Risk Factors for Developing Low Estimated Glomerular Filtration Rate and Albuminuria in Living Kidney Donors

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Rationale & Objective: Chronic kidney disease is associated with significant morbidity and mortality in the general population, but little is known about the incidence and risk factors associated with developing low estimated glomerular filtration rate (eGFR) and moderate-severe albuminuria in living kidney donors following nephrectomy.

Study Design: Retrospective, population-based cohort study.

Setting & Participants: Kidney donors in Alberta, Canada.

Exposure: Donor nephrectomy between May 2001 and December 2017.

Outcome: Two eGFR measurements <45 mL/min/1.73 m^2 or 2 measurements of moderate or severe albuminuria from 1-year postdonation onwards that were at least 90 days apart.

Analytical Approach: Associations between potential risk factors and the primary outcome were assessed using Cox proportional hazard regression analyses.

Results: Over a median follow-up period of 8.6 years (IQR, 4.7-12.6 years), 47 of 590 donors (8.0%) developed sustained low eGFR or moderate-severe albuminuria with an incidence rate of 9.2 per 1,000 person-years (95% confidence interval, 6.6-11.8). The median time for development of this outcome beyond the first year after nephrectomy was 2.9 years (IQR, 1.4-8.0 years). Within the first 4 years of follow-up, a 5 mL/min/1.73 m^2 lower predonation eGFR increased the hazard of developing postdonation low eGFR or moderate-severe albuminuria by 26% (adjusted HR, 1.26; 95% CI, 1.10-1.44). Furthermore, donors were at higher risk of developing low eGFR or albuminuria if they had evidence of predonation hypertension (adjusted HR, 2.52; 95% CI, 1.28-4.96) or postdonation diabetes (adjusted HR, 4.72; 95% CI, 1.54-14.50).

Limitations: We lacked data on certain donor characteristics that may affect long-term kidney function, such as race, smoking history, and transplant-related characteristics.

Conclusions: A proportion of kidney donors at an incidence rate of 9.2 per 1,000 person-years will develop low eGFR or albuminuria after donation. Donors with lower predonation eGFR, predonation hypertension, and postdonation diabetes are at increased risk of developing this outcome.

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Living donor kidney transplant is considered the optimal treatment for patients with kidney failure.[1] Kidney transplants from living donors offer additional benefits over transplants from deceased donors including shorter duration on dialysis (or even complete avoidance of dialysis in the case of pre-emptive transplants), longer graft survival, and less cold ischemia time, thereby reducing the risk of delayed graft function.[2,3]

Although donor nephrectomy is considered a relatively safe procedure, there are potential short- and long-term risks to the donors. Previous studies have shown increased rates of hypertension, gout, pre-eclampsia, and kidney failure in living kidney donors compared to matched, healthy, non-donor controls.[4–10] Gaining more information about the incidence and risk factors associated with sustained low estimated glomerular filtration rate (eGFR) and albuminuria in living kidney donors could better inform decisions about donation and improve the identification of higher risk individuals to protect these altruistic members of society.

In this study, we determined the incidence and risk factors associated with developing low eGFR and moderate-severe albuminuria after donor nephrectomy.

METHODS

Design and Setting

We conducted a retrospective, population-based cohort study using linked health care databases within the Alberta Kidney Disease Network.[11] Greater 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)[12,13] 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 (REB15-1575).

Data Sources

We ascertained baseline characteristics, information about covariates, and outcome data from linked administrative and laboratory data (Table S2). The Alberta Health database contains information on demographic data, vital statistics, and diagnostic and procedural information on inpatient and outpatient physician services. We linked these data sources to a provincial laboratory repository via unique,

PLAIN-LANGUAGE SUMMARY

The purpose of this study was to understand the risk of developing kidney disease in living kidney donors after donation. We followed 590 donors in Alberta, Canada for almost 9 years. Approximately 8% of donors developed reduced kidney function (low estimated glomerular filtration rate) or increased protein in the urine (albuminuria). Donors with lower kidney function before donation, hypertension before donation, or diabetes after donation had a higher likelihood of experiencing these kidney outcomes. This research provides important insights to patients and health care providers to better support the long-term kidney health of living kidney donors.

encoded patient identifiers. The serum creatinine measurements obtained in our databases have been standardized across provincial laboratories over time, reducing interlaboratory variation in measurements.[11] These databases have been previously used for research on health outcomes and services.[14,15]

Population

We identified all adult living kidney donors (≥18 years old) who underwent donor nephrectomy between May 1, 2001 and December 31, 2017 in Alberta, Canada (Fig S1). Living kidney donors were identified using an algorithm that required the presence of 1 diagnostic code for kidney donation (International Statistical Classification of Diseases, 9th Revision [ICD-9] V59.4 or 10th Revision [ICD-10] Z52.4) and 1 procedural code for kidney procurement or excision (for March 2002 or earlier [ICD-9], 55.51; for April 2002 onward Canadian Classification of Health Interventions [CCI] 1.PC.58, 1.PC.89, or 1.PC.91) (Table S2). Similar codes have been used in prior studies to identify living kidney donors.[14-16] This algorithm has been validated and found to have a sensitivity of 97% and a positive predictive value of 90% when compared with the gold standard of living kidney donor identification by the provincial tissue and organ agency and verification through manual perioperative chart review.[17]

We excluded pediatric donors (<18 years old), out-of-province donors, and a small proportion of donors (<2%) with missing data, such as sex or date of birth. Donors were also excluded if they died on or before the date of nephrectomy. To avoid the misclassification of kidney transplant recipients as donors, we excluded individuals with evidence of dialysis or kidney transplant before donation. To ensure that donors included in this study had reasonable laboratory follow-up data, patients were excluded if they did not have a minimum of 2 outpatient serum creatinine measurements in our database that were at least 1 year postdonation and a minimum of 90 days apart. We also excluded donors with evidence of dialysis, kidney transplant, death, or emigration within the first year after donation. Donors were followed from 1 year after their donation date until the first occurrence of any of the following events: death, emigration from the province, outcome of interest, or end of study period (March 31, 2019).

Baseline Characteristics and Medical Comorbid Conditions

Baseline demographics, including age and sex, were determined from Alberta Health administrative data files. Postal codes were linked to the Canadian census using the Postal Code Conversion file to determine median neighborhood household income quintile (level 5 being the highest) as well as rural versus urban location of residence and distance from transplant center. Hypertension (predonation and de novo postdonation) and diabetes (de novo postdonation only given that predonation diabetes is a contraindication to donation) were identified based on validated algorithms using hospital discharge records and physician claims (Table S2).[18,19] We also identified postdonation diabetes by evidence of a glycated hemoglobin A1c of ≥6.5%.[20] Postdonation characteristics were identified based on the presence of applicable data and codes from 1 year postdonation onward. Demographic data were complete except for income quintile (<0.5%); patients with missing income quintile were included in the middle (level 3) category.

Outcome

The primary outcome was defined by either 2 eGFR measurements <45 mL/min/1.73 m^2 or 2 measurements of moderate or severe albuminuria that were at least 90 days apart. The 90-day criteria aligns with the Kidney Disease: Improving Global Outcomes (KDIGO) definition of chronic kidney disease (CKD) to confirm chronicity.[21] The primary outcome also included the need for kidney replacement therapy, which was defined as maintenance dialysis or kidney transplant. The composite of eGFR <45 mL/min/1.73 m^2 and kidney failure was used given that postdonation kidney failure is a rare event and is typically preceded by a decline in eGFR.[22] Furthermore, only outpatient laboratory measurements of eGFR and albuminuria were used to identify the primary outcome to avoid capturing episodes of in-hospital acute kidney injury. Only laboratory data beyond the first year following donation were considered to ensure stable function of the remaining kidney following nephrectomy.[15] Therefore, for the purpose of survival analyses, time 0 was defined as 1 year postdonation, and the administrative censoring date was the end of the study period (March 31, 2019).

The eGFR was calculated using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation.[23]

Table 1. Baseline Characteristics at the Time of Donation and Medical Comorbid Conditions of Living Kidney Donors

Characteristic	Total (n = 590)
Age, y, mean [SD]	43.6 [11.7]
18-30	91 (15.4)
31-50	304 (51.5)
>50	195 (33.1)
Sex	
Male	194 (32.9)
Female	396 (67.1)
SES	
Level 1 (lowest)	101 (17.1)
Level 2	142 (24.1)
Level 3 (middle)	123 (20.8)
Level 4	94 (15.9)
Level 5 (highest)	130 (22.0)
Residence	
Urban	523 (88.6)
Rural	67 (11.4)
Distance to transplant center, km, median [IQR]	29.3 [13.9-165.4]
<50	359 (60.8)
50.1-150	76 (12.9)
150.1-300	66 (11.2)
>300	89 (15.1)
Year of nephrectomy	
2001-2009	330 (55.9)
2010-2017	260 (44.1)
Predonation eGFR, mL/min/1.73m², mean [SD]	98.5 [16.1]
≥90	358 (60.7)
80-89	98 (16.6)
70-79	49 (8.3)
60-69	24 (4.1)
≤59	0 (0)
Missing	61 (10.3)
Predonation albuminuria category	
None/Mild	439 (74.4)
Moderate	7 (1.2)
Severe	0 (0)
Missing	144 (24.4)
Predonation HbA1C, %, mean [SD]	5.5 [0.3]
<5.5	98 (16.6)
5.5-5.9	106 (18.0)
6.0-6.4	12 (2.0)
Missing	374 (63.4)
Comorbid conditions	
Predonation hypertension	67 (11.4)
Postdonation hypertension	83 (14.1)
Postdonation diabetes	23 (3.9)

Note: Data are presented as number (percent), mean [SD], or median [IQR]. Abbreviations: eGFR, estimated glomerular filtration rate; HbA1C, hemoglobin A1C; IQR, interquartile range; SES, socio-economic status; SD, standard deviation.

Because data on race were not available, recipients were assumed to be of non-African descent. Misclassification of eGFR was expected to be minimal because <4% of the Albertan population self-identified as "Black" in the Canadian census.[24] Albuminuria was ascertained using all available outpatient, random, spot urine measurements of the albumin-creatinine ratio (ACR) and the protein-creatinine ratio (PCR). The degree of albuminuria was categorized as normal to mild (A1: ACR <30 mg/g, PCR <15 mg/mmol), moderate (A2: ACR 30-300 mg/g, PCR 15-50 mg/mmol) or severe (A3: ACR >300 mg/g, PCR >50 mg/mmol).[21] An eGFR <45 mL/min/1.73 m^2 and moderate or severe (A2 or A3) albuminuria were selected as the composite primary outcome because this degree of abnormal kidney function places the nondonor population at moderate-high risk of progression to CKD and mortality.[21]

Statistical Analyses

Baseline characteristics were summarized using either mean and standard deviation (SD) or median and interquartile range (IQR) based on the normality of data distribution. We compared baseline characteristics and postdonation comorbid conditions of donors with and without low eGFR and albuminuria using χ^2 or Fisher exact tests for categorical variables and Kruskal-Wallis or t tests for continuous variables. We used univariate and multivariable Cox proportional hazard regression analyses to estimate the associations between the baseline characteristics in Table 1 and the primary outcome. To analyze the association between time-dependent postdonation risk factors (hypertension and diabetes) and the kidney outcome, we used extended Cox models, adjusting for age, sex, eGFR, and predonation hypertension (adjusted hazard ratio with 95% confidence intervals [aHR]; 95% confidence intervals [CI]). The extended Cox model has been shown to minimize immortal time bias more effectively compared with other traditional methods.[25,26] Missing eGFR values were imputed using multiple imputations from the AregImpute (R), based on predictive mean matching conditional on age, sex, socio-economic status, and hypertension, which uses the bootstrap to approximate the process of drawing predicted values from a full Bayesian predictive distribution. Five imputations were conducted, and the average of the predicted values was used in the final model. To satisfy the proportionality assumption in Cox models, we used logarithmic transformation of distance from transplant center. The step function was implemented for predonation eGFR to satisfy the proportional hazards assumption because the hazard ratio changed over time. This function divided follow-up time into 2 distinct periods, allowing the hazard ratio to vary across these intervals. We assessed model validity and goodness of fit by means of formal tests of significance and graphical methods based on residuals.[27] A Kaplan-Meier curve was created to show the probability of surviving without developing the kidney outcome postdonation. A P value of <0.05 was used to define statistical significance. All analyses were performed using R, version 4.1.1 (R-project.org).

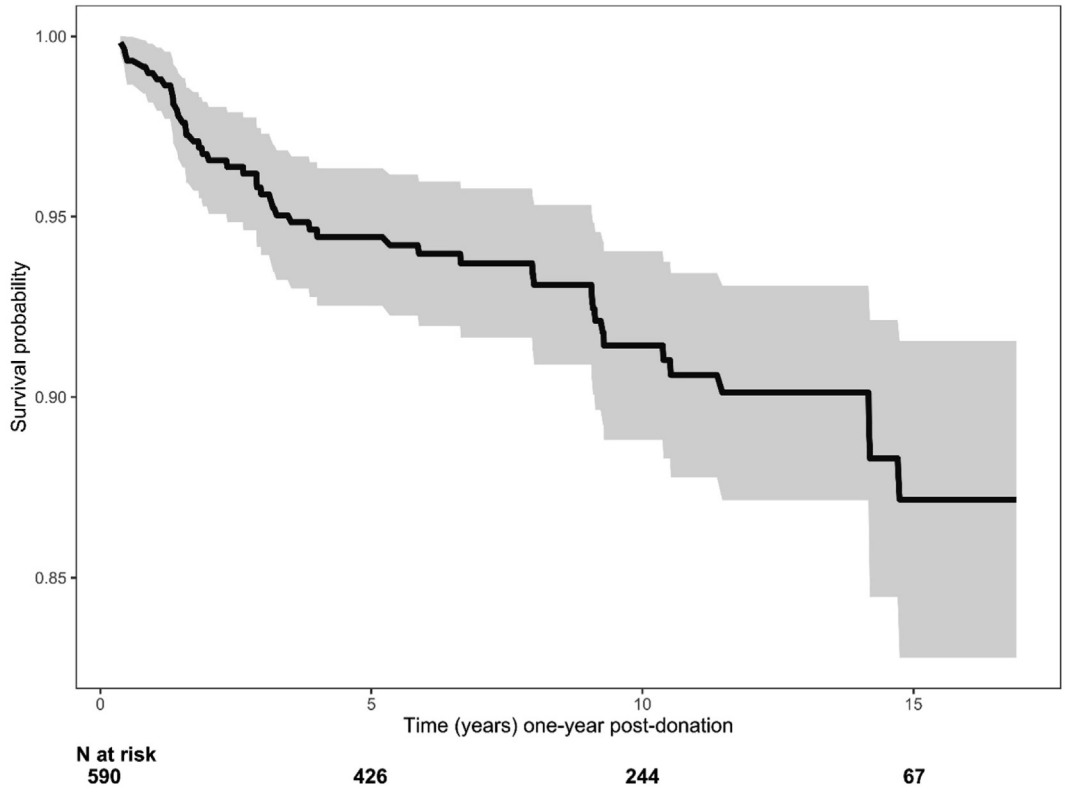

Figure 1. Kaplan-Meier curve with 95% confidence interval of estimated kidney outcome-free survival in living kidney donors from 1 year postdonation onward.

RESULTS

Baseline Characteristics

Between May 1, 2001 and December 31, 2017, there were 778 living kidney donor nephrectomies performed in Alberta. Of these, 188 donors were excluded, with the most common exclusion criterion being lack of 2 or more eligible postdonation eGFR measurements (n = 87), leaving 590 donors who met study inclusion criteria (Fig S1). The mean age at time of donation was 43.6 years (SD, 11.7), and 67.1% of donors were female (Table 1). The mean predonation eGFR was 98.5 mL/min/1.73 m^2 (SD, 16.1), and almost all donors with available laboratory data had none/mild albuminuria (98.4%) before donation.

Development of Low eGFR or Moderate-Severe Albuminuria Following Donor Nephrectomy

Of the 590 adults included in this study, 47 (8.0%) donors developed sustained low eGFR or moderate-severe albuminuria before the end of the follow-up period, with an incidence rate of 9.2 cases per 1,000 person-years (95% CI, 6.6-11.8). In our study, donors were classified as having the kidney outcome based on the condition they developed first during the follow-up period. According to this classification, 21 donors developed sustained low eGFR, 23 donors developed moderate-severe albuminuria, and 3 donors received dialysis. The median time for development of the primary outcome beyond the first year after nephrectomy was 2.9 years (IQR, 1.4-8.0). The probabilities of surviving 5 and 10 years beyond the first year postdonation without having the kidney outcome were 0.94 (95% CI, 0.93-0.96) and 0.91 (95% CI, 0.89-0.94), respectively (Fig 1).

The median follow-up time was 8.6 years (IQR, 4.7-12.6) with a maximum follow-up of 16.9 years. Before the end of the follow-period, 47 donors (8.0%) developed the primary outcome, 7 donors (1.2%) were censored because of death, and 11 donors (1.9%) were censored due to emigration.

Correlations of Baseline Characteristics and Low eGFR or Moderate-Severe Albuminuria

Compared to donors without the primary outcome, donors who developed low eGFR or moderate-severe albuminuria were more likely to be older (mean age 49.3 vs 43.1 years), male (48.9% vs 31.5%), and have predonation hypertension (25.5% vs 10.1%) (Table S3). Predonation eGFR was also lower in donors who developed the kidney outcome (mean 89.7 vs 99.2 mL/min/1.73 m^2).

In adjusted analyses, donors with lower predonation eGFR were at higher risk of developing the primary outcome. Within the first 4 years of follow-up, a 5 mL/min/1.73 m^2 lower predonation eGFR increased the hazard of developing postdonation low eGFR or moderate-

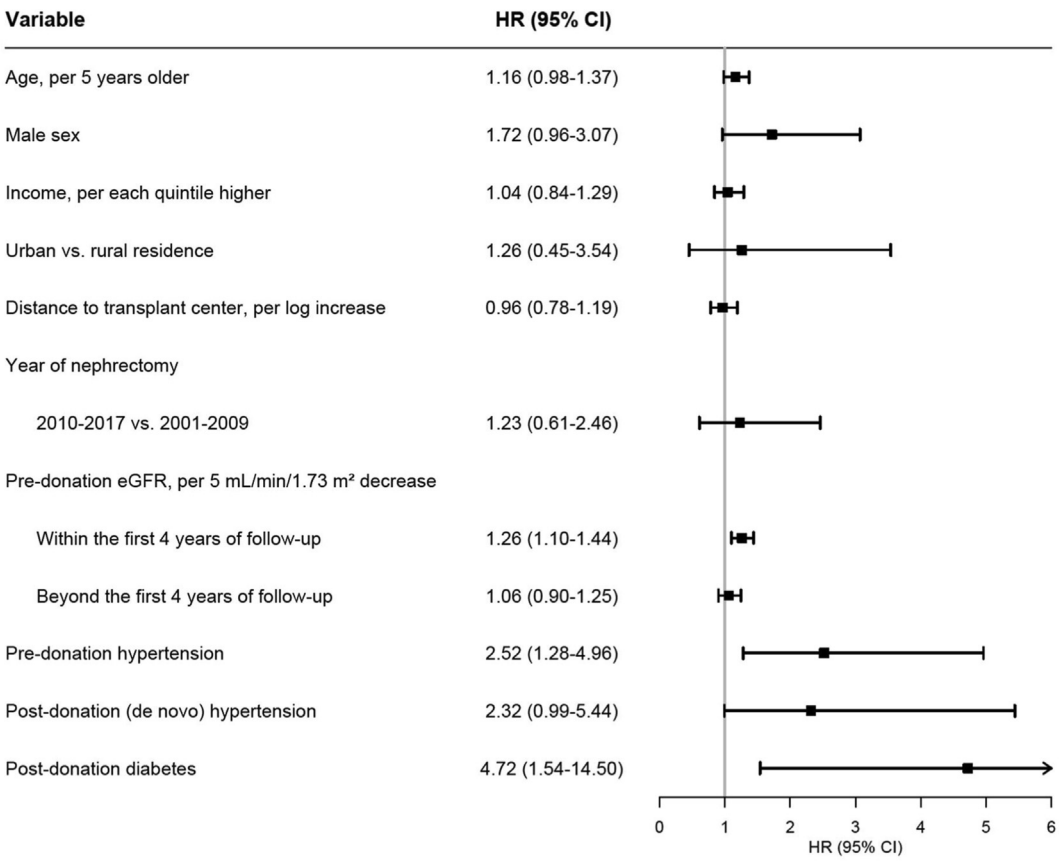

Figure 2. Adjusted hazard ratios of low eGFR or moderate-severe albuminuria following living donor nephrectomy. Data are adjusted for age, sex, predonation hypertension, and predonation eGFR. Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

severe albuminuria by 26% (aHR = 1.26; 95% CI, 1.10-1.44). Beyond the initial 4 years of follow-up, there was no statistically significant association between predonation eGFR and risk of postdonation kidney outcome (aHR = 1.06; 95% CI, 0.90-1.25). Donors with evidence of predonation hypertension had a 2.5-fold higher risk of developing low eGFR or moderate-severe albuminuria after donation compared with donors without predonation hypertension (aHR = 2.52; 95% CI, 1.28-4.96). The remainder of the baseline characteristics showed no significant association with risk of the kidney outcome in adjusted analyses (Fig 2). Sensitivity analysis with missing values excluded yielded similar results. Results from unadjusted analyses are shown in Figure S2.

Postdonation Risk Factors for Developing Low eGFR or Moderate-Severe Albuminuria

In adjusted analyses, there was no statistically significant association between postdonation (de novo) hypertension and the development of the primary outcome (aHR = 2.32; 95% CI, 0.99-5.44); however, donors who developed postdonation diabetes had a 4.7-fold higher risk of developing the kidney outcome compared to donors without diabetes (aHR = 4.72; 95% CI, 1.54-14.50).

DISCUSSION

In this retrospective cohort study of living donors in 1 large Canadian province, we found that over a median follow-up period of 8.6 years, 8.0% of living kidney donors developed low eGFR or moderate-severe albuminuria postdonation. The rates of kidney outcome-free survival after 5 and 10 years beyond the first year postdonation were 0.94 and 0.91, respectively. In adjusted analyses, lower predonation eGFR, presence of predonation hypertension, and the development of postdonation diabetes were risk factors for subsequent low eGFR or moderate-severe albuminuria.

Although the absolute risk of kidney failure is low in living kidney donors, prior studies have suggested that the relative risk is higher than that noted in nondonor controls.[5,28] Low eGFR and moderate-severe albuminuria are precursors to kidney failure and therefore serve as an early indicator of donors at risk.[29] Immediately after donor nephrectomy, there is a 25%-40% decrease in eGFR associated with hyperfiltration of the remaining kidney.[15,30-32] In a similar cohort of living kidney donors followed over a median period of 7 years (maximum 15 years), we found that from 6 weeks postdonation onward, eGFR increased by +0.35 mL/min per 1.73 m^2 per year.[15]

This increase in eGFR was greatest in the first 2 years postdonation (+1.06 mL/min per 1.73 m^2 per year) and began to plateau after 5 years (−0.06 mL/min per 1.73 m^2 per year).[15] Similarly, Kido et al.[33] found that in 8 donors who developed kidney failure, their kidney function initially remained stable over a long period following donation (mean 13 years). It was not until the development of a CKD progression risk factor, such as proteinuria or hypertension, or a CKD accelerating factor, such as a cardiovascular event, that the eGFR started to suddenly, and more rapidly, decline.[33] With regards to postdonation proteinuria, a meta-analysis of 3 studies comparing a total of 129 donors to 59 controls found that the 24-hour urine protein was higher in donors compared to nondonor controls an average of 11 years after donation (147 vs 83 mg/day), and this difference increased with time from donation ($P < 0.001$).[30] Thus, longer follow-up, beyond the first decade postdonation, is needed to better understand the trends in eGFR decline and increasing albuminuria leading to abnormal kidney function and, potentially, kidney failure.

Whether low eGFR and albuminuria in kidney donors warrants a clinical diagnosis of CKD is controversial.[34,35] Important implications of this diagnosis include the potential to provoke unnecessary anxiety among donors as well as the burden imposed on donors due to increased appointments, investigations, and health insurance and life insurance costs.[35] The expected benefit of identifying patients with evidence of low eGFR or albuminuria is that it provides an opportunity for early intervention to prevent progression of disease.[36] The 2017 KDIGO Guideline on the Evaluation and Care of Living Kidney Donors recommends that all donors undergo annual lifelong surveillance.[36] This recommendation is primarily grounded in ethical principles due to the lack of existing evidence that annual follow-up improves long-term outcomes.[36] However, there are significant constraints associated with implementation of these policies that must be considered, including systemic barriers, such as limited resources, infrastructure, and funds, as well as the added costs and inconveniences experienced by donors.[37,38] Selective close follow-up of donors with risk factors for developing abnormal kidney function may provide a balance between protecting overall donor health while minimizing costs on an individual and societal level.

An important aspect of our study was analyzing potential predonation risk factors for the development of low eGFR or moderate-severe albuminuria after donation which could provide valuable knowledge to guide informed decision making for prospective donors. In adjusted analyses, we found that donors with lower predonation eGFR were at higher risk of developing the primary outcome. Similar results were found in a Taiwanese study of 105 living kidney donors, in which a preoperative eGFR <90 ml/min/1.73 m^2 was significantly associated with CKD, defined as 2 eGFR measurements <60 mL/min/1.73 m^2 at least 3 months apart.[39] Another predonation risk factor identified in this study was hypertension, which was associated with a 2.6-fold higher risk of developing the kidney outcome in our cohort. Although we did not find a statistically significant association between de novo hypertension and the primary outcome, this may have been attributed to limited follow-up time and the small proportion of donors who developed de novo hypertension in our cohort. A recent US study of 3,700 kidney donors over a mean of 16.6 years found that hypertension developed in 4%, 10%, and 51% of donors at 5, 10, and 40 years postdonation, respectively, and was associated with low eGFR, proteinuria, and death.[40]

With regards to postdonation risk factors, donors who developed diabetes after nephrectomy had a 4.6-fold higher risk of subsequently developing the kidney outcome compared with donors without diabetes. It is likely that the kidney outcome in these donors with diabetes was attributed to the development of moderate-severe albuminuria, which typically precedes eGFR decline among the nondonor population with diabetes.[41,42] A US study of 4,014 donors also noted an association between diabetes and eGFR decline over a mean follow-up time of 9.2 years after a diagnosis of diabetes; however, the rate of eGFR decline only exceeded that of nondiabetic donors in those with concomitant proteinuria and hypertension.[43] Diabetic kidney disease in living kidney donors is more frequently a late rather than early cause of kidney failure; therefore, studies with follow-up times exceeding 10 years after donation may provide more clarity regarding the progression of disease in this unique population.

Our study has several strengths. It involves a large Canadian cohort of 590 donors followed for almost a decade postnephrectomy with little loss to follow-up. Furthermore, we were able to access all laboratory measurements performed within the province, and these measurements have been standardized across laboratories, thus, reducing interlaboratory variation. There are limitations worth noting. We lacked data on certain donor characteristics that may affect long-term kidney function, such as race; race-related biomarkers, such as *APOL1* genotype; smoking; and body mass index. However, we were able to identify and control for other important demographics. Unfortunately, we also did not have access to transplant-related characteristics, such as donor–recipient relationship, which precluded the evaluation of potential genetic predispositions to kidney disease among related donors and their influence on the outcome of interest. The median duration of follow-up in this study was 8.6 years; therefore, more donors may have developed the primary outcome with a longer follow-up time. An inherent limitation of our study stems from the application of multiple exclusion criteria during cohort creation due to missing demographic or laboratory data. While these criteria were essential to ensure robustness of outcome data, this approach does carry the potential for introducing selection bias. Although we only considered outpatient serum

creatinine and albuminuria measurements, we were not able to determine the indications for the serum creatinine and albuminuria measurements to differentiate between kidney function surveillance and medical illness or concern. Therefore, our study did have potential for ascertainment bias because follow-up laboratory measurements were not performed per a standardized protocol. Lastly, our results may not be generalizable to other countries or regions that do not have a similar universal health care system.

In conclusion, the results from our study show that a small proportion of kidney donors will develop low eGFR or moderate-severe albuminuria following donation. Donors were at higher risk of developing the kidney outcome if they had lower predonation eGFR, predonation hypertension, or postdonation diabetes. Further research is needed to determine whether donors with these risk factors would benefit from more diligent follow-up care as well as the effect of low eGFR and moderate-severe albuminuria on donor morbidity.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1: Cohort creation.

Figure S2: Unadjusted hazard ratios of kidney outcome following living donor nephrectomy.

Table S1: STROBE and RECORD Checklist.

Table S2: Databases and Coding Definitions for Inclusion/Exclusion Criteria, Baseline Characteristics, and Outcome Measurements.

Table S3: Baseline Characteristics at the Time of Donation and Medical Comorbid Conditions for Living Kidney Donors With and Without Evidence of the Primary Outcome (Low eGFR or Moderate-Severe Albuminuria).

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