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Renal Function, Albuminuria, and the Risk of Cardiovascular Events After Kidney Transplantation

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Background. The risk of mortality and graft loss is higher in kidney transplant recipients with reduced estimated glomerular filtration rate (eGFR) and albuminuria. It is unclear whether these markers are also associated with cardiovascular events. **Methods.** We examined linked healthcare databases in Alberta, Canada to identify kidney transplant recipients between 2002 and 2013 who had at least 1 outpatient serum creatinine and albuminuria measurement at 1-year posttransplant. We determined the relationship between categories of eGFR and albuminuria and the risk of subsequent cardiovascular events. **Results.** Among 1069 eligible kidney transplant recipients, the median age was 52 years, 37% were female, and 52% had eGFR ≥60 mL/min per 1.73 m^2. Over a median follow-up of 6 years, the adjusted rate of all-cause mortality and cardiovascular events was 2.7-fold higher for recipients with eGFR 15-29 mL/min per 1.73 m^2 and heavy albuminuria compared to recipients with eGFR ≥60 mL/min per 1.73 m^2 and normal albuminuria (rate ratio, 2.7; 95% confidence interval, 1.3-5.7). Similarly, recipients with heavy albuminuria had a threefold increased risk of all-cause mortality and heart failure compared with recipients with eGFR ≥60 mL/min per 1.73 m^2 and normal albuminuria. **Conclusions.** These findings suggest that eGFR and albuminuria should be used together to determine the risk of cardiovascular outcomes in transplant recipients.

(*Transplantation Direct* 2018;4: e389; doi: 10.1097/TXD.0000000000000828. Published online 6 September 2018.)

The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease includes albuminuria as part of the classification system for chronic kidney disease (CKD).[1,2] Albuminuria as a marker of kidney damage may also reflect systemic vascular disease burden. In the general population, the risk of cardiovascular outcomes (cardiovascular death, coronary artery disease, heart failure, ischemic stroke) at a given level of estimated glomerular filtration rate (eGFR) increases with higher levels of albuminuria.[3-5]

Only a few studies have reported the combined effects of lower eGFR and higher albuminuria on clinical outcomes in kidney transplant recipients.[6-8] Similar to the general population, the risk of death and kidney failure (return to dialysis or retransplantation) appears to increase with reduced eGFR and heavier albuminuria.[6-8] In our cohort of 900 kidney transplant recipients from Alberta, Canada, the risk of all-cause mortality was eightfold higher for recipients with eGFR 15 to 29 mL/min per 1.73 m^2 and heavy albuminuria compared with eGFR greater than 60 mL/min per 1.73 m^2 and normal albuminuria.[9] Similarly, the risk of death-censored graft loss was almost 50 times higher. The impact of renal function and degree of albuminuria on the risk of cardiovascular events in kidney transplant recipients is unknown. To address this knowledge gap, we examined associations of

eGFR and albuminuria with cardiovascular outcomes among a large cohort of kidney transplant recipients in a Canadian province.

MATERIALS AND METHODS

Design and Setting

We conducted a population-based, retrospective cohort study using linked healthcare databases within the Alberta Kidney Disease Network (AKDN) that incorporates data from Alberta Health, the provincial health ministry.[10] Over 99% of Alberta residents are registered with Alberta Health and have universal access to hospital care and physician services. This study followed guidelines for the reporting of observational studies (**Table S1 SDC,** http://links.lww.com/TXD/A134) and the protocol was approved by the research ethics boards at the University of Alberta and the University of Calgary, with a waiver of patient consent granted.

Data Sources

We ascertained baseline patient characteristics, covariate information, and outcome data from the AKDN records (**Table S2 SDC,** http://links.lww.com/TXD/A135). We identified kidney transplant recipients using the Northern and Southern Alberta Renal Program databases, which provide care to all patients treated with chronic dialysis or kidney transplant in the province. The Alberta Health database contains information on demographic data, vital statistics, and diagnostic and procedural information for inpatient and outpatient physician services. We linked these data sources to a provincial laboratory repository via unique, encoded, patient identifiers held by the AKDN. These databases have been previously used for research on health outcomes and services.[9,11-14]

Population

We included all adult kidney transplant recipients (≥18 years), who received their first kidney-only transplant between May 1, 2002 and March 31, 2013 in Alberta (**Figure S1 SDC,** http://links.lww.com/TXD/A130). We excluded pediatric recipients (<18 years) and those who had received a previous organ transplant or a simultaneous multiorgan transplant (eg, kidney-pancreas). Eligible recipients had at least 1 outpatient serum creatinine measurement and at least 1 outpatient measurement of albuminuria at approximately 1-year after transplantation. We chose to classify kidney function at this time to ensure stability of renal function and immunosuppression regimen and because this metric has been shown to be predictive of other clinical outcomes, such as mortality.[9,15-22] Thus, to be included in the study, recipients must have survived at least 1 year with a functioning graft. We excluded transplant recipients who had graft failure (death or return to dialysis) in the first year posttransplant or whose eGFR was less than 15 mL/min per 1.73 m^2. The index date was 1-year posttransplant, and this served as the start date for follow-up.

Measurement of Kidney Function and Albuminuria

The eGFR at 1-year posttransplant was estimated using the Chronic Kidney Disease-Epidemiology Collaboration equation.[23] Because data on race were not available, recipients were assumed to be non-African American. Misclassification of eGFR was expected to be minimal because less than 2% of the Alberta population are black. Baseline kidney function (index eGFR) was estimated using all outpatient serum creatinine measurements taken within a 3-month look-forward period of the creatinine measurement closest to the 1-year posttransplant date (index creatinine) (**Figure S2,** http://links.lww.com/TXD/A131). The index eGFR was calculated as the mean of these measurements within the 3-month period.[10] Index eGFR was categorized based on the 2012 KDIGO stages of CKD as 60 or higher, 45 to 59, 30 to 44, and 15 to 29 mL/min per 1.73 m^2.[1]

Albuminuria was ascertained from outpatient, random, spot urine measurements of albumin-creatinine ratio (ACR), protein-creatinine ratio (PCR), or urine dipstick and categorized based on the KDIGO definition as normal (A1: ACR <30 mg/g, PCR <15 mg/mmol, or dipstick negative), mild (A2: ACR 30-300 mg/g, PCR 15-100 mg/mmol, or dipstick trace or 1+) or heavy (A3: ACR >300 mg/g, PCR >100 mg/mmol, dipstick ≥2+).[1,10,24,25] Albumin-creatinine ratio was the primary measure of albuminuria, and if unavailable, was supplemented with PCR measurements. When both ACR and PCR were unavailable, dipstick urinalysis was used. All outpatient ACR or PCR measurements or urine dipsticks in the 3-month periods before and after the index creatinine value were used to establish baseline albuminuria. For recipients with multiple albuminuria measurements within the 3 months of the index creatinine value, the median value was calculated.

Baseline Characteristics

Baseline demographic data, including age and sex, were determined from the Alberta Health administrative data files. Indigenous race was retrieved from the First Nations status in the registry file. It was not possible to identify other race/ethnic groups, although more than 85% of the Alberta population is white. The presence of 1 or more diagnostic codes in the 3 years before the index date was used for identification of comorbidities according to validated International Classification of Diseases, Ninth Revision, Clinical Modification and International Statistical Classification of Diseases, Tenth Revision coding algorithms applied to physician claims and hospitalization data.[26,27] Hypertension and diabetes mellitus were identified from hospital discharge records and physician claims based on validated algorithms.[28,29] Data were complete except for income quintile (0.3% missing) and residence location (3.3% missing), which were imputed based on the previous year's values.

Outcomes

Recipients were followed up from the first posttransplant anniversary (index date) until death, emigration from the province, end of study (March 31, 2015), or outcome of interest. The primary outcome was a composite of all-cause mortality and cardiovascular event (defined as a hospitalization for myocardial infarction or ischemic stroke or a procedural code for percutaneous coronary intervention [PCI] or coronary artery bypass graft surgery [CABG]). Additional outcomes included death-censored cardiovascular event, a composite of all-cause mortality and heart failure, and lastly, death-censored heart failure.

Statistical Analyses

Poisson regression with sandwich estimator was used to evaluate the association between the baseline factors and

each outcome of interest, with rates expressed per 1000 person-years.[30] The 95% confidence interval (CI) was estimated using bootstrap techniques. If the primary assumption that variance equals the mean was not met, a negative binomial model or a generalized Poisson model was used. We calculated unadjusted rates for each of the outcomes by level of eGFR and albuminuria. We then calculated fully adjusted event rates for each outcome, adjusting for the sociodemographic variables and comorbidities listed in Table 1. Two-way interactions between eGFR and albuminuria were assessed for all clinical outcomes. Lastly, we calculated incidence rate ratios using the recipients with eGFR 60 mL/min per 1.73 m² or higher and normal albuminuria as the referent group.

For the primary analysis, we included all patients with at least 1 albuminuria measurement based on ACR, PCR, or urine dipstick. In sensitivity analyses, we included measurements based on ACR and PCR alone (not including urine dipstick). In all analyses, we tested for linear trends across categories of eGFR and albuminuria. The variables used to calculate the tests for trend in eGFR and ACR or PCR were defined by the median values of these parameters in each category. The variable used to calculate the test for trend in dipstick albuminuria were defined by values of 1, 2, and 3 for normal, mild, and heavy albuminuria, respectively. Statistical analyses were performed using Statistical Analysis Software STATA version 13.1 (STATA Corporation, College Station, TX). A P value less than 0.05 was used to define statistical significance.

RESULTS

Among 1387 kidney transplant recipients, 1069 were alive with graft function at the first posttransplant anniversary and had at least 1 outpatient serum creatinine and albuminuria measurement at the 1-year posttransplant date (**Figure S1 SDC,** http://links.lww.com/TXD/A130). Baseline characteristics of the recipients at their index date are shown in Table 1, according to level of eGFR and albuminuria. At 1-year posttransplant, 52.3% of the recipients had an eGFR of 60 mL/min per 1.73 m² or greater and 5.1% had an eGFR less than 30 mL/min per 1.73 m². The median age of the recipients was 52.2 years (interquartile range [IQR], 40.8-61.6) and 17.6% were older than 65 years. The median age increased across declining levels of eGFR (49.4 years for eGFR ≥60 mL/min per 1.73 m² vs 59.7 years for eGFR <30 mL/min per 1.73 m²). Less than half of the recipients were women (38.6%).

TABLE 1.

Demographic and clinical characteristics of recipients at 1 year posttransplant by level of kidney function and albuminuria

| Characteristics | Overall, n (%) | eGFR (mL/min per 1.73 m²) | | | | Albuminuria | | |
		≥60	45-59	30-44	15-29	Normal	Mild	Heavy
Recipients (n)	1069 (100)	559 (52.3)	303 (28.3)	152 (14.2)	55 (5.1)	659 (61.6)	358 (33.5)	52 (4.9)
Age (y)	52.2 [40.8-61.6]	49.4 [37.3-59.1]	54.1 [42.4-63.5]	55.7 [46.8-64.7]	59.7 [45.8-67.2]	51.0 [39.9-61.3]	55.1 [42.6-63.0]	50.8 [40.0-60.0]
>65 y	188 (17.6)	70 (12.5)	63 (20.8)	38 (25.0)	17 (30.9)	112 (17.0)	69 (19.3)	7 (13.5)
Female sex	393 (36.8)	216 (38.6)	97 (32.0)	63 (41.4)	17 (30.9)	254 (38.5)	123 (34.4)	16 (30.8)
Aboriginal race	61 (5.7)	40 (7.2)	12 (4.0)	6 (3.9)	3 (5.5)	25 (3.8)	31 (8.7)	5 (9.6)
Socioeconomic status[a]								
Lowest	250 (23.4)	131 (23.4)	70 (23.1)	34 (22.4)	15 (27.3)	148 (22.5)	91 (25.4)	11 (21.2)
Middle	217 (20.3)	120 (21.5)	59 (19.5)	30 (19.7)	8 (14.5)	127 (19.3)	76 (21.2)	14 (26.9)
Highest	194 (18.1)	88 (15.7)	57 (18.8)	35 (23.0)	14 (25.5)	123 (18.7)	61 (17.0)	10 (19.2)
Urban residence[b]	951 (89.0)	501 (89.6)	271 (89.4)	133 (87.5)	46 (83.6)	597 (90.6)	305 (85.2)	49 (94.2)
Pretransplant dialysis modality[c]								
Hemodialysis	632 (59.1)	334 (59.7)	165 (54.5)	97 (63.8)	36 (65.5)	387 (58.7)	214 (59.8)	31 (59.6)
Peritoneal	292 (27.3)	159 (28.4)	83 (27.4)	36 (23.7)	14 (25.5)	181 (27.5)	97 (27.1)	14 (26.9)
Preemptive	145 (13.6)	66 (11.8)	55 (18.2)	19 (12.5)	5 (9.1)	91 (13.8)	47 (13.1)	7 (13.5)
Dialysis duration (yr)	2.1 [1.2-3.3]	2.2 [1.2-3.3]	1.8 [1.1-2.9]	2.4 [1.5-3.6]	2.4 [1.4-3.9]	1.9 [1.1-3.1]	2.4 [1.4-3.9]	2.2 [1.4-3.1]
Northern Alberta	660 (61.7)	372 (66.5)	177 (58.4)	87 (57.2)	24 (43.6)	417 (63.3)	215 (60.1)	28 (53.8)
Comorbidities[d]								
Hypertension	979 (91.6)	514 (91.9)	276 (91.1)	138 (90.8)	51 (92.7)	604 (91.7)	325 (90.8)	50 (96.2)
Diabetes mellitus	423 (39.6)	228 (40.8)	99 (32.7)	63 (41.4)	33 (60.0)	232 (35.2)	160 (44.7)	31 (59.6)
Myocardial infarction	41 (3.8)	16 (2.9)	15 (5.0)	5 (3.3)	5 (9.1)	22 (3.3)	17 (4.7)	2 (3.8)
PCI/CABG	43 (4.0)	19 (3.4)	16 (5.3)	6 (3.9)	2 (3.6)	25 (3.8)	18 (5.0)	0 (0)
Heart failure	89 (8.3)	46 (8.2)	27 (8.9)	12 (7.9)	4 (7.3)	48 (7.3)	36 (10.1)	5 (9.6)
Atrial fibrillation	55 (5.1)	25 (4.5)	16 (5.3)	10 (6.6)	4 (7.3)	31 (4.7)	22 (6.1)	2 (3.8)
Stroke/TIA	42 (3.9)	26 (4.7)	9 (3.0)	4 (2.6)	3 (5.5)	30 (4.6)	12 (3.4)	0 (0)
PVD	65 (6.1)	29 (5.2)	20 (6.6)	9 (5.9)	7 (12.7)	33 (5.0)	26 (7.3)	6 (11.5)

[a] Income was categorized according to fifths of average neighborhood income (first quintile is the lowest and the fifth quintile is the highest).

[b] Urban location indicates a population > 10000 or a population > 1000 with population density > 400/km².

[c] Recipients identified as preemptive were assessed for the presence of dialysis codes and reclassified as hemodialysis (n = 16) or peritoneal dialysis (n = 14).

[d] Assessed by the presence of a diagnostic or procedural code in the 3 years before the index date except for hypertension and diabetes which are defined by a previously validated algorithm.[28,29]

Data are presented as number (%) except for age and dialysis duration, which are presented as median (IQR).

PVD, peripheral vascular disease; TIA, transient ischemic attack.

At 1 year, 61.6% of recipients had normal levels of albuminuria as measured by ACR, PCR, or urine dipstick. Compared with these recipients, the 725 recipients in the sensitivity analysis whose albuminuria was measured by ACR or PCR had higher proportions of mild (43.3% vs 33.5%) or heavy albuminuria (5.5% vs 4.9%) ($P < 0.01$) (**Table S3 SDC,** http://links.lww.com/TXD/A136).

Adjusted Likelihood of Clinical Outcomes by Level of eGFR and Albuminuria

After median follow-up of 6.0 years (IQR, 3.4-8.5 years), 13.5% (n = 144) recipients died, and 9.5% (n = 102) initiated dialysis. The unadjusted rate of all-cause mortality and cardiovascular events significantly increased as kidney function declined ($P = 0.002$) but this pattern was no longer significant after adjustment for recipient factors ($P = 0.37$) (Figure 1A). For eGFR 45 to 59 mL/min per 1.73 m^2 and 15 to 29 mL/min per 1.73 m^2, the adjusted incidence rates increased with worsening albuminuria ($P = 0.03$ and $P = 0.001$, respectively). Recipients with eGFR of 15 to 29 mL/min per 1.73 m^2 and heavy albuminuria had an almost threefold increased risk of all-cause mortality and cardiovascular events compared to recipients with eGFR of ≥60 mL/min per 1.73 m^2 and normal albuminuria (rate ratio, 2.7; 95% CI, 1.3-5.7) (Figure 2A). There did not appear to be any significant association between eGFR, albuminuria, and death-censored cardiovascular events; however, the number of events was lower (Figures 1A and 2B).

The rate of all-cause mortality and heart failure increased as kidney function declined. The adjusted incidence rate for eGFR ≥60, 45 to 59, 30 to 44, and 15 to 29 mL/min per 1.73 m^2 was 29.4, 28.2, 49.2, and 54.8 per 1000 person-years, respectively ($P = 0.004$) (Figure 1B). Except for eGFR ≥60 mL/min per 1.73 m^2, the adjusted incidence rates across the other eGFR categories significantly increased with worsening albuminuria ($P < 0.02$). For these recipients, the risk of all-cause mortality and heart failure was threefold higher for recipients with heavy albuminuria compared to recipients with eGFR ≥60 mL/min per 1.73 m^2 and normal albuminuria (rate ratio range, 3.1-3.8) (Figure 2C).

Similarly, the unadjusted rate of death-censored heart failure increased as kidney function declined ($P = 0.006$) but, again, the adjusted rate did not reach statistical significance ($P = 0.06$). Except for eGFR 45 to 59 mL/min per 1.73 m^2, the adjusted incidence rates across the other eGFR categories significantly increased with worsening albuminuria ($P < 0.05$). The risk of death-censored heart failure was sixfold higher in recipients with eGFR 15 to 29 mL/min per 1.73 m^2 compared with recipients with normal graft function and albuminuria (rate ratio 5.5, 95% CI 2.2-14.0) (Figure 2D). The analyses for the subgroup of recipients (n = 725) whose albuminuria was measured by ACR or PCR alone (not by urine dipstick) are presented in **Figure S3, SDC** (http://links.lww.com/TXD/A132 and http://links.lww.com/TXD/A133). The patterns were similar, although the smaller number of events led to wider CIs.

DISCUSSION

In this population-based study of 1069 kidney transplant recipients, we found that the risk of all-cause mortality and cardiovascular events significantly increased with worsening albuminuria for certain eGFR categories (45 to 59 and 15 to 29 mL/min per 1.73 m^2). The association was stronger for all-cause mortality and heart failure, where the adjusted incidence rate increased with worsening albuminuria for the lower eGFR categories. The risk of this composite outcome was threefold higher for recipients with heavy albuminuria compared with recipients with an eGFR of 60 mL/min per 1.73 m^2 or higher and normal albuminuria.

Cardiovascular disease remains the leading cause of death in kidney transplant recipients, accounting for 30% of deaths with a functioning graft.[31] Although the risk of cardiovascular death is significantly lower with transplantation compared to dialysis, the risk remains higher than the general population.[32] In a retrospective study of 4954 kidney transplant recipients from Ontario, Canada, we found that the 3-year cumulative incidence of death and major cardiovascular event (myocardial infarction, PCI, CABG, or ischemic stroke) was 9.0% (3.2 events per 100 person-years), and this was higher than the age- and sex-matched general population (2.6%, 0.89 events per 100 person-years).[33] For these reasons, the 2009 KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients suggests that recipients be considered to be at the highest risk for cardiovascular disease.[34] Cardiovascular events in kidney transplant recipients may be high due to the combination of traditional cardiovascular risk factors, such as hypertension and diabetes, and renal-specific cardiovascular risk factors, such as exposure to dialysis and immunosuppressive medications.[35,36] Our results likely underestimate the burden of vascular disease in this patient population, as our composite outcome did not include diagnoses such as arrhythmias, unstable angina, or peripheral vascular disease.

Our results expand on our previous findings that the combined assessment of graft function and albuminuria at 1 year posttransplantation was associated with the risks of all-cause mortality and graft loss.[9] Only a few other studies have examined the interactive effects of graft function and albuminuria on clinical outcomes; however, none of these prior studies have assessed cardiovascular outcomes, including heart failure.[6-8]

Lentine et al[37] reported that the 3-year incidence of de novo heart failure in 27 011 kidney transplant recipients from the United States from 1995 to 2001 was 18%. Risk factors for heart failure included older age, female sex, and pretransplant comorbidities, such as diabetes mellitus and myocardial infarction. Heart failure was associated with an almost threefold higher risk of death and death-censored graft failure. In a Canadian population from 1969 to 1999, Rigatto et al[38] reported that the incidence of de novo heart failure in 638 kidney transplant recipients was 1.3 per 100 patient-years and was associated with a 1.8-fold increased the risk of death posttransplantation. Graft function was not independently associated with heart failure although it was a strong univariate predictor. Neither the American nor Canadian study assessed the combined impact of graft function and albuminuria on the development of posttransplant heart failure. In our study, 11% of recipients had heart failure over a median follow-up of 6 years. Recipients with an eGFR of 15 to 29 mL/min per 1.73 m^2 and heavy albuminuria had an approximately sixfold higher risk of death-censored heart failure compared with recipients with eGFR ≥60 mL/min per 1.73 m^2 with normal albuminuria.

A

Rates of Clinical Outcomes by Level of eGFR and Albuminuria in Kidney Transplant Recipients, per 1,000 Person-years

eGFR	All-cause Mortality and Cardiovascular Events[a] (N=1,069)				Death-censored Cardiovascular Events[a] (N=1,069)			
	Albuminuria							
	Overall	Normal	Mild	Heavy	Overall	Normal	Mild	Heavy
≥60 mL/min/1.73 m²								
Events, n	108	68	35	5	65	43	19	3
Patients, n	559	379	163	17	559	379	163	17
Unadjusted	33.6 (22.2, 37.7)	29.9 (23.6, 37.0)	41.3 (29.1, 54.7)	53.4 (15.8, 122.5)	20.3 (15.4, 25.6)	18.9 (13.4, 25.1)	22.5 (13.3, 33.3)	32.0 (0, 87.7)
Adjusted[b]	37.3 (31.1, 46.7)	35.2 (27.3, 46.5)	42.0 (29.8, 60.1)	47.2 (13.0, 134.5)	24.6 (19.2, 33.3)	24.3 (17.5, 35.4)	25.4 (14.7, 40.9)	29.0 (0, 112.8)
45-59 mL/min/1.73 m²								
Events, n	49	26	19	4	29	16	11	2
Patients, n	303	194	96	13	303	194	96	13
Unadjusted	29.3 (22.2, 38.4)	23.0 (14.7, 31.9)	40.0 (24.0, 59.0)	61.9 (14.2, 153.3)	17.3 (11.3, 23.9)	14.1 (7.3, 21.7)	23.1 (10.8, 38.6)	31.0 (0, 100.3)
Adjusted[b]	29.6 (21.9, 38.8)	23.0 (14.9, 33.0)	43.1 (27.1, 64.1)	51.2 (8.7, 192.3)	17.8 (11.4, 25.6)	14.1 (7.6, 22.2)	25.8 (12.5, 45.6)	29.4 (0, 140.6)
30-44 mL/min/1.73 m²								
Events, n	43	19	20	4	26	10	13	3
Patients, n	152	71	70	11	152	71	70	11
Unadjusted	52.0 (38.4, 68.4)	44.9 (26.5, 68.4)	57.1 (35.3, 85.2)	74.2 (14.6, 186.5)	31.4 (20.8, 45.2)	23.6 (11.1, 39.1)	37.1 (19.2, 60.3)	55.7 (0, 163.7)
Adjusted[b]	47.5 (34.1, 64.7)	41.3 (24.1, 64.7)	51.8 (32.5, 83.0)	65.5 (18.6, 125.6)	30.4 (19.4, 45.1)	22.9 (10.7, 40.6)	35.7 (18.4, 64.2)	49.5 (0, 109.6)
15-29 mL/min/1.73 m²								
Events, n	23	5	11	7	9	3	4	2
Patients, n	55	15	29	11	55	15	29	11
Unadjusted	73.3 (48.4, 103.9)	52.3 (14.4, 99.9)	70.5 (34.0, 120.0)	112.8 (51.1, 225.6)	28.7 (10.6, 50.1)	31.4 (0, 72.9)	25.6 (0, 54.9)	32.2 (0, 103.1)
Adjusted[b]	44.4 (27.4, 71.3)	18.7 (5.7, 41.5)	57.8 (27.4, 105.6)	95.5 (41.1, 253.8)	17.6 (7.6, 30.9)	11.1 (0, 27.9)	20.9 (0, 48.5)	33.0 (0, 106.3)

Data is presented as rate (95% confidence interval).
[a] Cardiovascular event was defined as a hospitalization for myocardial infarction or ischemic stroke or a procedural code for PCI or CABG.
[b] Adjusted for age, sex, SES, urban residence, pre-transplant dialysis modality, dialysis duration, year of transplant, and a pre-transplant history of hypertension, diabetes mellitus, myocardial infarction, PCI or CABG surgery, heart failure, atrial fibrillation, stroke/TIA, and PVD.
For all-cause mortality and cardiovascular events, test results for linear trend were significant across albuminuria categories for eGFR 45 to 59 mL/min/1.73 m² (p=0.03) and 15 to 29 mL/min/1.73 m² (p=0.001).
Colors represent the ranking of adjusted rates (ranked from 1 [lowest] to 12 [highest]). The categories with rank numbers 1-3 are green, 4-6 are yellow, 7-9 are orange, and 10-12 are red.[45] Colors reflect the KDIGO categories of risk (green: low risk; yellow: moderately increased risk; orange: high risk; red: very high risk).[1]
Abbreviations: CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SES, socio-economic status.; TIA, transient ischemic attack.

B

Rates of Clinical Outcomes by Level of eGFR and Albuminuria in Kidney Transplant Recipients, per 1,000 Person-years

eGFR	All-cause Mortality and Heart Failure (N=1,069)				Death-censored Heart Failure (N=1,069)			
	Albuminuria							
	Overall	Normal	Mild	Heavy	Overall	Normal	Mild	Heavy
≥60 mL/min/1.73 m²								
Events, n	90	55	30	5	54	30	20	4
Patients, n	559	379	163	17	559	379	163	17
Unadjusted	27.8 (22.3, 33.4)	23.7 (17.7, 30.5)	35.6 (23.0, 48.8)	59.9 (14.1, 131.7)	16.7 (12.5, 21.4)	12.9 (8.6, 18.0)	23.7 (14.0, 35.0)	48.0 (9.4, 111.9)
Adjusted[a]	29.4 (23.8, 37.9)	26.9 (19.5, 37.3)	32.4 (22.6, 51.3)	67.4 (16.3, 238.1)	18.7 (19.2, 33.3)	15.7 (10.3, 23.9)	22.8 (13.9, 38.9)	56.8 (10.2, 228.2)
45-59 mL/min/1.73 m²								
Events, n	45	25	15	5	29	17	8	4
Patients, n	303	194	96	13	303	194	96	13
Unadjusted	26.7 (19.1, 35.1)	21.9 (14.0, 30.8)	30.9 (16.5, 47.9)	86.8 (20.4, 240.6)	17.2 (11.1, 23.1)	14.9 (8.3, 22.0)	16.5 (6.4, 28.2)	69.5 (10.9, 202.8)
Adjusted[a]	28.2 (20.0, 39.7)	22.2 (13.8, 34.4)	35.7 (20.6, 57.1)	84.6 (24.7, 306.4)	18.5 (11.4, 25.6)	15.6 (8.2, 26.6)	17.5 (6.8, 36.3)	81.6 (15.4, 278.4)
30-44 mL/min/1.73 m²								
Events, n	41	15	21	5	23	6	15	2
Patients, n	152	71	70	11	152	71	70	11
Unadjusted	49.3 (35.5, 66.3)	33.8 (17.8, 52.9)	62.2 (37.9, 92.1)	99.7 (27.8, 218.1)	27.7 (16.7, 39.4)	13.5 (4.1, 25.2)	44.4 (22.9, 71.5)	39.9 (0.0, 138.3)
Adjusted[a]	49.2 (34.0, 72.0)	32.0 (16.5, 54.5)	65.2 (39.8, 108.6)	85.9 (33.0, 195.4)	29.8 (19.4, 45.1)	13.2 (3.6, 31.2)	50.6 (29.2, 96.8)	34.7 (0.0, 139.9)
15-29 mL/min/1.73 m²								
Events, n	24	6	11	7	13	4	4	5
Patients, n	55	15	29	11	55	15	29	11
Unadjusted	78.4 (51.1, 112.0)	66.0 (21.2, 128.2)	70.1 (34.1, 117.8)	119.9 (52.6, 250.8)	42.5 (21.3, 67.5)	44.0 (0, 103.0)	25.5 (5.2, 51.5)	85.7 (25.8, 202.1)
Adjusted[a]	54.8 (35.3, 88.1)	30.2 (10.0, 71.7)	63.0 (29.2, 119.1)	101.0 (40.3, 261.2)	32.1 (7.6, 30.9)	21.1 (4.0, 70.3)	24.9 (5.2, 59.1)	87.2 (23.3, 243.5)

Data is presented as rate (95% confidence interval).
[a] Adjusted for age, sex, SES, urban residence, pre-transplant dialysis modality, dialysis duration, year of transplant, and a pre-transplant history of hypertension, diabetes mellitus, myocardial infarction, PCI or CABG surgery, heart failure, atrial fibrillation, stroke/TIA, and PVD.
For all-cause mortality and heart failure, test results for linear trend were significant across the overall eGFR categories (p=0.004) and across eGFR categories for mild albuminuria (p=0.015). Test results for linear trend were also significant across the albuminuria categories for eGFR 45 to 59 mL/min/1.73 m² (p=0.013), 30 to 44 mL/min/1.73 m² (p=0.005), and 15 to 29 mL/min/1.73 m² (p=0.014).
For death-censored health failure, test results for linear trend were significant across the albuminuria categories for eGFR ≥60 mL/min/1.73 m² (p=0.04), 30 to 44 mL/min/1.73 m² (p=0.01), and 15 to 29 mL/min/1.73 m² (p<0.05).
Colors represent the ranking of adjusted rates (ranked from 1 [lowest] to 12 [highest]). The categories with rank numbers 1-3 are green, 4-6 are yellow, 7-9 are orange, and 10-12 are red.[45] Colors reflect the KDIGO categories of risk (green: low risk; yellow: moderately increased risk; orange: high risk; red: very high risk).[1]
Abbreviations: CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SES, socio-economic status.; TIA, transient ischemic attack.

FIGURE 1. A and B, Rates of clinical outcomes by level of eGFR and albuminuria in kidney transplant recipients, per 1000 person-years.

In the nontransplant population, the risk of cardiovascular events at a given level of eGFR increases with worsening albuminuria. In a retrospective study of 1.5 million patients in Alberta, Canada, Bello et al[3] reported that after a median follow-up of 35 months, the rate of heart failure, peripheral vascular disease, and cerebral vascular accident or transient ischemic attack all increased with lower eGFR and heavier albuminuria. Similar results were found in larger,
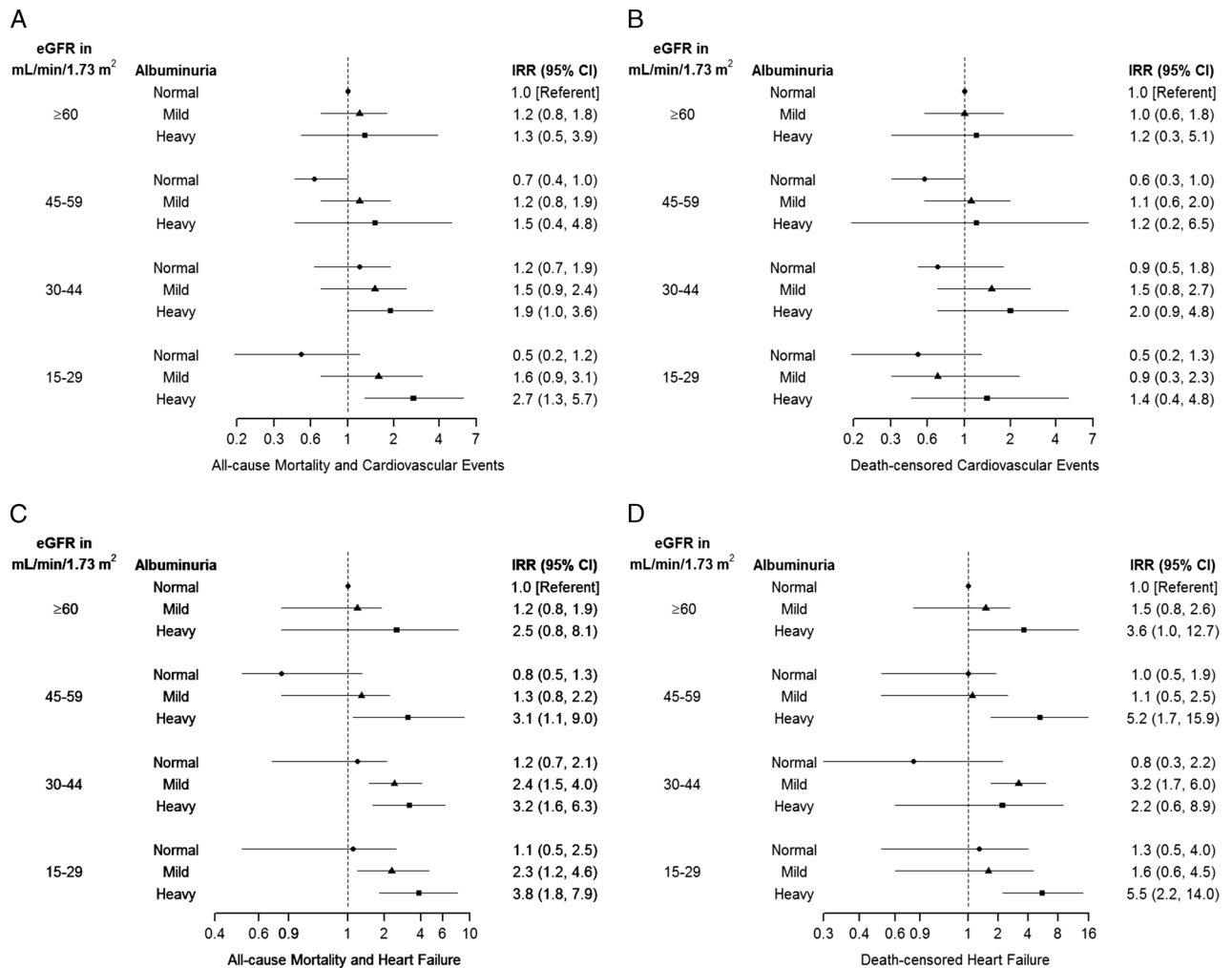
FIGURE 2. Adjusted Incidence rate ratios by Level of eGFR and Albuminuria in Kidney Transplant Recipients. All values ≥1, including point estimates and confidence limits, are plotted on log scale. All values <1 are plotted on –(1/3*x) scale for outcomes of all-cause mortality and cardiovascular events and death-censored cardiovascular events, and are plotted on –(1/x) scale for outcomes of all-cause mortality and heart failure and death-censored heart failure. IRR, incidence rate ratio.

collaborative meta-analyses of the general population, high-risk population, and CKD population.[4,5,39]

We assessed albuminuria at 1-year posttransplantation and its association with cardiovascular events. Albuminuria from the native kidneys typically declines within the first 3 weeks after transplantation, due to the reduction in glomerular filtration.[40] Thus, albuminuria detected at 1 year likely represents allograft pathology, and prior studies have shown this to be a predictor of long-term graft outcomes.[41,42] Currently, it is unclear whether or not interventions aimed at improving posttransplant albuminuria lead to improved clinical outcomes. In a randomized controlled trial of 213 kidney transplant recipients with albuminuria (≥0.2 g/d), Knoll et al[43] did not show a reduction in the composite outcome of doubling of serum creatinine, end-stage renal disease, or death for ramipril compared with placebo. Due to the number of recipients enrolled in the study, there may have been insufficient power to detect a treatment effect.[44]

Our study population represents a large Canadian cohort of recipients (>1000) followed up over a 13-year period. The serum creatinine measurements in our study have been standardized across provincial laboratories, reducing interlaboratory

variation in measurements. In addition to this, we allowed for multiple measurements of albuminuria, reducing the risk of misclassification. Our outcomes were based on diagnostic and procedural codes that have been shown to have good validity in previous validation studies (**Table S2 SDC,** http://links.lww.com/TXD/A135).[26,45-47] There are, however, limitations worth noting. Given that we included recipients with a functioning graft and blood and urine tests at 1 year, there is a risk of survival and selection bias. Recipients eligible for study inclusion may have differed from recipients who experienced graft failure, died, or were lost to follow-up within a year of transplant. We based graft function on serum creatinine with GFR estimation rather than cystatin C, because this was not available in our data sets. We also lacked data on certain baseline characteristics (eg, smoking, blood pressure measurements, body mass index), cardiovascular and immunosuppressive medications (eg, renin-angiotensin system inhibitors, sirolimus), and cardiovascular investigation results done as part of the transplant assessment (eg, echocardiography, coronary angiogram). We were able to incorporate other important comorbidities associated with cardiovascular events, such as hypertension and diabetes mellitus. Unfortunately,

we were not able to accurately determine the cause of death, including cardiovascular death, in our data sets. Lastly, our results include kidney transplant recipients from 1 large Canadian province, and it is unclear whether these results are generalizable to other recipients, particularly those of non-Caucasian race.

In summary, in a Canadian cohort of over 1000 incident kidney transplant recipients, we found that the combined effects of eGFR and albuminuria at 1 year posttransplant were associated with higher risk of all-cause mortality and cardiovascular events, including heart failure. These results suggest that in kidney transplant recipients, albuminuria provides additional information to eGFR on the prognosis of clinically important outcomes.

ACKNOWLEDGMENTS

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