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Risk Factors and Outcomes of Early Hospital Readmission in Canadian Kidney Transplant Recipients: A Population-Based Multi-Center Cohort Study

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Abstract

Background: Early hospital readmissions (EHRs) occur commonly in kidney transplant recipients. Conflicting evidence exists regarding risk factors and outcomes of EHRs.

Objective: To determine risk factors and outcomes associated with EHRs (ie, hospitalization within 30 days of discharge from transplant hospitalization) in kidney transplant recipients.

Design: Population-based cohort study using linked, administrative health care databases.

Setting: Ontario, Canada.

Patients: We included 5437 kidney transplant recipients from 2002 to 2015.

Measurements: Risk factors and outcomes associated with EHRs. We assessed donor, recipient, and transplant risk factors. We also assessed the following outcomes: total graft failure, death-censored graft failure, death with a functioning graft, mortality, and late hospital readmission.

Methods: We used multivariable logistic regression to examine the association of each risk factor and the odds of EHR. To examine the relationship between EHR status (yes vs no [reference]) and the outcomes associated with EHR (eg, total graft failure), we used a multivariable Cox proportional hazards model.

Results: In all, 1128 kidney transplant recipients (20.7%) experienced an EHR. We found the following risk factors were associated with an increased risk of EHR: older recipient age, lower income quintile, several comorbidities, longer hospitalization for initial kidney transplant, and older donor age. After adjusting for clinical characteristics, compared to recipients without an EHR, recipients with an EHR had an increased risk of total graft failure (adjusted hazard ratio [aHR]: 1.46, 95% CI: 1.29, 1.65), death-censored graft failure (aHR: 1.62, 95% CI: 1.36, 1.94), death with graft function (aHR: 1.34, 95% CI: 1.13, 1.59), mortality (aHR: 1.41, 95% CI: 1.22, 1.63), and late hospital readmission in the first 0.5 years of follow-up (eg, 0 to <0.25 years: aHR: 2.11, 95% CI: 1.85, 2.40).

Limitations: We were not able to identify which readmissions could have been preventable and there is a potential for residual confounding.

Conclusions: Results can be used to identify kidney transplant recipients at risk of EHR and emphasize the need for interventions to reduce the risk of EHRs.

Trial registration: This is not applicable as this is a population-based cohort study and not a clinical trial.

Abrégé

Contexte: Les réadmissions précoces à l'hôpital (RPH) sont fréquentes chez les receveurs d'une greffe rénale. Les données sur les facteurs de risque d'une RPH et sur les résultats qui y sont associés restent toutefois contradictoires.

Objectif: Définir les facteurs de risque et les effets associés à une RPH (soit une hospitalization dans les 30 jours suivant la sortie de l'hôpital après la transplantation) chez les receveurs de greffe rénale.

Type d'étude: Étude de cohorte représentative d'une population, réalisée à partir des bases de données administratives en santé.

Cadre: Ontario, Canada.

Sujets: Ont été inclus 5 437 adultes receveurs d'une greffe rénale entre 2002 et 2015.
Mesures: Les facteurs de risque et les résultats associés à une RPH. Nous avons évalué les facteurs de risque du donneur, du receveur et de la transplantation. Nous avons également évalué les résultats suivants : l'échec du greffon, l'échec du greffon censuré par le décès, le décès avec un greffon fonctionnel, la mortalité et les réadmissions tardives.
Méthodologie: Nous avons utilisé la régression logistique multivariée pour examiner l'association de chaque facteur de risque et les probabilités de RPH. Un modèle multivarié des risques proportionnels de Cox a par ailleurs servi à examiner la relation entre le statut des RPH (oui vs non [référence]) et les résultats associés à celles-ci (p. ex., l'échec de la greffe).
Résultats: Dans la cohorte étudiée, 1 128 receveurs d'une greffe rénale (20,7 %) ont été réadmis précocement à l'hôpital. Les facteurs de risque suivants ont été associés à un risque accru de RPH : âge plus avancé du receveur, provenance d'un quartier au quintile de revenu inférieur, présence de plusieurs comorbidités, hospitalization initiale plus longue pour la transplantation rénale et âge plus avancé du donneur. Après ajustement pour les caractéristiques cliniques, par rapport aux receveurs de greffe qui n'avaient pas été réadmis précocement, les patients avec une RPH présentaient un risque accru d'échec du greffon (risque relatif corrigé [RRc] : 1,46; IC 95 % : 1,29-1,65), d'échec du greffon censuré par le décès (RRc: 1,62; IC 95 % : 1,36-1,94), de décès avec un greffon fonctionnel (RRc: 1,34; IC 95 % : 1,13-1,59), de mortalité (RRc: 1,41; IC 95 % : 1,22-1,63) et de réadmission tardive au cours des premiers six mois de suivi (p. ex., entre 0 et moins de 0,25 an de suivi, le RRc était de 2,11; [IC 95 % : 1,85-2,40]).
Limites: Nous n'avons pas été en mesure d'identifier les réadmissions qui auraient pu être prévenues et il existe un risque de facteurs de confusion résiduels.
Conclusion: Ces résultats peuvent être employés pour identifier les receveurs d'une greffe rénale susceptibles d'être réadmis rapidement à l'hôpital. Ces résultats soulignent en outre la nécessité d'interventions pour réduire le risque de RPH.
Enregistrement de l'essai: Sans objet puisqu'il s'agit d'une étude de cohorte basée sur la population et non d'un essai clinique.

Keywords
early hospital readmission, kidney transplant recipient, risk factors, outcomes, graft failure

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Introduction

Early hospital readmission (EHR) can be defined as an admission occurring within 30 days of discharge from transplant surgery.[1] EHRs commonly occur in kidney transplant recipients with as many as one-third of recipients experiencing these events.[1] Several studies have found an association between EHR and mortality, morbidity, and graft loss.[2-6] For example, Harhay et al, found that recipients with an EHR had a 41% higher rate of mortality compared to recipients with no EHR.[3] Moreover, EHRs are associated with high economic costs with the average cost per recipient estimated at more than USD10 000 and more than CAD11 000.[7,8]

We conducted a comprehensive search of bibliographic databases (PubMed and Medline) in March 2021, finding several studies examining risk factors and outcomes of EHR (summary of previously conducted studies in Supplementary Tables S1a and S1b).[2-20] However, risk factors and outcomes associated with EHR remain uncertain with many risk factors (eg, body mass index, delayed graft failure, weekend discharge for kidney transplantation, comorbidities) and outcomes (ie, graft loss) inconsistently associated with EHR. Furthermore, there are several notable limitations of previous studies. First, there have been limited multi-center studies conducted in health care

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systems outside the United States and results may vary by country with differences in recipient, transplant, and donor characteristics across health care systems.[21,22] Second, previous studies have limited generalizability, with most being single-centered. Third, many studies assessing risk factors had a relatively small number of EHR events, which resulted in imprecise estimates.

An understanding of risk factors associated with EHR is important to identify kidney transplant recipients who may benefit from increased monitoring post-transplant and guides the development of interventions aimed to reduce EHRs and its consequences. Given the limitations of previous studies, we conducted this multi-center study using data from Canada's unique universal health care system, to identify risk factors associated with EHR after kidney transplantation. We also compare recipients with an EHR to recipients without an EHR on several important post-transplant outcomes, including total graft failure (ie, return to chronic dialysis, pre-emptive re-transplantation, or death), death-censored graft failure, death with a functioning graft, all-cause mortality, and late hospital readmission.

Methods

Design and Setting

We conducted a population-based cohort study using provincial administrative health care databases in Ontario, Canada. These datasets were linked using unique, encoded identifiers and analyzed at ICES (ices.on.ca). The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board. To report this study, we followed guidelines for observational studies (Supplementary Table S2).[23]

Data Sources

We used the Canadian Organ Replacement Register (CORR) to create our cohort of kidney transplant recipients. When compared to chart review, CORR accurately captures kidney transplantation with more than 95% sensitivity.[24] The Registered Persons Database provided information on vital status and patient demographics. We used the Canadian Institute for Health Information (CIHI) Discharge Abstract Database to identify hospitalization-associated procedural and diagnostic codes, while same day surgeries were identified from CIHI Same Day Surgery. To identify emergency department visits we used the CIHI National Ambulatory Care Reporting System. Physician submitted billing and diagnostic codes were obtained from the Ontario Health Insurance Plan. Our data sources are largely complete with emigration from the province being the only reported reason for loss to follow-up ($<0.5\%$ annually).[25]

Cohort Creation

We included kidney transplant recipients who were discharged from one of the Ontario's 6 transplant hospitals for their kidney transplant from April 1, 2002 to February 28, 2015. We excluded the following individuals: aged <18 years on the date of transplant, died on or before the discharge date for the hospitalization for their kidney transplant surgery, simultaneous multi-organ transplant recipient (eg, kidney-pancreas transplant), and missing donor type (living vs deceased). We have used this cohort in a previously published study.[26]

Early Hospital Readmission

We defined EHR as an admission to an acute care hospital within 30 days of hospital discharge for the initial kidney transplant. We excluded admissions for elective procedures (Supplementary Table S3). Hospital transfers were considered to be part of the same episode of care and were not counted as an EHR.[26]

Risk Factors

We considered multiple recipient, donor, and transplant characteristics, including initial transplant hospitalization characteristics and post-operative complications to potentially be associated with EHR (Table 1). Risk factors were selected based on the literature from the kidney transplant[1] and general population,[27] clinical expertise, and data availability. Further details on the administrative database codes used to identify risk factors are described in Table S3. We defined frailty using the Johns Hopkins Adjusted Clinical Group (ACG)® System Version 10.[28] Frailty was defined as a binary variable (yes vs no) based on 12 clusters of diagnoses, including malnutrition, dementia, impaired vision, decubitus ulcer, incontinence of urine, loss of weight, incontinence of feces, obesity (morbid), poverty, access to care barriers, difficulty in walking, and falls. Individuals were considered frail if they were in ≥ 1 of the aforementioned diagnosis clusters.[28] The index date (cohort entry date) for the risk factor analysis was the date of discharge from the hospital for the initial kidney transplant. The maximum follow-up date for an EHR was March 30, 2015 (ie, 30 days after discharge for the kidney transplant surgery).

Outcomes After Early Hospital Readmission

When assessing the association between EHR and post-transplant outcomes, our primary outcome was total graft failure which we defined as a composite of death or graft failure (ie, return to chronic dialysis or pre-emptive kidney re-transplantation). Secondary outcomes included death-censored graft failure, death with graft function, all-cause mortality, and late hospital readmission. We defined

Table 1. Characteristics of Kidney Transplant Recipients Classified by Early Hospital Readmission Status.[a]

Characteristic	No early hospital readmission (N = 4309)	Early hospital readmission (N = 1128)	Standardized difference[b] (%)
Recipient characteristics			
Age, years	52 (41, 61)	54 (44, 63)	**16**
Female	1590 (36.9)	400 (35.5)	3
Race			
White	2742 (63.6)	731 (64.8)	2
Asian	309 (7.2)	56 (5.0)	9
Black	311 (7.2)	85 (7.5)	1
Other	579 (13.4)	155(13.7)	1
Unknown or Missing	368 (8.5)	101 (9.0)	1
Income quintile[c]			
Quintile 1, low	929 (21.6)	252 (22.3)	2
Quintile 2	873 (20.3)	268 (23.8)	8
Quintile 3, middle	896 (20.8)	232 (20.6)	1
Quintile 4	849 (19.7)	186 (16.5)	8
Quintile 5, high	762 (17.7)	190 (16.8)	2
Urban residence[d]	3823 (88.7)	995 (88.2)	2
Cause of ESKD			
Glomerulonephritis	1356 (31.5)	322 (28.5)	6
Cystic kidney disease	544 (12.6)	111 (9.8)	9
Diabetes	751 (17.4)	236 (20.9)	9
Renal vascular disease	424 (9.8)	105 (9.3)	2
Other	580 (13.5)	173 (15.3)	5
Unknown or missing	654 (15.2)	181 (16.0)	2
Comorbidities			
Coronary artery disease w/o angina	1690 (39.2)	457 (40.5)	3
Myocardial infarction	113 (2.6)	46 (4.1)	8
Heart failure	626 (14.5)	207 (18.4)	**10**
Hypertension[e]	2,645 (61.4)	690 (61.2)	0
Diabetes[e]	1,235 (28.7)	371 (32.9)	9
Stroke/TIA	72 (1.7)	26 (2.3)	5
Major Cancers[f]	280 (6.5)	90 (8.0)	6
Chronic Liver Disease	493 (11.4)	152 (13.5)	6
Peripheral Vascular Disease	423 (9.8)	163 (14.5)	**14**
Chronic obstructive pulmonary disease	46 (1.1)	27 (2.4)	**10**
Frailty[g]	198 (4.6)	81 (7.2)	**11**
Arrhythmia	279 (6.5)	94 (8.3)	7
Charlson Comorbidity Score[h]	2 (2, 3)	2 (2, 4)	**16**
Hospitalization in the year prior to transplant	2,568 (59.6)	716 (63.5)	8
Transplant characteristics			
Dialysis modality[i]			
Hemodialysis	2934 (68.1)	814 (72.2)	9
Peritoneal dialysis	959 (22.3)	223 (19.8)	6
Preemptive[j]	416 (9.7)	91 (8.1)	6
Dialysis vintage (pre-transplant)[k], years	3 (1, 6)	4 (2, 6)	**11**
Delayed graft function[l]	1080 (25.1)	313 (27.7)	6
History of organ transplant[m]	394 (9.1)	114 (10.1)	3
Transplant era			
2002-2004	683 (15.9)	204 (18.1)	6
2005-2007	951 (22.1)	259 (23.0)	2
2008-2010	1148 (26.6)	258 (22.9)	9
2011-2014	1527 (35.4)	407 (36.1)	1

(continued)

Table 1. (continued)

Characteristic	No early hospital readmission (N = 4309)	Early hospital readmission (N = 1128)	Standardized difference[b] (%)
Donor characteristics			
Donor type			
Living donor	1790 (41.5)	418 (37.1)	9
Deceased donor	2,519 (58.5)	710 (62.9)	9
Donor age, years	47 [36-55]	49 [37-57]	**15**
Donor age, ≥60 years	623 (14.5)	216 (19.1)	**13**
Initial transplant hospitalization characteristics			
Length of stay >7 days	2402 (55.7)	773 (68.5)	**27**
Weekend discharge for kidney transplant surgery	508 (11.8)	121 (10.7)	3
Season discharged			
Summer	1072 (24.9)	264 (23.4)	3
Autumn	1143 (26.5)	309 (27.4)	2
Spring	1048 (24.3)	282 (25.0)	2
Winter	1046 (24.3)	273 (24.2)	0
Post-operative complications[n]			
Sepsis	28 (0.6)	8 (0.7)	1
Myocardial infarction	78 (1.8)	36 (3.2)	9

Note. Data presented as number (percentage) or median (25th, 75th percentile). Bold standardized differences represent a meaningful difference (ie, difference ≥ 10%). ESKD = end-stage kidney disease; TIA = transient ischemic attack

[a]All baselines assessed 3 years prior to the discharge date for the initial kidney transplant hospitalization unless otherwise indicated.

[b]Standardized differences were used to compare early hospital readmission to no early hospital readmission; a value ≥10% is interpreted as a meaningful difference between groups.

[c]Income is represented according to fifths of average neighborhood income.

[d]Urban residence defined as a population >10 000.

[e]Hypertension and diabetes defined as 2 Ontario Health Insurance Plan codes or one hospitalization with a diagnosis of hypertension or diabetes, in the 3 years prior to the discharge date for the initial kidney transplant.

[f]Major cancers defined as a composite of lung/bronchi, colon/rectum, breast, pancreas, prostate, leukeumia, non-Hodgkin lymphoma, liver, ovarian, esophageal, bowel, breast, lung, and prostate cancers.

[g]Frailty defined based on 12 clusters of diagnoses associated with frailty.

[h]Recipients with a Charlson comorbidity index score of 0 were given a score of 2 and recipients with a score of 1 were given a score of 3; kidney disease is a variable in the Charlson which results in all recipients receiving a minimum score of 2.

[i]Dialysis modality selected based on the modality the recipient was on closest to their transplant date.

[j]Preemptive kidney transplant defined as no dialysis prior to the kidney transplant date.

[k]Dialysis vintage was defined as the kidney transplant date—dialysis initiation date. Recipients with no history of dialysis prior to transplant (ie, preemptive kidney transplant) were given a dialysis vintage of 0.

[l]Delayed graft function defined as evidence of dialysis within the first 7 days of transplantation but no dialysis in the 90-150 days.

[m]History of transplant defined as receipt of any solid organ transplant type (eg, kidney, liver) prior to the kidney transplant date.

[n]Post-operative complications occurred from the kidney transplant date to the date of hospital discharge.

death-censored graft failure as graft failure with death treated as a censoring event. Death with graft function was defined as death occurring after kidney transplantation but prior to graft failure, with the latter treated as a censoring event if it occurred prior to death. Finally, we defined late hospital readmission as an admission to an acute care hospital (excluding elective admissions) in the 31 to 396 days after discharge from the hospital for the initial kidney transplant. The index date for all outcomes was 30 days after discharge from the hospital for the initial kidney transplant. We excluded patients who died within the first 30 days of discharge in this analysis (n = 16). The maximum follow-up date for all outcomes was March 31, 2016.

Statistical Analysis

We described categorical variables as proportions and continuous variables as medians (25th, 75th percentile). We used standardized differences to examine meaningful differences (ie, difference ≥ 10%) in baseline characteristics between recipients with and without an EHR.[29]

We used logistic regression to examine the association of each risk factor and the odds of EHR. Selecting risk factors that were statistically significant in the univariable logistic model, we used backward elimination to determine risk factors for inclusion in our final multivariable logistic model. To decrease the possibility of missing potentially important risk factors for EHR a P value <.2 was decided a priori to select

risk factors to include in our final model.[30] To account for time-to-event and censoring (ie, death), in an additional analysis we used the Cox proportional hazards model to examine the relationship between risk factors (independent variables) and EHR (dependent variable). For each risk factor, we assessed violations in the proportional hazards assumption. For continuous variables, we also assessed linearity using Martingale residuals. We considered a two-tailed *P* value $<.05$ to indicate violations using the Kolmogorov-type supremum test. No important violations were noted.

When examining outcomes associated with EHR, we used the Kaplan–Meier product limit method to determine the cumulative probability of remaining event-free for our primary outcome of total graft failure. We curtailed our curve when approximately 10% of the cohort remained at risk.[31] The associated log-rank test was used to compare total graft failure across EHR status (yes vs no). To examine the relationship between EHR status (yes vs no [reference]) and the outcomes associated with EHR (eg, total graft failure), we used the Cox proportional hazards model. No important departures from the proportional hazard assumption, using the Kolmogorov-type supremum test, were noted except when examining the outcome of late hospital readmission. To account for the lack of proportionality, we fit an extended Cox model with a Heaviside function, stratifying hazard ratios by periods of follow-up time.[32] Using clinical expertise and a literature review, we adjusted for the following covariates: age (continuous), sex, race (White, Black, Asian, other), rurality (urban vs rural residence), neighborhood income quintile, cause of end-stage kidney disease (ESKD) (glomerulonephritis/autoimmune diseases, cystic kidney disease, diabetes, renal vascular disease, other), dialysis vintage (ie, time on dialysis prior to transplant), Charlson comorbidity index, history of organ transplant, delayed graft function (ie, evidence of dialysis in the first 7 days after transplant but no dialysis in the 90-150 days), donor type (living vs deceased), donor age (<60 vs ≥ 60 years), and length of initial hospitalization for kidney transplant. In an additional analysis, we used the Fine and Gray model to account for competing risks. For death-censored graft failure we treated death with graft function as a competing event, while for death with graft function, graft failure prior to death was considered a competing event. The maximum follow-up date for this analysis was March 31, 2016.

Data were missing for the following variables income quintile ($<1\%$), race (8.6%), and cause of ESKD (15.4%). For missing income quintile, we imputed quintile 3, for race we imputed White race, and for missing cause of ESKD we imputed glomerulonephritis. We performed all analyses using SAS (Statistical Analysis Software) version 9.4 *(SAS Institute, Cary, NC).*

Results

Baseline Characteristics

In our cohort, there were 5437 kidney transplant recipients (Figure S1), of which 20.7% (n = 1128) had an EHR and 79.3% (n = 4309) did not have an EHR.[26] As we previously reported, the most common diagnoses for readmission were failure and rejection of transplanted organs and tissues (18.7%); complications of procedures, not elsewhere classified (13.6%); acute renal failure (5.7%); other disorders of urinary system (4.3%); and post-procedural disorders of genitourinary system, not elsewhere classified (2.6%).[26] Compared to recipients who did not have an EHR, recipients who did have an EHR were older (median age: 54 vs 52 years), were more likely to be frail (7.2% vs 4.6%), and were more likely to have a length of hospital stay for the kidney transplant surgery >7 days (vs ≤ 7 days; 68.5 vs 55.7%; Table 1).

Risk Factors for Early Hospital Readmission

Results from the univariable and multivariable logistic regression models, with EHR as the outcome, are displayed in Table 2. In the multivariable analysis, we found that the only recipient characteristics associated with EHR were age, income quintile, peripheral vascular disease, chronic obstructive pulmonary disease, and frailty. For every 5-year increase in recipient age there was a 4% increased odds of EHR (adjusted odds ratio [aOR]: 1.04, 95% CI: 1.01, 1.07). Recipients in income quintile 2 had a 26% increased odds of EHR compared to recipients in higher income quintiles (3 to 5; aOR: 1.26, 95% CI: 1.07, 1.49). Recipients with peripheral vascular disease, chronic obstructive pulmonary disease, and frailty had an increased odds of EHR (aOR: 1.39, 1.75, and 1.35, respectively). Compared to recipients of a donor aged <60 years, those who received a kidney from a donor aged ≥ 60 years had a 26% increased odds of EHR (aOR: 1.26, 95% CI: 1.05, 1.50). A longer length of hospitalization for the initial kidney transplant (ie, >7 days) compared to a shorter length of hospitalization (ie, ≤ 7 days) had a 55% increased odds of EHR (aOR 1.55, 95% CI: 1.34, 1.79). No transplant characteristics or post-operative complications were independently associated with EHR. We found similar results from our Cox proportional hazards model (Supplementary Table S4).

Outcomes After Early Hospital Readmission

Over a total of 31 880 person-years of follow-up (median follow-up: 5.46 years: 25th, 75th percentile 3.01, 8.44), we observed 1320 (24.3%) total graft failure events. The incidence rate (per 100 person-years) for total graft failure was higher in recipients with an EHR compared to recipients with no EHR (6.01 vs 3.71; Table 3). Similar results were found for death-censored graft failure (2.87 vs 1.68), death with graft function (3.14 vs 2.02), all cause-mortality (3.94 vs 2.40), and late hospital readmission (73.75 vs 38.83; Table 3).

Compared to recipients with no EHR, recipients with an EHR had a significantly lower probability of remaining event-free from total graft failure ($P<.001$; Figure 1). In the unadjusted and adjusted Cox proportional hazards models,

Table 2. Univariable and Multivariable Logistic Regression Analysis of Risk Factors for Early Hospital Readmission.

Risk factors	Univariable analysis OR (95% CI)	Multivariable analysis OR (95% CI)
Characteristics		
Recipient characteristics		
Age (per 5-year increase)	1.06 (1.04-1.09)	1.04 (1.01-1.07)
Sex		
Men	Reference	
Female	0.94 (0.82-1.08)	
Race		
White	Reference	
Asian	0.68 (0.51-0.91)	
Black	1.02 (0.79-1.31)	
Other	1.00 (0.83-1.21)	
Income quintile[a]		
Quintile 1, low	1.12 (0.95-1.32)	1.06 (0.90-1.26)
Quintile 2	1.27 (1.08-1.49)	1.26 (1.07-1.49)
Quintiles 3 to 5, middle to high	Reference	Reference
Residency		
Urban[b]	Reference	
Rural	1.05 (0.86-1.29)	
Cause of ESKD		
Glomerulonephritis	Reference	Reference
Cystic kidney disease	0.83 (0.66-1.04)	0.81 (0.65-1.02)
Diabetes	1.29 (1.08-1.54)	1.10 (0.92-1.33)
Renal vascular disease	1.00 (0.79-1.26)	0.87 (0.69-1.11)
Other	1.21 (1.00-1.46)	1.20 (0.99-1.46)
Comorbidities		
Coronary artery disease	1.06 (0.92-1.21)	
Myocardial infarction	1.58 (1.11-2.24)	
Heart failure	1.32 (1.11-1.57)	1.16 (0.97-1.39)
Hypertension	0.99 (0.87-1.13)	
Diabetes	1.22 (1.06-1.40)	
Stroke/TIA	1.39 (0.88-2.19)	
Major Cancers	1.25 (0.98-1.60)	
Chronic Liver Disease	1.21 (0.99-1.47)	
Peripheral Vascular Disease	1.55 (1.28-1.89)	1.39 (1.14-1.69)
Chronic obstructive pulmonary disease	2.27 (1.41-3.67)	1.75 (1.07-2.86)
Frailty	1.61 (1.23-2.10)	1.35 (1.03-1.78)
Arrhythmia	1.31 (1.03-1.68)	
Charlson Comorbidity Score	1.13 (1.07-1.19)	
Hospitalization in the year prior to transplant		
No	Reference	
Yes	1.18 (1.03-1.35)	
Transplant Characteristics		
Dialysis modality		
Hemodialysis	Reference	
Peritoneal dialysis	0.84 (0.71-0.99)	
Preemptive	0.79 (0.62-1.00)	
Dialysis vintage (pre-transplant), years	1.02 (1.01-1.03)	1.01 (1.00-1.02)
Delayed graft function		
No	Reference	
Yes	1.15 (0.99-1.33)	
History of organ transplant		
No	Reference	
Yes	1.12 (0.90-1.39)	

(continued)

Table 2. (continued)

Risk factors	Univariable analysis OR (95% CI)	Multivariable analysis OR (95% CI)
Transplant era		
2002-2004	1.12 (0.93-1.36)	1.05 (0.86-1.28)
2005-2007	1.02 (0.86-1.22)	0.99 (0.83-1.19)
2008-2010	0.84 (0.71-1.00)	0.85 (0.71-1.01)
2011-2014	Reference	Reference
Donor characteristics		
Donor type		
Living donor	Reference	
Deceased donor	1.21 (1.05-1.38)	
Donor age		
<60 years	Reference	Reference
≥60 years	1.40 (1.18-1.66)	1.26 (1.05-1.50)
Initial transplant hospitalization characteristics		
Length of hospital stay for transplantation, days		
≤7 days	Reference	Reference
>7 days	1.73 (1.50-1.99)	1.55 (1.34-1.79)
Day of week discharged for kidney transplant surgery		
Weekday	1.11 (0.90-1.37)	
Weekend	Reference	
Season discharged		
Summer	0.94 (0.78-1.14)	
Autumn	1.04 (0.86-1.24)	
Spring	1.03 (0.86-1.24)	
Winter	Reference	
Post-operative complications		
Sepsis		
No	Reference	
Yes	1.09 (0.50-2.40)	
Myocardial infarction		
No	Reference	
Yes	1.79 (1.20-2.67)	

Note. OR = odds ratio; CI = confidence interval; ESKD = end stage kidney disease; TIA = transient ischemic attack.
[a]Income presented as quintiles of average neighborhood income.
[b]Urban defined as living in an area with a population >10 000.

we found a statistically significant relationship between EHR and total graft failure (aHR: 1.46, 95% CI: 1.29, 1.65; Table 4). Similarly, we found that EHR was associated with an increased rate of death-censored graft failure, death with graft function, and all-cause mortality. For example, recipients with an EHR had a 41% increased rate of all-cause mortality (aHR: 1.41, 95% CI: 1.22, 1.63). Similar results for death-censored graft failure and death with graft function were found when the Fine and Gray model was compared to the primary analysis. For late hospital readmission, we found in the first 0.5 years of follow-up, individuals with an EHR had a significantly higher rate of late hospital readmission (Table 5). For example, in follow-up years 0 to <0.25, recipients with an EHR had a 111% increased rate of late hospital readmission compared to recipients without an EHR (aHR: 2.11, 95% CI: 1.85, 2.40). However, recipients with an EHR did not have a significantly higher rate of late hospital readmission for follow-up years 0.5 to 1 (aHR: 1.14, 95% CI: 0.90, 1.45).

Discussion

In this study, we found that approximately 21% of kidney transplant recipients had an EHR and these individuals were more likely to be older, living in a lower neighborhood income quintile, have comorbidities, a longer length of hospitalization for their initial kidney transplant, and have received a kidney from an older donor. Kidney transplant recipients with an EHR had worse post-transplant outcomes compared to recipients with no EHR, including an increased

Table 3. Incidence Rate for Total Graft Failure, Death-Censored Graft Failure, Death With Graft Function, All-Cause Mortality, and Late Hospital Readmission After Kidney Transplantation by Early Hospital Readmission Status.[a]

Outcomes	No early hospital readmission (N = 4303)	Early hospital readmission (N = 1118)
Total Graft Failure		
No. events (%)	958 (22.3)	362 (32.4)
No. events per 100 person-years[b] (95% CI)	3.71 (3.48-3.95)	6.01 (5.42-6.65)
Death-censored Graft Failure		
No. events (%)	435 (10.1)	173 (15.5)
No. events per 100 person-years[b] (95% CI)	1.68 (1.53-1.85)	2.87 (2.47-3.33)
Death with Graft Function		
No. events (%)	523 (12.2)	189 (16.9)
No. events per 100 person-years[b] (95% CI)	2.02 (1.86-2.20)	3.14 (2.71-3.61)
All-cause Mortality		
No. events (%)	655 (15.2)	260 (23.3)
No. events per 100 person-years[b] (95% CI)	2.40 (2.22-2.59)	3.94 (3.48-4.44)
Late Hospital Readmission		
No. events (%)	1321 (30.7)	525 (47.0)
No. events per 100 person-years[b] (95% CI)	38.83 (36.78-40.97)	73.75 (67.64-80.27)

Note. CI = confidence interval.
[a]Denominator is different from risk factor analysis (n = 5421) as the index date was 30 days after discharge from the transplant admission. Therefore, patients who died in this 30-day period were excluded.
[b]Incidence rates are unadjusted.

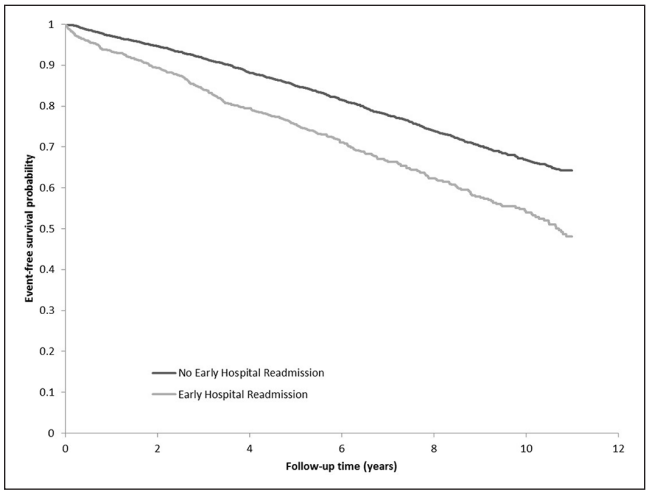

Figure 1. Kaplan-Meier survival curve for total graft failure, comparing kidney transplant recipients with and without an early hospital readmission.

rate of total graft failure, death with graft function, death-censored graft failure, all-cause mortality, and late hospital readmission. These results identified some risk factors that should be considered by clinicians when evaluating a patient's EHR risk and highlight the need to develop interventions to decrease the EHR burden.

We found that frailty was the only potentially modifiable risk factor independently associated with an increased risk of EHR. Previous studies in the dialysis population suggest components of frailty may be modifiable (eg, physical function) through exercise rehabilitation programs.[33-35] Similar to our findings, McAdams-DeMarco et al conducted a single-center study in the United States (n = 383) and found that frail kidney transplant recipients (defined using criteria established by Fried et al,)[36] were 1.6 times more likely to experience an EHR compared to recipients who were not frail.[11] With an increase in the average age and comorbidities in the kidney transplant population, frailty is a growing concern.[37] These results suggest that frailty may be a useful marker to identify kidney transplant recipients who might benefit from rehabilitation prior to transplant and interventions post-transplant to reduce EHR.[11]

Despite the lack of modifiable risk factors found in this study, risk factors can still help identify recipients at increased risk for EHR. Although few risk factors have been found to be consistently associated with an increased risk of EHR across studies, a longer length of hospitalization for the initial kidney transplant was associated with EHR in this study and several others.[7,10,20] While there are multiple reasons for a recipient to have a longer length of hospitalization (eg, post-operative complications, underlying comorbidities, frailty), hospitalization length could be used as a marker to identify patients at increased risk of EHR. Future studies should develop and validate clinical prediction models for EHR in kidney transplant recipients. However, in the general population, EHR prediction models have demonstrated widely variable discriminative ability, with many predictive models having poor predictive performance.[38,39] In the kidney transplant population, Taber et al, attempted to develop a

Table 4. Univariable and Multivariable Cox Proportional Hazards Model for Total Graft Failure, Death-Censored Graft Failure, Death With a Functioning Graft, All-Cause Mortality, and Late Hospital Readmission After Kidney Transplantation by EHR Status.[a]

			Outcomes		
EHR status	Total graft failure	Death-censored graft failure	Death with a functioning graft	All-cause mortality	Late hospital readmission
Unadjusted					
No EHR	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
EHR	1.64 (1.45, 1.85)	1.72 (1.44, 2.05)	1.57 (1.33, 1.86)	1.66 (1.44, 1.92)	1.82 (1.64, 2.01)
Adjusted[b]					
No EHR	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	[c]
EHR	1.46 (1.29, 1.65)	1.62 (1.36, 1.94)	1.34 (1.13, 1.59)	1.41 (1.22, 1.63)	[c]

Note. EHR = early hospital readmission.
Data are presented as hazard ratios (95% confidence interval).
[a]Denominator is different from risk factor analysis (n = 5421) as the index date was 30 days after discharge from the transplant admission. Therefore, patients who died in this 30-day time period were excluded.
[b]Adjusted for age, sex, race, rurality, income quintile, cause of end-stage kidney disease, dialysis vintage, Charlson co-morbidity index, history of organ transplant, delayed graft function, donor type, donor age, and length of initial hospitalization for kidney transplant.
[c]No estimate is provided due to non-proportionality. Table 5 presents the results stratified by follow-up time due to non-proportionality.

Table 5. Adjusted Hazard Ratios for Late Hospital Readmission for Recipients With an EHR Compared to Recipients Without EHR. Results Presented Stratified by Follow-Up Time Due To Non-Proportionality.[a]

EHR vs no EHR (reference)	Adjusted hazard ratio[b]
Follow-up time	
0 to <0.25 years	2.11 (1.85, 2.40)
0.25 to <0.50 years	1.27 (1.01, 1.62)
0.50 to 1 years	1.14 (0.90, 1.45)

Note. Data are presented as hazard ratios (95% confidence interval). EHR = early hospital readmission.
[a]Denominator is different from risk factor analysis (n = 5421) as the index date was 30-days after discharge from the transplant admission. Therefore, patients who died in this 30-day time period were excluded.
[b]Results presented using the extended Cox model stratified by follow-up time due to non-proportionality. Adjusted for age, sex, race, rurality, income quintile, cause of end-stage kidney disease, dialysis vintage, Charlson co-morbidity index, history of organ transplant, delayed graft function, donor type, donor age, length of initial hospitalization for kidney transplant.

risk prediction model for EHR with an area under the curve value of 0.73.[9] However, this was a single-center study with only 123 EHR events.[9] Similarly, Hogan et al, created a prediction model for EHR; however, the area under the curve value was only 0.61.[40] It has been suggested that the inclusion of more granular data, such as data available in electronic medical records, might be required to improve the predictive accuracy of these models.[40]

Similar to previous studies, we found that kidney transplant recipients with an EHR had worse post-transplant outcomes compared to recipients without an EHR, even after adjustment for clinical characteristics.[2-4,10,12,15] The poor post-transplant outcomes observed in kidney transplant recipients with an EHR highlight the need to better understand the causes of readmission to guide the development and testing of interventions to prevent readmissions. However, there are limited published studies on interventions aimed to reduce EHR in kidney transplant recipients. Hu et al conducted a randomized controlled trial and found that a transitional care intervention comprised a risk assessment for EHR, health education, individualized discharge planning, and post discharge follow-up significantly reduced EHR in kidney transplant recipients.[41] In patients hospitalized for medical or surgical reasons (excluding kidney transplant recipients), a meta-analysis found that interventions aimed to reduce EHR are effective, with complex interventions being the most effective.[42] Several non-randomized studies have been conducted in the kidney transplant population suggesting that hospital readmissions can be reduced through several methods including increased care post-discharge, education to improve medication knowledge, and decreasing anxiety upon discharge.[5,6,20]

This study has several strengths. There were minimal concerns about selection bias, with universal health care benefits allowing us to include all kidney transplant recipients from the 6 transplant centers in Ontario. This is the largest Canadian study to identify risk factors and outcomes of EHRs in kidney transplant recipients. This is important as Canada has a universal health care system which may result in differences in patient outcomes as has been found when comparing mortality in kidney transplant recipients between Canada and the United States.[21] Two single-center Canadian studies has been conducted examining predictors of hospital readmissions in Canadian kidney transplant recipients; however, one study combined early and late hospital readmissions when examining predictors[43] and the other study was not able to capture readmissions to hospitals outside the transplant hospital.[8] The inclusion of multiple transplant centers in our study extends the generalizability of our findings. Finally, loss to follow-up in our study was minimal with less than 0.5% emigrating from the province each year.[25]

Several limitations of our study deserve to be mentioned. First, given that Canada has a unique publicly funded health care system and with previous research suggesting differences in kidney transplant recipient outcomes between the United States and Canada,[21] our results may not be generalizable to other countries. Second, due to data availability, we were not able to assess several risk factors (eg, cold ischemia time, human leukocyte antigen mismatch, social support, non-compliance). Third, although we accounted for many clinical characteristics, residual confounding remains a concern due to insufficient capture of known (eg, smoking status) and unknown potential confounders. Fourth, we were not able to accurately identify which readmissions were preventable, as this would require medical chart abstraction. Fifth, we were not able to determine which transplant centers, if any, implemented initiatives to reduce EHR; however, our previous work suggests there has been no change in the incidence of EHR during our study period.[26] Finally, not all of our outcomes have undergone a formal validation (ie, graft failure date).[44]

In conclusion, several risk factors can be used to help identify kidney transplant recipients at risk of EHR. Many recipients with EHR experience poor post-transplant outcomes, including total graft failure, death with graft function, death-censored graft failure, all-cause mortality, and late hospital readmission. Our results serve as a call to action to develop and validate prediction models (using more detailed datasets, with adequate statistical power, and state-of-the-art modeling approaches such as machine learning) to accurately identify kidney transplant recipients at increased risk of EHR and to enter these individuals in clinical trials to prevent EHR.

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Ethics Approval and Consent to Participate

ICES is a prescribed entity under section 45 of Ontario's Personal Health Information Protection Act. Section 45 authorizes ICES to collect personal health information, without consent, for the purpose of analysis or compiling statistical information with respect to the management of, evaluation or monitoring of, the allocation of resources to or planning for all or part of the health system. Projects conducted under section 45, by definition, do not require review by a Research Ethics Board. This project was conducted under section 45, and approved by ICES' Privacy and Compliance Office.

Consent for Publication

All authors consent to the publication of this study.

Availability of Data and Materials

The dataset from this study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the data set publicly available, access can be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS. The full data set creation plan and underlying analytic code are available from the authors upon request, understanding that the programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

Declaration of Conflicting Interests

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Supplemental Material

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