1.35 (1.13-1.61)	1.35 (1.13-1.61)	1.35 (1.13-1.61)
African	1.19 (0.92-1.53)	1.19 (0.92-1.53)	1.19 (0.92-1.54)
Asian	1.24 (0.96-1.61)	1.24 (0.96-1.61)	1.23 (0.95-1.60)
Other[1]	Reference	Reference	Reference
Cause of ESRD: GN	0.85 (0.72-1.00)	0.85 (0.72-1.01)	0.85 (0.72-1.01)
Diabetes	1.08 (0.89-1.32)	1.08 (0.89-1.32)	1.08 (0.89-1.32)
Cystic	0.63 (0.51-0.78)	0.63 (0.51-0.78)	0.63 (0.51-0.78)
RVD	0.99 (0.81-1.21)	0.99 (0.81-1.21)	0.99 (0.81-1.21)
Other	Reference	Reference	Reference
BMI	1.01 (1.00-1.02)	1.01 (1.00-1.02)	1.01 (1.00-1.02)
Charlson Index	1.14 (1.09-1.20)	1.14 (1.09-1.20)	1.14 (1.09-1.20)
Preemptive transplant	0.82 (0.65-1.05)	0.82 (0.65-1.05)	0.82 (0.65-1.05)
Pretransplant dialysis[2]	Reference	Reference	Reference
Time on dialysis pretransplant (per 1 yr increase)	1.05 (1.03-1.07)	1.05 (1.03-1.07)	1.05 (1.03-1.07)
Donor type; Living	0.79 (0.69-0.90)	0.79 (0.69-0.90)	0.78 (0.68-0.90)
Deceased	Reference	Reference	Reference
Donor age (per 5 year increase)	1.04 (1.03-1.06)	1.04 (1.03-1.06)	1.04 (1.03-1.06)
Time era of transplant: 2000-2004	Reference	Reference	Reference
2005-2009	0.95 (0.84-1.08)	0.97 (0.84-1.11)	0.94 (0.82-1.09)
2009-2013	0.78 (0.67-0.91)	0.81 (0.66-0.99)	0.79 (0.63-0.98)

Centre: 1 2 3 4 5	0.95 (0.86-1.04) 0.93 (0.83-1.05) 1.12 (1.00-1.25) 0.98 (0.88-1.09) 1.03 (0.93-1.14)	0.97 (0.84-1.12) 0.91 (0.79-1.05) 1.11 (0.99-1.25) 0.97 (0.87-1.09) 1.04 (0.93-1.17)	0.96 (0.82-1.12) 0.93 (0.79-1.08) 1.12 (0.99-1.27) 0.98 (0.87-1.10) 1.03 (0.91-1.16)
Centre volume (per 25 patients)		0.97 (0.87-1.08)	0.98 (0.88-1.10)
Average provider experience (per 5 years experience)			1.02 (0.98-1.05)
Provider Type: Urologist General Surgeon Fellow Nephrologist Internist			 0.99 (0.83-1.20) 0.97 (0.80-1.18) 1.15 (0.95-1.40) 0.89 (0.76-1.04) 0.94 (0.72-1.24)

Other[1] includes Aboriginal, Indian subcontinent, Pacific Islander,other/Multiracial.

Pretransplant dialysis[2] includes both peritoneal dialysis and hemodialysis.

Centre[3] -the reference is the average across all centres.

Abbreviations: ESRD, end stage renal disease; GN, glomerulonephritis; RVD, renal vascular disease; BMI, body mass index

Table S7.Centre-specific patient case mix hazard ratios from multivariable Cox Proportional hazards regression analysis for death with graft function over full follow up (Number of events=Cannot report due to privacy rules)

	Adjusting for patient case mix only (n=5037)	Adjusting for patient case mix and centre volume (n=5037)	Adjusting for patient case mix, centre volume and provider characteristics (5037)
Covariate			
Age, (per 5 year increase)	1.33 (1.28-1.39) p<0.0001	1.33 (1.28-1.39) p<0.0001	1.34 (1.27-1.39) p<0.0001
Sex ; Female	0.82 (0.70-0.97) p=0.02	0.82 (0.70-0.97) p=0.02	0.83 (0.70-0.98) p=0.03
Male	Reference	Reference	Reference
Race; Caucasian	1.73 (1.27-2.37)	1.74 (1.27-2.37)	1.72 (1.26-2.35)
African	0.95 (0.59-1.53)	0.95 (0.59-1.54)	0.94 (0.58-1.52)
Asian	1.41 (0.92-2.17)	1.41 (0.92-2.17)	1.41 (0.91-2.16)
Other[1]	Reference p=0.12	Reference p=0.12	Reference p=0.12
Cause of ESRD: GN	0.73 (0.57-0.94)	0.73 (0.57-0.94)	0.73 (0.56-0.93)
Diabetes	1.39 (1.06-1.83)	1.39 (1.05-1.83)	1.38 (1.05-1.82)
Cystic	0.64 (0.47-0.89)	0.64 (0.47-0.88)	0.64 (0.46-0.88)
RVD	0.99 (0.74-1.33)	0.99 (0.74-1.33)	0.99 (0.74-1.33)
Other	Reference p=0.97	Reference p=0.96	Reference p=0.95
BMI	1.01 (0.99-1.02) p=0.40	1.01 (0.99-1.02) p=0.40	1.01 (0.99-1.02) p=0.40
Charlson Index	1.17 (1.08-1.25) p<0.0001	1.16 (1.08-1.25) p<0.0001	1.16 (1.08-1.25) p<0.0001
Preemptive transplant	0.92 (0.63-1.34) p=0.66	0.92 (0.63-1.34) p=0.66	0.93 (0.64-1.37) p=0.66
Pretransplant dialysis[2]	Reference	Reference	Reference
Time on dialysis pretransplant (per 1 yr increase)	1.07 (1.04-1.10) p<0.0001	1.07 (1.04-1.10) p<0.0001	1.07 (1.05-1.10) p<0.0001
Donor type; Living	0.86 (0.71-1.05) p=0.14	0.87 (0.71-1.06) p=0.16	0.87 (0.71-1.06) p=0.16
Deceased	Reference	Reference	Reference
Donor age (per 5 year increase)	1.03 (1.01-1.06) P=0.01	1.03 (1.01-1.06) P=0.01	1.03 (1.01-1.06) P=0.01
Time era of transplant: 2000-2004	Reference	Reference	Reference
2005-2009	0.82 (0.68-0.99)	0.80 (0.65-0.98)	0.78 (0.63-0.97)
2009-2013	0.71 (0.55-0.91)	0.66 (0.48-0.90)	0.63 (0.45-0.88)
Centre 1	0.79 (0.68-0.92)	0.75 (0.60-0.93)	0.78 (0.62-0.99)
2	1.09 (0.93-1.29)	1.15 (0.93-1.42)	1.18 (0.95-1.47)

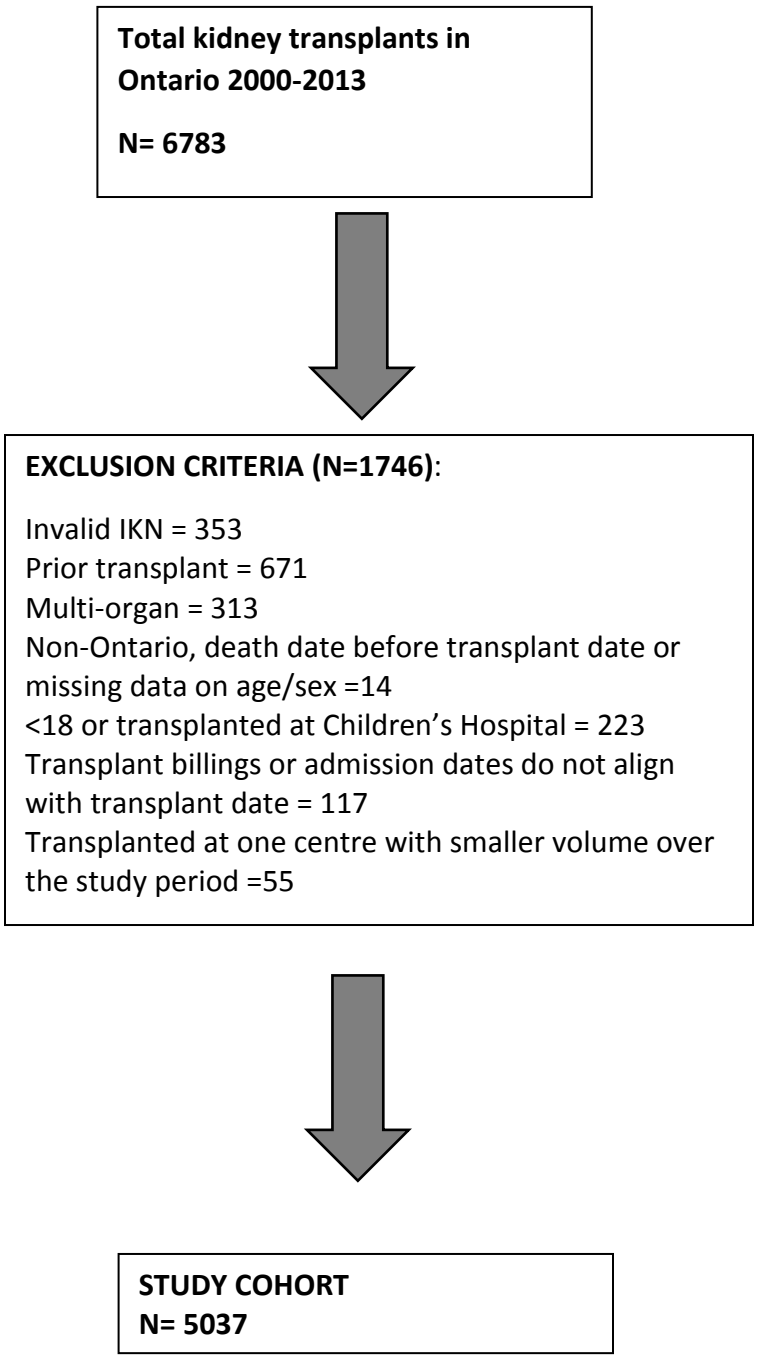
3	1.09 (0.92-1.29)	1.11 (0.93-1.33)	1.12 (1.08-1.17)
4	1.08 (0.93-1.25)	1.08 (0.93-1.25)	1.07 (0.91-1.26)
5	0.98 (0.84-1.15)	0.95 (0.80-1.13)	0.90 (0.75-1.09)
Centre Volume: (per 25 patients)		1.07 (0.90-1.26)	1.08 (0.84-1.29)
Average provider experience (per 5 years experience)			0.98 (0.92-1.03)
Provider Type:			
Urologist			0.96 (0.73-1.27)
General Surgeon			0.90 (0.67-1.20)
Fellow			1.07 (0.77-1.49)
Nephrologist			0.82 (0.65-1.04)
Internist			0.96 (0.65-1.42)

Other[1] includes Aboriginal, Indian subcontinent, Pacific Islander,other/Multiracial.

Pretransplant dialysis[2] includes both peritoneal dialysis and hemodialysis.

Abbreviations: ESRD, end stage renal disease; GN, glomerulonephritis; RVD, renal vascular disease; BMI, body mass index

Figure S1. Cohort Creation



CHAPTER 6 –DISCUSSION

Kidney transplantation is the optimal treatment for patients with end stage renal disease (ESRD). Transplant outcomes may be influenced by: patient risk factors, factors related to the provider caring for the patient, as well as centre related practices. In the United States, understanding differences in performance among many centres (with the objective of improving quality of care across centres) has become a priority especially in the field of transplant medicine. In Canada, while graft survival rates are documented and published, such rates are not usually adjusted for patient factors; furthermore, potential transplant centre differences have not been examined.

The overall aim of this thesis was to examine centre variation post kidney transplantation in the province of Ontario, Canada; and to understand which factors beyond patient related variables may explain centre variability. This thesis consisted of two parts. The first included a systematic review of the literature published to date on this topic. The second part included analysis of a study cohort consisting of primary solitary kidney transplant recipients in Ontario using linked administrative database to address the following objectives: i) describe differences at the patient, centre and provider level among Ontario kidney transplant centres, ii) compare observed graft and patient survival rates at end of follow up, iii) determine which patient factors are associated with increased graft loss and patient mortality, iv) assess whether significant variation in graft and patient survival rates persist after adjusting for patient characteristics and v) determine whether centre volume and/or provider characteristics (such as: type of provider and provider experience) are associated with graft and patient outcomes and explain centre variation.

6.1 *Summary of Research findings*

The first study of this thesis entitled "*Centre Variation and the Effect of Centre and Provider Characteristics on Clinical Outcomes in Kidney Transplantation: A Systematic Review"* has been accepted for publication in the Canadian Journal of Kidney Health and Disease. This systematic review summarized the literature on centre effect in kidney transplantation published from inception until June 2016. In this manuscript we included 24 observational studies, 15 of which assessed centre variation in graft survival and 7 of which assessed centre variation in patient survival. Seventeen of the included studies assessed for a volume-outcome association. Due to heterogeneity in the included studies we were unable to meta-analyze our data, nevertheless, the findings from the systematic review are important because they demonstrate strong evidence supporting the phenomenon of centre variation unaccounted for by case-mix. Further our systematic review highlights the strong need for future research into this area of transplant medicine.

The second study of this thesis entitled "*Case-mix, patterns of care and in-patient outcomes among Ontario renal transplant centres: a population-based study"* is in press at the Canadian Journal of Kidney Health and Disease. This study included a cohort of over 5000 kidney transplant recipients transplanted across 5 Ontario centres between January 1st 2000 to December 31st 2013. It describes differences across centres at the patient level and at the centre and provider levels. A majority of patient outcomes, including: length of initial transplant admission, proportion of patients requiring in-hospital dialysis and proportion of patients requiring intensive care unit admission during their initial post-transplant period varied

significantly across the centres. Additionally, to compare case-mix adjusted differences in the length of stay across centres, multivariable Cox proportional hazards regression was used. We found that the variation seen across centres in the length of stay was not explained by patient case mix, centre volume or provider characteristics alone. This study demonstrates that Ontario transplant centres vary substantially in the type of patient deemed acceptable for transplantation.

The third study of this thesis is titled "*Graft and Patient Survival Rates Across Kidney Transplant Programs in Ontario, Canada accounting for Patient Case mix*". This study examined variation in observed survival rates and case mix-adjusted centre specific hazard ratios across kidney transplant centres in Ontario. The follow-up period was long including patients contributing data up to 15 years post kidney transplantation. This study found that observed one, five and ten year graft and patient survival rates varied across transplant centres. Cox proportional hazards regression was used to obtain HRs for each centre relative to the average across all centres. After adjusting for patient case mix, centre-specific HRs for death with graft function varied substantially from a low of 0.51 (95% CI 0.20-1.33) (i.e., the centre hazard was 49% below the average) to a high of 1.24 (95% CI 0.88-1.44) (i.e., the centre hazard was 24% above the average), p=0.17; HRs were similarly variable for total mortality 0.74 (95% CI 0.38-1.45) to a high of 1.18 (95% CI 0.91-1.43),p=0.38. Centre HRs varied to a lesser degree for total graft loss, ranging from a minimum of 0.85 (95% CI 0.54-1.35) to a maximum of 1.16 (95% CI 1.00-1.35),

p=0.50. These findings imply that additional factors potentially at the centre or provider level, may be contributing to these differences.

The fourth study of this thesis, titled "*Variation in Post-kidney transplantation outcomes between centres is not due to centre volume and provider characteristics*" examined centre variation across transplant centres accounting for patient factors, centre volume and provider characteristics (years of experience and type). Outcomes were assessed at 1 year post transplantation and at the end of study follow up. At one year follow-up, after adjusting for patient case mix, as well as centre and provider factors, hazard ratios for graft loss censored at the time of death ranged between 0.73 (95% CI 0.51-1.04) and 1.41 (95% CI 1.08-1.83) across centres, and for total mortality between 0.78 (95% CI 0.43-1.42) and 1.43 (0.92-2.21). At the end of total follow up, after adjusting for patient case mix, as well as centre and provider factors, HRs for graft loss censoring at time of death ranged from 0.72 (95% CI 0.58-0.90) to 1.18 (95% CI 1.00-1.40), and for total mortality from 0.85 (95%CI 0.70-1.04) to 1.14 (95%CI 0.98-1.33). Centre volume and provider type were not independently associated with any outcome. Despite the fact that the overall p values for centre hazard ratios were not significant after adjustment for casemix, centre volume and provider factors, the confidence intervals were wide and contained some clinically relevant values in terms of variation. This suggests that more studies should be performed to understand the importance and determinants of centre variation in graft outcomes.

6.2 *Overall strengths and limitations of this thesis*

This thesis has several strengths and limitations specific to each study which have been outlined within each manuscript. The following section presents the overall strengths and limitations of the thesis work overall.

The strengths of the systematic review (manuscript 1) lie in its robust methods producing a summary of the totality of the existing topical literature leading to the important conclusion that there remains a strong need for more robust and updated studies evaluating the centre effect in kidney transplantation. The main limitations relate to our inability to pool and meta-analyze data across studies due to the significant clinical, methodological, and analytical heterogeneities observed. For example, explanatory variables, such as centre volume, differed in their definition across studies (using different categorical volume thresholds). Not all of the studies adjusted for patient case mix or when adjustment was performed, different patient and recipient factors were used (with adjusting performed independently for age and sex or improper definitions being used for comorbidities) allowing for residual confounding. The length of study follow up time and outcome definition endpoints varied across studies and thus we were unable to assess centre variation in longer term graft and patient survival rates.

There are several strengths to our population based cohort study (manuscripts 2-4) that warrant mention. This large analysis is the first Canadian study to examine centre variation post kidney transplantation in a cohort of patients who were transplanted exclusively beyond the year 2000. This is relevant given that short term patient and graft survival rates have ameliorated with improvements in the newer immunosuppressive therapies. We included a

large sample size of patients who had more than ten years of follow up enabling assessment at 1-, 5-, and 10 years post-transplant. This is important as a prior Canadian study found greater variation in survival rates across centres with increasing time from transplantation.[1] Our study had minimal loss to follow up (less than 1.5%), which is in contrast to prior studies examining centre variation which either have made no mention of percentage of patients lost to follow-up[1-4] or have had up to 20% attrition within the first year alone.[5] The data for our study was obtained from the Canadian Organ Replacement Registry (CORR) which is the national database for organ failure in Canada. The quality of the data collected has been compared with medical charts of patients and although it was found that co-morbid conditions were under-reported, the risks of mortality were similar in the database and charts. Furthermore CORR was found to have 98.5% agreement with Canadian institute for health information discharge abstract database (CIHI DAD) for transplant procedures.[6-8] As CORR includes information from patients transplanted from all centres in Ontario with universal health care the findings of this study are generalizable to the province and are free of selection bias.

Manuscripts 3 and 4 of this thesis used a different analytical approach to examine centre variation compared to what is reported in the American literature.[7-9] The Scientific Registry of Transplant Recipients (SRTR) uses adjusted standardized ratio (SR) of observed to expected events (graft losses and deaths) for each centre compared to the national average in order to identify centre outliers. Our study used multivariable Cox proportional hazards regression to obtain risk adjusted HR for each centre relative to the average across included transplant centres in order to identify between centre differences.[10] Given the small sample number of

transplant centres in Ontario we used fixed effects modelling and elected to evaluate the effect of each centre relative to the average. This methodology allows one to detect significant between centre differences that occur from an accumulation of small differences rather than identifying one outlier.[11,12]

There are several limitations to the population based cohort study of this thesis. Firstly, using retrospective data collected for administrative databases meant that not all potential covariates of interest were included in the datasets and therefore we were unable to adjust for potential confounding variables such as expanded criteria donor[13], ABO incompatibility[14] and cold ischemia times[15] which have been found to influence graft outcome. Furthermore, important clinical process variables such as immunosuppressive protocols that may vary slightly at a particular institution are not provided. Secondly, the estimate used for provider experience was taken as the average of all the physicians (surgical and medical) who completed a transplant specific billing code for each patient at the time of transplantation. This was necessary because it was impossible to identify one specific responsible physician and we were therefore unable to examine individual providers or provider to patient ratios. Thirdly, our inability to detect statistically significant differences for all outcomes of interest may relate to the small number of centres we included in our study. The small number of centres also precluded the use of random effects regression analysis and the quantification of between-centre differences using intra-centre correlation coefficients (i.e., the proportion of variation that is between centres). Lastly, but most importantly, there was a high percentage of missing data for certain covariates. For example, individual covariates had up to 16% missing data and

those with >20% missing data were necessarily excluded. This meant covariates such as cold ischemia time and panel reactive antibody which have been found to impact graft survival[15,16] could not be analyzed. In order to account for missing data in those covariates with <20% missing data, prior to performing our analyses we included a robust method of multiple imputation analysis using the fully conditional specification (FCS) method.[17] We conducted ten imputations using 100 burn-in iterations. Multivariable analyses were conducted for each imputation dataset and combined across datasets using Rubin's rules.[18] This is in contrast to prior studies which have typically used complete case analysis only.[1,19]

6.3 Implications for kidney transplant recipients in Ontario and future research

As the number of patients with ESRD in Ontario continues to increase and the number of available kidneys for transplantation remains steady, optimizing graft survival rates is essential. This thesis project found significant heterogeneity across kidney transplant centres in case mix, practice patterns, in-patient outcomes, and survival rates. While identification of patient factors that affect transplant outcomes is important, such factors are not always modifiable. Examining centre and provider level factors in association with transplant outcomes is important as some of these variables may be modifiable. For example, learning that centre transplant volume was not associated with graft or patient survival rates is a key finding and reassuring for patients.

While the results from this thesis are meaningful, they will need to be confirmed using a larger sample of transplant centres. Our inability to detect statistically significant variation for all included outcomes may have been related to the small number of transplant centres included.

It will therefore be important to conduct a similar study using data from all transplant centres across Canada. Furthermore, our inability to discern associations between centre volume or provider characteristics with one year outcomes may relate to the small number of events that occurred at that time point and a lack of statistical power. Therefore this relationship should also be assessed with larger sample size of patients. Alternatively, additional patient outcomes which occur closer to the time of kidney transplantation may be considered, such as readmission rates post transplantation.

Given the importance of improving long term graft survival in order to avoid the need for re-transplantation and increased risk of death associated with a failed graft, it is imperative to also examine differences in provider care post hospital discharge. For example, examining the associations between patient outcomes and the frequency of clinic visits after hospital discharge and location of transplant follow up care (transplant centre compared to the community) is important. This could be done through the use of the administrative databases utilized for this thesis project and it is our intention to perform such analyses as a next step. Additionally, conducting a prospective observational study in order to collect more detailed clinical data from centres across Ontario will provide important additional information.

6.4 Conclusions

In summary, our study found clinically significant variation in patient outcomes across Ontario transplant centres that is not explained by patient factors alone. Centre volume and provider experience are not significantly associated with graft and patient survival rates. This thesis

project was conducted using administrative databases and thus subject to limitations of retrospective data. It will be important to conduct a prospective observational study across Ontario collecting more detailed information on post transplantation care in order to better understand what may be contributing to centre variation.

6.5 REFERENCES

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