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Progression of Kidney Disease in Kidney Transplant Recipients With a Failing Graft: A Matched Cohort Study

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Abstract

Background: Few studies have assessed outcomes in transplant recipients with failing grafts as most studies have focused on outcomes after graft loss.
Objective: To determine whether renal function declines faster in kidney transplant recipients with a failing graft than in people with chronic kidney disease of their native kidneys.
Design: Retrospective cohort study.
Setting: Alberta, Canada (2002-2019).
Patients: We identified kidney transplant recipients with a failing graft (2 estimated glomerular filtration rate [eGFR] measurements 15-30 mL/min/1.73 m^2 ≥90 days apart).
Measurements: We compared the change in eGFR over time (eGFR with 95% confidence limits, ${}_{LCL}eGFR_{UCL}$) and the competing risks of kidney failure and death (cause-specific hazard ratios [HRs], ${}_{LCL}HR_{UCL}$).
Methods: Recipients (n = 575) were compared with propensity-score-matched, nontransplant controls (n = 575) with a similar degree of kidney dysfunction.
Results: The median potential follow-up time was 7.8 years (interquartile range, 3.6-12.1). The hazards for kidney failure ($HR_{1.10}1.33_{1.60}$) and death ($HR_{1.21}1.59_{2.07}$) were significantly higher for recipients, while the eGFR decline over time was similar (recipients vs controls: ${}_{-2.60}{-}2.27_{-1.94}$ vs ${}_{-2.52}{-}2.21_{-1.90}$ mL/min/1.73 m^2 per year). The rate of eGFR decline was associated with kidney failure but not death.
Limitations: This was a retrospective, observational study, and there is a risk of bias due to residual confounding.
Conclusions: Although eGFR declines at a similar rate in transplant recipients as in nontransplant controls, recipients have a higher risk of kidney failure and death. Studies are needed to identify preventive measures to improve outcomes in transplant recipients with a failing graft.

Abstract

Abrege Contexte: Peu d'études ont évalué les résultats chez les patients transplantés dont le greffon est défaillant; la majorité des études s'étant plutôt concentrées sur les résultats après la perte du greffon.
Objectif: Vérifier si la fonction rénale décline plus rapidement chez les patients transplantés dont le greffon est défaillant que chez les personnes souffrant d'une insuffisance chronique sur reins natifs.
Conception: Étude de cohorte rétrospective.
Cadre: Alberta, Canada (2002 à 2019).
Sujets: Nous avons identifié des patients transplantés dont le greffon est défaillant (défini par deux mesures du débit de filtration glomérulaire estimé [DFGe] de 15-30 ml/min/1,73 m^2 à au moins 90 jours d'intervalle).
Mesures: Nous avons comparé l'évolution du DFGe dans le temps (DFGe avec intervalles de confiance [IC] à 95 % inférieur et supérieur: ${}_{ICI}DFGe_{ICS}$) et les rapports de risque d'insuffisance rénale et de décès (intervalles de rapport de risque (RR) lié à la cause: ${}_{ICI}RR_{ICS}$).
Méthodologie: Les transplantés dont le greffon est défaillant (n=575) ont été comparés à des témoins non transplantés (n=575) appariés selon le score de propension et présentant un niveau similaire de dysfonctionnement rénal.

Résultats: Le temps médian de suivi potentiel était de 7,8 ans (ÉIQ: 3,6 à 12,1). Les risques d'insuffisance rénale (RR: $_{1,10}$1,33$_{1,60}$) et de décès (RR: $_{1,21}$1,59$_{2,07}$) étaient significativement plus élevés chez les transplantés dont le greffon est défaillant, mais le déclin du DFGe au fil du temps était similaire dans les deux groupes (receveurs: $_{-2,60}$-2,27$_{-1,94}$ ml/min/1,73 m^2 par an; témoins: $_{-2,52}$-2,21$_{-1,90}$ ml/min/1,73 m^2 par an). Le taux de déclin du DFGe a été associé à une insuffisance rénale terminale, mais pas au décès.

Limites: Il s'agit d'une étude observationnelle rétrospective et il existe un risque de biais dû à des facteurs de confusion résiduels.

Conclusion: Bien que le DFGe décline à un rythme similaire chez les transplantés dont le greffon est défaillant et les témoins non transplantés, le risque d'insuffisance rénale terminale et de décès est plus élevé pour les transplantés. D'autres études sont nécessaires pour identifier les mesures préventives qui pourraient améliorer les résultats des patients transplantés dont le greffon est défaillant.

Keywords

Alberta, chronic kidney disease, estimated glomerular filtration rate, kidney transplantation, mortality

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Introduction

Modern immunosuppression regimens have improved graft survival following kidney transplantation,[1] yet most kidney allografts will still fail at some point during the lifetime of the recipient.[2] Previous studies have not adequately assessed outcomes in transplant recipients with failing grafts as most studies have focused on outcomes after graft loss.[3,4]

There is a lack of data comparing transplant recipients with a failing graft to nontransplant controls with chronic kidney disease (CKD). Previously, we have shown that kidney transplant recipients with a failing graft had a higher hazard of death and a higher rate of all-cause hospitalization compared with matched, nontransplant controls.[5] It is unclear whether kidney disease progresses more quickly in transplant recipients with a failing allograft compared with nontransplant controls with similar levels of kidney function. Given the high risk of adverse events associated with severe kidney dysfunction (ie, estimated glomerular filtration rate [eGFR] below 30 mL/min/1.73 m^2), information on kidney disease progression in failing grafts may have prognostic and clinical implications.[6,7]

We performed a retrospective cohort study to determine whether the rate of progression of kidney disease is greater among patients with a failing kidney allograft than in nontransplant controls with a similar degree of native kidney dysfunction. We also studied the absolute risks of kidney failure and death without kidney failure and how eGFR decline may impact these risks.

Methods

Design and Setting

We conducted a population-based cohort study using linked health care databases within the Alberta Kidney Disease Network, which receives data from Alberta Health, the provincial health ministry.[8] More than 99% of Alberta residents are registered with Alberta Health and have universal access to hospital care and physician services. We followed guidelines for the reporting of observational studies (Table S1) and a protocol approved by the research ethics boards at the University of Alberta and the University of Calgary, with a waiver of patient consent.

Data Sources

We ascertained baseline characteristics, information about covariates, and outcome data from database records (Table S2). The Alberta Health database contains information on demographic data, vital statistics, and diagnostic and procedural information for inpatient and outpatient physician services. We identified kidney transplant recipients from the Alberta Kidney Care—North and South databases, which provide care to all patients treated with maintenance dialysis or kidney transplantation in the province. We linked these data sources to a provincial laboratory repository via unique, encoded, patient identifiers. The serum creatinine measurements obtained in our databases have been standardized across provincial laboratories over time, reducing interlaboratory variation in measurements.[8] We identified comorbidities

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using diagnostic or procedural codes from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and International Statistical Classification of Diseases, Tenth Revision (ICD-10) in the 3 years prior to the index date using validated algorithms, whenever possible (Table S2).[9,10]

Populations

Kidney transplant recipient population. We considered all kidney transplant recipients alive with a functioning graft between May 1, 2002, and December 31, 2017, in Alberta. We excluded pediatric recipients (<18 years old), recipients with a previous organ transplant, and recipients who had received a simultaneous multiorgan transplant (eg, kidney-pancreas).

We used laboratory data to identify kidney transplant recipients who achieved a functioning graft post-transplant and then experienced a loss of graft function during the study period. We calculated the eGFR using the CKD-EPI equation ignoring the coefficient for race (2009 Chronic Kidney Disease Epidemiology Collaboration). We included recipients who survived at least 1 year with a functioning graft defined as at least 1 eGFR >30 mL/min/1.73 m^2 measurement after the first transplant year. We considered only eGFR measurements beyond the first year post-transplant to ensure the stability of graft function and the immunosuppression regimen.[6,11] We excluded recipients who had graft failure (death or return to dialysis) within a year post-transplant or whose baseline eGFR was <30 mL/min/1.73 m^2 throughout the entire follow-up period. From this initial cohort, we identified an incident cohort of recipients who experienced a decline in graft function based on at least 2 outpatient eGFR measurements between 15 and 30 mL/min/1.73 m^2 that were obtained between 90 and 365 days apart (sustained G4 or stage IV CKD). We excluded recipients who had an eGFR <15 mL/min/1.73 m^2 or who received dialysis in between these 2 measurements. We used the second of the 2 eGFR measurements as the index date for follow-up. Finally, we excluded recipients who did not have evidence of an outpatient nephrology visit within a year prior to the index date.

CKD population. We identified members of the general population in Alberta with a similar degree of CKD between May 1, 2002, and December 31, 2018. As in the transplant recipient population, we identified adults (≥18 years old at first eGFR >30 mL/min/1.73 m^2) with at least 2 outpatient eGFR measurements between 15 and 30 mL/min/1.73 m^2 that were obtained between 90 and 365 days apart, without dialysis or an eGFR <15 mL/min/1.73 m^2 between measurements, to ensure chronicity. The date of the second of these 2 measurements was used as the index date for follow-up. We excluded patients who had evidence of a previous kidney or other organ transplant or were on maintenance dialysis prior to their index date. To enhance comparability, we excluded people with CKD who did not have evidence of an outpatient nephrology visit within a year prior to the index date.

Matching

We used propensity-score methods to match kidney transplant recipients with a failing graft to nontransplant controls with CKD in a 1:1 ratio. We estimated the propensity score as the conditional probability of receiving a transplant using a logistic regression model in which we regressed transplant status on the following baseline covariates: age (and its squared term), sex, socioeconomic status (quintile of neighborhood income), location of residence (urban vs rural), distance from home to transplant center, index eGFR, index albuminuria, and baseline comorbidities. We modeled age, distance from the patient's home to the transplant center, and index eGFR as continuous variables. To enhance group comparability, we specified exact matching for categories of index year (<2005, 2005-2009, 2010-2014, and ≥2015), age (<65 and ≥65 years), sex (men and women), nonmetastatic cancer (present and absent), and albuminuria.

For matching, demographic data were complete except for socioeconomic status, location of residence, and index albuminuria (≤5% missing in the kidney transplant recipient cohort). Those with missing socioeconomic data were reclassified in the third (middle) quintile of neighborhood income and those with missing location of residence data were reclassified as urban. Due to its potential to indicate a lower level of quality of care, we treated missing index albuminuria as a separate category such that the resulting variable was categorical with 4 levels (ie, none/mild, moderate, severe/nephrotic, or missing). We matched transplant recipients to nontransplant controls on the propensity score using a caliper width equal to 0.2 of the standard deviation of the propensity score. We matched without replacement using a greedy nearest neighbor algorithm in random order. We compared differences in baseline characteristics between transplant recipients and nontransplant CKD patients using graphical methods and standardized differences. A standardized difference less than 10% was considered to be indicative of a negligible difference between groups.[12] We used the *MatchIt* package (version 3.0.2) in R (version 4.0.2) for matching.[13,14]

Follow-up and Outcomes

We followed participants from their index date until the first of all-cause mortality (death before kidney failure), kidney failure, or a censoring event (emigration from the province or end of study, March 31, 2019). The primary outcome was the change in eGFR over time. The secondary outcomes were kidney failure and death before kidney failure. We defined kidney failure as the earlier of the initiation of kidney replacement therapy (maintenance dialysis or kidney

transplantation) or sustained eGFR <10 mL/min/1.73 m^2 (based on 2 eGFR measurements <10 mL/min/1.73 m^2 that were 90-365 days apart). In a sensitivity analysis, we defined kidney failure as the initiation of kidney replacement therapy only.

Statistical Analysis

We compared baseline characteristics between recipients and matched controls using standardized differences, using a cut-off of 10% for meaningful imbalance.[12] We determined the quantiles of the potential follow-up time distribution based on the Kaplan-Meier method applied to the censored times, reversing the roles of event status and censoring.

We used a linear mixed-effects model with a random intercept and slope to estimate the change in eGFR per year accounting for within-person correlations in the measurements. To improve model convergence, we used semester means (the average of eGFR measurements within a 6-month period) for each person. We used joint modeling (JM package in R) to estimate the longitudinal outcome (eGFR with 95% confidence limits, ${}_{LCL}eGFR_{UCL}$) and the event outcomes (kidney failure and death without kidney failure) to account for possible informative censoring.

We summarized the competing risks of kidney failure and death using nonparametric cumulative incidence functions. We estimated the hazard ratios (${}_{LCL}HR_{UCL}$) for kidney failure and death using cause-specific Cox regression. We assessed model validity and goodness of fit by means of formal tests and graphical methods based on residuals. We accounted for the matched nature of the sample using robust variance estimation.[15] We used R version 4.0.2 (R-project.org) for all analyses.

Results

Baseline Characteristics

There were 2875 prevalent kidney transplant recipients in Alberta, Canada, between May 1, 2002, and December 31, 2017. Of these, 624 (22%) recipients met the study inclusion criteria (Figure S1). We were able to match 575 recipients with a failing graft (92%) to 575 nontransplant controls who had a similar degree of chronic kidney dysfunction (Figure S2). As expected, the 2 populations were substantially different prior to matching (Table S3), but were comparable after matching with all measured standardized differences <10% (Table 1).

The baseline characteristics for the cohort are presented in Table 1. For the matched kidney transplant recipients, the median age was 57 years (interquartile range [IQR], 46-67) and 39% of participants were women. The index eGFR was 27 mL/min/1.73 m^2 (IQR, 24-29). The median time from transplant to the index date for the recipients was 6 years (IQR, 2-10).

The median potential follow-up time was 7.8 years (IQR, 3.6-12.1) for kidney transplant recipients and 7.9 years (IQR, 3.7-12.2) for nontransplant controls. Of the 1150 total individuals, 221 (19%) died (125 recipients vs 96 controls), 294 (26%) started kidney replacement therapy (182 vs 112), 156 (14%) reached sustained eGFR <10 mL/min/1.73 m^2 (54 vs 102), 15 (1%) emigrated from the province (5 vs 10), and 464 (40%) were event-free at the study end date (209 vs 255).

Change in Kidney Function

The median number of eGFR measurements was 32 for transplant recipients and 23 for nontransplant controls, while the median number of semester measurements was 6 and 7, respectively. The average decrease in eGFR was over 2 mL/min/1.73 m^2 per year, which was similar between the 2 groups in both the separate linear model and the joint model (joint model results for recipients vs controls: ${}_{-2.60}{-}2.27_{-1.94}$ vs ${}_{-2.52}{-}2.21_{-1.90}$ mL/min/1.73 m^2 per year; $P = .73$; Figure 1 and Table 2).

Mortality and Kidney Replacement Therapy

The overall rate of kidney failure was higher in transplant recipients than in nontransplant controls (recipients vs controls: ${}_{9.29}10.64_{12.00}$ vs ${}_{6.97}8.05_{9.13}$ per 100 person-years) as was the rate of death without kidney failure (recipients vs controls: ${}_{4.65}5.64_{6.63}$ vs ${}_{2.89}3.61_{4.34}$ per 100 person-years). The absolute risks of kidney failure and death were higher in the transplant recipient cohort (Figure 2). The cause-specific HRs of kidney failure and death of transplant recipients compared with nontransplant controls were ${}_{1.10}1.33_{1.60}$ and ${}_{1.21}1.59_{2.07}$, respectively (Table 2). In the joint model, the conditional HR of death remained the same, while the HR of kidney failure was higher. According to this model, for every 1 mL/min/1.73 m^2 eGFR decrease per year, there was a ${}_{1.37}1.42_{1.47}$-fold increase in the hazard of kidney failure in both transplant recipients and nontransplant controls; whereas there was no significant association between eGFR decline and death without kidney failure (${}_{0.99}HR_{1.01}$) (Table 2). Results were similar when kidney failure was restricted to kidney replacement therapy only (Table S4).

Discussion

In this study of 575 recipients and 575 nontransplant controls, we found that although kidney function declines at a similar rate between the 2 groups, the hazards for both kidney failure and death without kidney failure were significantly higher for kidney transplant recipients. In both groups, the rate of eGFR decline was associated with kidney failure, but not with death. This suggests that transplant recipients have a higher risk of progression to kidney failure than

Table 1. Baseline Characteristics of Kidney Transplant Recipients With a Failing Graft and Matched Nontransplant Controls With Chronic Kidney Disease at the Time of Cohort Entry.[a]

Characteristic	Transplant recipients (n = 575)	Nontransplant controls (n = 575)	Standardized difference[b]
Age, y	57.0 [46.4-66.7]	57.4 [47.5-66.7]	3.6
≥65	178 (31)	178 (31)	0
Women	225 (39)	225 (39)	0
Socioeconomic status[c]			
Lowest quintile	139 (24)	151 (26)	4.8
Second quintile	149 (26)	147 (26)	0.8
Middle quintile	111 (19)	107 (19)	1.8
Fourth quintile	84 (15)	84 (15)	0
Highest quintile	92 (16)	86 (15)	2.9
Urban residence[d]	464 (81)	468 (81)	1.8
Distance to transplant center, km[e]	25.5 [13.8 - 160.9]	24.8 [13.3 - 161.9]	1
<50	361 (63)	360 (63)	0.4
50.1-150	65 (11)	65 (11)	0
150.1-300	76 (13)	73 (13)	1.6
>300	73 (13)	77 (13)	2.1
Transplant era			
1994-2000	142 (25)	N/A	N/A
2001-2010	254 (44)	N/A	N/A
2011-2017	93 (16)	N/A	N/A
Missing	86 (15)	N/A	N/A
Transplant to index date, y	6.1 [2.4-10.1]	N/A	N/A
Index date			
<2005	72 (13)	63 (11)	4.9
2005-2009	172 (30)	181 (31)	3.4
2010-2014	161 (28)	161 (28)	0
≥2015	170 (30)	170 (30)	0
Index eGFR, mL/min/1.73 m^2	26.8 [24.1-28.6]	27.1 [24.0-28.7]	1.4
26-30	389 (68)	386 (67)	1.1
21-25	134 (23)	151 (26)	6.9
15-20	52 (9)	38 (7)	9.1
Index albuminuria			
None/mild	174 (30)	174 (30)	0
Moderate	158 (27)	158 (27)	0
Severe	218 (38)	218 (38)	0
No measurement	25 (4)	25 (4)	0
Comorbidities[f]			
Hypertension	395 (69)	387 (67)	3
Diabetes mellitus	226 (39)	227 (39)	0.4
Myocardial infarction	34 (6)	31 (5)	2.3
PCI/CABG	21 (4)	23 (4)	1.8
Heart failure	71 (12)	85 (15)	7.1
Atrial fibrillation	39 (7)	40 (7)	0.7
Stroke/ TIA	33 (6)	24 (4)	7.2
Peripheral vascular disease	24 (4)	36 (6)	9.4
Chronic pulmonary disease	77 (13)	63 (11)	7.5
Peptic ulcer disease	13 (2)	14 (2)	1.1
Liver disease	18 (3)	22 (4)	3.8
Dementia	9 (2)	8 (1)	1.4
Lymphoma	11 (2)	2 (0)	14.8
Cancer (nonmetastatic)	43 (7)	43 (7)	0

(continued)

Table 1. (continued)

Characteristic	Transplant recipients (n = 575)	Nontransplant controls (n = 575)	Standardized difference[b]
Cancer (metastatic)	4 (1)	4 (1)	0
HIV/AIDS	2 (0)	2 (0)	0

Data are presented as number (%) or as median [interquartile range].

AIDS = acquired immunodeficiency syndrome; CABG = coronary artery bypass graft; eGFR = estimated glomerular filtration rate; HIV = human immunodeficiency virus; N/A = not applicable; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.
[a]The time of cohort entry is the date of the second of 2 eligible eGFR measurements.
[b]Standardized differences provide a measure of the difference between groups divided by the pooled standard deviation; >10% is interpreted as a meaningful difference between the groups.
[c]Income was categorized according to fifths of average neighborhood income (1 = low, 5 = high).
[d]Urban indicates a population >10 000 or a population >1000 with a population density >400/km^2.
[e]Values >500 km were imputed as 500 km.
[f]Assessed by the presence of diagnostic or procedural codes in the 3 years prior to the index date, based on validated algorithms, where applicable (Table S2).

Table 2. Model Results for Change in eGFR and Hazard of Kidney Failure or Death Comparing Transplant Recipients With a Failing Graft to Matched Nontransplant Controls With Chronic Kidney Disease at the Time of Cohort Entry.

	Linear mixed-effects model	Cause-specific Cox model	Joint model
Change in eGFR (mL/min/1.73 m^2 per year)			
Transplant recipients	$_{-1.90}-1.64_{-1.37}$	N/A	$_{-2.60}-2.27_{-1.94}$
Nontransplant controls	$_{-2.03}-1.78_{-1.53}$	N/A	$_{-2.52}-2.21_{-1.90}$
Hazard ratios of kidney failure and death in transplant recipients versus nontransplant controls			
Kidney failure	N/A	$_{1.10}1.33_{1.60}$	$_{2.05}2.68_{3.49}$[a]
Death	N/A	$_{1.21}1.59_{2.07}$	$_{1.23}1.61_{2.11}$[a]
Hazard ratios of kidney failure and death for every 1 unit decline in eGFR in transplant recipients versus nontransplant controls			
Kidney failure	N/A	N/A	$_{1.37}1.42_{1.47}$
Death	N/A	N/A	$_{0.99}1.01_{1.02}$

Data are presented as eGFR with 95% confidence limits ($_{LCL}$eGFR$_{UCL}$) or hazard ratios with 95% confidence limits ($_{LCL}$HR$_{UCL}$). eGFR = estimated glomerular filtration rate; HR = hazard ratios; N/A = not applicable.
[a]Conditional (as opposed to marginal) HRs reflect the individual tendency to experience the event of interest as opposed to the population average tendency to fail.

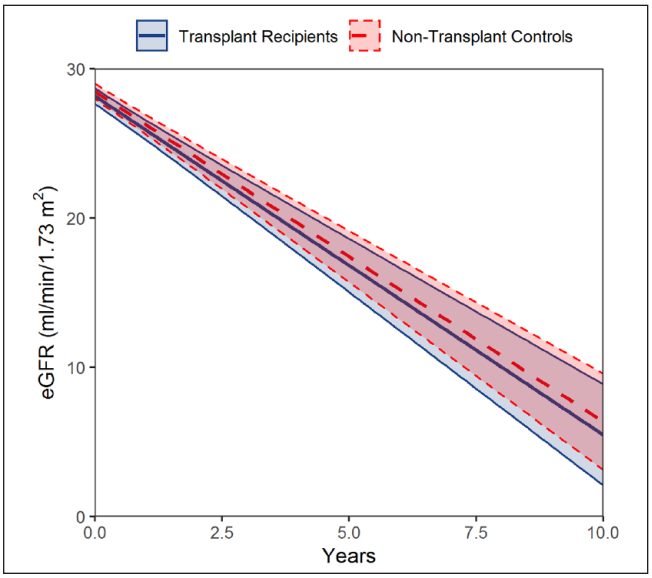

Figure 1. Mean decline in eGFR in transplant recipients and nontransplant controls (joint model).
eGFR = estimated glomerular filtration rate.

nontransplant controls, independent of eGFR decline. Targeted interventions to prevent sudden drops in eGFR may prolong graft survival.

These results build upon our previous study in which we reported that kidney transplant recipients with a failing graft had a higher hazard of death (HR $_{1.28}1.54_{1.85}$) and a higher rate of all-cause hospitalization (rate ratio $_{1.42}1.67_{1.97}$), compared with nontransplant controls, over a median follow-up of 5 years.[5] In that study, we considered outcomes that occurred before and after the initiation of kidney replacement therapy. In this study, we found that the 2 competing risks of kidney failure and death without kidney failure were higher in recipients compared with nontransplant controls. The risk of kidney failure was higher regardless of how we defined kidney failure and initiation of kidney replacement therapy alone or in combination with a sustained drop in eGFR <10 mL/min/1.73 m^2. Urgent actions are needed to narrow this gap in outcomes and ensure optimal use of scarce resources.

Transplant recipients may be more likely to initiate kidney replacement therapy given their familiarity with

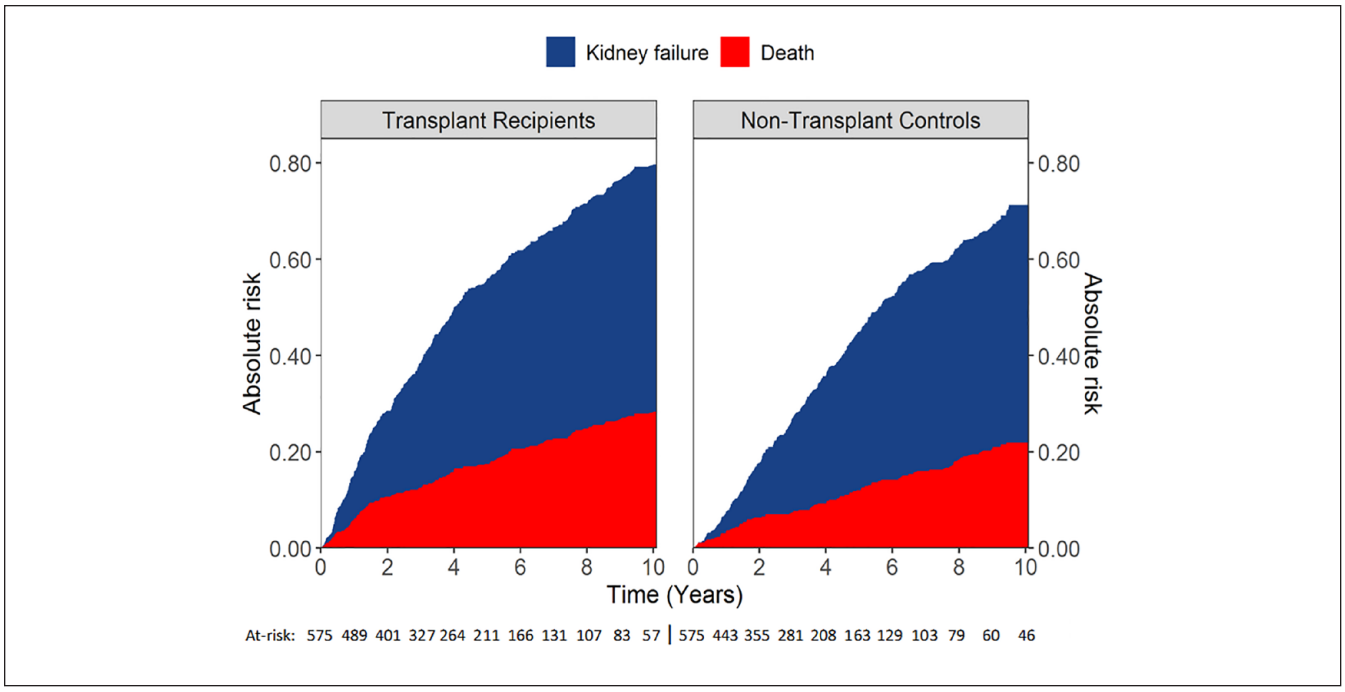

Figure 2. Absolute risk of kidney failure and death in kidney transplant recipients and nontransplant controls (cumulative incidence functions).

treatment options, including the transplant referral and assessment process. Although this could lead to a higher number of pre-emptive retransplantations, it is unlikely to have a significant impact on our results. The majority of kidney replacement therapy in our cohort was initiation of dialysis, and transplant recipients are more likely to initiate dialysis for many reasons. In addition to being familiar with dialysis treatment options, they are followed closely by nephrologists and may have a functioning fistula in place from their previous time on dialysis. At a given eGFR, nephrologists may be more likely to start dialysis in a transplant recipient compared with a patient with CKD who is dialysis-naïve as optimal timing of dialysis initiation in the recipient population has not been well studied.[16] The IDEAL study (Initiating Dialysis Early and Late study), which included transplant recipients with a failed graft (<4%), found comparable survival between planned early (eGFR between 10 and 14 mL/min) versus late dialysis (eGFR between 5 and 7 mL/min) in patients with severe CKD.[17] In contrast, a propensity-score analysis using the Scientific Registry of Transplant Recipients (SRTR) of 747 failed kidney transplant recipients found that those who restarted dialysis early (eGFR >10.5 mL/min/1.73 m^2) had an increased risk of death, especially among healthier, younger, female recipients.[18]

In our study, kidney transplant recipients had an increased risk of kidney replacement therapy despite a similar rate of eGFR decline in follow-up. We hypothesized that due to the adverse effects of immunosuppression, recipients would have a more rapid decline in eGFR compared with nontransplant controls. Although we found no differences in the rate of eGFR decline, transplant recipients may be at a higher risk of sudden drops in eGFR and/or more severe acute kidney injury, resulting in urgent dialysis. One Canadian study of 1164 kidney transplant recipients with a failed graft found that more than half (56%) of the recipients initiated dialysis as an inpatient, which was also associated with increased mortality compared with initiating dialysis as an outpatient.[19] These results are surprising given that transplant recipients are followed by specialists with expertise in CKD care but are consistent with studies showing that recipients with a failed graft returning to dialysis have suboptimal clinical targets.[20] In consideration of this issue, we ensured that both cohorts in this study had evidence of an outpatient nephrology visit in the year prior to the index date. In addition to specialized CKD care, there are opportunities to use a multidisciplinary approach to improve the patient experience and outcomes of kidney transplant recipients with a failing graft as they transition care.[19-21]

Our study has many strengths including having robust data on more than 1000 kidney transplant recipients and nontransplant controls with follow-up in a large Canadian province. We compared outcomes to nontransplant controls with a similar degree of CKD to assess kidney function decline and the excess risk of kidney failure and death among recipients, which has been identified as a significant knowledge gap.[3] There are study limitations that should be considered. This was a retrospective, observational study and there is a

risk of bias due to residual confounding. To minimize the risk of confounding, we used propensity-score matching to compare outcomes among groups that were balanced on measured baseline characteristics. In addition, we lacked granular data such as cause of death, race, smoking history, blood pressure control, transplant-related factors (ie, donor type and cause of kidney failure, such as chronic rejection), and kidney biopsy results. Despite this, we were able to control for several factors which may be associated with progression to kidney failure. For the main analysis, we defined kidney failure as both initiation of kidney replacement therapy and sustained eGFR <10 mL/min/1.73 m^2 as a surrogate for conservative management. We did not have details on the decisions around timing or reasoning behind kidney failure treatment; however, results were no different when we considered kidney failure as the initiation of kidney replacement therapy alone. Finally, our population has access to universal health care, which may limit the generalizability of our results.

In summary, among 575 kidney transplant recipients with a failing graft, the rate of kidney function decline was similar, but the risk of kidney failure and death was higher when compared with matched nontransplant controls. The higher risk of kidney failure in transplant recipients cannot be explained by eGFR decline alone, and further interventions to mitigate the risk of acute kidney injury resulting in graft loss are needed. This has implications in terms of prognosis discussion with kidney transplant recipients and highlights an area where specific health care interventions can be targeted to improve graft survival.

Author Contributions

NNL and PR participated in research design. AC, PR, and HA participated in data analysis. NNL and JK drafted and revised the manuscript. All authors were involved in data interpretation and final approval of the manuscript.

Declaration of Conflicting Interests

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Data Sharing Statement

This study is based in part on data provided by Alberta Health and Alberta Health Services. The interpretation and conclusions contained herein are those of the researchers and do not necessarily represent the views of the Government of Alberta or Alberta Health Services. Neither the Government of Alberta nor Alberta Health or Alberta Health Services express any opinion in relation to this study. We are not able to make our data set available to other researchers due to our contractual arrangements with the provincial health ministry (Alberta Health), who is the data custodian.

Supplemental Material

Supplemental material for this article is available online.

References

1. Halloran PF. Immunosuppressive drugs for kidney transplantation. *N Engl J Med*. 2004;351(26):2715-2729. doi:10.1056/NEJMra033540.
2. Canadian Institute for Health Information. Treatment of end-stage organ failure in Canada, Canadian Organ Replacement Register, 2010 to 2019: end—stage kidney disease and kidney transplants—data tables. Published 2020. Accessed April 9, 2022. https://www.cihi.ca/en/organ-replacement-in-canada-corr-annual-statistics-2020.
3. Kabani R, Quinn RR, Palmer S, et al. Risk of death following kidney allograft failure: a systematic review and meta-analysis of cohort studies. *Nephrol Dial Transplant*. 2014;29(9):1778-1786. doi:10.1093/ndt/gfu205.
4. Rao PS, Schaubel DE, Jia X, Li S, Port FK, Saran R. Survival on dialysis post–kidney transplant failure: results from the Scientific Registry of Transplant Recipients. *Am J Kidney Dis*. 2007;49(2):294-300. doi:10.1053/j.ajkd.2006.11.022.
5. Lam NN, Boyne DJ, Quinn RR, et al. Mortality and morbidity in kidney transplant recipients with a failing graft: a matched cohort study. *Can J Kidney Health Dis*. 2020;7:2054358120908677. doi:10.1177/2054358120908677.
6. Lam NN, Tonelli M, Lentine KL, et al. Albuminuria and posttransplant chronic kidney disease stage predict transplant outcomes. *Kidney Int*. 2017;92(2):470-478. doi:10.1016/j.kint.2017.01.028.
7. Hemmelgarn BR, Manns BJ, Lloyd A, et al. Relation between kidney function, proteinuria, and adverse outcomes. *JAMA*. 2010;303(5):423-429. doi:10.1001/jama.2010.39.

8. Hemmelgarn BR, Clement F, Manns BJ, et al. Overview of the Alberta Kidney Disease Network. *BMC Nephrol*. 2009;10:30. doi:10.1186/1471-2369-10-30.
9. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43(11):1130-1139. doi:10.1097/01.mlr.0000182534.19832.83.
10. Tonelli M, Wiebe N, Fortin M, et al. Methods for identifying 30 chronic conditions: application to administrative data. *BMC Med Inform Decis Mak*. 2015;15(1):31. doi:10.1186/s12911-015-0155-5.
11. Schnitzler MA, Johnston K, Axelrod D, et al. Associations of renal function at 1-year after kidney transplantation with subsequent return to dialysis, mortality, and healthcare costs. *Transplantation*. 2011;91(12):1347-1356. doi:10.1097/TP.0b013e31821ab993.
12. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun Stat Simul Comput*. 2009;38:1228-1234. doi:10.1080/03610910902859574.
13. Ho DE, Imai K, King G, et al. MatchIt: nonparametric preprocessing for parametric causal inference. *J Stat Softw*. 2011;42(8):1-28. doi:10.18637/jss.v042.i08.
14. R Foundation for Statistical Computing. *R: A Language and Environment for Statistical Computing*. Published 2017. Accessed May 22, 2018. https://www.r-project.org/about.html.
15. Austin PC. The performance of different propensity score methods for estimating marginal hazard ratios. *Stat Med*. 2013;32(16):2837-2849. doi:10.1002/sim.5705.
16. Pham P-T, Everly M, Faravardeh A, et al. Management of patients with a failed kidney transplant: dialysis reinitiation, immunosuppression weaning, and transplantectomy. *World J Nephrol*. 2015;4(2):148-159. doi:10.5527/wjn.v4.i2.148.
17. Cooper BA, Branley P, Bulfone L, et al. A randomized, controlled trial of early versus late initiation of dialysis. *N Engl J Med*. 2010;363(7):609-619. doi:10.1056/NEJMOA1000552.
18. Molnar MZ, Streja E, Kovesdy CP, et al. Estimated glomerular filtration rate at reinitiation of dialysis and mortality in failed kidney transplant recipients. *Nephrol Dial Transplant*. 2012;27(7):2913-2921. doi:10.1093/NDT/GFS004.
19. Naylor KL, Knoll GA, McArthur E, et al. Outcomes of an inpatient dialysis start in patients with kidney graft failure: a population-based multicentre cohort study. *Can J Kidney Health Dis*. 2021;8:2054358120985376. doi:10.1177/2054358120985376.
20. Gill JS, Abichandani R, Khan S, Kausz AT, Pereira BJ. Opportunities to improve the care of patients with kidney transplant failure. *Kidney Int*. 2002;61(6):2193-2200. doi:10.1046/j.1523-1755.2002.00373.x.
21. Lubetzky M, Tantisattamo E, Molnar MZ, et al. The failing kidney allograft: a review and recommendations for the care and management of a complex group of patients. *Am J Transplant*. 2021;21(9):2937-2949. doi:10.1111/ajt.16717.