Predicting Graft Loss Following Acute Kidney Injury in Patients With a Kidney Transplant

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Synopsis:

Acute kidney injury (AKI), characterized by an abrupt loss of kidney function with retention of nitrogenous waste products, is common in the months to years following kidney transplantation and is associated with an increased risk of transplant failure (graft loss). Kidney transplant patients who experience graft loss and return to dialysis have an increased mortality risk and a lower quality of life. Research involving kidney transplant patients can prove challenging, as they are relatively small in number. To increase statistical power, researchers may utilize administrative databases. However, these databases are not designed primarily for research, and knowledge of their limitations is needed, as significant bias can occur. When using administrative databases to study AKI in kidney transplantation, the method used to define AKI should be carefully considered. The power of a study may be greatly increased if AKI can be accurately defined using administrative diagnostic codes because data on AKI will be universally available for all patients in the database. However, the methods by which diagnostic codes are assigned to a patient allow for error to be introduced. We confirmed that, when compared to the gold standard definition for AKI of a rise in serum creatinine, the diagnostic code for AKI has low sensitivity but high specificity in the kidney transplant population (the best performing coding algorithm had a sensitivity of 42.9% (95% CI 29.7, 56.8) and specificity of 89.3% (95% CI 86.2, 91.8) (Chapter 3). We therefore determined that for the study outlined in Chapter 4, defining AKI using diagnostic codes would significantly under-capture AKI and misclassify patients. We decided to define AKI using only serum creatinine criteria even though this would limit our sample size (creatinine data was only available for a subset of patients in the administrative databases). In Chapter 4, we derived an index score to predict the risk of graft loss in kidney transplant

patients following an admission to hospital with AKI. The index includes six readily available, objective clinical variables that increased the risk of graft loss: increasing age, increased severity of AKI (as defined by the AKIN staging system), failure to recover from AKI, lower baseline estimated glomerular filtration rate, increased time from kidney transplant to AKI admission, and deceased donor. The derived index requires validation in order to assess its utility in the clinical realm.

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Author Contributions:

The questions addressed in this thesis arose following initial discussions between Dr. Greg Knoll and me in 2013.

Manuscript one (Chapter 3):

Dr. A. Molnar is the principal author and Dr. G. Knoll the senior author (primary thesis supervisor) of this manuscript to be submitted for publication. Dr. C. van Walraven (thesis co-supervisor and ICES Scientist) contributed to the study design, analysis and drafting of the manuscript. Dr. D. Fergusson (thesis advisory committee) contributed to the study design, analysis and drafting of the manuscript. Dr. A. Garg is an ICES Scientist and lead of the ICES Kidney Dialysis Transplantation Program and contributed to the study design and drafting of the manuscript. E. McCarthur is an ICES analyst and contributed to the analysis and drafting of the manuscript.

Manuscript two (Chapter 4):

Dr. A. Molnar is the principal author and Dr. G. Knoll (primary thesis supervisor) is the senior author of this manuscript to be submitted for publication. Dr. C. van Walraven (thesis co-supervisor and ICES Scientist) contributed to the study design, analysis and drafting of the manuscript. Dr. D. Fergusson (thesis advisory committee) contributed to the study design and drafting of the manuscript. Dr. A. Garg is an ICES Scientist and lead of the ICES KDT Program and contributed to the study design and drafting of the manuscript. E. McCarthur is an ICES analyst and contributed to the analysis and drafting of the manuscript.

Dr. A. Molnar was involved in all aspects of both manuscripts from start to finish. Research Ethics Board Approval (REB) through the Ottawa Hospital Research Institute (OHRI), a data sharing agreement (DSA) between OHRI and the Institute for Clinical Evaluative Sciences (ICES) and ICES privacy approval were obtained by A. Molnar with Dr. Knoll as the Principal Investigator on the REB and DSA applications and Dr. van Walraven as the Principal Investigator on the ICES application (REB- 20130462-02H; DSA-agreement made June 10, 2014; ICES project number 2015 0901 054000). Dr. Knoll supervised all stages of both studies from start to completion and provided invaluable input and support into the design, analysis and discussion relating to the final manuscripts.

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Table of contents

List of Tables

Glossary:

1. Ace inhibitor……Angiotensin converting enzyme inhibitor
2. AKI……Acute kidney injury
3. AKIN……Acute Kidney Injury Network
4. ARB……..Angiotensin receptor blocker
5. ATN……..Acute tubular necrosis
6. BMI……Body mass index
7. CHF……Congestive heart failure
8. CIHI-DAD……..Canadian Institute for Health Information Discharge Abstract Database
9. CKD……Chronic kidney disease
10. CORR……Canadian Organ Replacement Registry
11. DGF……Delayed graft function
12. DSA……Donor specific antibody
13. eGFR……Estimated glomerular filtration rate
14. ESRD……End stage renal disease
15. HLA……Human leukocyte antigen
16. HR……Hazard ratio
17. HRA……..Health records abstractor
18. ICD……International Classification of Diseases
19. ICES……Institute for Clinical Evaluative Sciences
20. IQR……Interquartile range
21. NPV……Negative predictive value
22. OHDW……Ottawa Hospital Data Warehouse
23. PPV……Positive predictive value
24. PRA……Panel reactive antibody
25. RPDB……Registered Persons Database
26. SCr……Serum creatinine

Chapter 1: Thesis Introduction and Overview

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Problem:

Acute kidney injury (AKI) is characterized by an abrupt loss of kidney function with retention of nitrogenous waste products [1, 2]. The diagnosis of AKI, (formerly referred to as acute renal failure), is based on a specific increase in serum creatinine or a defined reduction in urine output [3, 4]. Studies in the general population have found that AKI affects between 2 and 12% of all hospitalized patients, [5-9] with an increased incidence in more recent years [10, 11, 7]. When AKI is severe enough to result in kidney failure, renal replacement therapy (RRT) (usually in the form of dialysis) is initiated [12, 4]. AKI requiring dialysis has been the focus of many studies in the general population, all of which show a heightened risk of subsequent poor long-term outcomes, specifically death and the development of chronic kidney disease [13-16]. There is now increasing evidence that less severe in-hospital AKI is also associated with an increased risk of poor long-term outcomes, even if kidney function fully recovers by the time of discharge [17-19, 5, 20, 21].

Compared to the general population, there is a paucity of published data on the incidence and consequences of AKI in the kidney transplant population. Patients with a kidney transplant comprise a relatively small subset of the population and are commonly excluded from studies in the general population. Only two studies to date have examined the consequences of AKI in kidney transplant patients, with both demonstrating an increased risk of kidney transplant failure (graft loss) associated with AKI [22, 23]. One study was small (289 patients) and the other study, although large (greater than 27,000 patients), used administrative diagnostic codes, as opposed to the gold standard of serum creatinine, to define AKI.

Purpose and Rationale:

There is an important need for research to better understand the consequences of AKI in the kidney transplant population. We sought to develop a foundation that would facilitate the study of AKI in kidney transplant patients using healthcare administrative databases and to identify risk factors for graft loss among kidney transplant patients with in-hospital AKI.

Healthcare administrative databases offer an efficient means of conducting large observational studies; however, the validity of such studies is largely dependent on the accuracy of the diagnostic codes used to study the outcome(s) or exposure(s) of interest [24-27]. Due to limited laboratory data availability (i.e. serum creatinine values), defining AKI using administrative diagnostic codes can greatly enhance the power of a study. This is demonstrated by the Mehrotra *et al*. study, which examined AKI in kidney transplant patients using diagnostic codes as opposed to serum creatinine values and achieved a sample size of more than 27,000 patients [22]. However, administrative diagnostic codes for AKI have never been validated in the kidney transplant population. To potentially enhance the power of our study and also to facilitate the conduct of future studies in this area, we sought to determine the validity of identifying kidney transplant patients with AKI using administrative database codes.

The overarching purpose of this thesis was to identify, among kidney transplant patients with in-hospital AKI, which patients are most likely to experience graft loss. If we are able to better identify high-risk patients, this will hopefully lead to improved outcomes

through closer follow-up, translational and basic science studies examining mechanisms of graft loss, and ultimately, interventions to improve graft survival.

Objectives:

There are two specific objectives of this thesis, which will be explored in two separate but related manuscripts in Chapters 3 and 4.

1. The first objective of this thesis was to determine the validity of the *International classification of diseases* (*ICD*)-9 and *ICD*-10 administrative diagnostic codes for in-hospital AKI in the kidney transplant population (Chapter 3).
2. The second objective of this thesis was to develop a risk score that would predict the probability of graft loss following an episode of in-hospital AKI in kidney transplant recipients (Chapter 4).

Overview of Submitted Thesis and Manuscripts:

We developed this thesis with the aim of examining AKI in kidney transplant patients using healthcare administrative databases. Outlined below are the stages of research in this thesis, coupled with the relevant chapters.

The first stage involved the creation of a solid foundation of background evidence. "Chapter 2-Background" provides the background information required by the reader to better understand the advantages and limitations of using healthcare administrative databases for clinical research, the epidemiology of AKI in kidney transplant patients, and the burden of graft loss.

Chapter 3-"Recognizing the limitations and potential for bias when using healthcare administrative databases for research: AKI defined by diagnostic codes", begins with a review of the validity of administrative diagnostic codes for AKI in the general and chronic kidney disease populations. This chapter also includes a paragraph summarizing the manuscript being submitted for publication, "Validity of the *International Classification of Diseases, Tenth Revision* code for acute kidney injury in kidney transplant patients during a hospital admission six months or greater post transplant". References will be made to supporting appendices. The manuscript in this chapter highlights the limited sensitivity of the *ICD-10* code for AKI in the kidney transplant population, identifying the potential for biased results due to under capturing of AKI by the *ICD-10* code.

Chapter 4-" Derivation of a risk score to predict graft loss following AKI in kidney transplant patients". This chapter begins with a literature review summarizing known risk factors for graft loss and the ability to accurately identify these risk factors within healthcare administrative databases. This chapter integrates the evidence gathered on the epidemiology of AKI and graft loss in the kidney transplant population, the advantages and limitations of healthcare administrative databases, and the limitations of the *ICD-10* AKI code described in Chapter 3, and applies the compilation of evidence towards the derivation of a risk score to predict graft loss in kidney transplant patients following in-hospital AKI. The risk score and the methods used to derive it are outlined in the manuscript to be submitted for publication entitled: "Derivation of a risk score to predict graft loss following acute kidney injury in patients with a kidney transplant". Additional appendices are included.

Chapter 5-“Discussion”, summarizes the thesis, reviews the novel concepts presented, limitations and provides an overall direction and next steps in the program of research.

Chapter 2: Background

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Introduction

As described in Chapter 1, there are relatively few studies published about AKI in the kidney transplant population. Research involving kidney transplant patients can be challenging given that they represent a small subset of the general population. However, healthcare administrative databases can facilitate clinical research involving kidney transplant patients and can serve as an efficient means to increase the power of studies. This current chapter highlights the limitations of using administrative databases for research; the epidemiology of AKI in kidney transplantation; and the clinical importance of graft loss.

Healthcare administrative data for clinical research

Healthcare administrative databases are created by the routine collection of information on a patient's healthcare encounter. The data collected include, for example, the dates of contact, type of surgery, admission diagnosis, and hospital length of stay. The data are collected primarily for management and accounting purposes, not research [24-26]. The administrative datasets for Ontario are contained at the Institute for Clinical Evaluative Sciences (ICES). Given that Ontario provides universal healthcare coverage for all its residents, data on each and every healthcare encounter in the province are housed at ICES. This allows for the availability of an enormous amount of data that can potentially be leveraged for large observational studies at a low cost. However, given that the data are not primarily collected for research purposes, one must be aware of some important limitations at the time of study design and when interpreting results [28, 29, 26].

Detailed clinical data, such as blood pressure values and physical exam findings, will not be found in health administrative datasets. Test results, such as diagnostic imaging and bloodwork, are also not typically available. However, if a laboratory database containing all laboratory test results for a hospital can be made available by download from the laboratory information system, these data can then be linked to the administrative data [25, 26]. One must be very familiar with the available data at the time of study design, as this greatly impacts the questions that can be posed as well as the quality of the study. If data on important confounding factors are missing, this will limit the validity of the results [29]. If data on a key exposure or outcome are missing or cannot be determined in a sufficiently accurate manner, administrative data may not be appropriate for the research question [28, 29].

The validity of laboratory databases is generally not of concern as one would expect the data to be highly accurate and complete [26]. Concerns regarding the validity of administrative data arise when diagnoses are represented by codes. There are several steps in the allocation of a diagnostic code where errors can be introduced, as described by van Walraven and Austin: "(1) the physician must recognize and diagnose the disease; (2) the physician must legibly document "disease X" in the chart; (3) this documentation must be recognized and correctly interpreted by the health records abstractor (HRA); and (4) the HRA must identify the proper code for disease X" [26]. An error at any one of these steps could result in a diagnosis being missed or incorrectly assigned [26]. In order to properly interpret results and to determine the degree of bias, the accuracy of the administrative diagnostic codes used in a study should be known [26, 27]. For this thesis, the use of codes

to diagnose AKI has the potential advantage of increasing power, but the validity of the codes was unknown.

AKI in the Kidney Transplant Population

Causes of AKI

AKI in a kidney transplant patient can occur for a variety of reasons, many of which are similar to those in the general population. Immediately after transplant, AKI can occur due to a lack of adequate blood perfusion to the transplanted kidney prior to and during the transplant surgery, resulting in organ damage (acute tubular necrosis (ATN)), referred to as delayed graft function. Other important factors, such as volume depletion and medication toxicity, are also potential causes of AKI immediately after transplant. AKI in kidney transplantation that occurs months to years after transplant is often due to factors that are also common in the general population, such as another illness or infection, or dehydration/volume depletion. There are also transplant-specific causes of AKI such as recurrence of the original cause of kidney failure in the transplant; obstruction related to surgical complications; or acute rejection, where the immune system of the transplant recipient attacks the transplanted kidney [30]. AKI immediately after transplant, as well as acute rejection and surgical complications, which more commonly occur in the weeks to months after kidney transplant, are not the focus of this thesis [30, 31]. This project focuses on AKI that occurs beyond the first 6 months post-transplantation.

Incidence and Consequences of AKI

Only three studies to date have examined AKI in kidney transplant patients [22, 23, 32]. Nakamura *et al.* studied AKI in an outpatient setting among 289 patients at least 3 months post-transplant and found an incidence of 20.4% over 5.5 years (AKI defined by a 50% or greater rise in serum creatinine above the baseline value). The most common cause of AKI was a bacterial infection [23]. Bardak *et al.* also found that infections were a common cause of AKI in kidney transplant patients. In a very small study (n=19 patients with 79 AKI episodes), they found that an infection was a contributor in more than half of AKI episodes [32]. Mehrotra *et al.* studied AKI in an inpatient setting with AKI defined by *ICD-9* administrative diagnostic codes. The study was very large, including over 27,000 patients, and found an incidence of 11.3% between 6 months and 3 years post-transplant. They also found that the incidence of AKI was higher in more recent years and that patients with lower baseline transplant function had a higher risk of AKI [22]. Both Mehrotra *et al.* and Nakamura *et al.* showed that AKI was associated with an increased risk of graft loss; the highest risk was among those with more severe AKI [22, 23]. The details, strengths and limitations of these two studies are outlined in Table 2.

Table 1: Summary of Published Studies on the Association of AKI with Graft Loss

Study	Definition of AKI	Definition of Graft loss	Association of AKI with Graft Loss	Strengths	Limitations
Nakamura *et al.* [23]	50% or greater increase in serum creatinine above baseline	Reaching an eGFR <15 ml/min/1.73 m^2 or requiring	Adjusted HR 3.72 (2.3-6.3)	Had specific clinical data, such as cause of AKI. A clinical database/chart	Small sample size. Single Centre

	(outpatient lab values included)	dialysis		review was used. Defined AKI using serum creatinine.	Only included living donor transplant recipients. Unclear what method was used for the survival analysis. Do not specify how the event of death was treated in the analysis.
Mehrotra *et al.* [22]	Presence of an *ICD*-9 administrative diagnostic codes for AKI during a hospital admission.	Graft loss or death Death with a functioning transplant Death censored transplant loss All outcomes were >90 days after admission with AKI	Adjusted HR 2.74 (2.6-2.9) Adjusted HR 2.36 (2.1-2.6) Adjusted HR 3.17 (2.9-3.5)	Very large sample size, multi-centre, American data. Excluded patients with acute rejection (tracked in one of the administrative databases). Baseline eGFR was available. Examined death and transplant failure as separate outcomes. AKI treated as a time-varying covariate.	Do not have detailed data, such as cause of AKI—use of administrative data. AKI defined using administrative diagnostic codes, which are not validated in kidney transplants and are known to have limited sensitivity in the general population. Competing risk survival analysis not used for the outcomes of graft loss and death

eGFR: estimated glomerular filtration rate

HR: hazard ratio

Burden of Graft Loss

Short-term graft survival has improved extensively in recent years, likely due to better immunosuppressive medications and less acute rejection. However, we have failed to achieve any significant improvement in long-term graft survival, likely due to the multitude of factors that contribute over time to the survival of a graft and a relatively poor understanding of why grafts fail over the long-term [33, 34]. The receipt of a kidney transplant (compared to dialysis) is known to improve the quality of life and survival of patients with kidney failure [35, 36]. Kidney transplant failure requiring a return to dialysis is associated with increased mortality and a reduced quality of life compared to kidney transplant patients with a functioning graft and transplant naïve dialysis patients [37, 38]. As well, extending graft survival is of utmost importance given the scarcity of organ donors.

Summary

AKI is common in kidney transplant patients and increases the risk of long-term graft loss. A better understanding of the factors contributing to the relationship between AKI and graft loss is needed.

Chapter 3: Recognizing the Limitations and Potential for Bias When Using Healthcare Administrative Databases for Research: AKI Defined by Diagnostic Codes

This chapter incorporates the manuscript: "Validity of the *International Classification of Diseases, Tenth Revision* code for acute kidney injury in kidney transplant patients during a hospital admission six months or greater post transplant**".**

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Introduction:

When studying kidney transplant patients, administrative databases can increase power and permit the conduct of research that otherwise would not be possible. However, as outlined in Chapter 2, one must recognize the limitations and potential for bias when using administrative databases. In order to increase the power of our study, we considered using administrative diagnostic codes to diagnose AKI, as performed by Mehrotra *et al* [22]. As described in Chapter 2, the accuracy of diagnostic codes should be known before they are used in a study.

Accuracy of AKI Administrative Codes

The accuracy of AKI diagnostic codes has been determined in the general and chronic kidney disease (CKD) populations, but not in the kidney transplant population. When a diagnosis of AKI not requiring dialysis is considered, codes are found to be extremely insensitive, leading to inaccurate exposure classification [39-41]. *ICD*-9 (used in hospital admissions prior to April 1st, 2003) and *ICD*-10 diagnostic codes for AKI have both been validated in the general population, and *ICD*-10 codes in the CKD population. When compared to a reference standard of a rise in serum creatinine OR chart re-abstraction, a meta-analysis of validation studies in the general population found that the specificity and negative predictive values of AKI diagnostic codes were high across studies (median specificity 99%; negative predictive value 95%); however, the sensitivity and positive predictive value were generally poor (median sensitivity 29%; median positive predictive value 67%) [40]. AKI diagnostic codes are more sensitive but less specific when examined in an elderly (age >65) CKD population (sensitivity 36%, specificity 92%, compared to a

reference standard of a 50% or greater increase in serum creatinine; sensitivity 76%, specificity 84%, compared to a reference standard of at least a doubling in serum creatinine) [39]. Studies reporting the accuracy of AKI codes in the general population compared to the gold standard test for AKI of a rise in serum creatinine are summarized in Table 3. The higher sensitivity of *ICD-10* codes (compared to *ICD-9)* reported in the Hwang *et al.* study could be due to the fact that the cohort was restricted to elderly patients [39].

Table 2: Accuracy of Administrative Diagnostic Codes for AKI Among Studies Using a Reference Standard of Serum Creatinine Criteria (Adapted from Vlasschaert et al[40])

Study	Codes	Reference Standard	Sample Size	Sensitivity	Specificity	PPV	NPV
Waikar *et al* [41]	*ICD-9*	Change in creatinine of 100%	97,705	35 (34-37)	98 (98-98)	48 (46-49)	96 (96-96)
Waikar *et al* [41]	*ICD-9*	Hou criteria[a]	97,705	28 (28-29)	99 (99-99)	80 (79-81)	91 (90-91)
Waikar *et al* [8]	*ICD-9*	Change in creatinine of 100% (nadir to peak)	19,206	29 (27-31)	97 (97-98)	59 (56-62)	92 (91-92)
Liangos *et al* [6]	*ICD-9*	Hou criteria[a]	13,237	19 (17-21)	99 (99-99)	88 (84-91)	90 (90-91)
Wald *et al* [16]	*ICD-9*	Hou criteria[a]	8,451	19 (18-21)	99 (99-99)	89 (85-92)	84 (83-85)
Wald *et al* [16]	*ICD-9*	Rise in creatinine ≥2x nadir	8,451	29 (25-32)	98 (98-98)	55 (49-60)	94 (94-94)
Grams *et al* [42]	*ICD-9 and ICD-10*	50% change from outpatient sCr, or ≥0.5-mg/dl increase if peak sCr is >4 mg/dl, or 0.3-mg/dl	1,970	17 (13-21)	99 (98-99)	72 (62-82)	84 (82-86)

		increase in ≤48 hr					
Hwang[b] *et al* [39]	*ICD-10*	Rise in creatinine ≥2x nadir	38,566	62 (58-66)	96 (95-96)	17 (16-19)	99 (99-100)

[a]Hou criteria: creatinine increases by 0.5 mg/dL if baseline creatinine ≤1.9 mg/dL; increases 1.0 mg/dL if baseline creatinine 2.0-4.9 mg/dL; increases 1.5 mg/dL if baseline creatinine ≥5 mg/dL

[b]Study restricted to elderly individuals > age 65 years.

PPV: positive predictive value

NPV: negative predictive value

sCr: serum creatinine. To convert mg/dL to µmol/L, multiply by 88.4.

Validation Study of AKI Administrative Diagnostic Codes in the Kidney Transplant Population

We had limited creatinine data available to define AKI. Our laboratory databases were restricted to the Ottawa Hospital in Ottawa, Ontario and the London Health Sciences Centre in London, Ontario, which would exclude kidney transplant patients from two large Ontario transplant centres: Hamilton and Toronto. Defining AKI using serum creatinine also restricted the dates of inclusion for our study. All of these factors made the power of our study a significant concern. Therefore, we sought to examine the validity of AKI diagnostic codes in the kidney transplant population in the ICES administrative datasets. This validation study was designed to help us determine if administrative diagnostic codes could be used to define AKI in the study outlined in Chapter 4, and also to facilitate future administrative database studies examining AKI in kidney transplantation.

The specific objectives of this validation study were to determine, among kidney transplant patients admitted to hospital six months or greater following transplant: (1) the sensitivity, specificity, positive predictive value and negative predictive value of *ICD-9* and *ICD-10* diagnostic codes for AKI (compared to the gold standard of a rise in serum creatinine); and (2) compare the rise in creatinine observed during a hospital admission for patients with and without a diagnostic code for AKI.

Validation studies of AKI codes performed in the general population, as outlined in the previous section, have shown poor sensitivity. However, improved sensitivity of AKI codes has been found in more restricted populations (such as those with CKD and the elderly) [39]. We hypothesized that AKI codes would also have a higher sensitivity and positive predictive value in the kidney transplant population because kidney transplant patients have a higher incidence of AKI, are more likely to have their kidney function followed closely, and to have a nephrologist involved in their care during a hospital admission [43].

The validation study had three significant findings. First, we were unable to validate the *ICD-9* diagnostic codes because the number of patients with hospital admissions prior to April 1st, 2003 was too small. If small cells are created during the analysis, the results cannot be disclosed due to ICES privacy regulations. Second, we examined various coding algorithms of the *ICD-10* diagnostic code for AKI against various reference standards (all serum creatinine based). All coding algorithms had fairly low sensitivity but high specificity. The positive predictive value was quite variable, depending on the reference standard used, and the negative predictive value was moderate to high. The most sensitive coding

algorithm had a sensitivity of 42.9% (95% confidence interval (CI) 29.7, 56.8), specificity of 89.3% (95% CI 86.2, 91.8), positive predictive value 32.4% (95% CI 22.9, 43.7), and negative predictive value 92.9% (95% CI 90.1, 94.9), (AKI defined by a ≥2 fold increase in serum creatinine, *ICD-10* code present in any diagnostic field). Less sensitive coding algorithms were more specific (Table 2, manuscript 1). Third, the presence or absence of an *ICD-10* diagnostic code for AKI differentiates two groups of patients with distinct changes in serum creatinine at the time of hospital admission (median rise in creatinine 104.2 µmol/L (IQR 57 to 158) *vs.* 16 µmol/L (IQR -3 to 41) for code positive and code negative patients, respectively (*ICD-10* code present in any diagnostic field)) (Table 3, Supplementary Figures 1 and 2, manuscript 1).

We concluded that no matter which coding algorithm or reference standard was used, we would be significantly under-capturing AKI and misclassifying patients. We also wondered if certain types of transplant patients, such as those admitted to surgical services, were more likely to be under captured by the AKI code (false negatives), which would introduce bias for the project outlined in Chapter 4. As well, details with respect to the AKI event, such as the severity of AKI, would be lost if diagnostic codes were used to define AKI. Recognizing the limitations and potential for bias with the AKI diagnostic codes, we decided to only define AKI using serum creatinine values, knowing that this would limit the size of our cohort. While the precision of the AKI code was insufficient for the derivation of a risk score (outlined in Chapter 4), this does not necessarily preclude its use in other projects, as long as the limitations are understood. The code is quite specific and identifies two populations with distinct rises in serum creatinine. As well, we found a precision similar

to that of the AKI codes validated in the general population, and diagnostic codes for AKI have been used in a number of studies in the general population [44-46].

Limitations of the AKI Administrative Code Validation Study

The validation study had some important limitations. First, for the reference standard used to define AKI, we adapted the creatinine-based component of the AKIN classification system (see Appendix 1), which defines AKI using both serum creatinine and urine output measurements [4]. It is also recommended that the AKIN classification system be applied only after a patient has achieved an optimal state of hydration. Unfortunately, urine output measurements and clinical data, such as hydration status and the administration of intravenous fluids, were not available in the ICES datasets. However, even if urine output data were available, urine output measurements are difficult to obtain and are poorly documented outside of the intensive care setting. As well, the sole use of serum creatinine criteria is a commonly accepted method of defining AKI, used in previous studies [47, 23, 48]. Second, there is no consensus definition for AKI that has been validated in the kidney transplant population [49, 50]. However, all consensus definitions apply similar serum creatinine and urine output criteria [50, 12], AKI is defined similarly for transplant and non-transplant patients in the clinical setting, and the AKIN staging system was used to define AKI and correlated with poor outcomes in a prior study that included kidney transplants [23]. Third, the majority of the cohort had AKIN stage 1 (mild AKI) (Table 1, manuscript 1), which likely explains the very low positive predictive value seen when AKIN stage 3 or greater was used as the reference standard. Finally, data on cause of AKI was not available. The accuracy of diagnostic codes for AKI may differ depending on the cause,

especially for kidney transplants, where a diagnosis of acute rejection may be coded as such instead of AKI. However, our analysis was limited to events beyond the first 6 post-transplant months where the incidence of acute rejection is much less common.

Manuscript One:

Validity of the *International Classification of Diseases, Tenth Revision* code for acute kidney injury in kidney transplant patients during a hospital admission six months or greater post-transplant

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Running Title: Accuracy of AKI administrative codes and kidney transplant

Abstract

Objective: To evaluate the accuracy of the *International Classification* of Diseases*, Tenth Revision* (*ICD-10*) code N17x for acute kidney injury (AKI) in kidney transplant patients in the setting of a hospital admission six months or greater post kidney transplant.

Methods: A population-based retrospective cohort validation study using databases in Southwestern Ontario and Ottawa, Ontario, Canada from 2003 to 2012. We included first-time kidney transplant recipients for whom serum creatinine data were available during an applicable hospital admission and within 6 months prior (n=524). The sensitivity, specificity, and negative and positive predictive values of *ICD-10* coding algorithms for AKI (*ICD-10* code present as the main diagnosis, an admission diagnosis, or any diagnosis) were determined using a reference standard of change in serum creatinine (Acute Kidney Injury Network classification) during a hospital admission compared to a baseline value prior to hospitalization. Median changes in serum creatinine of patients who were code positive and code negative for AKI were also examined.

Results: The most sensitive coding algorithm had a sensitivity of 42.9% (95% CI 29.7, 56.8) and specificity of 89.3% (95% CI 86.2, 91.8), (AKI defined by a ≥2 fold increase in serum creatinine, *ICD-10* code of N17x present in any diagnostic field). Less sensitive coding algorithms were more specific. The median (IQR) rise in serum creatinine from baseline in patients who were code positive and code negative for AKI was 104 (57 to 158) µmol/L and 16 (-3 to 41) µmol/L, respectively.

Conclusions: Similar to the general population, the ICD-10 N17x code for AKI in the kidney transplant population underestimates the true incidence of AKI due to limited sensitivity.

Introduction

Healthcare administrative databases house an enormous amount of data, allowing one to conduct large observational studies in an efficient, relatively low-cost manner [24, 25]. However, researchers utilizing such databases must be aware of the limitations of the data and the potential for biased results [28, 29, 26]. In particular, if a key exposure or outcome of a study is identified using diagnostic or procedural codes, the validity of the results will depend upon the accuracy of such codes [26, 27]. Ideally, when used for clinical research, the accuracy of diagnostic and procedural codes should be known and reported.

The accuracy of diagnostic codes for many commonly studied medical diagnoses, such as myocardial infarction, congestive heart failure and stroke, has been determined [51-53]. Acute kidney injury (AKI) is characterized by an abrupt decline in kidney function, and the gold standard for diagnosis is a rise in serum creatinine, which is determined using a simple blood test [54, 2, 4]. Therefore, if one has access to a database with serum creatinine values, the accuracy of AKI diagnostic codes can be determined with relative ease since the need for chart review or abstraction is eliminated.

The diagnostic codes for AKI have been validated in the general population, showing low sensitivity (approximately 30%) and high specificity (generally >95%) [40]. A recently published study examined the incidence of AKI and outcomes associated with AKI in the kidney transplant population wherein AKI was defined using diagnostic codes [22]. However, the accuracy of diagnostic codes for AKI has never been determined in the kidney transplant population.

We therefore undertook a study with the aim of determining the accuracy of the *International Classification of Diseases, Tenth Revision* (*ICD-10*) code N17x for AKI in kidney transplant recipients. We compared the N17x code against changes in serum creatinine during a hospital admission. We anticipated that the *ICD-10* code for AKI would have a higher sensitivity and positive predictive value in the kidney transplant population compared to the general population because kidney transplant patients have a higher prevalence of AKI, are more likely to have their kidney function followed closely and to have a nephrologist involved in their care during a hospital admission [22, 23, 43]. The results of our study can be applied to future health services and clinical research involving the study of AKI in kidney transplants.

Methods

Study Design and Setting

We conducted a retrospective validation study in the province of Ontario, Canada by linking laboratory data from the Ottawa Hospital Data Warehouse (OHDW) with the healthcare administrative databases housed at the Institute for Clinical Evaluative Sciences (ICES). Residents of Ontario have universal access to hospital care and physician services. The study was conducted according to a pre-specified protocol that was approved by the Ottawa Hospital Research Ethics Board. The reporting of this study follows guidelines set out for studies assessing diagnostic accuracy (Appendix 2) [55].

Data Sources

We ascertained patient characteristics, diagnostic codes and laboratory data by linking 7 databases. We identified patients with a history of a kidney transplant using the Canadian Organ Replacement Register (CORR). Outpatient and inpatient laboratory data were obtained from the OHDW for Ottawa patients, and from Cerner and Gamma-Dynacare for Southwestern Ontario patients. OHDW houses lab information for individuals who had bloodwork drawn at one of three hospitals in Ottawa, Ontario. Cerner is a hospital network in Southwestern Ontario, housing data from 12 hospitals. Gamma-Dynacare is a laboratory service provider that contains outpatient lab information for individuals who had bloodwork drawn at any of their 148 collection sites in Ontario. Demographics and vital status information were obtained from the Ontario Registered Persons Database and CORR. Diagnostic and procedural information from all hospitalizations was determined using the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD). Information was also obtained from the Ontario Health Insurance Plan database, which contains all health claims for inpatient and outpatient physician services. These datasets were linked using unique encoded identifiers (IKN) and analyzed at ICES. We have previously used these databases to research kidney health outcomes and health services [46, 56, 57].

Study Cohort

We included patients with the following characteristics: (a) first kidney only transplant recipients; (b) hospital admission occurring 6 months or later from the transplantation date; (c) at least one serum creatinine value available during the hospital admission; (d) discharge date prior to the end date of laboratory data availability; and (e)

serum creatinine data available anytime between two weeks to 6 months prior to the admission date to determine baseline creatinine. If multiple baseline creatinine values were available, the most recent one was used, except if drawn less than 2 weeks prior to admission. Creatinine values drawn very close to admission were excluded due to a heightened chance of the patient being unwell at the time of the bloodwork; the result may therefore not reflect a true baseline value but possibly the beginning of the AKI episode.

Hospital admissions occurring between April 1, 2003 and December 31st, 2012 (Ottawa) and March 31st, 2012 (Southwestern Ontario) were eligible for inclusion. Hospital admissions with an admission date prior to April 1st, 2003 were excluded due to the use of *ICD-9* diagnostic codes prior to this date. Originally, *ICD-9* codes were included as a separate analysis, but this analysis had to be suppressed due to the presence of small cells (total n=118 patients). Presenting these data would be a breach of ICES privacy regulations. A look-back period of three years from the date of hospital admission was used to determine co-morbidities. Codes used to define co-morbidities of interest are outlined in Appendix 5. When multiple eligible hospital admissions were available for a patient, one was selected at random in order to avoid clustering in the analysis.

The reference standard: serum creatinine based definitions of AKI

We used the Acute Kidney Injury Network (AKIN) staging system to define AKI [4]. AKIN stage 1 or greater is defined by an increase in serum creatinine ≥26.4 umol/L (0.3 mg/dL) or a 1.5 to 2-fold increase from baseline. AKIN stage 2 is defined by a 2 to 3-fold increase in serum creatinine from baseline. AKIN stage 3 is defined by an increase in serum

creatinine >3-fold from baseline, or if the baseline creatinine is greater than 354 umol/L, an acute increase of at least 44 umol/L (0.5 mg/dL) [4]. The urine output criteria for the AKIN staging system was not used as data on urine output were not available in our databases. The peak creatinine during a hospital admission was used to define the presence or absence of AKI and the AKIN stage.

ICD-10 coding administrative database algorithms for AKI

Trained coders review all charts to record appropriate diagnosis codes and their associated attributes following a discharge from hospital. Coders follow the Canadian Coding Standards developed by CIHI [58]. According to CIHI's guidelines, the coders are not permitted to interpret laboratory tests; however, they can record a condition based on laboratory measurements if a physician documents the condition in the patient's chart. For hospitalization records (included in the CIHI-DAD), coders may record up to 25 conditions using *ICD-10* diagnostic codes. They must also indicate the diagnosis type. A diagnosis type 'M' is the main or most responsible diagnosis, which is the condition that contributed most to the hospital length of stay or used the greatest amount of resources. An admission diagnosis is any condition that existed prior to the admission and was treated during the hospital stay [58].

In our study, we tested three unique coding algorithms to identify patients with AKI during a hospital admission. Each algorithm used the *ICD-10* code N17x, which is defined as 'acute renal failure', but varied the diagnosis code type. We examined three possible code

types: 1. diagnosis type 'M' or most responsible/main diagnosis, 2. admission diagnosis, or 3. all diagnoses (present in any one of the 25 potential diagnosis fields).

Statistical Analysis

For each diagnostic coding algorithm, we calculated the sensitivity, specificity, positive and negative predictive values for AKI (using code N17x) compared to a reference standard of changes in serum creatinine using the AKIN staging system for AKI (formulas and a sample 2x2 table are presented in Appendix 3). We calculated 95% confidence intervals for single proportions using the Wilson Score method [59]. We calculated the positive likelihood ratio using the sensitivity and specificity (Appendix 3). We also compared the change in serum creatinine between patients who were N17x code positive and those who were N17x code negative. Changes in serum creatinine from baseline were expressed as median (IQR) and the mean changes were compared using the Mann-Whitney test. We conducted all analyses using the SAS software, version 9.4 (SAS institute Inc., Cary, NC, USA).

Results

We identified a total of 524 kidney transplant patients with eligible hospital admissions from 2003 to 2012 that met our inclusion criteria. Patient selection is outlined in Supplementary Figure 1. Baseline characteristics are outlined in Table 1. The mean age was 57.7 years (standard deviation (SD) 12.1). The median time from kidney transplant to the index hospital admission was 3.5 years. The baseline serum creatinine was measured a median of 34 days (IQR 22, 68) prior to hospital admission. 45.1% of the cohort had a

diagnosis of AKI (based on serum creatinine values) and 14.1% of the cohort were coded with ICD-10 N17x in any position. Nearly all patients with AKI had mild AKI (34.4% of the total cohort) (AKIN stage 1 defined by an increase in serum creatinine ≥26.4 umol/L (0.3 mg/dL) or a 1.5 to 2-fold increase from baseline).

The diagnostic performance of the various coding algorithms is presented in Table 2. The diagnostic coding algorithm of 'all diagnoses' performed the best. Compared to a reference standard of AKIN stage1, the *ICD-10* N17x code for AKI showed a sensitivity of 28% (95% CI 22.6, 34.0) and specificity of 97.2% (95% CI 94.6, 98.6). Compared to a reference standard of AKIN stage 2 (at least a 2 fold or doubling of the serum creatinine compared to baseline), the *ICD-10* code showed a sensitivity of 42.9% (95% CI 30.8, 55.9) and a specificity of 89.3% (95% CI 86.2, 91.8). The sensitivity of the code improved with more severe definitions of AKI. Overall, specificity was high, >90% for most coding algorithms and definitions of AKI. The positive predictive value (PPV) decreased significantly with increasing severity of AKI (AKIN stage 1 PPV 89.2 (95% CI 80.1, 94.4); AKIN stage 2 PPV 32.4 (95% CI 22.9, 43.7); AKIN stage 3 PPV 14.9 (95% CI 8.5, 24.7), coding algorithm all diagnoses).

The absolute and relative changes in serum creatinine for patients that were code positive and code negative are presented in Table 3 and Supplementary Figures 2 and 3. When considering a coding algorithm of 'all diagnoses', 74 patients (14.1%) were code positive for AKI during the index hospital admission. In patients who were code positive and code negative for AKI, the median (IQR) absolute rise in serum creatinine from baseline was 104 (57 to 158) umol/L and 16 (-3 to 41) umol/L, respectively. The median (IQR) percent

relative change was 56.9 (35 to 111) and 12.9 (-2.2 to 31), for code positive and code negative patients, respectively. The difference between the mean absolute and relative changes in serum creatinine between code negative and code positive patients was statistically significant when the means were compared using the Mann-Whitney test ($p<0.0001$).

Discussion

In this retrospective study, we measured the accuracy of the *ICD-10* N17x code for the diagnosis of AKI in the kidney transplant population. The best performing coding algorithm was when the code was expressed as 'all diagnoses' (i.e. present in any diagnostic field during a hospital admission). All coding algorithms, when compared to all reference standards, showed a low to moderate sensitivity but high specificity. For AKI AKIN stage 1 or greater, the PPV or post-test probability of the code was high at almost 90%. This suggests that the code would be reasonable for cohort selection if only kidney transplant patients with AKI were of interest. It should however be recognized that the low sensitivity of the code would result in the exclusion of many patients who truly have AKI, in other words a high number of false negatives. Also, if only more severe forms of AKI (AKIN stage 2 or 3) were of interest, the code would not be appropriate for cohort creation due to the low PPV or post-test probability.

The code performed poorly when a coding algorithm of the 'main or most responsible diagnosis' was used (the condition that contributed most to the hospital length of stay or used the greatest amount of resources). This could be due to the fact that AKI

often occurs in the setting of another illness, such as an infection [32, 23], which may be coded as the main diagnosis as opposed to AKI. The PPV of the code was quite variable depending on the reference standard used. A low PPV for severe AKI (AKIN stage 3) was found with all coding algorithms. This is likely due to the very low prevalence of AKIN stage 3 (5%) in our cohort; the PPV of a test (in this case the code) is known to vary significantly depending on the prevalence of the disease [60]. Specificity was quite high for all coding algorithms; however, was slightly lower for more sensitive coding algorithms. All coding algorithms were more sensitive (less false negatives) when a higher stage of AKI was used as the reference standard. This is to be expected because more severe AKI is more clinically apparent and therefore more likely to be recorded in the chart. No matter which coding algorithm was used, sensitivity was reasonably low (highest value 43%; all diagnoses, reference ≥2x increase in serum creatinine).

Overall, the sensitivity of the code was lower than expected. When examined in elderly patients and elderly patients with CKD (both at higher risk for AKI [11, 61, 9], similar to kidney transplant patients), the *ICD-10* code for AKI had a sensitivity of 62% and 76% compared to a reference of at least a doubling in serum creatinine, respectively [39]. However, the PPV of the code was higher in the kidney transplant population (32%, compared to 10% for elderly CKD and 19% for elderly). As expected, the sensitivity of the code was slightly better in the kidney transplant population compared to the general population (sensitivity 30% compared to at least a doubling in serum creatinine, general population) [40]. One possible reason for the lower than expected sensitivity of the code, is that acute rejection, although presenting as an acute rise in creatinine and thus AKI, has its

own diagnostic code. Although we could not verify the true incidence of acute rejection in our study, it should be very low given that the median time from transplant to index admission was 3.5 years and acute rejection is very infrequent beyond the first year [30]. Nonetheless, a small proportion of AKI episodes (determined based on the reference standard of a rise in creatinine) were likely assigned a code for acute rejection as opposed to AKI. The specificity of the code in the kidney transplant population was worse than in the general or elderly population [40], suggesting that kidney transplant patients are more likely to have a code assigned for AKI when their kidney function is actually stable. Despite the limited sensitivity and PPV of the code, it was still able to distinguish two populations with distinctly different rises in serum creatinine ($p<0.0001$).

To our knowledge, this is the first study to measure the accuracy of the *ICD-10* diagnostic code for AKI in the kidney transplant population. Prior studies have examined the accuracy of AKI codes, mostly *ICD-9,* in the general, elderly and elderly CKD populations [39, 40, 42]. We studied transplant patients from two healthcare regions in the province of Ontario, making the sample more representative and thus generalizable. We had creatinine values available, making it possible to compare the administrative diagnostic code to the gold standard for diagnosing AKI, as opposed to relying on chart re-abstraction.

Our study has some important limitations. First, for the reference standard used to define AKI, we adapted the creatinine-based component of the AKIN classification system, which defines AKI using both serum creatinine and urine output measurements [4]. It is also recommended that the AKIN classification system be applied only after a patient has achieved an optimal state of hydration. Unfortunately, urine output measurements and

clinical data, such as hydration status and the administration of intravenous fluids, were not available in the administrative datasets that we used for this study. However, even if urine output data were available, urine output measurements are difficult to obtain and are poorly documented outside the intensive care setting. In addition, the sole use of serum creatinine is a commonly accepted method of defining AKI both clinically and for research purposes [47, 23, 48]. Second, there is no consensus definition for AKI that has been validated in the kidney transplant population [49, 50]. However, all established classification systems apply similar serum creatinine and urine output criteria [50, 12]; AKI is defined similarly for transplant and non-transplant patients in the clinical setting; and the AKIN staging system was used to define AKI and correlated with poor outcomes in a prior study of kidney transplant patients [23]. Finally, data on the cause of AKI was not available. The accuracy of administrative coding for AKI may differ depending on the cause, especially in transplantation, where a diagnosis of acute rejection may be coded preferentially over a diagnosis of AKI.

In summary, healthcare administrative databases house an enormous amount of data on a large number of patients and can therefore serve as a low-cost, efficient method of conducting large observational studies. The use of these databases for research requires knowledge of the inherent limitations, in particular the accuracy of administrative diagnostic codes. Our data demonstrate that identifying AKI in kidney transplant patients using administrative diagnostic codes will result in an underestimation of the true incidence and misclassification of patients with AKI, making it less than ideal for determining the incidence and consequences of AKI in hospitalized kidney transplant patients. The code may

however be reasonable for cohort selection if only kidney transplant patients with AKI are of interest, due to the high PPV for any AKI.

Table 1: Baseline Characteristics

Total n= 524	
Demographics	
Mean Age (SD), years	57.7 (12.1)
Age (n (%))	
18-34	23 (4.4)
35-59	262 (50)
60-69	151 (28.8)
>=70	88 (16.8)
Women (n (%))	185 (35.3)
Race	
Caucasian	374 (71.4)
Asian	15 (2.9)
Black	19 (3.6)
Indian Sub-continent	12 (2.3)
Aboriginal	9 (1.7)
Other	16 (3.1)
Unknown	34 (6.5)
Missing	45 (8.6)
Income Quintile (n (%))	
One (lowest)	114 (21.8)
Two	106 (20.2)
Three	102 (19.5)
Four	83 (15.8)
Five (highest)	119 (22.7)
Rural location (n (%))	102 (19.5)
Year of cohort entry (n (%))	
2003-2006	149 (28.4)
2007-2009	159 (30.4)
2010-2012	216 (41.2)
Median time since transplant (IQR), years	3.5 (1.5, 7.1)
Year of kidney transplant (n (%))	
1988-1992	18 (3.4)
1993-1997	39 (7.45)
1998-2002	147 (28.1)
2003-2007	205 (39.1)
2008-2012	115 (21.9)
Median time on dialysis prior to transplant (IQR), years	2.0 (0.9, 3.5)
Time on dialysis prior to transplant (n (%)), years	
0-0.9	121 (23.1)
1-1.9	118 (22.5)
2-2.9	82 (15.7)
3-3.9	57 (10.9)

>=4	98 (18.7)
Cause of end stage renal disease (n (%))	
Glomerulonephritis	148 (28.2)
Hypertension	49 (9.4)
Pyelonephritis/Interstitial	35 (6.7)
Cystic kidney disease	61 (11.6)
Diabetes	108 (20.6)
Other	29 (5.5)
Unknown	94 (17.9)
Type of donor (n (%))	
Deceased	347 (66.2)
Living	165 (31.5)
Missing	12 (2.3)
Comorbidities (n (%))	
Coronary artery disease	156 (29.8)
Diabetes	243 (46.4)
Hypertension	489 (93.3)
Congestive heart failure	88 (16.8)
Chronic liver disease	36 (6.9)
Chronic obstructive pulmonary disease	20 (3.8)
Peripheral vascular disease	28 (5.3)
Stroke/transient ischemic attack	12 (2.3)
Baseline laboratory measurements	
Median serum creatinine (IQR), umol/L	133 (103, 173.9)
Median eGFR (IQR), ml/min/1.73 m^2**	46.1 (33.4, 62.8)
eGFR category (n (%)), ml/min/1.73 m^2	
<15	21 (4.0)
15 to <30	84 (16.0)
30 to <45	146 (27.9)
45 to <60	116 (22.1)
>=60	157 (30.0)
AKI definitions (n (%))	
Any AKI	236 (45.0)
AKIN stage 1	180 (34.4)
AKIN stage 2	30 (5.7)
AKIN stage 3	26 (5.0)

*Only available for those age >65 years (n=153). Look back for comorbidities was 3 years.

**Estimated glomerular filtration rate (eGFR) was calculated using the CKD epi equation. CKD epi equation: CKD-Epi equation:$141*\min((\text{serum creatinine in } \mu mol/L/88.4)/\kappa, 1)^{\alpha*}\max((\text{serum creatinine in } \mu mol/L/88.4)/\kappa, 1)^{-1.}209*0.993Age*1.018(\text{if female})*1.159$ (if an African–American) κ=0.7 for females and 0.9 for males, α=−0.329 for females and −0.411 for males, min=the minimum of Scr/κ or 1, max=the maximum of Scr/κ or 1. All patients were assumed to be of non-African Canadian race. This was thought to be a reasonable assumption given the low prevalence of African-Canadians in Ontario. Source: http://www12.statcan.ca/census-recensement/2006/dp-pd/hlt/97-562/index.cfm?Lang=E. This is confirmed by the low prevalence (<4 %) in our dataset.

Table 2: Diagnostic performance characteristics of three different algorithms for *ICD-10* code N17x using the AKIN staging system for AKI as the reference standard

Diagnostic Coding Algorithm	AKIN Stage	Diagnostic Performance Characteristics (95% CI)
All diagnoses	**AKIN stage 1 or greater**	Sn= 28.0 (22.6, 34.0)*
		Sp= 97.2 (94.6, 98.6)
		PPV= 89.2 (80.1, 94.4)
		NPV= 62.2 (57.7, 66.6)
		LR+= 10.0
	AKIN stage 2 or greater	Sn=42.9 (30.8, 55.9)
		Sp=89.3 (86.2, 91.8)
		PPV=32.4 (22.9, 43.7)
		NPV=92.9 (90.1, 94.9)
		LR+= 4.0
	AKIN stage 3	Sn=42.3 (25.5, 61.1)
		Sp= 87.4 (84.1, 90.0)
		PPV=14.9 (8.5, 24.7)
		NPV=96.7 (94.6, 98.0)
		LR+= 3.4
Admission diagnosis	**AKIN stage 1 or greater**	Sn=20.3 (15.7, 25.9)
		Sp=97.9 (95.5, 99.0)
		PPV=88.9 (77.8, 94.8)
		NPV=60.0 (55.5, 64.3)
		LR+= 9.7
	AKIN stage 2 or greater	Sn=35.7 (24.5, 48.8)
		Sp=92.7 (90.0, 94.8)
		PPV=37.0 (25.4, 50.4)
		NPV=92.3 (89.6, 94.4)
		LR+= 4.9
	AKIN stage 3	Sn=38.5 (22.4, 57.5)
		Sp=91.2 (88.4, 93.4)
		PPV=18.5 (10.4, 30.8)
		NPV=96.6 (94.5, 97.9)
		LR+= 4.4
Main diagnosis/most responsible diagnosis	**AKIN stage 1 or greater****	
	AKIN stage 2 or greater	Sn=16.1 (8.7, 27.8)
		Sp=96.6 (94.5, 97.9)
		PPV=36.0 (20.3, 55.5)
		NPV=90.6 (87.7, 92.8)
		LR+= 4.7
	AKIN stage 3	Sn=23.1 (11.0, 42.1)
		Sp= 96.2 (94.1, 97.5)
		PPV= 24.0 (11.5, 43.4)
		NPV= 96.0 (93.9, 97.4)

		LR+= 6.1

*used the Wilson 95% confidence interval

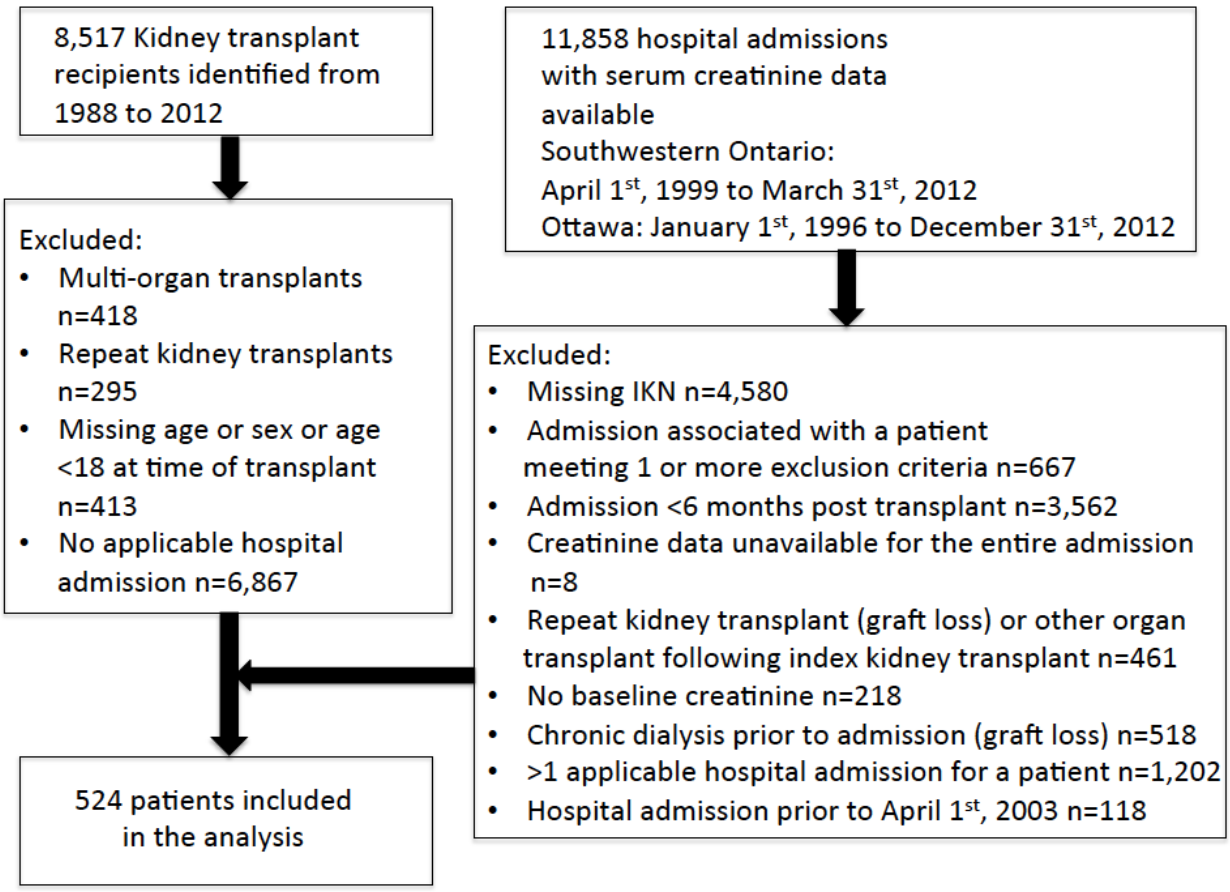
**Results suppressed as per ICES privacy regulations, due to the presence of small cells.

Sn=sensitivity, Sp=specificity, PPV=positive predictive value, NPV=negative predictive value, LR+= positive likelihood ratio

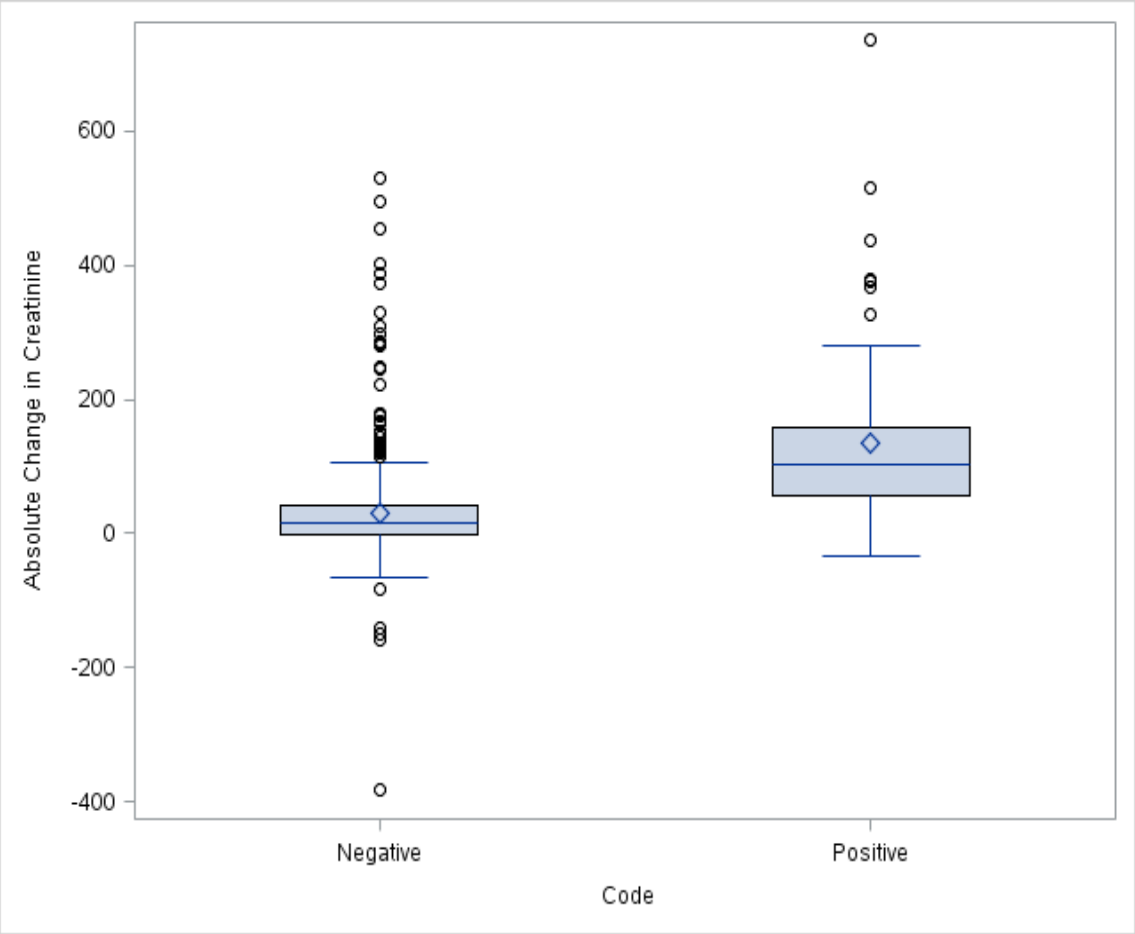
Table 3: Change in serum creatinine from baseline in all patients with and without an ICD-10 N17x code for AKI (referred to as code positive or code negative)

Diagnostic Coding Algorithm	Code	N	Absolute change (µmol/L) Median (IQR)	Relative change (%)*
All diagnoses	+	74	104.2 (57 to 158)	56.9 (35.0 to 111.4)
	-	450	16 (-3 to 41)	12.9 (-2.2 to 30.5)
Admission diagnosis	+	54	109 (62 to 161)	64.0 (35.0 to 122.1)
	-	470	18 (-2.0 to 45.0)	13.8 (-1.5 to 32.5)
Main diagnosis/most responsible diagnosis	+	25	128 (57.0 to 160.0)	71.3 (27.4 to 122.1)
	_	499	19 (-1.0 to 51)	15.3 (-0.7 to 37.4)

*Relative change= (Peak serum creatinine- baseline serum creatinine)/baseline serum creatinine*100.



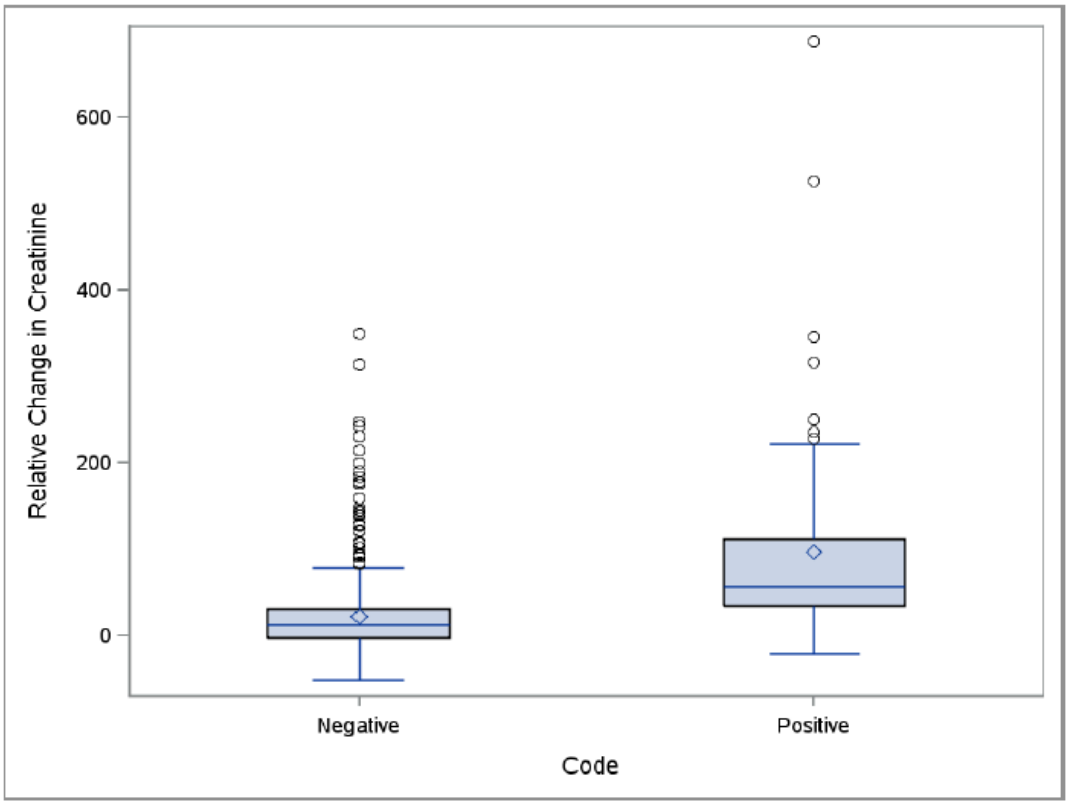
Supplementary Figure 1: Patient Selection



Supplementary Figure 2: Absolute changes in serum creatinine among patients who were code negative and code positive for AKI.*

The boxes represent the interquartile range (50% of the values). The line across the box indicates the median. The diamond indicates the mean. The whiskers extend to the 95th and 5th percentiles.

*The *ICD-10* N17x coding algorithm considered is all diagnoses.



Supplementary Figure 3: Relative changes in serum creatinine among patients who were code negative and code positive for AKI.*

The boxes represent the interquartile range (50% of the values). The line across the box indicates the median. The diamond indicates the mean. The whiskers extend to the 95th and 5th percentiles.

*The *ICD-10* N17x coding algorithm considered is all diagnosis.

Chapter 4: Derivation of a risk score to predict graft loss following AKI in kidney transplant patients

This chapter incorporates the manuscript: "Derivation of a risk score to predict graft loss following acute kidney injury in patients with a kidney transplant".

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Introduction:

Chapter 2 highlighted the advantages and disadvantages of using healthcare administrative databases for clinical research, as well as the evidence supporting the association of AKI with graft loss in kidney transplant patients and the poor prognosis associated with graft loss. Next, Chapter 3 presented the validation study of the *ICD-10* N17x diagnostic code for AKI in kidney transplant patients and highlighted one major limitation of administrative databases - the accuracy of diagnostic codes. The limited sensitivity of the AKI code had been previously demonstrated in the general population [42, 39]. The study in Chapter 3 identified that the AKI *ICD-10* diagnostic code also has limited sensitivity in the kidney transplant population. The findings in Chapter 3, coupled with the background presented in Chapter 2, helped inform the design of a study that would utilize administrative and laboratory databases to derive an index score to predict the risk of graft loss following in-hospital AKI in kidney transplant patients. This chapter will present background literature on risk factors for graft loss in kidney transplant patients and comment on the ability to include these risk factors in the derivation of our index score, recognizing the limitations of our datasets. The chapter will finish with the manuscript: "Derivation of a risk score to predict graft loss following acute kidney injury in patients with a kidney transplant".

Risk factors for graft loss in kidney transplant patients

Factors associated with an increased risk of graft loss and references to the published studies are presented in Table 3. The presence of proteinuria post-transplant, even a small amount, is associated with an increased risk of graft loss, as is a decreased

baseline transplant function (estimated glomerular filtration rate (eGFR)). Both are accepted risk factors for subsequent graft loss, with several published studies demonstrating an increased risk associated with these factors [62-71] [72-75, 31, 76, 77, 69, 78, 79]. A prior history of acute rejection is associated with an increased risk of subsequent graft loss [80-85, 71, 31, 77, 86-90], as are several factors associated with acute rejection, such as the presence of donor specific antibody (DSA) [91], non-adherence with immunosuppression [92, 93], immunosuppressant drug level variability [94, 95], panel reactive antibody (PRA) [96, 97] and human leukocyte antigen (HLA) mismatch [97, 98].

The role of transplant recipient age is less clear. Some studies demonstrate an increased risk of graft loss in younger recipients [72, 77], while others demonstrate an increased risk in older recipients [99, 71, 89]. The studies examining age that are listed in Table 3 did not all use the same definition for graft loss; some studies included death with graft function in the definition of graft loss while others did not, which may be a reason for the conflicting results. Older patients may be more likely to experience death with graft function (in other words, graft loss secondary to death), because older individuals are more likely to die [72, 77, 69]. However, younger individuals may be more likely to experience graft loss that is defined by a return to dialysis or repeat kidney transplant, likely due to the fact that they live longer [69]. Moreover, younger recipients may be more prone to graft loss from acute rejection [100, 86], potentially secondary to non-adherence [92].

Some studies have shown an increased risk of graft loss associated with male sex and the type of donor (deceased) [77, 89, 84]. Delayed graft function (DGF), generally defined by AKI and the requirement for dialysis immediately post-transplant, is also

associated with an increased risk of long-term graft loss [101, 71, 102]. Whether DGF is an independent risk factor is unclear; DGF is generally associated with graft loss when it is not transient and results in a lower baseline eGFR or triggers acute rejection [96, 103]. The role of body mass index (BMI) is less clear; some studies show that a lower BMI poses an increased risk [104, 105, 77], while others show an increased risk with a higher BMI [106, 77, 107]. The type of immunosuppression may be of importance [108]. A meta-analysis of randomized controlled trial data showed that tacrolimus reduces the risk of acute rejection compared to cyclosporine [109]; however, the differential effect on long-term graft survival is less clear [110].

Hypertension, as with native kidney disease, is associated with an increased risk of graft loss [80, 71, 111, 77]. The cause of end stage renal disease may play a role, as certain kidney diseases can recur in the transplant [112]. Congestive heart failure [101], diabetes [81, 71] and time spent on the transplantation wait list [99, 71, 113] likely increase the risk of death with graft function. A higher serum calcium and phosphate, hyperlipidemia, lower serum albumin, and anemia are other potential risk factors, but their role is less clear [80, 114, 115, 77, 116, 117, 90]. There is data suggesting that anemia is associated with an increased risk of acute rejection [114].

Potential limitations of identifying known risk factors for graft loss in the administrative and laboratory datasets

Due to the retrospective nature of our study, data on many of the risk factors listed above and in Table 3 will not be available. The availability of each risk factor is listed in Table 3. One of the most important risk factors, baseline eGFR, can be calculated from

serum creatinine values in the laboratory datasets. The availability of baseline eGFR will, in part, adjust for the effect of prior acute rejection episodes and DGF, neither of which is available in the datasets. Many of the factors that are unavailable in the datasets are essentially risk factors for acute rejection. Unfortunately, proteinuria, which is an established risk factor, although available in the Ottawa Hospital laboratory database (OHDW), is not universally available in the other laboratory datasets and therefore the number of missing values will be too great to include it in the index score. Other laboratory measures, such as serum calcium and phosphate, are not universally available but are likely of lesser importance.

Table 3: Risk factors for graft loss in the kidney transplant population

Risk factor	Studies demonstrating an association with graft loss	Available in datasets
Older recipient Age	[99, 71, 89]	Yes
Younger recipient Age	[72, 77]	Yes
Male sex	[77, 89]	Yes
Deceased donor	[84, 89]	Yes
Cause of ESRD	[101]	Yes
Proteinuria	[62-71]	Only available for a portion of the cohort
Baseline eGFR	[72-75, 31, 76, 77, 69, 78, 79]	Yes
History of DGF	[101, 71, 102]	No, but baseline eGFR should at least in part account for this
History of acute rejection	[80-85, 71, 31, 77, 86-90]	No
Hypertension	[80, 71, 111, 77]	Yes (by diagnostic codes)
High BMI	[106, 77, 107]	Yes, but a lot of missing values

Low BMI	[104, 105, 77]	Yes, but a lot of missing values
Non-adherence with immunosuppression	Systematic review of 36 studies [118] [92, 93]	No
Kidney biopsy showing fibrosis	[119]	No
Anemia	[114, 77, 116]	Only available for a portion of the cohort
Hyperlipidemia	[80]	Only available for a portion of the cohort
Serum albumin	[77, 117, 90]	Only available for a portion of the cohort
DSA	[91]	No
HLA mismatch	[97, 98]	No
PRA	[96, 97]	No
Time spent on wait list	[99, 71, 113]	Cannot determine this but can use time on dialysis as a surrogate
Smoking	Systematic review of 12 studies [120]	No
Serum calcium	[115]	Only available for a portion of the cohort
Serum phosphate	[115]	Only available for a portion of the cohort
Type of immunosuppression	[108]	No
Drug level variability	[94, 95]	No
Diabetes	[81, 71]	Yes (by diagnostic codes)
CHF	[101]	Yes (by diagnostic codes)
Ace inhibitor or ARB use	[121]	Yes, but only for age >65

ESRD: end stage renal disease, eGFR: estimated glomerular filtration rate, DGF: delayed graft function, BMI: body mass index, HLA: human leukocyte antigen, PRA: panel reactive antibody, CHF: congestive heart failure, Ace inhibitor: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker

Derivation of an index score to predict graft loss following in-hospital AKI in kidney transplants

In the general population, the association of AKI with poor long-term outcomes, such as CKD and increased mortality, has been reported in several studies [17, 122, 13, 15, 20, 16]. More recently, AKI, independent of DGF and acute rejection, has been recognized as a potential important contributor to poor outcomes, such as graft loss, in the kidney transplant population [22, 23]. The findings, strengths and limitations of the two studies reporting on the association of AKI with graft loss in kidney transplant are reported in Chapter 2, Table 2.

Index scores predicting the risk of graft loss following kidney transplant have been published [90, 123, 124]. However, these scores pertain to all transplant recipients and have not accounted for the specific effect of AKI. Our index will be the first to focus specifically on kidney transplant patients with AKI and to incorporate AKI specific factors, such as stage of AKI and recovery from AKI.

The risk score study presented in manuscript two included kidney transplant patients admitted to hospital with AKI six months or greater post-transplant and had three main objectives. The first objective was to identify the factors associated with an increased risk of subsequent graft loss or death. The second objective was to determine factors associated with an increased risk of graft loss (repeat transplant or return to dialysis) and factors associated with death with graft function. If factors were found to be differentially associated with each outcome, then a composite outcome of graft loss or death would be

inappropriate for the risk score. The third objective was to derive a risk score for the selected outcome (either graft loss or graft loss or death).

The main findings of the study are as follows. The median follow-up time was 6.7 years from the AKI event. From a cohort of 315 patients, 87 patients (27.6%) experienced graft loss and 71 patients (22.5%) died prior to experiencing graft loss. Younger age, increased time from transplant to admission with AKI, a lower baseline eGFR, AKIN stage 3 AKI, failure to recover from AKI, and a history of CHF were independently associated with graft loss or death ($p<0.05$). Younger age, AKIN stage 3 AKI, and a lower baseline eGFR were independently associated with graft loss ($p<0.05$). Older age, increased time from transplant to AKI admission, increased time on dialysis prior to transplant and a history of diabetes were independently associated with death with graft function ($p<0.05$) (Table 2, Supplementary Figs 2 to 6, Manuscript 2). A highly discriminative risk score composed of readily available, objective clinical data was derived to predict graft loss in kidney transplant patients within 5 years of an admission with AKI. The expected risk fell within the 95% confidence interval of the observed risk; however, the confidence intervals were wide due to the small sample size (Fig 1, Manuscript 2). The risk score includes the following factors: age, time from kidney transplant to AKI admission, baseline eGFR, recovery from AKI, AKIN stage of AKI, and type of donor (Table 3, Manuscript 2).

We concluded that kidney transplant patients who experience in-hospital AKI are at high risk for graft loss or death. There are distinct risk factors for graft loss and death with graft function; the use of death or graft loss as a composite outcome will lead to biased

results. A risk score was derived that can prognosticate kidney transplant patients following an admission with AKI. This risk score requires validation.

Limitations of the risk score

The derived risk score has some important limitations. This was a retrospective study. As a result, data on important factors, such as proteinuria, were not available for inclusion in the analysis. Missing data on prior acute rejection episodes and DGF would be partially accounted for by the inclusion of baseline eGFR. Cause of AKI could not be determined; however, acute rejection this far out from kidney transplant is rare [30, 31] (median time post-transplant to AKI admission 2 years). Prior studies on AKI in this setting suggest that infection is the most common cause [32, 23]. The sample size was relatively small (n=315 patients); nevertheless, this is still the largest study that we are aware of to examine AKI in the kidney transplant population defined by serum creatinine values [32, 22, 23]. Moreover, this was a high-risk population with a high event rate. Due to the limited sample size, we were unable to internally validate the risk score. The risk score also requires external validation.

Manuscript Two:

Derivation of a Risk Score to Predict graft loss following acute kidney injury in patients with a kidney transplant

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Abstract

Introduction: Acute kidney injury (AKI) is common in the kidney transplant population and is associated with an increased risk of long-term graft loss.

Methods: Using retrospective data, we derived a multivariable survival model predicting time to graft loss (repeat kidney transplant or return to dialysis) in 315 kidney transplant patients who had a hospitalization with AKI six months or greater following transplant. We performed a competing risk survival regression analysis using the Fine and Gray method, with death as the competing event. We modified the model into a simple point-system index.

Results: Graft loss occurred in 27.6 % of the cohort. The final competing risk model included six variables that increased the risk of graft loss: increasing age, increased severity of AKI (as defined by the AKIN staging system), failure to recover from AKI, lower baseline estimated glomerular filtration rate, increased time from kidney transplant to AKI admission, and deceased donor. The index separated patients into seven groups having significantly unique risks of graft loss, ranging from 0% in the lowest-risk group to 84% in the highest risk group. The model generated 5-year risk of graft loss always fell within the 95% confidence interval of the observed risk; however, due to the small size of the cohort, the 95% confidence intervals were quite wide, especially at the highest risk scores.

Conclusions: Our prognostic index uses commonly available information to predict graft loss in kidney transplant patients hospitalized with AKI six months or greater after kidney transplant. The index requires validation in order to determine its clinical utility.

Introduction

Studies excluding kidney transplant patients show that acute kidney injury (AKI) affects between 2 and 12% of all hospitalized patients [5, 6, 125, 8, 9] and is associated with an increased risk of subsequent chronic kidney disease (CKD) and death [17, 18, 13, 19, 14, 15, 20, 16]. A study in kidney transplant patients found that hospitalizations with AKI occurred in 11% of patients between 6 months and 3 years post-transplant, and that AKI was increasingly common in more recent years [22]. This reported rate is likely an underestimate given that AKI was defined using administrative diagnostic codes, which are known to have low sensitivity [42, 40]. There is limited data on the consequences of AKI in kidney transplantation. However, recent data suggest that AKI is associated with an increased risk of subsequent graft loss and death [22, 23].

Graft loss resulting in a return to dialysis is associated with a 3-fold increased risk of mortality and a reduction in quality of life [37, 38]. Prognostic scores are available to predict a patient's risk of graft loss following kidney transplant [124, 90, 123]. However, these scores were derived in kidney transplant patients who survive up to one year post-transplant. There is no such score that specifically predicts the risk of graft loss following AKI or incorporates AKI specific factors.

We aimed to derive a new risk score to quantify the risk of subsequent graft loss for a kidney transplant patient following an admission to hospital with a diagnosis of AKI. We based the risk score on readily available data so that it could be easily implemented in a clinical setting. The model was modified into a simple scoring system to quantify graft loss

risk following AKI. Our goal is to guide and improve the care of kidney transplant patients following AKI by identifying those at highest risk for graft loss.

Methods

Design and Setting

We conducted a retrospective cohort study in the province of Ontario, Canada by linking laboratory data from the Ottawa Hospital Data Warehouse (OHDW) with the healthcare databases housed at the Institute for Clinical Evaluative Sciences (ICES). Residents of Ontario have universal access to hospital care and physician services and individuals 65 years of age or older have universal prescription coverage. The study was conducted according to a pre-specified protocol that was approved by the Ottawa Hospital Research Ethics Board. The reporting of this study follows the STROBE guidelines for observational studies (Appendix 4) [126].

Data Sources

We ascertained patient characteristics, laboratory data, and outcome data from 8 linked databases. We identified patients with a history of a kidney transplant using the Canadian Organ Replacement Register (CORR). Outpatient and inpatient laboratory data were obtained from the OHDW for Ottawa patients, and Cerner and Gamma-Dynacare for Southwestern Ontario patients. OHDW houses lab information for individuals who had bloodwork drawn at one of three hospitals in Ottawa, Ontario. Cerner is a hospital network in Southwestern Ontario, housing data from 12 hospitals. Gamma-Dynacare is a laboratory

service provider that contains outpatient lab information for individuals who had bloodwork drawn at any of their 148 collection sites in Ontario. Demographics and vital status information were obtained from the Ontario Registered Persons Database and CORR. Diagnostic and procedural information from all hospitalizations was determined using the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD). Information was also obtained from the Ontario Health Insurance Plan database, which contains all health claims for inpatient and outpatient physician services. Outcome data was obtained using RPDB, CORR and the Ontario Renal Reporting System. These datasets were linked using unique encoded identifiers (IKN) and analyzed at ICES. We have previously used these databases to research renal health outcomes and health services [46, 56, 57]. Whenever possible, we defined patient characteristics and outcomes using validated codes (Appendix 5).

Study Cohort

We included patients with the following characteristics: (a) First time kidney only transplant recipients; (b) hospital admission occurring 6 months or greater from the transplantation date; (c) at least one serum creatinine value available during the hospital admission; (d) discharge date prior to the end date of laboratory data availability; and (e) serum creatinine data available anytime between two weeks to 6 months prior to the admission date to determine baseline creatinine. If multiple baseline creatinine values were available, the most recent one was used. Creatinine values drawn less than two weeks prior to admission were excluded due to a heightened chance of the patient being unwell at the time of the bloodwork. We included patients with admissions between January 1st, 1996

and December 31st, 2012 (Ottawa) and between April 1st, 1999 and March 31st, 2012 (Southwestern Ontario). These dates were selected due to lab data availability. Due to the unavailability of laboratory data, patients with admissions to 2 of the 3 hospitals in Ottawa prior to July 1st, 2002 were excluded prior to data linkage (n=117). We wanted to ensure that the first episode of AKI was captured for all patients. Kidney transplants with AKI (based on AKIN stage 1 or greater: rise in serum creatinine ≥26.4 μmol/L or ≥ 50% increase[4]) during an applicable hospital admission were included. The peak creatinine value present during a hospital admission was used to define the presence or absence of AKI and the AKIN stage of AKI. Only the first admission with AKI was included in the analysis. Complete recovery from AKI was defined by a last available admission creatinine <26.4 umol/L above the baseline value. A look back period of 3 years from date of admission was used to determine co-morbidities.

Outcomes

Patients were followed until December 31st, 2013. This was the final date for which outcome data was available. The primary outcome was a composite endpoint comprising graft loss (defined by a return to dialysis or repeat kidney transplant) or death. Secondary outcomes included death with graft function with graft loss as a competing event and graft loss with death as a competing event.

Statistical Analysis

We used Cox regression analyses to determine the independent association between potentially prognostic covariates and time to graft loss or death. Competing risk

regression analysis using the Fine and Gray method was used to determine potentially prognostic covariates associated with time to graft loss and with time to death [127]. Observation of patients started when they were diagnosed with AKI and ended when patients died, had graft loss or were censored at the study end date. The following pre-specified variables were included in all three regression models: Age (by decade), year of kidney transplant (1996 to 1998 and 2010 to 2012 were grouped together due to a lower number of patients), time on dialysis prior to transplant, time from transplant to admission with AKI, baseline eGFR, AKIN stage of AKI (stage 1 as the referent), recovery from AKI (y/n; yes as the referent), CHF (y/n), diabetes (y/n), and type of donor (living vs. deceased; living as the referent). Due to the small size of the cohort, we decided not to divide the cohort into derivation and validation groups. Due to ICES privacy regulations, small cells equal to or less than five have been suppressed.

We used fractional polynomial functions to determine the best linear or nonlinear form for continuous variables [128-130]. Type of donor was the only covariate with missing values. Missing values for donor status were imputed using a logistic regression model derived from the cohort to predict donor status (Appendix 6). The competing risk model examining an outcome of graft loss was used for the creation of the index score. Covariates with a $p<0.05$ were kept in the model. Certain covariates with a larger p value, such as type of donor, were retained in the model, as they were thought to be clinically significant based on prior data [84, 89].

Details pertaining to the creation and assessment of the index score are available in Appendix 7. Discrimination of the risk score was assessed by grouping risk scores with

similar graft survival together and examining the Gray's test for equality of the cumulative incidence functions. We conducted all analyses with the SAS software, version 9.4 (SAS institute Inc., Cary, NC, USA).

Results

Our cohort included 315 first time kidney only transplant recipients admitted to hospital with a diagnosis of AKI 6 months or greater following transplant. Patient selection is described in Supplementary Figure 1.

Baseline Characteristics

Baseline characteristics are outlined in Table 1. The mean age was 55 years. The majority of patients were male and Caucasian. The median time from transplant to a first hospitalization with AKI was 2 years. The median baseline eGFR and serum creatinine were 46 ml/min/1.73 m^2 and 134 µmol/L, respectively. The majority of patients experienced mild AKI (AKIN stage 1), (80.6%). No patients required acute dialysis. The median rise in creatinine and ratio of peak creatinine to baseline creatinine for patients with AKIN stages 1, 2 and 3 was 50 µmol/L (interquartile range (IQR) 37, 72) and 1.4 (IQR 1.3, 1.6), 147 µmol/L (IQR 122, 193) and 2.3 (IQR 2.1, 2.5), and 304 µmol/L (IQR 245, 385) and 3.5 (IQR 3.3, 3.5), respectively. Although the focus of our analysis was on the first admission with AKI, 171 patients (54%) had more than one admission with AKI. The median length of hospital stay was 4 days (IQR 2, 8).

Outcomes

The median follow-up time was 6.7 years (IQR 3.3, 10.3) and total person-years of observation 1377. Eighty-seven (27.9%) patients had graft loss (incidence rate (IR) 63.2 per 1000 person years; 95% confidence interval (CI) (51.2, 78.0)), and 71 (22.5%) patients died prior to experiencing graft loss (IR 51.6 per 1000 person years; 95% CI (40.9, 65.1)). 157 patients (49.8%) were censored at the study end date.

Regression model for the composite outcome of graft loss or death

Age, time from transplant to admission with AKI, baseline eGFR, AKIN stage 3, failure to recover from AKI, and a history of CHF were independently associated with the composite outcome of graft loss or death ($p<0.05$) (Table 2, Supplementary Figs 2-6). The presence of AKIN stage 3 AKI, failure to completely recover from AKI and a history of CHF increased the risk of graft loss or death.

All continuous variables, except baseline eGFR, required transformation. To allow for interpretation, the adjusted hazard ratios of continuous variables were plotted (Supplementary Figures 2-6). A higher baseline eGFR was significantly protective against the composite outcome of graft loss or death (HR 0.97 (95% CI 0.96, 0.98), $p<.0001$). A longer time between transplant and AKI significantly increased the risk of graft loss or death. The adjusted hazard ratio for death or graft loss declined with increasing age (age 20 to 29 treated as the referent group; age 30 to 39, HR 0.54; age 40 to 49, HR 0.43, age 50 to 59, HR 0.39; age 60 to 69, HR 0.37; age 70 to 79, HR 0.36; age 80 to 89, HR 0.35; $p=0.02$).

Regression model for graft loss with death as a competing event

To further explore the unexpected protective effect of increasing age on the composite outcome of graft loss or death, we performed a competing risk analysis with graft loss as the outcome of interest and death as a competing event. In this model, age, AKIN stage 3 AKI, and baseline eGFR were independently associated with graft loss ($p<0.05$). Failure to recover from AKI significantly increased the risk of graft loss on univariate regression (HR 1.72 (95% CI 1.13, 2.61), p=0.01); however, this association was somewhat attenuated upon adjustment (HR 1.58 (95% CI 1.01, 2.46), p=0.05) (Table 2, Supplementary Figs 2-6).

Baseline eGFR and age had the strongest association with graft loss. Higher baseline eGFR was protective against graft loss; each increase of 1 umol/L in baseline eGFR was associated with a 5% (95% CI 3% to 6%) reduction in the risk of graft loss. Similarly, older age was protective against graft failure. Compared to the referent group aged 20-29 years, the following hazard ratios were found: age 30-39, HR 0.22; age 40-49, HR 0.13; age 50-59, HR 0.10; age 60-69, HR 0.09; age 70-79, HR 0.08; age 80-89, HR 0.08; $p<.0001$ (Supplementary Figs 2 and 6). A history of CHF and time from transplant to admission with AKI, although associated with an increased risk of the composite outcome of graft loss or death, were not significantly associated with graft loss on its own (Table 2, Supplementary Fig 5). The regression model used to create the index score for graft loss is presented in Supplementary Table 2.

Regression model for death with graft function

Age, time from transplant to AKI admission, time on dialysis prior to transplant and diabetes were independently associated with death with graft function ($p<0.05$). A history of diabetes increased the risk of death with graft function (HR 1.76 (95% CI 1.04, 2.99), p=0.04) (Table 2). Increased time between kidney transplant and AKI admission and increased time on dialysis prior to transplant increased the risk of death with graft function (p=0.02 and p=0.04, respectively). Increasing age was associated with an increased risk of death with graft function (age 20 to 29 as the referent; age 30-39, HR 1.73; age 40-49, HR 2.54; age 50-59, HR 3.43; age 60 to 69, HR 4.39; age 70 to 79, HR 5.40; age 80 to 89, HR 6.46) (Supplementary Figs 2-6).

Prognostic index for graft loss with death as a competing event

A prognostic index was derived with graft loss as the outcome of interest. The final prognostic index variables, along with the scoring system, are presented in Table 3. Potential index scores ranged from -4 to 25 corresponding to a 5-year probability of graft loss between 1.2% and 100% respectively (Supplementary Table 3).

An individual patient's index score can be calculated by summing up the points for each risk factor presented in Table 3. For example, a 55 year old woman (-3) with AKI AKIN stage 2 (0) and a baseline eGFR of 45 mL/min/1.73 m^2 (5) who had a deceased donor kidney transplant (1) performed 3 years ago (1) and has not completely recovered back to her baseline kidney function at the time of discharge (2) has an index score of 6 with an expected risk of graft loss in 5 years of 13.7%.

The prognostic index was highly discriminative for graft survival. Patients with higher scores had more graft loss, and graft survival was significantly different between index score groupings. The index separated patients into 7 different groupings, with all but one having three or less discrete index scores (Gray's test for equality of the cumulative incidence functions, p<.0001) (Supplementary Fig 7). The expected and observed risks of graft loss for each prognostic index score are presented in Fig 1 and Supplementary Table 3. The model generated 5-year risk of graft loss always fell within the 95% confidence interval of the observed risk; however, due to the small size of the cohort, the 95% confidence intervals were quite wide, especially at the highest risk scores. Overall, the observed risk tended to be greater than the expected risk. The observed risk could not be calculated for index scores of 16 or greater, as no patients in the cohort had a score this high.

Discussion

We derived an index score that predicts graft loss following a hospitalization with AKI in kidney transplant patients. The score uses objective, readily available information to estimate the risk of graft loss at five years after the AKI event. Our index score requires validating; however, it serves as a first step towards prognosticating kidney transplant patients who develop AKI in the months to years following transplant and was highly discriminative in our derivation cohort. The ability to easily identify patients at high risk of graft loss will hopefully lead to improved outcomes through closer follow-up, translational and basic science studies examining mechanisms of graft loss, and ultimately, interventions to improve graft survival.

The majority of covariates had a differential effect depending on the outcome of interest. The most striking differential effect was for age. When a composite outcome of death or graft loss was considered, the risk decreased with increasing age, contrary to what was expected. When a competing risk analysis was performed with graft loss as the outcome of interest, the risk increased as age decreased. As expected, older age was associated with increased death with graft function. Older age being protective against graft loss has been demonstrated in prior studies [72, 77]. Younger individuals may be more likely to experience graft loss defined by a return to dialysis or repeat kidney transplant due to the fact that they live longer [69]. Moreover, younger recipients may be more prone to acute rejection [100, 86]. Although the rate of acute rejection was likely very low in our cohort due to the timing of the AKI events [30, 31], the youngest patients may have had proportionately more AKI caused by late acute rejection from non-adherence [92].

Similar to previously published studies, reduced baseline eGFR was a strong predictor for graft loss [72-75, 31, 76, 77, 69, 78, 79]. Baseline eGFR was not associated with death with graft function, which is potentially unique to this selected cohort. Reduced eGFR has been previously associated with increased mortality in kidney transplant patients, but only at an eGFR <45 ml/min/1.73 m^2 [131]. Congestive heart failure and diabetes, representative of patients with greater cardiovascular risk, were associated with a higher risk of death with graft function but not graft loss. Receipt of a deceased donor kidney transplant was not significantly associated with any of the outcomes of interest. Based on prior nationally collected Canadian data, we expected that receipt of a deceased donor kidney would increase the risk of graft loss [132]. Our results may conflict with prior data

due to a number of reasons: statistical power; previously published national data were unadjusted; and donor type may have less of an effect on graft loss in high-risk transplant patients (i.e. patients admitted with AKI). Due to type of donor being commonly accepted as a risk factor for graft loss, it was maintained in the risk score despite the lack of statistical significance. Although not statistically significant, there was a trend toward an increased risk of death with graft function in more recent transplant years. We suspect that this is due to the transplantation of older individuals and those with more co-morbidities in more recent years. Although the analysis is adjusted, residual confounding may remain. Time spent on dialysis prior to transplant increased the risk of death with graft function but not graft loss. This is likely due to the fact that a patient who spends more time on dialysis probably has more co-morbidities and will be older at the time of transplant [113]. More severe AKI was associated with an increased risk of graft loss but not death with graft function. Studies excluding kidney transplants have failed to show a consistent association between severe AKI and death [13, 16].

Our study has several strengths. First, prognostic scores have been previously developed to predict the risk of graft loss following kidney transplant [124, 90, 123]; however, to our knowledge, none have included AKI specific factors or quantified the risk of graft loss following an admission to hospital with AKI. Second, to our knowledge, our study is the first to derive a risk score that predicts graft loss in kidney transplants using a competing risk model. Many studies in kidney transplantation use a composite outcome of death or graft loss or a “pseudo-competing event” model with an outcome of death censored graft loss [101, 71, 22, 78, 124, 90, 123]. As demonstrated in our study, the risk

factors for graft loss and for death may differ significantly; combining the two outcomes will then lead to a biased estimate. Performing a death-censored analysis will also lead to a biased estimate, in particular if the mortality rate is high, as it was in our cohort [127, 133]. Third, despite the relatively small sample size (n=315 patients), this is the largest study, that we are aware of, to examine AKI in the kidney transplant population defined by serum creatinine values [32, 22, 23]. Moreover, this was a high-risk population with a high event rate. Lastly, all of the variables included in our index are objective and readily available to clinicians.

There are important limitations worth noting. First, this was a retrospective study. As a result, data on important factors, such as proteinuria [62-71], were not available. Missing data on prior acute rejection episodes and delayed graft function would be partially accounted for by the inclusion of baseline eGFR. Second, cause of AKI could not be determined; however, acute rejection this far out from kidney transplant is rare [30, 31] (median time post transplant to AKI admission 2 years). Prior studies on AKI in this setting suggest that infection is the most common cause [32, 23]. Third, due to the limited sample size, we were unable to internally validate the index score. Lastly, our cohort only included in-hospital AKI; as a result, our index may not apply to outpatient AKI.

In conclusion, kidney transplant patients admitted with AKI are at high risk for poor outcomes. Our prognostic index serves as a first step towards identifying transplant patients at the highest risk for graft loss. The derived index requires validation in order to determine its clinical utility.

Table 1: Baseline Characteristics

Total n= 315	
Demographics	
Mean Age (SD), years	55.1 (12.9)
Age (n (%))	
18-34	27 (8.6)
35-59	162 (51.4)
60-69	90 (28.6)
>=70	36 (11.4)
Women (n (%))	121 (38.4)
Race	
Caucasian	243 (77.1)
Asian	12 (3.8)
Black	11 (3.5)
Other	22 (7.0)
Unknown	34 (8.6)
Income Quintile (n (%))	
One (lowest)	68 (21.6)
Two	66 (21.0)
Three	58 (18.4)
Four	50 (15.9)
Five (highest)	73 (23.2)
Rural location (n (%))	58 (18.4)
Year of cohort entry (n (%))	
1997-2002	52 (16.5)
2003-2007	117 (37.1)
2008-2012	146 (46.3)
Median time since kidney transplant (IQR), years	2.1 (0.9, 4.4
Year of kidney transplant (n (%))	
1996-1998	22 (7.0)
1999-2001	92 (29.2)
2002-2004	66 (21.0)
2005-2007	76 (24.1)
2008-2012	59 (18.7)
Median time on dialysis prior to transplant (IQR), years	2.0 (1.1, 3.5)
Time on dialysis prior to transplant (n (%)), years	
0-0.9	64 (20.3)
1-1.9	75 (23.8)
2-2.9	48 (15.2)
3-3.9	40 (12.7)
>=4	56 (17.8)
Cause of end stage renal disease (n (%))	

Glomerulonephritis	89 (28.3)
Hypertension	31 (9.8)
Pyelonephritis/Interstitial	20 (6.4)
Cystic kidney disease	33 (10.5)
Diabetes	69 (21.9)
Other	20 (6.4)
Unknown	53 (16.8)
Type of donor (n (%))*	
Deceased	218 (69.2)
Living	97 (30.8)
Comorbidities (n (%))	
Coronary artery disease	93 (29.5)
Diabetes	136 (43.2)
Hypertension	285 (90.5)
Congestive heart failure	53 (16.8)
Chronic liver disease	22 (7.0)
Chronic obstructive pulmonary disease	11 (3.5)
Peripheral vascular disease	22 (7.0)
Stroke/transient ischemic attack	8 (2.5)
Baseline laboratory measurements	
Median serum creatinine (IQR), umol/L	134.0 (107.0, 171.0)
Median eGFR (IQR), ml/min/1.73 m2**	46.0 (34.0, 60.4)
eGFR category (n (%)), ml/min/1.73 m2**	
<30*	51 (16.2)
30 to <45	99 (31.4)
45 to <60	84 (26.7)
>=60	81 (25.7)
AKI definitions (n (%))	
AKIN stage 1	254 (80.6)
AKIN stage 2	36 (11.4)
AKIN stage 3	25 (7.9)
Median time from baseline creatinine measurement to admission with AKI (IQR), days	32 (22, 65)
Complete recovery from AKI^	180 (57.1)

*≤5 individuals had a missing value for donor type. Missing values have been grouped together with the deceased or living categories. The number missing could not be reported on its own due to privacy reasons. Missing values for donor type were imputed in the analysis (see methods).Look back for comorbidities was 3 years. **Estimated glomerular filtration rate (eGFR) was calculated using the CKD epi equation.(ref) All patients were assumed to be of non-African Canadian race. This was thought to be a reasonable assumption given the low prevalence of African-Canadians in Ontario. Source: http://www12.statcan.ca/census-recensement/2006/dp-pd/hlt/97-562/index.cfm?Lang=E. This is confirmed by the low prevalence (<4 %) in our dataset. ^Complete recovery from AKI defined by the last available admission creatinine <26.4 umol/L above the baseline creatinine.

Table 2: Multivariate Regression Analysis, Categorical Variables

Variable	Death or graft loss	Graft loss	Death with graft function
	Adjusted Hazard Ratio (95% CI)	**Adjusted Hazard Ratio (95% CI)**	**Adjusted Hazard Ratio (95% CI)**
AKIN stage 2*	1.14 (0.67, 1.95)	1.04 (0.46, 2.39)	0.76 (0.36, 1.63)
AKIN stage 3*	1.93 (1.09, 3.42)	2.89 (1.49, 5.60)	0.77 (0.26, 2.28)
Failure to recover from AKI*	1.48 (1.06, 2.06)	1.58 (1.01, 2.46)	1.25 (0.74, 2.12)
Congestive heart failure	1.58 (1.05, 2.38)	1.02 (0.58, 1.47)	1.56 (0.87, 2.81)
Diabetes	1.27 (0.91, 1.77)	0.92 (0.58, 1.78)	1.76 (1.04, 2.99)
Type of donor*	1.14 (0.75, 1.74)	1.23 (0.75, 2.01)	1.03 (0.57, 1.85)

*****AKIN stage 1, complete recovery from AKI, and living donor as the referent groups. Complete recovery defined by the last available admission creatinine <26.4 umol/L above the baseline creatinine.

Table 3: Prognostic variables and scoring system of index for the prediction of graft loss among kidney transplants hospitalized with AKI ≥6 months following transplant

Variable	Points*
Age (years)	
20-29	6
30-39	0
40-49	-2
50-59	-3
≥60	-4
Time since kidney transplant	
6 months to 2 years	0
>2 years	1
Baseline eGFR (mL/min/1.73 m^2)	
<30	11
30-44	8
45-59	5
≥60	0
Complete recovery from AKI**	
Yes	0
No	2
AKIN stage	
1 or 2	0
3	4
Type of donor	
Living	0
Deceased	1

*To calculate the index score, points for all factors are summed.

**Complete recovery defined by the last available admission creatinine being <26.4 umol/L above the baseline creatinine.

eGFR, estimated glomerular filtration rate

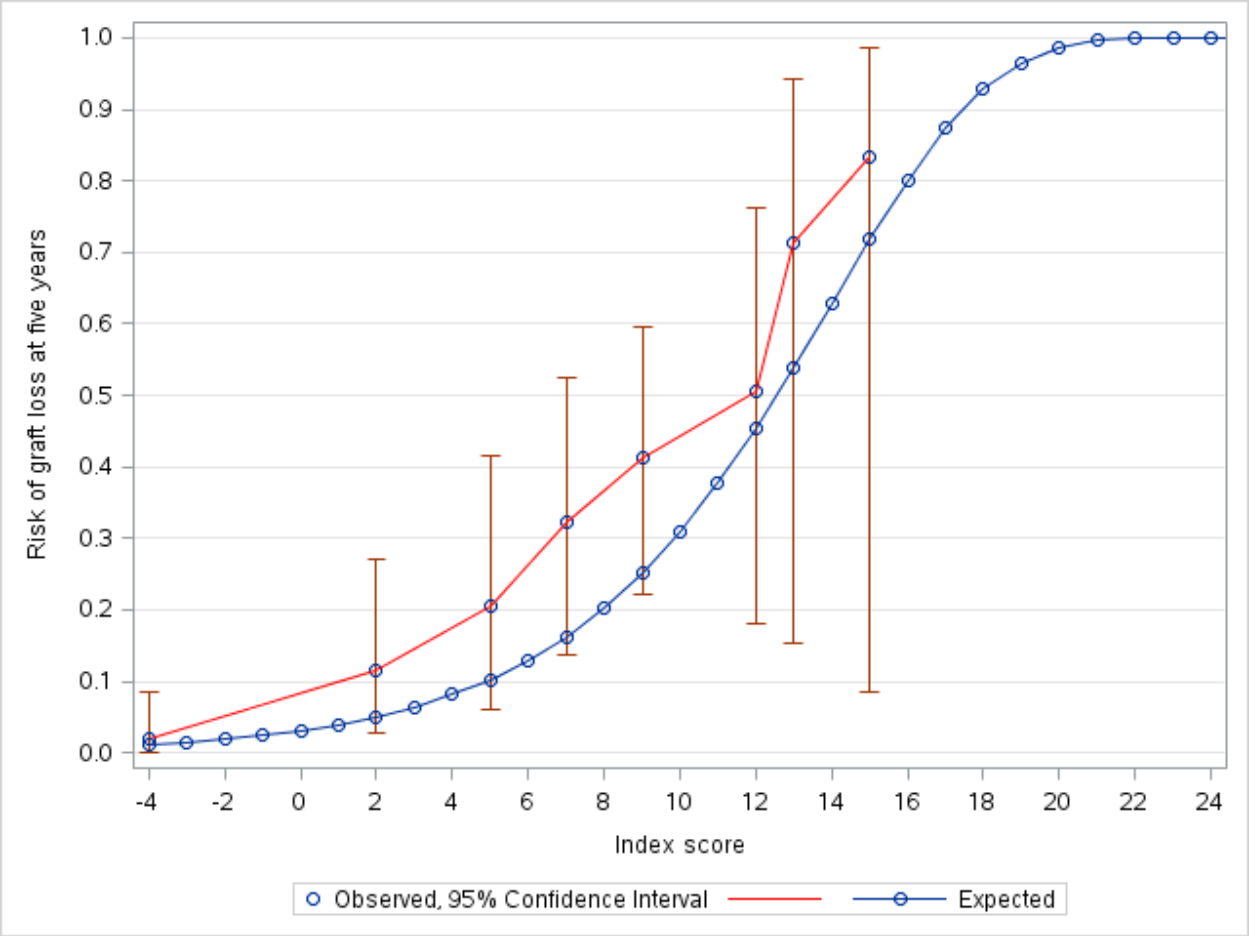
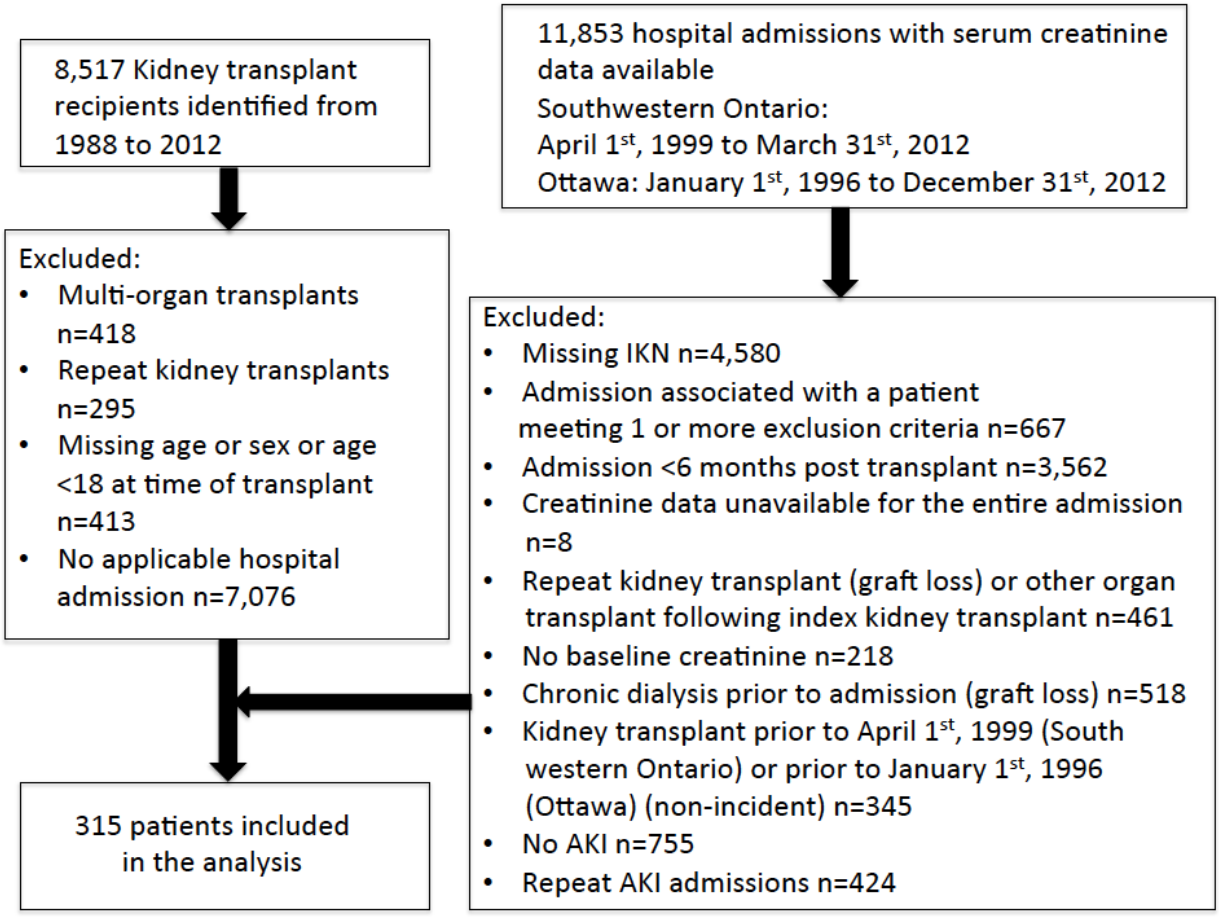
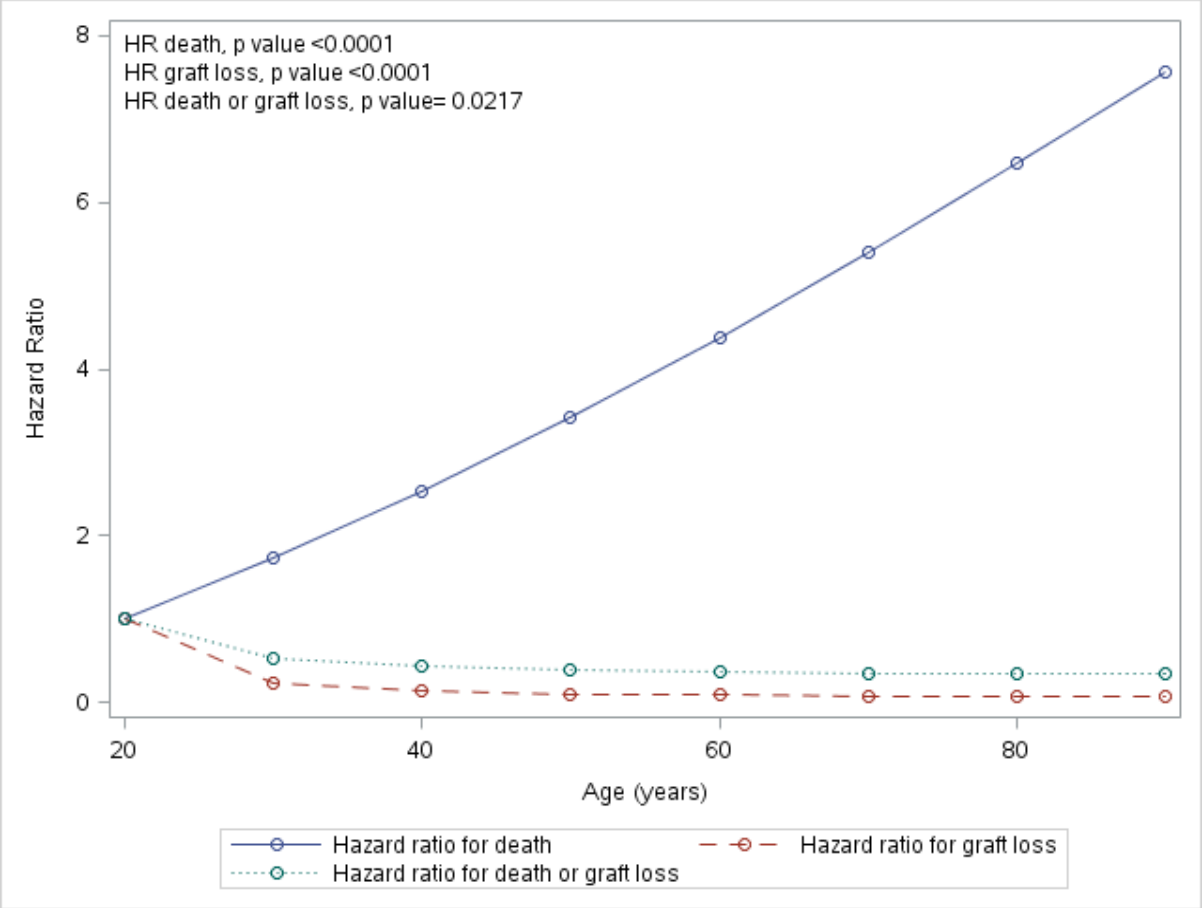


Figure 1: Comparison of expected and observed risk of graft loss at five years by index score.

The expected (blue line) and observed (red line) graft loss rates for each prognostic index score are shown. Vertical bars= 95% confidence intervals for the observed graft loss rates. Due to small numbers and low event rates, patients with the lowest and highest risk scores were grouped together (scores of -4 to 0, 1 to 2, and 14 to 15 were grouped together).

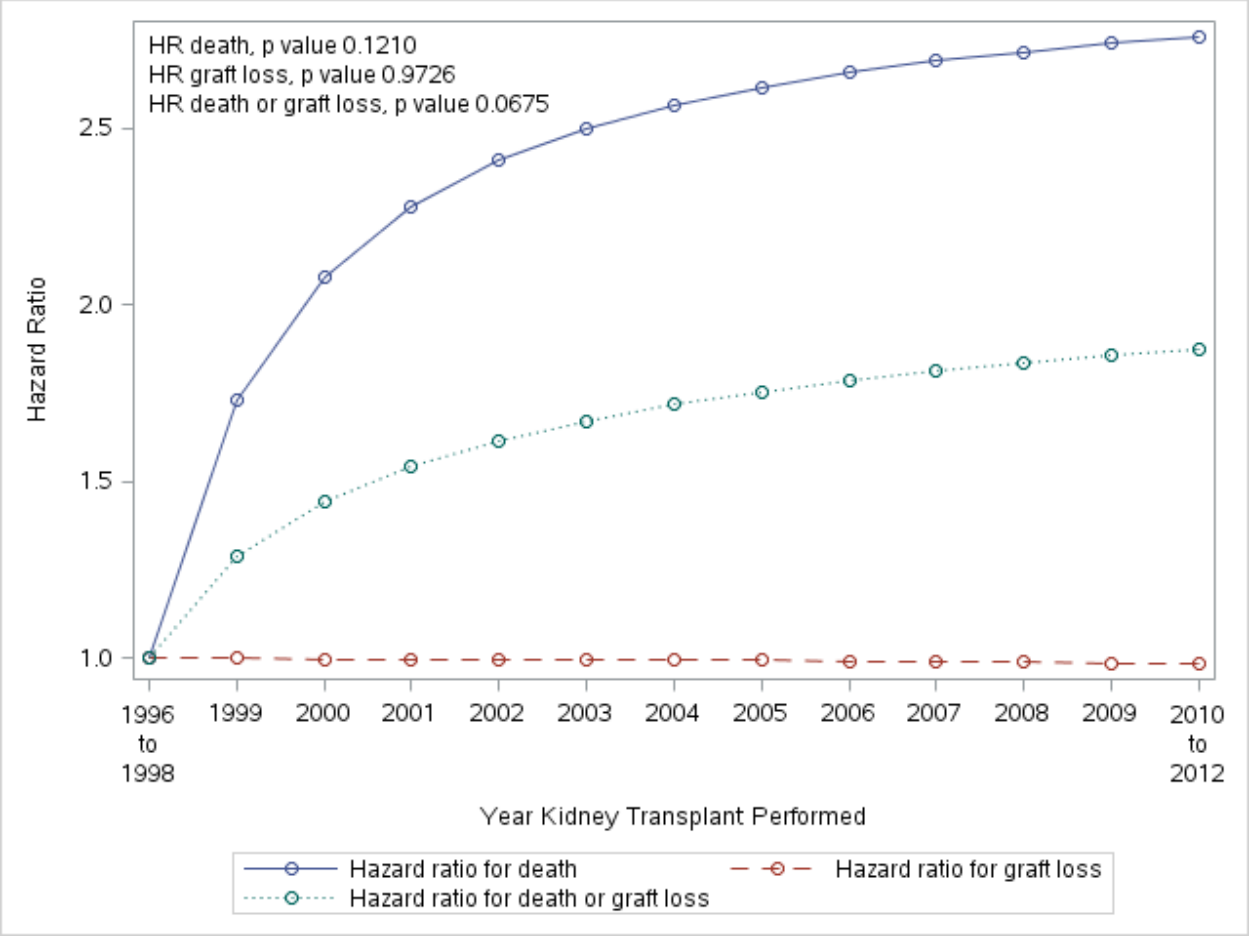


Supplementary Figure 1: Patient selection



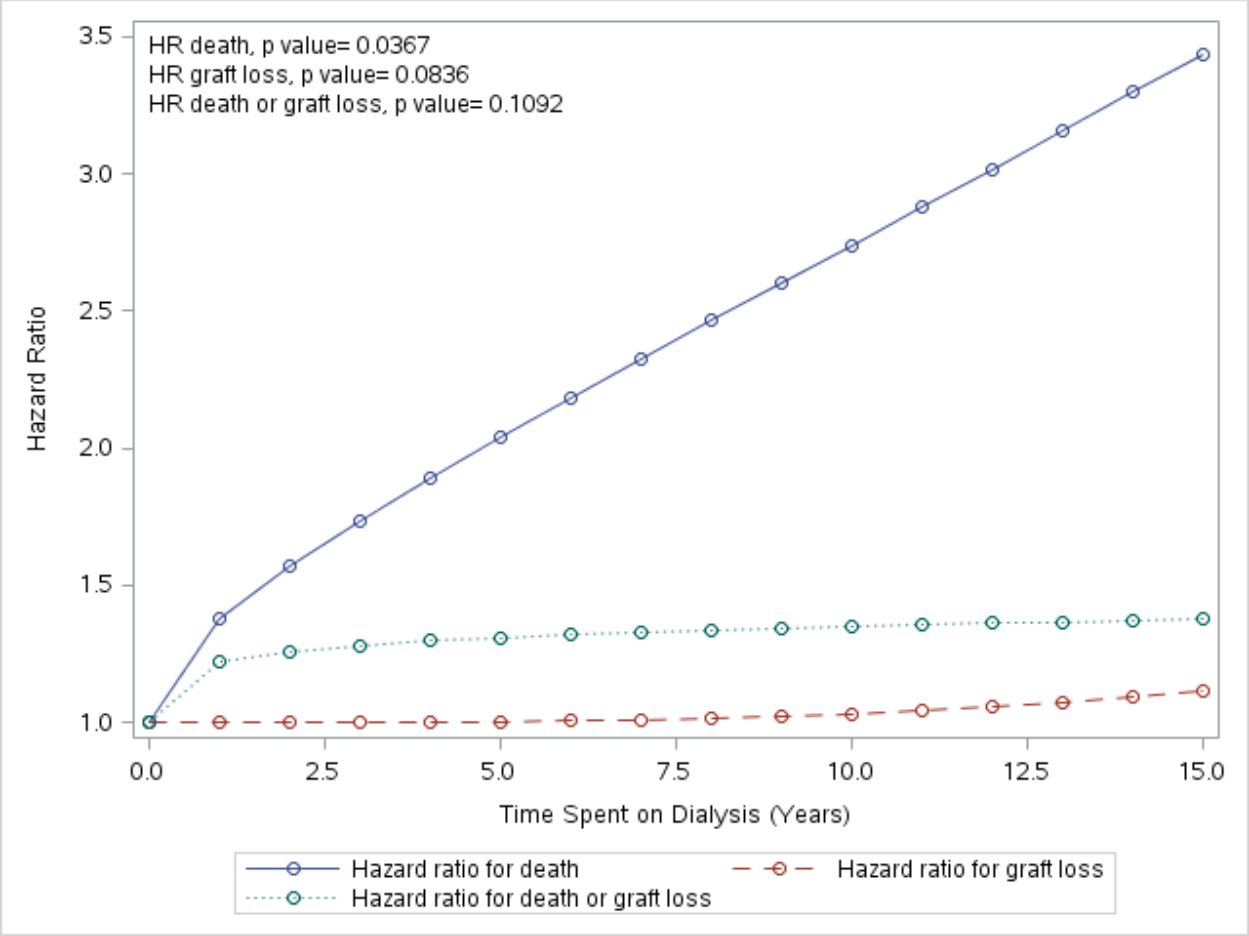
Supplementary Figure 2: Adjusted hazard ratios for age by outcome

Age was transformed to $(1/age)^2$ for the outcomes of death or graft loss and graft loss. Age was log transformed for the outcome of death with graft function.



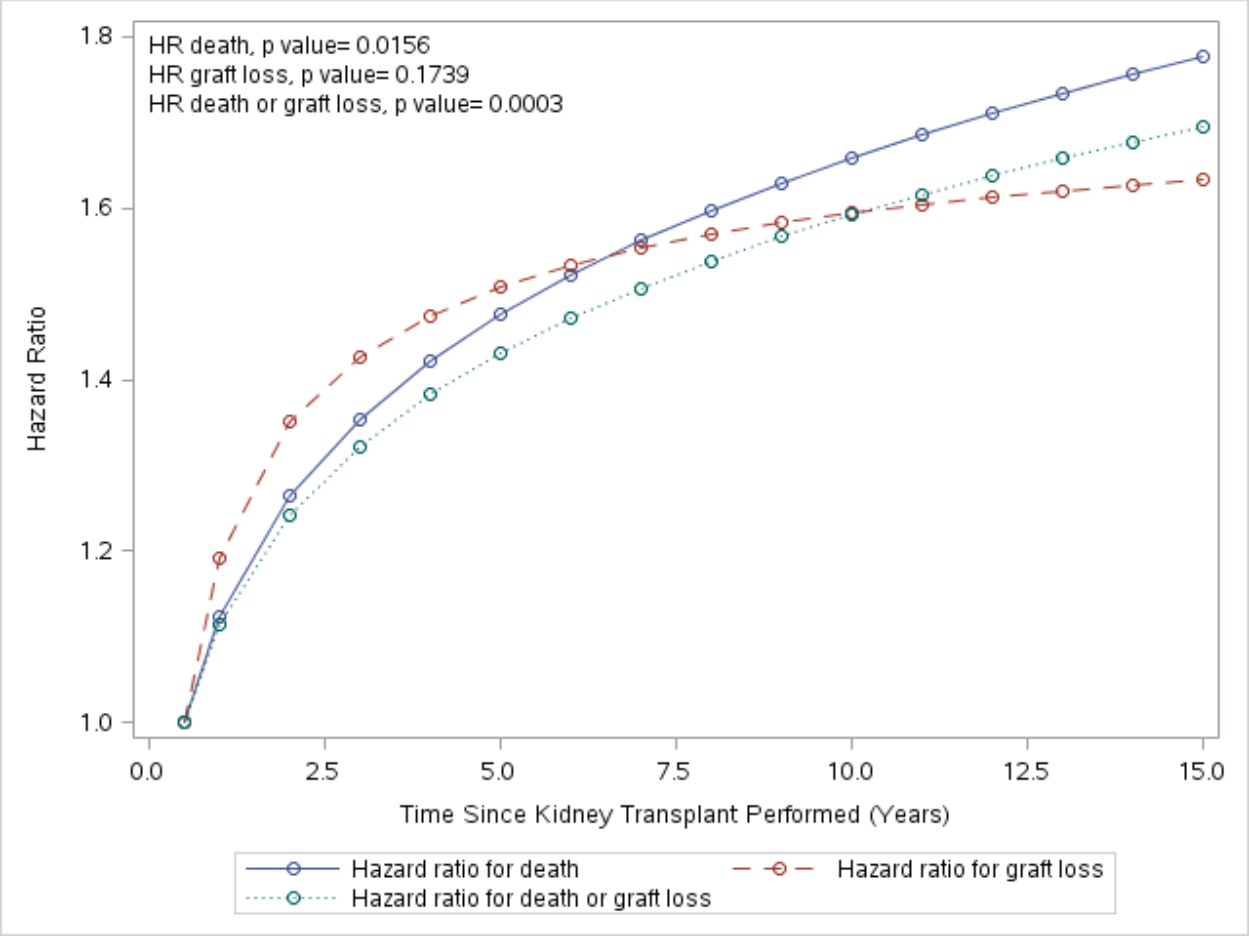
Supplementary Figure 3: Adjusted hazard ratios for year of kidney transplant for all outcomes

Year of kidney transplant was transformed to (1/√year of transplant) for the outcome of death or graft loss, $(\text{year of transplant})^2$ for graft loss, and (1/year of transplant) for death with graft function.



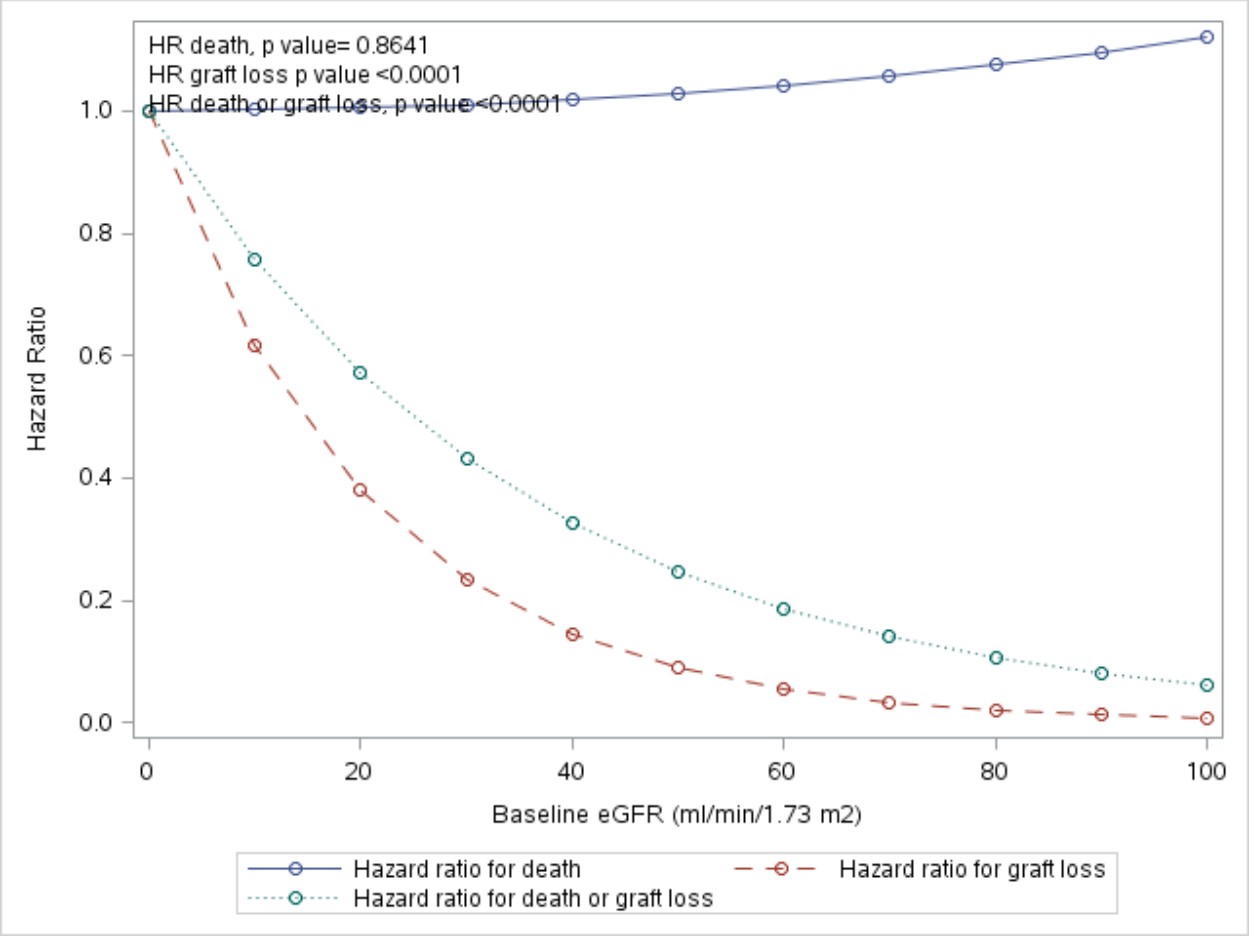
Supplementary Figure 4: Adjusted hazard ratios for time on dialysis prior to transplant for all outcomes

Time on dialysis prior to transplant was log transformed for the outcome of death or graft loss, transformed to $(\text{time on dialysis})^3$ for graft loss, and $\sqrt{}$time on dialysis for death with graft function.



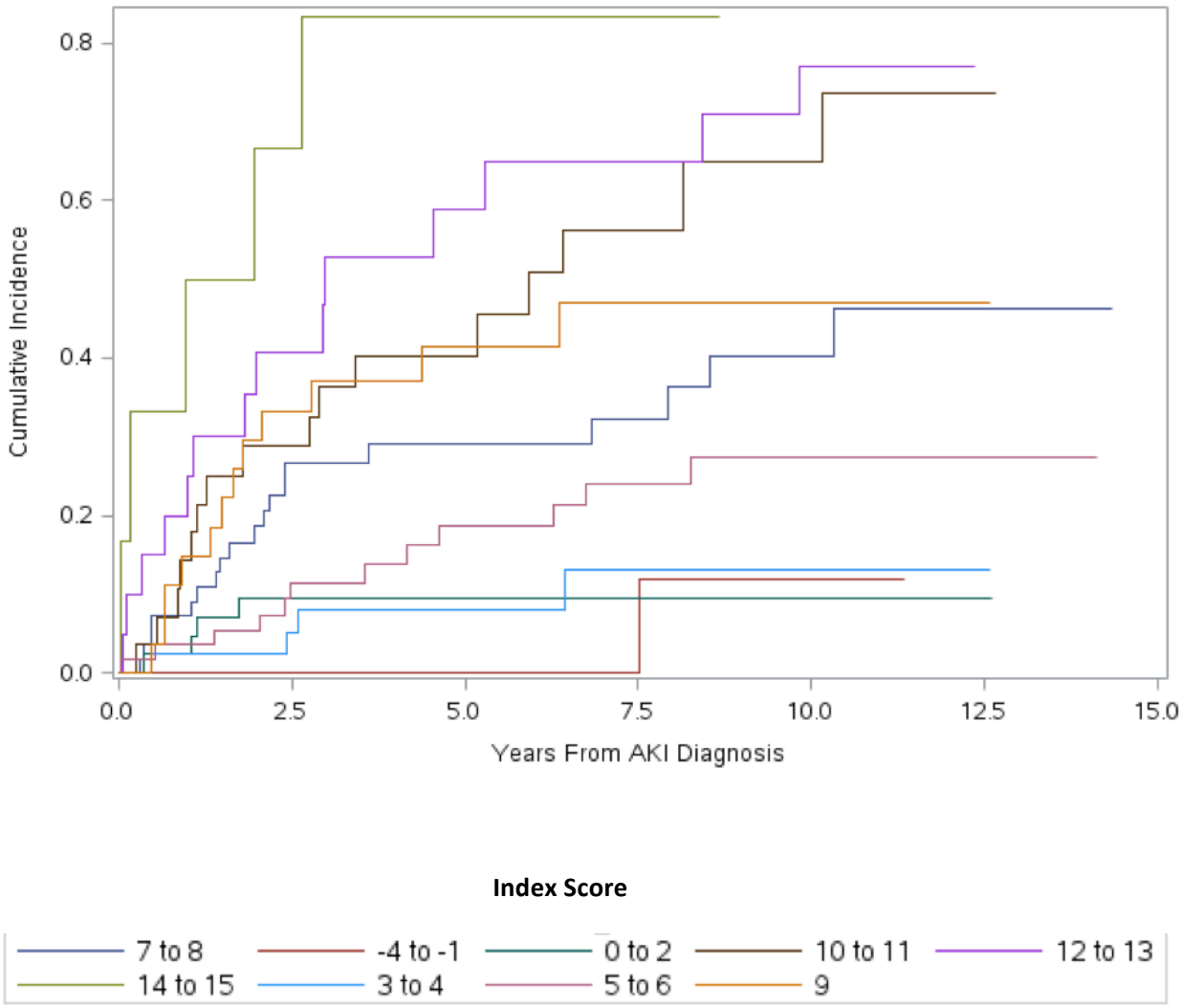
Supplementary Figure 5: Adjusted hazard ratios for time since kidney transplant performed for all outcomes

Time since kidney transplant was log transformed for the outcomes of death or graft loss and death with graft function, and transformed to (1/√time since kidney transplant) for graft loss.



Supplementary Figure 6: Adjusted hazard ratios for baseline eGFR for all outcomes

Baseline eGFR did not require transformation for the outcomes of death or graft loss and graft loss. Baseline eGFR was transformed to $(eGFR)^2$ for the outcome of death with graft function.



Supplementary Figure 7: Observed graft loss stratified by index score. This plot presents the proportion of patients with graft loss (vertical axis) at years after a first hospital admission with AKI (horizontal axis). The index scores within each group are presented in the legend.

Index scores 9 to 11 can be combined and 0 to 4 can be combined (overlapping 5 year cumulative incidence). This gives seven distinct index score groupings.

Supplementary Table 2: Regression model used for the index score to predict graft loss

Variable	Parameter Estimate	Standard Error	Chi-Square	Graft loss Adjusted Hazard Ratio (95% CI)	P value
AKIN stage 2*	0.03055	0.41886	0.0053	1.03 (0.45, 2.34)	0.94
AKIN stage 3*	1.06478	0.33393	10.1674	2.90 (1.51, 5.58)	0.001
Failure to recover from AKI*	0.43062	0.22554	3.6455	1.54 (0.99, 2.39)	0.06
Age**	10.8206	1.75606	37.9686	-	<.0001
Baseline eGFR	-0.04912	0.00733	44.8812	0.95 (0.94, 0.97)	<.0001
Time since kidney transplant**	-0.42611	0.30848	1.9081	-	0.17
Type of donor*	0.17905	0.24814	0.5207	1.20 (0.74, 1.95)	0.47

*****AKIN stage 1, complete recovery from AKI, and living donor as the referent groups. Complete recovery defined as the last available admission creatinine <26.4 umol/L above the baseline creatinine.

**Hazard ratios are not presented. Age and time since transplant were transformed; therefore, their hazard ratios cannot be directly interpreted. Age was transformed to $1/age^2$ and time since transplant was transformed to $1/\sqrt{}$time since transplant.

Supplementary Table 3: Expected and observed 5 year risk of graft loss (death as a competing event) by index score

Index Score	% Patients with Score	5-year graft loss risk	
		Expected	Observed (95% CI)
-4	0.32	1.3%	-
-3	2.86	1.6%	-
-2	5.08	2.0%	-
-1	5.08	2.6%	-
0	5.08	3.3%	6.3% (0.4, 26.0)
1	2.86	4.2%	-
2	5.40	5.4%	17.7% (4.1, 39.1)
3	5.40	6.8%	5.9% (0.3, 24.3)
4	7.30	8.6%	9.2% (1.5, 26.1)
5	8.25	10.9%	20.7% (5.9, 41.4)
6	9.21	13.7%	17.6% (6.2, 33.8)
7	7.30	17.2%	32.3% (13.7, 52.6)
8	10.16	21.5%	26.9% (12.3, 44.1)
9	8.57	26.6%	41.4% (22.3, 59.5)
10	5.40	32.6%	49.0% (22.4, 71.2)
11	3.49	39.6%	40.9% (9.4, 71.4)
12	4.13	47.5%	50.6% (18.0, 76.2)
13	2.22	56.2%	71.4% (15.3, 94.1)
14	0.95	65.1%	66.7% (0.2, 97.3)
15	0.95	74.0%	100.0%
16	0	82.1%	-
17	0	88.9%	-
18	0	94.0%	-
19	0	97.3%	-
20	0	99.0%	-
21	0	99.8%	-
22	0	100.0%	-
23	0	100.0%	-
24	0	100.0%	-
25	0	100.0%	-

For each possible index score, the table presents the expected 5-year risk of graft loss along with that observed in the cohort. Observed values are left empty if no patient in the cohort had an event or no patient in the cohort had that particular index score.

Chapter 5: Discussion

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Summary

This thesis presents a program of research examining AKI in kidney transplantation using administrative and laboratory databases. Background evidence outlining the advantages and limitations of using administrative databases for clinical research along with the existing data on AKI in kidney transplantation, in particular the association of AKI with graft loss, was first presented (Chapter 2). Next, the accuracy of the *ICD-10* code for AKI in the kidney transplant population was confirmed and the limitations of using this code to define AKI in a research setting were discussed (Chapter 3, manuscript 1). Finally, a risk score predicting graft loss following an admission to hospital with AKI 6 months or greater after kidney transplant was presented in Chapter 4 (manuscript 2). This discussion will highlight the novel findings presented in this thesis and the key limitations of the two studies. We will also discuss future plans to expand on the research presented in this thesis.

Novel Findings:

This thesis had two primary objectives. The first objective was to determine the accuracy of the *International Classification of Diseases* (*ICD*)-9 and *ICD*-10 administrative diagnostic codes for AKI in kidney transplant patients admitted to hospital six months or greater following transplant (Chapter 3). This section of the thesis was novel for three main reasons. First, using administrative and laboratory data from Ottawa and Southwestern Ontario, it was demonstrated that the *ICD-10* administrative diagnostic code for AKI has a low sensitivity but high specificity in the kidney transplant population, when compared to a gold standard of a rise in serum creatinine. The most sensitive coding algorithm had a sensitivity of 42.9% (95% CI 29.7, 56.8) and specificity of 89.3% (95% CI 86.2, 91.8), (AKI

defined by a ≥2 fold increase in serum creatinine, *ICD-10* code present in any diagnostic field). Unfortunately, due to small numbers, we were unable to determine the accuracy of *ICD-9* AKI diagnostic codes in the kidney transplant population. Second, the presence or absence of an *ICD-10* diagnostic code for AKI differentiated two groups of patients with distinct changes in serum creatinine at the time of hospital admission (median rise in creatinine 104.2 µmol/L (IQR 57 to 158) *vs.* 16 µmol/L (IQR -3 to 41) for code positive and code negative patients, respectively). Third, this is the first study to determine the accuracy of the *ICD-10* diagnostic code for AKI in the kidney transplant population. The findings demonstrate that using the *ICD-10* code to define AKI in kidney transplant patients will underestimate the true incidence and misclassify patients. The high PPV for mild AKI suggests that the code could be used to define a cohort of kidney transplant patients with AKI.

The second objective of this thesis was to develop a risk score that would predict the risk of graft loss following an admission to hospital with AKI 6 months or greater after receipt of a kidney transplant (Chapter 4). This section of the thesis was novel for three main reasons. First, the presented study is the largest to date to examine AKI in the kidney transplant population with AKI defined using serum creatinine values. The previously published study by Mehrotra *et al.* was very large with over 27, 000 patients [22]; however, AKI was defined using administrative diagnostic codes, which we demonstrated to be very insensitive, potentially introducing bias into their study results. Second, this is the first risk score in kidney transplantation to predict the risk of graft loss following an AKI event 6 months or greater after transplant. The derived risk score is highly discriminative and

incorporates AKI specific factors, such as severity of AKI and recovery from AKI. Third, this is the first risk score in kidney transplantation derived using a competing risk model. We demonstrate that performing a Cox proportional hazards survival analysis with a combined outcome of death or graft loss or an outcome of death censored graft loss introduces bias, as the majority of factors were differentially associated with death and with graft loss. The effect of age best demonstrates the potential for bias if a combined outcome is used. The risk of graft loss clearly decreases with older age while the risk of death clearly rises with older age.

Limitations:

The research presented in this thesis has several limitations that warrant discussion. These limitations have been previously discussed in the introductions and manuscripts presented in Chapters 3 and 4 and will be reviewed in this section. A minor limitation of the validation study (Chapter 3) is the reference standard used to define AKI. Only the creatinine-based component of the AKIN classification system was used to define AKI [4], as urine output measurements were not available. However, the sole use of serum creatinine criteria is a commonly accepted method of defining AKI that has been used in prior studies [47, 23, 48]. As well, the AKIN staging system has not been validated in the kidney transplant population. However, it has been used to define AKI and correlated with poor outcomes in a prior study including kidney transplants [23]. Lastly, the accuracy of the AKI diagnostic code may differ depending on the cause of AKI. Unfortunately, data on cause of AKI was not reliably available.

The primary limitation of the study presented in Chapter 4 (derivation of a risk score to predict graft loss) is that it utilized retrospective datasets that were not primarily created for research. As a result, data on important factors associated with graft loss, such as proteinuria, were missing. Cause of AKI was also not available in the datasets, in particular data on acute rejection. However, acute rejection so far out from kidney transplant is rare, and prior studies on AKI in this timeframe post transplant suggest that infection is the most common cause [30-32, 23]. The second key limitation is the relatively small sample size, which meant that we could not internally validate the risk score. This also affected the precision of our estimates. The score requires validation before it can be reliably used by clinicians. Despite the relatively small number of patients, our study is still the largest, that we are aware of, to examine AKI in the kidney transplant population defined by serum creatinine values [32, 22, 23].

Plans for future research:

The results of the validation study presented in Chapter 3 can be used to inform future studies in kidney transplantation using administrative datasets. There was concern that the limited sensitivity of the *ICD-10* AKI diagnostic code would introduce bias if used to define AKI for the study outlined in Chapter 4; however, the degree and type of bias introduced may be less problematic for other research questions and study designs.

Currently, laboratory data is only available for kidney transplant patients in the Ottawa and London, Ontario areas. This greatly limited the size of our cohort. We are presently working on a data sharing agreement that would allow access to laboratory data

from Toronto kidney transplant patients. This data could be used to validate our risk score for graft loss following AKI.

Conclusion

Administrative and laboratory databases can be used to study AKI in kidney transplantation, but their limitations must be recognized. The validation study in Chapter 3 demonstrated that using a diagnostic code to identify AKI in kidney transplant patients would significantly under capture AKI and misclassify patients. Using this information, we determined that AKI would be best defined using serum creatinine values and not diagnostic codes for the risk score study, recognizing that this would limit the power of the study. In the risk score study, we derived an index to predict the risk of graft loss following an admission to hospital with AKI 6 months or greater after transplant. The index incorporates 6 objective and readily available clinical factors and is highly discriminative. Validation of the risk score is required.

Appendices

Appendix 1: AKIN Classification system for AKI

Acute Kidney Injury Network (AKIN) Classification (taken from Mehta *et al.*)[4]

Stage	Serum creatinine criteria	Urine output criteria
1	Increase in serum creatinine of more than or equal to >=26.4 umol/l or increase to more than or equal to 150% to 200% (1.5 to 2 fold) from baseline	Less than 0.5 mg/kg/hour for more than 6 hours
2	Increase in serum creatinine to more than 200% to 300% (>2 to 3 fold) from baseline	Less than 0.5 mg/kg/hour for more than 12 hours
3	Increase in serum creatinine to more than 300% (>3 fold) from baseline or if baseline serum creatinine >=354 umol/L, an acute increase of at least 44 umol/L or requirement of renal replacement therapy	Less than 0.3 ml/kg/hour for 24 hours or anuria for 12 hours

Appendix 2: STARD (STAndards for the Reporting of Diagnostic accuracy studies) checklist, manuscript one

Section and Topic	Item #		Page
TITLE/ABSTRACT/ KEYWORDS	1	Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity').	23-24
INTRODUCTION	2	State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.	26-27
METHODS			
Participants	3	The study population: The inclusion and exclusion criteria, setting and locations where data were collected.	27-29
	4	Participant recruitment: Was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?	28-29
	5	Participant sampling: Was the study population a consecutive series of participants defined by the selection criteria in item 3 and 4? If not, specify how participants were further selected.	N/A
	6	Data collection: Was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?	27
Test methods	7	The reference standard and its rationale.	29-30

	8	Technical specifications of material and methods involved including how and when measurements were taken, and/or cite references for index tests and reference standard.	29-30
	9	Definition of and rationale for the units, cut-offs and/or categories of the results of the index tests and the reference standard.	29-31
	10	The number, training and expertise of the persons executing and reading the index tests and the reference standard.	29-31
	11	Whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers.	N/A
Statistical methods	12	Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals).	31, Appendix 3
	13	Methods for calculating test reproducibility, if done.	N/A
RESULTS			
Participants	14	Report when study was done, including beginning and ending dates of recruitment.	29, Supplementary Fig 1
	15	Report clinical and demographic characteristics of the study population (e.g. age, sex, spectrum of presenting symptoms, comorbidity, current treatments, recruitment centers).	31, Table 1
	16	Report the number of participants satisfying the criteria for inclusion that did or did not undergo the index tests and/or the reference standard; describe why participants failed to receive either test (a flow diagram is strongly recommended).	Supplementary Figure 1
Test results	17	Report time interval from the index tests to the reference standard, and any treatment administered between.	33-36***
	18	Report distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition.	34, 36, Table 1
	19	Report a cross tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard.	37, Table 2, Table 3
	20	Report any adverse events from performing the index tests or the reference standard.	N/A
Estimates	21		
	22	Report estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals).	37, Table 2, Table 3, Supplementary Figs 2 and 3
	23	Report how indeterminate results, missing responses and outliers of the index tests were handled.	N/A
	24	Report estimates of variability of diagnostic accuracy between subgroups of participants, readers or centers, if	N/A
DISCUSSION	25	Report estimates of test reproducibility, if done.	N/A

Appendix 3: Sample 2 by 2 table for assessing diagnostic performance characteristics (sensitivity, specificity, positive predictive value, and negative predictive value) for *ICD-10* code N17x

	Reference Standard: AKIN definition of AKI	
	≥ 2-fold increase in serum creatinine concentration from baseline	< 2-fold increase in serum creatinine concentration from baseline
Code N17x positive	True Positive (TP)	False Positive (FP)
Code N17x negative	False Negative (FN)	True Negative (TN)

Sensitivity (Sn) = TP ¸ (TP + FN); the proportion of patients with ≥ 2-fold increase in serum creatinine concentration from baseline who are code N17x positive
Specificity (Sp) = TN ¸ (FP + TN); the proportion of patients with < 2-fold increase in serum creatinine concentration from baseline who are code N17x negative
Positive Predictive Value (PPV) = TP ¸ (TP + FP); the proportion of patients who are code N17x positive with ≥2-fold increase in serum creatinine concentration from baseline
Negative Predictive Value (NPV) = TN ¸ (FN + TN); the proportion of patients who are code N17x negative with <2-fold increase in serum creatinine concentration from baseline
Positive likelihood ratio (LR+) = sensitivity/ (1-specificity)

Appendix 4: STROBE Guidelines checklist, manuscript two

	Item No.	Recommendation	Reported
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	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 and design
Setting	5	Describe the setting, locations and relevant dates, including periods of recruitment, exposure, follow-up and data collection	Methods – setting and design; data sources
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods-Study Cohort, Supplementary Fig 1
		(b) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods, appendices
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	Methods – data sources; appendices
Bias	9	Describe any efforts to address potential sources of bias	Methods – statistical analysis; Discussion
Study size	10	Explain how the study size was arrived at	n/a
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods-Statistical analysis
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Methods
		(b) Describe any methods used to examine subgroups and interactions	Methods
		(c) Explain how missing data were addressed	Methods, appendices
		(d) If applicable, explain how loss to follow-up was addressed	n/a
		(e) Describe any sensitivity analyses	n/a
Results			
Participants	13	(a) Report numbers of individuals at each stage of study – e.g. numbers potentially eligible, examined	Results; Supplementary Fig

		for eligibilty, confirmed eligible, included in the study, completing follow-up, and analysed	1
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	Supplementary Fig 1
Descriptive data	14	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	Results, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (e.g. average and total amount)	Results
Outcome data	15	Report numbers of outcome events or summary measures over time	Results
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	Results
		(b) Report category boundaries when continuous variables were categorized	Results
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Results
Other analyses	17	Report other analyses done – e.g. analyses of subgroups and interactions, and sensitivity analyses	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. Discuus 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
Gerneralisability	21	Discuss the gerneralisability (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	Acknowledgments

Appendix 5: Coding definitions

Coding definitions for demographic, co-morbid conditions, and AKI characteristics

Characteristic	Database	Codes
Age, Sex, Income, Rural	RPDB	
Race, Time on dialysis prior to transplant, Date of kidney transplant, Type of donor, Cause of ESRD	CORR	
Diabetes Mellitus	CIHI-DAD/OHIP	ICES derived cohort-ODD
Hypertension	CIHI-DAD/OHIP	ICES derived cohort-HYPERTENSION
Congestive Heart Failure	CIHI-DAD/OHIP	ICD9: 425, 5184, 514, 428 ICD10: I500, I501, I509, I255, J81 CCP: 4961, 4962, 4963, 4964 CCI: 1HP53, 1HP55, 1HZ53GRFR, 1HZ53LAFR, 1HZ53SYFR OHIP fee codes: R701, R702, Z429 OHIP diagnosis code: 428
Coronary Artery Disease	CIHI-DAD/OHIP	ICD9: 412, 410, 413, 414, 4292, 4295, 4296, 4297 ICD10: I21, I22, Z955, Z958, Z959, R931, T822 CCI: 1IJ26, 1IJ27, 1IJ50, 1IJ54, 1IJ57, 1IJ76 CCP: 4801, 4802, 4803, 4804, 4805, 481, 482, 483 OHIP: R741, R742, R743, G298, E646, E651, E652, E654, E655, G262, Z434, Z448 OHIP diagnosis code: 410, 412, 413
Stroke/TIA	CIHI-DAD	ICD9: 430, 431, 4340, 4341, 4349, 436, 435, 3623 ICD10: H341, I630, I631, I632, I633, I634, I635, I638, I639, G45, I629, I64, G45", H340, I600, I601, I602, I603, I604, I605, I606, I607, I607, I609, I61
Chronic obstructive pulmonary 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, 571, 2750, 2751, 7891, 7895

		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
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 feecode: 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, R813, R867, E649
AKI requiring acute dialysis	OHIP	OHIP fee: R849, G323, G866, G330, G331, G093, G095, G294, G295

Abbreviations: RPDB, Registered Persons Database; CIHI-DAD, Canadian Institute for Health Information Discharge Abstract Database; OHIP, Ontario Health Insurance Plan; CCP, Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures; CCI, Canadian Classification of Interventions; CORR, Canadian Organ Reporting Register; TIA, transient ischemic attack; AKI: acute kidney injury

Coding definitions for outcomes

Outcome	**Database**	**Codes**
Death	RPDB	
Return to chronic dialysis (graft loss)	CORR, ORRS	CORR: (Treatment_Code): 111, 112, 113, 121, 122, 123, 131, 132, 133, 211, 221, 231, 311, 312, 313, 321, 322, 323, 331, 332, 333, 413, 423, 433, 141, 151, 152, 241, 242, 251, 252, 443, 453, 060 ORRS: Treatmentchangecd: RR, F, N, M
Repeat kidney transplant (graft loss)	CORR, ORRS	CORR: (Treatment_code): 171 (Transplanted_Organ_type_code) [1-3]: 10, 11, 12, 18, 19 ORRS: Treatmentchangecd= TX

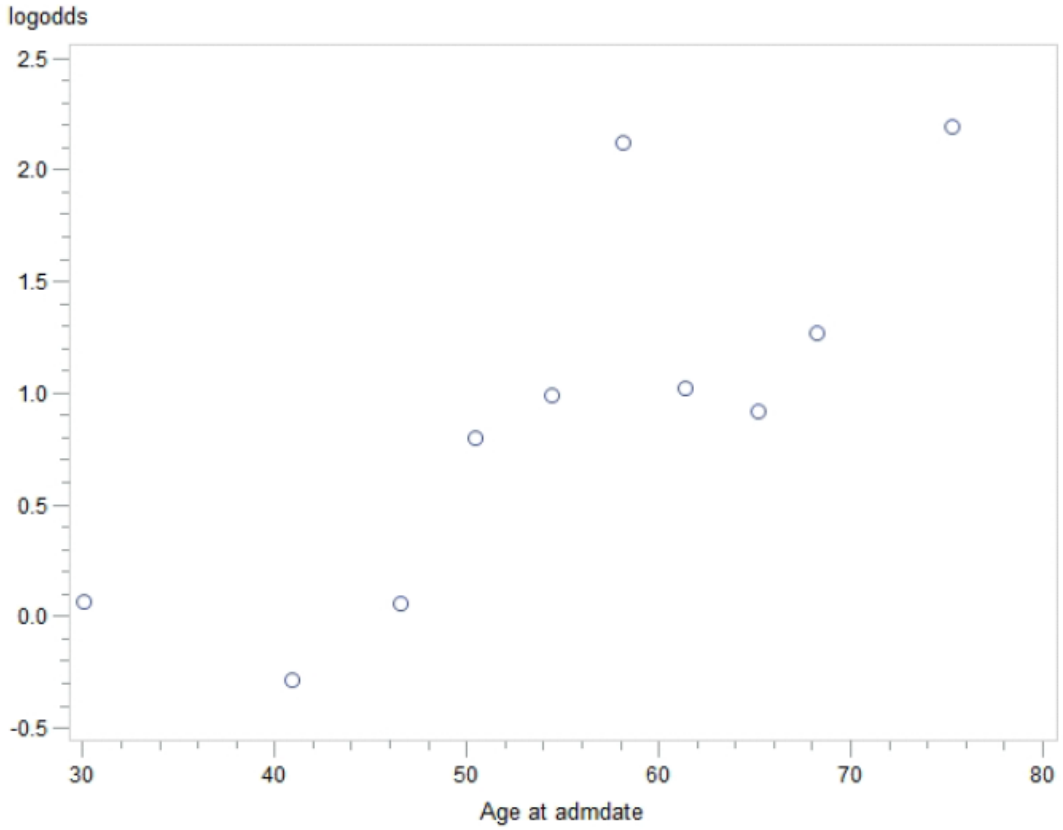
Abbreviations: CORR, Canadian Organ Reporting Register; ORRS, Ontario Renal Reporting System

Appendix 6: Logistic regression model to impute missing values for type of donor

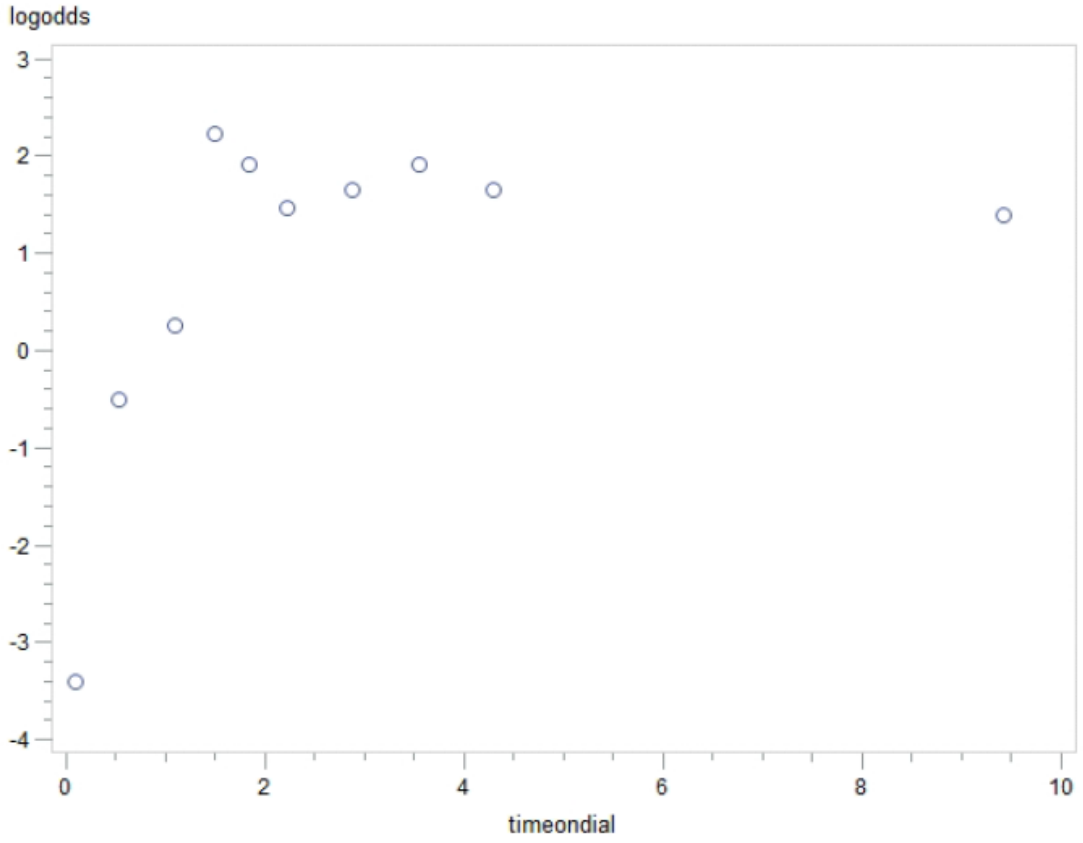
Based on clinical experience, the following variables were included in the logistic regression model to predict donor status: Age, time on dialysis prior to transplant, year of kidney transplant, and income quintile (created a dichotomous variable with income quintiles 1,2 and 3 in one group and income quintiles 4 and 5 in the other).

Continuous variables were plotted against the log odds of donor type to determine if transformation was required (see below). Based on the plots, age was kept in linear form, time on dialysis and year of transplant were transformed. Different transformations were entered into the model. The transformation that provided the lowest AIC value was selected. In the final model, time on dialysis was log transformed. Year of transplant was not transformed. If the logistic regression model predicted that a patient had a ≥50 % chance of receiving a deceased donor kidney and their donor status was missing, the status was imputed as deceased.

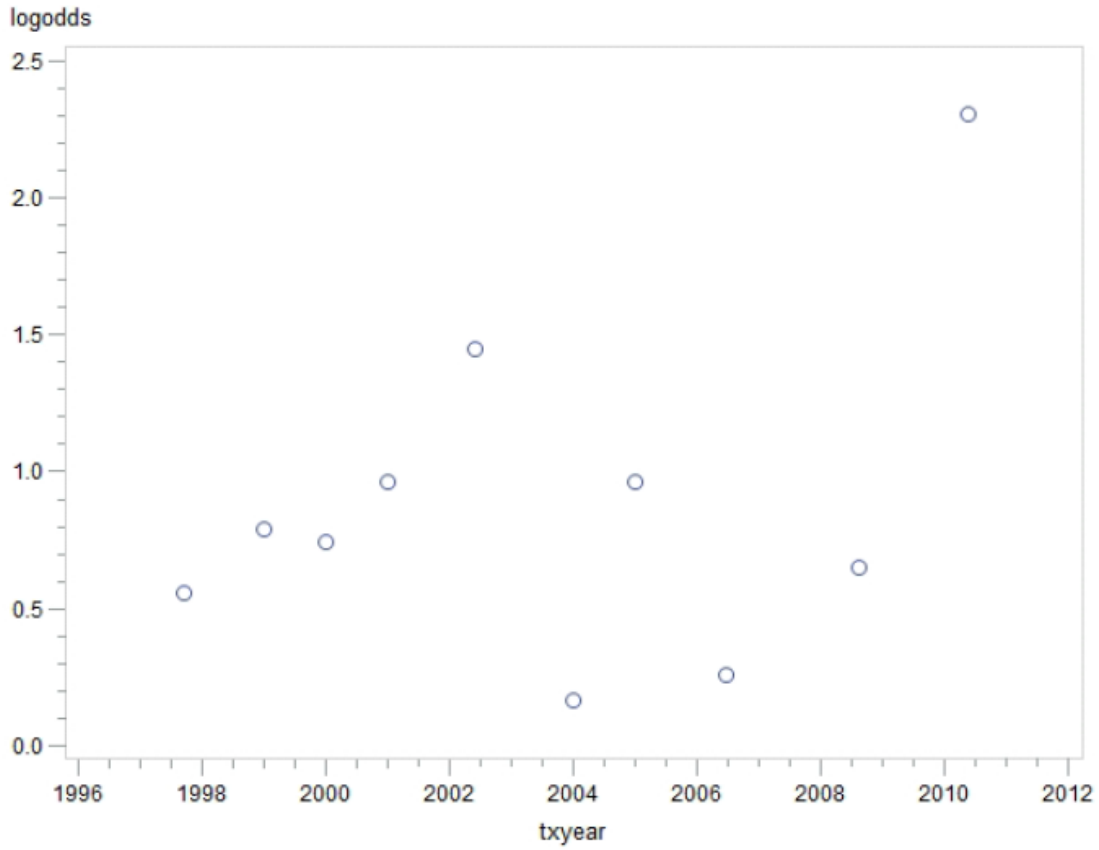
Plot for Age



Plot for Time on Dialysis Prior to Transplant



Plot for Year of Kidney Transplant



Appendix 7: Details regarding prognostic index creation and assessment

We used the methods described by Sullivan *et al.* [134] to modify the regression model into a prognostic index to predict the 5-year risk of graft loss. This time point was chosen because it was close to the median follow-up time of the cohort. The number of points assigned to each covariate in the regression model equalled its coefficient divided by the parameter estimate for the covariate with the smallest absolute value, rounded to the nearest whole number. For the creation of our index, each coefficient was divided by the absolute value of the coefficient for baseline eGFR multiplied by 5 (also referred to as the constant or B). Continuous variables were categorized. Categories with the same point value were combined. Each person's final index score was then calculated by summing up the points for each factor that applied to that person. The 5-year graft survival estimate for each possible score was calculated as 1 minus the following:

$$S_0(t)^{\exp\left(\sum_{i=1}^{p} \beta_i X_i - \sum_{i=1}^{p} \beta_i \bar{X}_i\right)}$$

S_0 is the average 5-year graft survival of the cohort (calculated by 1- 5-year cumulative incidence for graft loss), and p is the point total.

$\sum_{i=1}^{p} \beta_i \bar{X}_i$ was calculated once by summing the regression coefficients multiplied by the means (continuous variables) or proportions (categorical variables) of each risk factor.

$$\sum_{i=1}^{p} \beta_i X_i$$

was calculated for each point total and is ≈ the regression coefficient of the covariate used to calculate the constant (which in our case was baseline eGFR)*the selected baseline value for eGFR + B*p.

To measure the discrimination of the index, we grouped the prognostic index scores in the cohort together so that their cumulative incidence significantly differed from that in all other index score groups by $p<0.01$ using the Gray's test for equality of the cumulative incidence functions.

To measure calibration of the index, we compared the model-based expected and observed 5-year graft survival in the cohort at each prognostic index score. Expected and observed graft loss rates were deemed similar if the 95% confidence interval for the observed graft loss rate included the expected rate.

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