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Risk of Kidney Failure, Death, and Cardiovascular Events After Lower Limb Complications in Patients With CKD

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Objective: Lower limb complications are major adverse events in patients with peripheral artery disease (PAD) and chronic kidney disease (CKD). These complications can lead to morbidity, disability, reduced quality of life, and higher health care costs. We sought to determine how interim lower limb complications modify the subsequent risk of progression to kidney failure, all-cause mortality before kidney failure, and cardiovascular (CV) events in a cohort of patients with CKD stages G3 to G5.

Methods: We performed a retrospective cohort study using patient-level data obtained by linking several administrative databases from Manitoba, Canada. We used Fine and Gray regression models for the primary outcomes of (1) kidney failure adjusted for the competing risk of all-cause mortality, (2) death before kidney failure, and (3) cardiovascular-related hospitalization with the competing risk of non-CV death.

Results: A total of 92,618 patients were included in the final cohort, with a median follow-up time of 2.56 years. Compared with patients who did not experience an interim lower limb complication, there was a higher risk of kidney failure (adjusted hazard ratio [HR] 2.51, 95% confidence interval [CI] 2.10–3.00), all-cause mortality before kidney failure (adjusted HR 2.73, 95% CI 2.55–2.92), and CV events (adjusted HR 2.12, 95% CI 1.90–2.38).

Conclusions: Interim lower limb complications are associated with an increased risk of kidney failure, all-cause mortality before kidney failure, and cardiovascular-related hospitalization. Clinical trials of screening and treatment strategies for patients with CKD at risk for lower limb complications may help determine optimal strategies to manage this risk.

CKD is an emerging public health problem worldwide with an increasing incidence and prevalence largely driven by the epidemic of diabetes.[1,2] These patients are often at risk for many adverse complications, including increased mortality, increased risk of hospitalization, risk of kidney failure, and complications associated with the vascular system, including PAD.[3,4] PAD has been associated with considerable additional complications among patients with CKD, including foot ulcers and nontraumatic lower limb amputations.[4–6]

Once they develop, lower limb complications lead to morbidity, disability, reduced quality of life, and higher health care costs.[1] Recurrence of foot ulcers in patients with CKD and PAD is more than 50% within 3 years of initial healing.[1] This high recurrence rate can be explained by reduced blood flow from PAD, immune compromise from CKD, and lack of protective sensations from neuropathy.[1] Patients with kidney failure receiving dialysis have a 10-fold higher incidence of lower limb amputation compared with the general diabetic population.[3] Studies have shown that as many as two-thirds of patients with kidney failure receiving dialysis die within 2 years of their first lower limb amputation.[7] These findings illustrate the severity of risk that lower limb complications pose for patients with kidney failure.

Over the past decade, multiple studies have shown an association between CKD and PAD, and have identified kidney failure requiring dialysis as an important risk factor in the development of lower limb complications.[7–11] However, gaps in knowledge still exist about how lower limb complications as an interim event affect CKD progression and adverse events. The aim of this study was to determine how a lower limb complication modifies the subsequent risk of progression to kidney failure, all-cause mortality before kidney failure, and cardiovascular-related hospitalization, in a cohort of patients with CKD stages G3 to G5.

MATERIALS AND METHODS

Study Design

We performed a retrospective cohort study analyzing patient-level data obtained by linking several administrative databases housed at the Manitoba Centre for Health Policy in Manitoba, Canada, an organization that has for the past 25 years housed and integrated several administrative databases related to social and health services provided to Manitoba residents.[12] Included databases were the Manitoba Health Insurance Registry (patient demographics and follow-up information), the Discharge Abstract Database (hospital admissions), Medical Services (physician claims), Vital Statistics (cause-specific mortality), and Diagnostic Services of Manitoba (laboratory results). The study protocol was reviewed and approved by the University of Manitoba Health Research Ethics Board (Ethics # HS18574). All data provided were de-identified using a scrambled personal health identifier and patient consent was waved.

Study Cohort

We included all adult (age 18+) patients from Manitoba, Canada (population 1.3 million), with Stage G3 or higher CKD using serum creatinine tests from the Diagnostic Services of Manitoba database, taking the first recorded estimated glomerular filtration rate (eGFR) less than 60 ml/min per $1.73m^2$ between January 1, 2007, and October 31, 2014, with the study entry (index date) defined as the date of first serum creatinine test. The eGFR was calculated using the Chronic Kidney Disease–Epidemiology Collaboration study equation.[13] Patients receiving dialysis or with a functioning transplant at baseline were excluded, as ascertained by physician claims (Supplementary Table S1). In addition, patients without valid Manitoba Health registration data (e.g., invalid health coverage dates) and those who died or were censored on the same day as the index eGFR test were excluded.

Outcomes

The primary outcomes of interest in our study included (1) kidney failure adjusted for the competing risk of all-cause mortality, (2) death before kidney failure, and (3) cardiovascular-related hospitalization in the presence of the competing risk of non-CV death. Kidney failure was established as the first claim for chronic dialysis or a renal transplant using tariff codes from the Manitoba Physician's Manual[14] (Supplementary Table S1). CV-related hospitalizations were ascertained using *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) and *International Classification of Diseases, 10th Revision, Canadian version* (ICD-10-CA) codes and included either a primary or secondary diagnosis in the Discharge Abstract Databases (Supplementary Table S2).[15] CV-related mortality was established using the Vital Statistics database with a cause of death attributed to any ICD-10-CA code starting with I (diseases of the circulatory system).

Exposures

Baseline characteristics and comorbidities were ascertained between January 1, 2004, and the date of entry into the study cohort. The primary exposure of interest was an interim lower limb complication, defined as a diabetic foot ulcer or nontraumatic lower limb amputation in hospital records from the Discharge Abstract Database (ICD-9 and ICD-10-CA codes provided in Supplementary Table S3) and evaluated a time-dependent variable. Baseline characteristics included the following: demographic information (age and sex), laboratory data (eGFR, urine albumin-to-creatinine ratio, and hemoglobin A1C), and comorbid conditions (myocardial infarction, congestive heart failure, PAD, cerebrovascular disease, chronic pulmonary disease, and diabetes). ICD-9-CM and ICD-10-CA codes used to define comorbid conditions are presented in Supplementary Table S4.

Statistical Analysis

Descriptive statistics were presented as means and SDs or medians and interquartile ranges for continuous variables and percentages for categorical data. Comparisons were evaluated between individuals who had an interim lower limb complication (between the index date and the outcome of mortality or kidney failure) and those who did not by using the appropriate statistical test (e.g., t-test, Wilcoxon rank sum test, and the χ^2 test).

We developed Fine and Gray regression models to evaluate the outcome of kidney failure in the presence of the competing risk of death and CV-related hospitalization in the presence of the competing risk of non-
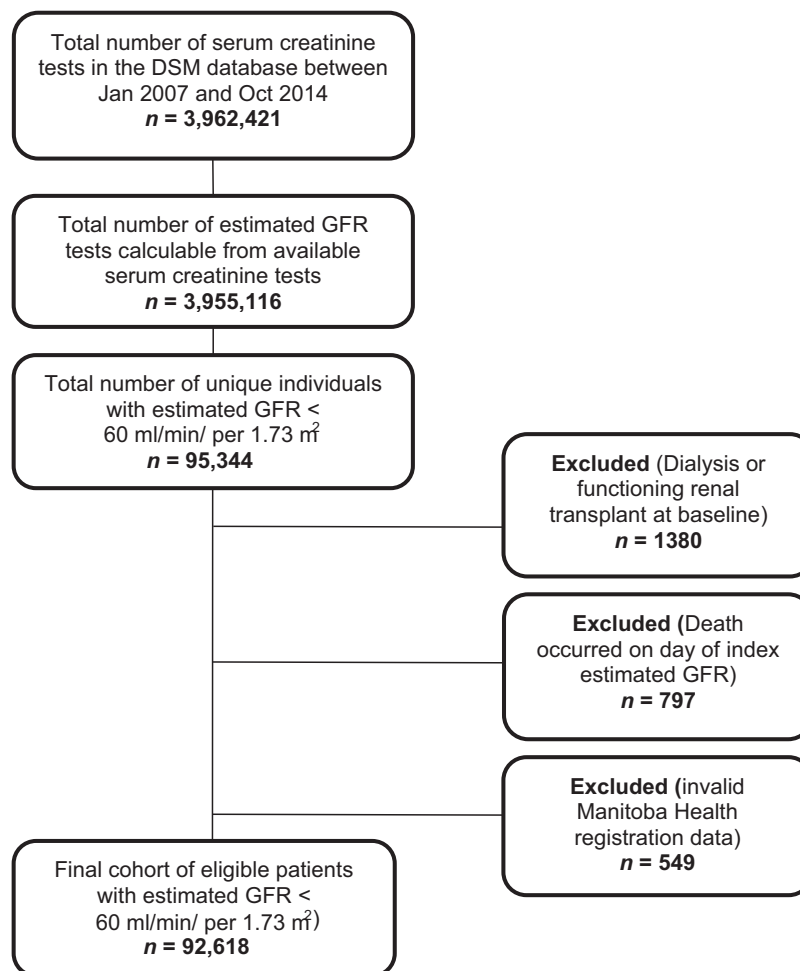
Figure 1. Overview of the cohort selection process. DSM, Diagnostic Services of Manitoba.

CV death. A Cox proportional hazards model was evaluated for the outcome of all-cause mortality before kidney failure. The primary exposure variable of interest, interim lower limb complication, was treated as a time-dependent variable in all regression models, which were also adjusted for baseline demographics (age, sex), baseline eGFR, and comorbid conditions (myocardial infarction, congestive heart failure, PAD, cerebrovascular disease, chronic pulmonary disease, and diabetes) as time-independent covariates. Assessment of proportionality was performed by visual inspection of scaled Schoenfeld residuals plotted over time. Multi-collinearity was assessed using a linear regression model and evaluating variance inflation factors. All statistical analysis was performed with SAS version 9.4 (SAS Institute Inc., Cary, NC) and we used a 2-sided significance level of $P < 0.05$.

Subgroup and Sensitivity Analyses

We performed several sensitivity analyses. First, we further adjusted models for urine albumin-to-creatinine values in patients where the test was available. Second, we performed a sensitivity analysis where models were

also adjusted for the presence of a prior lower limb complication before the index date. Third, interaction analyses were performed for age (<65 and ≥ 65 years), eGFR groups (<30 ml/min per 1.73 m^2 and ≥ 30 ml/min per 1.73 m^2), and the presence of comorbid diabetes. Last, we performed an additional sensitivity analysis using inverse probability of exposure weighting, determining the propensity to have a lower limb complication based on the covariates adjusted for in the primary analyses (age, sex, baseline eGFR, myocardial infarction, congestive heart failure, PAD, cerebrovascular disease, chronic pulmonary disease, and diabetes) and using logistic regression.

RESULTS

Cohort Selection and Population Characteristics

Our final cohort included 92,618 individuals with an eGFR <60 ml/min per 1.73 m^2. An outline of the selection process is provided in Figure 1.

The mean age of our cohort was 72 years and mean eGFR 46.5 ml/min per 1.73 m^2. At the time of inclusion, 12% of individuals had previous myocardial infarction, 23% had congestive heart failure, 13% had PAD,

Table 1. Baseline characteristics compared by the presence of interim lower limb complication before mortality or kidney failure

	All patients	Interim lower limb complication	No interim lower limb complication
Total *n*	92,618	1739	90,879
Demographics			
Age, mean (SD)	72.0 (14.5)	68 (13.7)	72.1 (14.5)
Male sex (%)	42,818 (46.2)	1045 (60.1)	41,773 (46.0)
Laboratory values			
Estimated GFR (ml/min per 1.73 m^2), mean (SD)	46.5 (12.5)	43.9 (13.3)	46.5 (12.5)
Urine ACR (mg/mmol), median (interquartile range)	2.8 (0.7–15.0) *n* = 18,372	13.0 (2.7–84.7) *n* = 686	2.7 (0.6–14.1) *n* = 17,686
HbA1C (%), mean (SD)	7.0 (1.8) *n* = 31,346	8.4 (2.3) *n* = 1255	6.9 (1.7) *n* = 30,091
Comorbidities, *n* (%)			
Acute myocardial infarction	11,073 (12.0)	373 (21.5)	10,700 (11.8)
Congestive heart failure	21,674 (23.4)	662 (38.1)	21,012 (23.1)
Peripheral artery disease	12,374 (13.4)	637 (36.6)	11,737 (12.9)
Cerebrovascular disease	16,367 (17.7)	373 (21.5)	15,994 (17.6)
Diabetes	31,290 (33.8)	1436 (82.6)	29,854 (32.9)
Chronic pulmonary disease	33,695 (36.4)	569 (32.7)	33,126 (36.5)
Prior lower limb complication	1610 (1.7)	474 (27.3)	1136 (1.3)
Prior lower limb amputation	753 (0.8)	216 (12.4)	537 (0.6)
Prior diabetic foot ulcer	1287 (1.4)	418 (24.0)	869 (1.0)

ACR, albumin-to-creatinine ratio; GFR, glomerular filtration rate; HbA1C, hemoglobin A1C.
All percentages were calculated based on the total n in each column. Descriptive statistics presented as means (standard deviation) for continuous, normally distributed variables, and median (interquartile range) for continuous, non-normally distributed variables.

18% had cerebrovascular disease, 36% had chronic pulmonary disease, and 34% had diabetes.

Individuals with interim lower limb complications before the outcomes of interest were younger (68 years vs. 72 years) and a greater proportion were men (60% vs. 46%). The eGFR in these individuals was lower whereas the urine albumin-to-creatinine ratio was higher. The prevalence of comorbid conditions was higher in those with interim lower limb complications compared with those who did not experience interim lower limb complications. Prior lower limb complications (amputations, and diabetic foot ulcers) were significantly more prevalent in individuals who experienced an interim lower limb event (all *P* values < 0.001). Descriptive statistics are summarized in Table 1.

Outcomes in Patients With and Without Interim Lower Limb Complications

Kidney Failure Competing With All-Cause Mortality

A total of 2946 (3%) patients developed kidney failure over a median follow-up 2.56 years (interquartile range 0.80 to 5.05). Among those with an interim lower limb complication, 195 (11%) patients developed kidney failure in comparison with 2751 (3%) of those without. The event rate per 100 person-years was 1.07 for the entire cohort, 3.16 among those with an interim lower limb complication and 1.02 in those without. In the fully adjusted model and accounting for the competing risk of all-cause mortality, the presence of an interim lower limb complication was associated with an HR of

2.51 (95% CI 2.10–3.00) for the outcome of kidney failure.

All-Cause Mortality Before Kidney Failure

A total of 32,863 (35%) patients died before kidney failure over a median follow-up of 2.56 years (interquartile range 0.80 to 5.05). Among those with an interim lower limb complication, 897 (52%) patients died before kidney failure in comparison with 31,996 (35%) of those without. The event rate per 100 person-years was 11.91 for the entire cohort, 14.52 among those with an interim lower limb complication, and 11.85 in those without. In the fully adjusted model, censoring for the outcome of kidney failure, the presence of an interim lower limb complication was associated with an HR of 2.73 (95% CI 2.55–2.92) for the outcome of all-cause mortality.

CV Hospitalization Competing With Non–CV-Related Mortality

A total of 19,717 (21%) patients experienced a CV-related hospitalization over a median follow-up of 2.56 years (interquartile range 0.80 to 5.05). Among those with an interim lower limb complication, 382 (31%) patients experienced a CV-related hospitalization before non–CV-related mortality in comparison with 19,335 (21%) of those without. The event rate per 100 person-years was 7.98 in the entire cohort, 21.67 among those with an interim lower limb complication, and 7.62 in those without. In the fully adjusted model and accounting for the competing risk of non-CV mortality, the presence of an interim lower limb complication was

Table 2. Association of interim LLC with adverse events

	Kidney failure with the competing risk of all-cause mortality			All-cause mortality before kidney failure			CV hospitalization with the competing risk of non–CV-related mortality		
	Incidence	Event rate	Hazard ratio (95% CI)	Incidence	Event rate	Hazard ratio (95% CI)	Incidence	Event rate	Hazard ratio (95% CI)
All patients (n = 92,618)	2946 (3%)	1.07	2.51 (2.10–3.00)	32,863 (35%)	11.91	2.73 (2.55–2.92)	19,717 (21%)	7.98	2.12 (1.90–2.38)
LLC yes (n = 1739)	195 (11%)	3.16		897 (51.6%)	14.52		382 (31%)	21.67	
LLC no (n = 90,879)	2751 (3%)	1.02		31,966 (35%)	11.85		19,335 (21%)	7.62	

CI, confidence interval; LLC, lower limb complication.
Models are adjusted for age, sex, estimated glomerular filtration rate, and comorbidities (myocardial infarction, congestive heart failure, peripheral artery disease, chronic pulmonary disease, cerebrovascular disease, and diabetes).
Event rates provided per 100 person-years.

associated with an HR of 2.12 (1.90–2.38) for the outcome of CV-related hospitalization.

An overview of event rates and model outcomes is provided in Table 2. Details of model parameter estimates are provided in Supplementary Table S5.

Subgroup and Sensitivity Analyses

Adjustment for urine albumin-to-creatinine ratio ($n = 18,370$) attenuated the association between interim limb complications and all outcomes: HRs were 1.74 (1.30–2.33) for kidney failure in the presence of the competing risk of all-cause mortality; 2.57 (2.27–2.92) for the outcome of death before kidney failure; and 1.73 (1.42–2.11) for the outcome of CV-related hospitalization in the presence of the competing risk of non-CV death. Additional descriptive statistics for this subcohort are provided in Supplementary Table S6.

After adjustment for prior lower limb complications, we found similar results to the baseline analysis with interim lower limb complications being associated with an HR of 2.42 (1.99–2.93) with respect to the outcome of kidney failure in the presence of the competing risk of all-cause mortality; an HR of 2.53 (2.35–2.71) for the outcome of death before kidney failure; and an HR of 1.92 (1.71–2.16) for the outcome of CV-related hospitalization in the presence of the competing risk of non-CV death.

In interaction analyses, we found a statistically significant interaction between eGFR groups for the outcome of kidney failure in the presence of the competing risk of death, with those having an eGFR <30 ml/min per 1.73 m² having an HR of 1.35 (1.05–1.75) for the outcome after an interim lower limb complication versus 4.47 (3.67–5.44) among those with an eGFR ≥30 ml/min per 1.73 m² ($P < 0.01$). For the outcome of all-cause mortality before kidney failure, there was also a statistically significant interaction between eGFR groups, with an HR after an interim lower limb complication of 2.04 (1.74–2.39) among those with eGFR <30 ml/min per 1.73 m² versus 2.97 (2.76–3.20) among those with an eGFR ≥30 ml/min per 1.73 m² ($P < 0.01$). We also observed a statistically significant interaction between age groups for the outcome of a

cardiovascular-related hospitalization in the presence of the competing risk of non-CV death, with an HR following an interim lower limb complication of 1.77 (1.53–2.06) among those aged 65+ versus an HR of 2.77 (2.35–3.26) among those younger than 65 ($P < 0.01$). All other interactions evaluated were not statistically significant. A summary of these analyses is presented in Figure 2. Parameter estimates for models including interaction terms are provided in Supplementary Table S7.
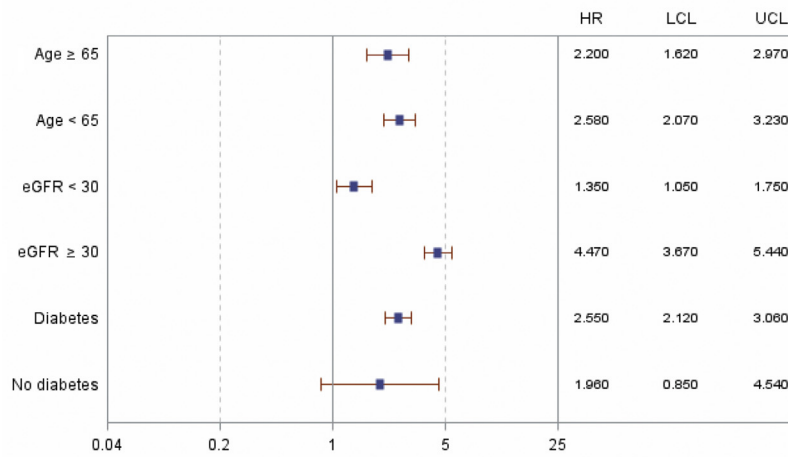
In our sensitivity analysis applying inverse probability of exposure weights, we found similar findings for the outcome of kidney failure, with an odds ratio of 2.80 (2.38–3.28), and the outcome of all-cause mortality, with an odds ratio of 2.18 (2.00–2.37). For the outcome of CV-related hospitalization, we found a slightly higher risk than the primary analysis, with an odds ratio of 3.96 (3.64–4.31).
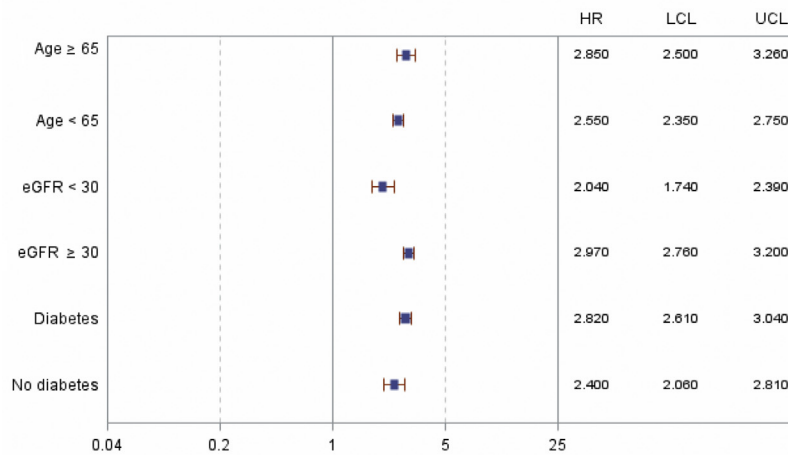
DISCUSSION

In our province-wide population study of 92,618 individuals with CKD stages G3 to G5, we found that interim lower limb complications were associated with greater than a 2-fold higher risk of progressing to kidney failure, death before kidney failure, or the risk of a CV-related hospitalization. These findings highlight the burden of lower limb complications in the CKD population and suggest early primary and secondary interventions are needed to prevent, both lower limb complications and consequent downstream events in the CKD population.

The effect of CKD progression and kidney failure on development of lower limb complications (diabetic foot ulcers and lower extremity amputations) has been studied.[8,10,11] In a cohort study of 90,617 participants with diabetes in The Health Information Network from the United Kingdom, investigators examined the association of foot ulcers and lower limb amputations and the relationship with CKD in patients with diabetes. Their findings show a strong association between CKD severity and development of diabetic foot ulcers and lower extremity amputations. However, the study
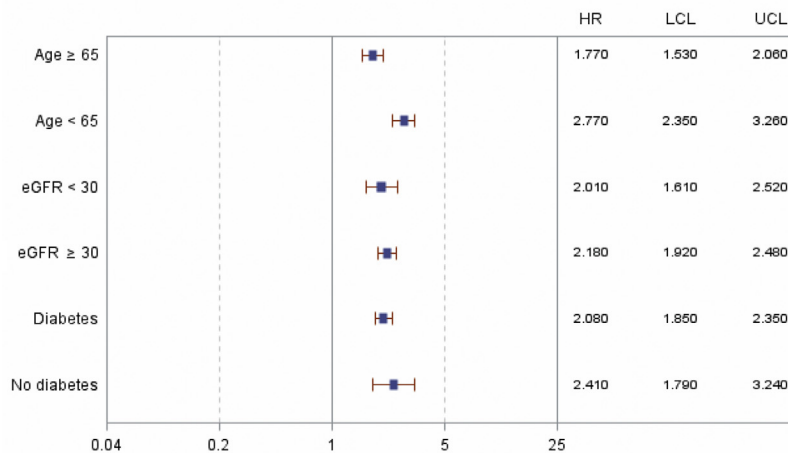
Figure 2. Adjusted risk of competing outcomes in proportional hazards models after interim lower limb complication in interaction analyses. eGFR, estimated glomerular filtration rate; HR, hazard ratio; LLC, lower limb complication; ULC, upper limb complication.

population included only individuals with diabetes, making it difficult to apply these findings to patients with non-diabetic CKD.[11] In another cohort study of

669 individuals from the Netherlands, investigators examined the incidence of foot ulceration and lower extremity amputation in all individuals with CKD

stages G4-G5 and individuals receiving dialysis, with CKD stage G3 as the comparator. Their findings showed a 4-fold and 8-fold increased risk of foot ulceration in individuals with CKD stages G4-G5 and those on dialysis, respectively.[10] Several other studies examining the relationship between CKD and dialysis treatment and the risk of developing lower limb complications report similar findings.[3,8,16]

To our knowledge, no previous studies have examined the association between lower limb complications and the risk of progression to kidney failure in patients with CKD. Furthermore, although there are data examining the survival rates of individuals with diabetes following an amputation, there are no data on how lower limb complications modify the risk of all-cause mortality before kidney failure.[3] There are also few published data examining the effect of lower limb complications on the development of CV events requiring hospitalization. Interestingly, our data suggest that, in a cohort of patients with stages G3 to G5 CKD, the presence of a lower limb complication is a stronger risk factor for development of CV events than a history of myocardial infarction, PAD, or cerebrovascular disease.

It is important to note that we found interactions between the effect of lower limb complications and younger age and lower eGFR for the outcomes of kidney failure, CV hospitalizations, and all-cause mortality. In nearly all cases, the interaction analyses showed higher relative risks in individuals with relatively preserved kidney function (eGFR) or those at a younger age, when compared with individuals with eGFR <30 ml/min per 1.73 m^2 or those older than 65 years. These findings suggest that when the baseline risk of events is already high, such as with all-cause death in older individuals, or with kidney failure risk in those with CKD stage G4+, the harm associated with lower limb complications may be incremental (on the relative scale), rather than catastrophic, such as in cases with preserved kidney function and younger age. This further highlights the opportunity to act early and focus on primary prevention of risk factors in these individuals.

The results from our population-wide study have clinically important implications. As rates of foot salvage in patients with established foot ulcers and kidney failure are low,[17–20] it seems reasonable to focus clinical efforts on early prevention, detection, and management of underlying risk factors. Clinicians should therefore consider careful clinical monitoring and treatment of risk factors for lower limb complications, such as vascular insufficiency, peripheral neuropathy, and skin/nail deformity.[21] It is relevant to note that interventions, such as foot care examinations,

provision of foot care services, and aggressive management of complications, have shown promise in improving clinical outcomes and preventing hospitalization in patients with diabetes and for those requiring dialysis.[21,22] As the increased risk of kidney failure, mortality, and CV-related hospitalization following a lower limb complication was observed irrespective of diabetic status, we would suggest clinicians consider similar foot care and vascular interventions in all patients with CKD, not only patients with diabetes. Indeed, guidelines recommend statin therapy for all patients with CKD, irrespective of cause.

Our retrospective cohort study has several strengths. By using a provincial data repository spanning more than a decade, our sample is both large and population based. We used a well-validated set of administrative codes to define exposure, adjustment, and outcome variables. The use of a competing risk model for the analysis of our data permits a more accurate determination of how lower limb complications modify the risk of 3 clinically important outcomes in patients with CKD.

There are also limitations to our study. Due to the retrospective nature of our study, all variables were accessed from administrative data, and by design we were unable to estimate disease severity or duration. Although we accounted for confounders, such as diabetes and preexisting PAD, it is possible that lower limb complications are a noncausal marker for other factors such as poorly controlled diabetes, rather than a causal event themselves. Future interventional studies will need to examine whether interventions that prevent lower limb complications will also reduce the risk of kidney failure, hospitalization, and death.

In conclusion, lower limb complications are common in patients with CKD. An incident lower limb complication increases the risk of progressing to kidney failure, all-cause mortality before kidney failure, and CV-related hospitalization by more than 2-fold. Clinical trials of screening and treatment strategies for lower limb complications in patients with CKD may help determine optimal strategies to manage this risk.

DISCLOSURES

ACKNOWLEDGMENTS

Policy for use of data contained in the Manitoba Population Research Data Repository under project # HS18574 (H2015: 153) (HIPC File No. 2015/2016–20). The results and conclusions are those of the authors and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health, or other data providers is intended or should be inferred. Data used in this study are from the Manitoba Population Research Data Repository housed at the Manitoba Centre for Health Policy, University of Manitoba, and were derived from data provided by Manitoba Health, Diagnostic Services of Manitoba, and the Winnipeg Regional Health Authority.

AUTHOR CONTRIBUTIONS

TF, NT, CR, PK, and JE designed the study; KL, TF, NT, CR, PK, and JE analyzed the data; KL and TF made the figures; KL, TF, NT, CR, PK, and JE drafted and revised the paper; all authors approved the final version of the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Tariff codes used to define dialysis and transplantation in the Manitoba Physician's Manual.

Table S2. ICD-9-CM and ICD-10-CA codes used to define cardiovascular-related hospitalizations in the Discharge Abstract Database.

Table S3. ICD-9-CM and ICD-10-CA codes used to define diabetic foot ulcers and nontraumatic lower limb amputations in the Discharge Abstract Database.

Table S4. ICD-9-CM and ICD-10-CA codes used to define comorbid conditions.

Table S5. Parameter estimates for proportional hazards models.

Table S6. Baseline characteristics compared by the presence of interim lower limb complications before mortality or kidney failure in a subcohort of individuals with available urine albumin-to-creatinine ratio test results.

Table S7. Parameter estimates for proportional hazards models in sensitivity and subgroup analyses.

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