

# Metabolic Acidosis is Associated With Acute Kidney Injury in Patients With CKD



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**Introduction:** Metabolic acidosis in patients with chronic kidney disease (CKD) results from a loss of kidney function. It has been associated with CKD progression, all-cause mortality, and other adverse outcomes. We aimed to determine whether metabolic acidosis is associated with a higher risk of acute kidney injury (AKI).

**Methods:** This was a retrospective cohort study. Using electronic health records and administrative data, we enrolled 2 North American cohorts of patients with CKD Stages G3–G5 as follows: (i) 136,067 patients in the US electronic medical record (EMR) based cohort; and (ii) 34,957 patients in the Manitoba claims-based cohort. The primary exposure was metabolic acidosis (serum bicarbonate between 12 mEq/l and <22 mEq/l). The primary outcome was the development of AKI (defined using ICD-9 and 10 codes at hospital admission or a laboratory-based definition based on Kidney Disease: Improving Global Outcomes guidelines). We applied Cox proportional hazards regression models adjusting for relevant demographic and clinical characteristics.

**Results:** In both cohorts, metabolic acidosis was associated with AKI: hazard ratio (HR) 1.57 (95% confidence interval [CI] 1.52–1.61) in the US EMR cohort, and HR 1.65 (95% CI 1.58–1.73) in the Manitoba claims cohort. The association was consistent when serum bicarbonate was treated as a continuous variable, and in multiple subgroups, and sensitivity analyses including those adjusting for albuminuria.

**Conclusion:** Metabolic acidosis is associated with a higher risk of AKI in patients with CKD. AKI should be considered as an outcome in studies of treatments for patients with metabolic acidosis.

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KEYWORDS: acute kidney injury; bicarbonate; chronic kidney disease; metabolic acidosis

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Metabolic acidosis is a common complication of advanced CKD and is associated with increased bone demineralization, muscle catabolism, CKD progression, and mortality.<sup>1–5</sup> It occurs in approximately 15% of patients with CKD (when defined as serum bicarbonate <22 mEq/l), with prevalence increasing among those with worsening kidney function.<sup>1,6</sup>

In response to metabolic acidosis, compensatory mechanisms are deployed by the kidney to maintain acid-base homeostasis.<sup>7</sup> Nevertheless, animal studies have demonstrated that these mechanisms ultimately make kidneys more prone to injury and disease progression.<sup>8,9</sup> In response to a high dietary acid load, the

remnant kidney increases ammoniogenesis per nephron to facilitate acid excretion in the setting of nephron loss.<sup>10</sup> This results in a high intrarenal concentration of ammonia, which activates an alternative complement pathway that promotes tubulointerstitial fibrosis.<sup>1,8</sup> In addition, upregulation of endothelin-1 facilitates acid excretion by stimulating proximal and distal Na<sup>+</sup>/H<sup>+</sup> exchange, reducing distal bicarbonate secretion, and stimulating H<sup>+</sup>-ATPase activity via adrenal aldosterone.<sup>11,12</sup> Nevertheless, endothelin-1 promotes kidney injury, proteinuria, inflammation, and kidney fibrosis.<sup>13,14</sup> Finally, systemic and renal angiotensin II levels are elevated in the setting of interstitial acid accumulation.<sup>15,16</sup> Treatment of acidosis lowers angiotensin II levels and conserves glomerular filtration rate in animal models.<sup>15,16</sup>

No previous studies have demonstrated an association between metabolic acidosis and AKI. Nevertheless, risk factors that predispose individuals to CKD

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progression have often been found to increase the risk of AKI. This has been shown to be true for albuminuria, which confers a 4-fold greater risk of admission for AKI, as well as diabetes.<sup>17,18</sup> This phenomenon likely occurs because the presence of these risk factors reflects kidneys that are vulnerable to insults. As a result, it is likely that the same acidosis-induced compensatory mechanisms, which increase risk for CKD progression, also increase risk for AKI. This study aims to investigate this hypothesis.

The objective of this study was to determine the association of metabolic acidosis with the development of AKI in patients with CKD stages G3–G5 in a large retrospective cohort study.

## METHODS

### Study Design and Data Sources

This was a retrospective study of 2 North American cohorts of patients with CKD. A US EMR cohort across all 50 states and Puerto Rico was derived from the Optum EHR+ Integrated Database (OptumLabs, Cambridge, MA). The Optum database contains comprehensive electronic health records from 103 million patients from a variety of health care providers and health insurance plans (including patients who are uninsured). We extracted longitudinal records from January 1, 2007 to June 30, 2019 which included laboratory results, ICD-9 and 10 codes from outpatient visits and inpatient admissions, and prescription drug records. Neither informed consent nor Institutional Review Board approval was required because the US EMR cohort includes deidentified information in compliance with the Health Insurance Portability and Accountability Act regulations and requirements.

A Canadian cohort was derived from a population-level data repository in Manitoba, a province of approximately 1.3 million people. Longitudinal records from April 1, 2006 to March 31, 2018 were extracted from several population-level administrative health databases housed at the Manitoba Center for Health Policy at the University of Manitoba. Databases included the following: (i) Manitoba Health Insurance Registry (age, sex, and start and end dates of health coverage); (ii) medical services and claims (diagnoses and billings related to general practitioner and specialist visits); (iii) Canadian Institute for Health Information Discharge Abstract Database (inpatient hospital admissions and day surgeries); (iv) Shared Health Diagnostic Services of Manitoba (outpatient and inpatient laboratory test results); and (v) Drug Program Information Network (outpatient drug prescriptions). Information corresponding to the same patient was linked across databases using a deidentified version of

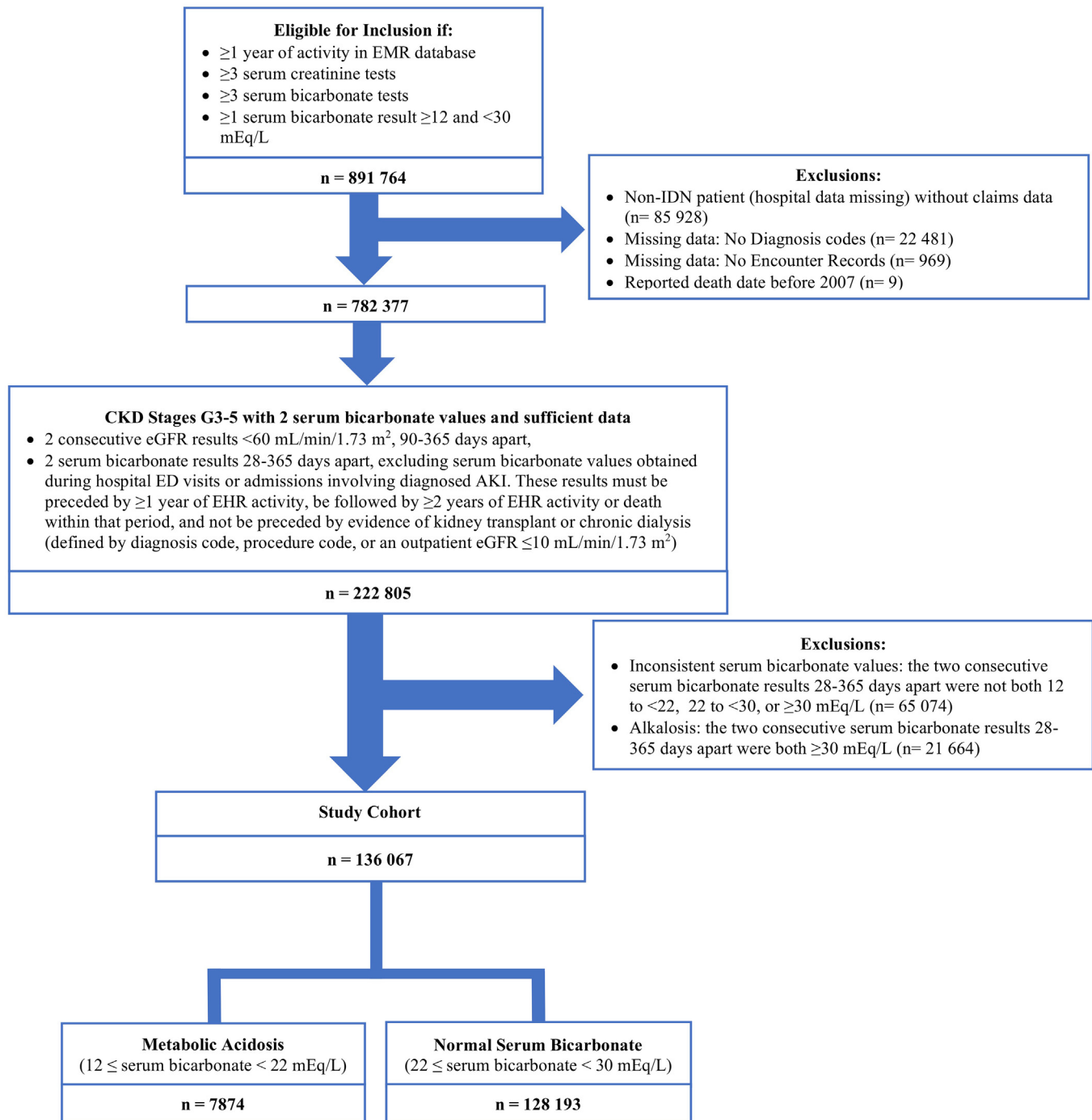
the personal health identification number, a unique number assigned to every Manitoban resident.<sup>19,20</sup> Ethics approval was obtained from the University of Manitoba Health Research Ethics Board (#HS22714).

### Study Population

All individuals in the Optum database along with at least 3 serum bicarbonate tests and 3 serum creatinine tests in any setting were eligible for inclusion in the US EMR cohort (Figure 1). Patients included in the study cohort had 2 consecutive estimated glomerular filtration rate (eGFR) results  $<60$  ml/min per  $1.73$  m<sup>2</sup> 90 to 365 days apart. Individuals with at least 1 serum bicarbonate test and 1 serum creatinine test performed in an outpatient setting were eligible for inclusion in the Manitoba claims cohort (Figure 2). The study cohort patients were established by identifying the first eGFR within the study period for each eligible individual and including only those with an eGFR  $<60$  ml/min per  $1.73$  m<sup>2</sup>. All eGFRs were calculated using the CKD Epidemiology Collaboration equation.<sup>21</sup> Participants of all ages (1 to 90 or more) were included in the US EMR cohort, whereas adults aged more than or equal to 18 (18 to 109) were included in the Manitoba claims cohort. The age of patients who were more than 90 years old was artificially constrained to 90 to ensure the Health Insurance Portability and Accountability Act compliance in the US EMR cohort.

Each cohort was subsequently divided into 2 groups based on serum bicarbonate values (measured in mEq/l and approximated by total CO<sub>2</sub>) as follows: (i) with metabolic acidosis (serum bicarbonate  $\geq 12$  and  $<22$ ); and (ii) without metabolic acidosis (serum bicarbonate  $\geq 22$  and  $<30$ ). In the US EMR cohort, 2 consecutive serum bicarbonate results 28 to 365 days apart that occurred after the date CKD was confirmed and fell within the intervals of 1 of the groups were required for cohort entry. In the Manitoba claims cohort, a serum bicarbonate level between 12 and less than 30 mEq/l within 180 days of their serum creatinine test (before or after) was required for cohort entry. For each included Manitoba patient, the serum bicarbonate level that was measured closest in time to the date of the serum creatinine test was used.

In the Manitoba claims cohort, the date of the serum bicarbonate test that confirmed metabolic acidosis status was designated as the index date. In the US EMR cohort, the index date was the first of the 2 serum bicarbonate tests. Additionally, those with a history of kidney failure were excluded (dialysis claim, transplant, or eGFR  $\leq 10$  ml/min per  $1.73$  m<sup>2</sup>), as well as those with less than 1 year of activity preindex date. In the US EMR cohort, those with less than 2 years of



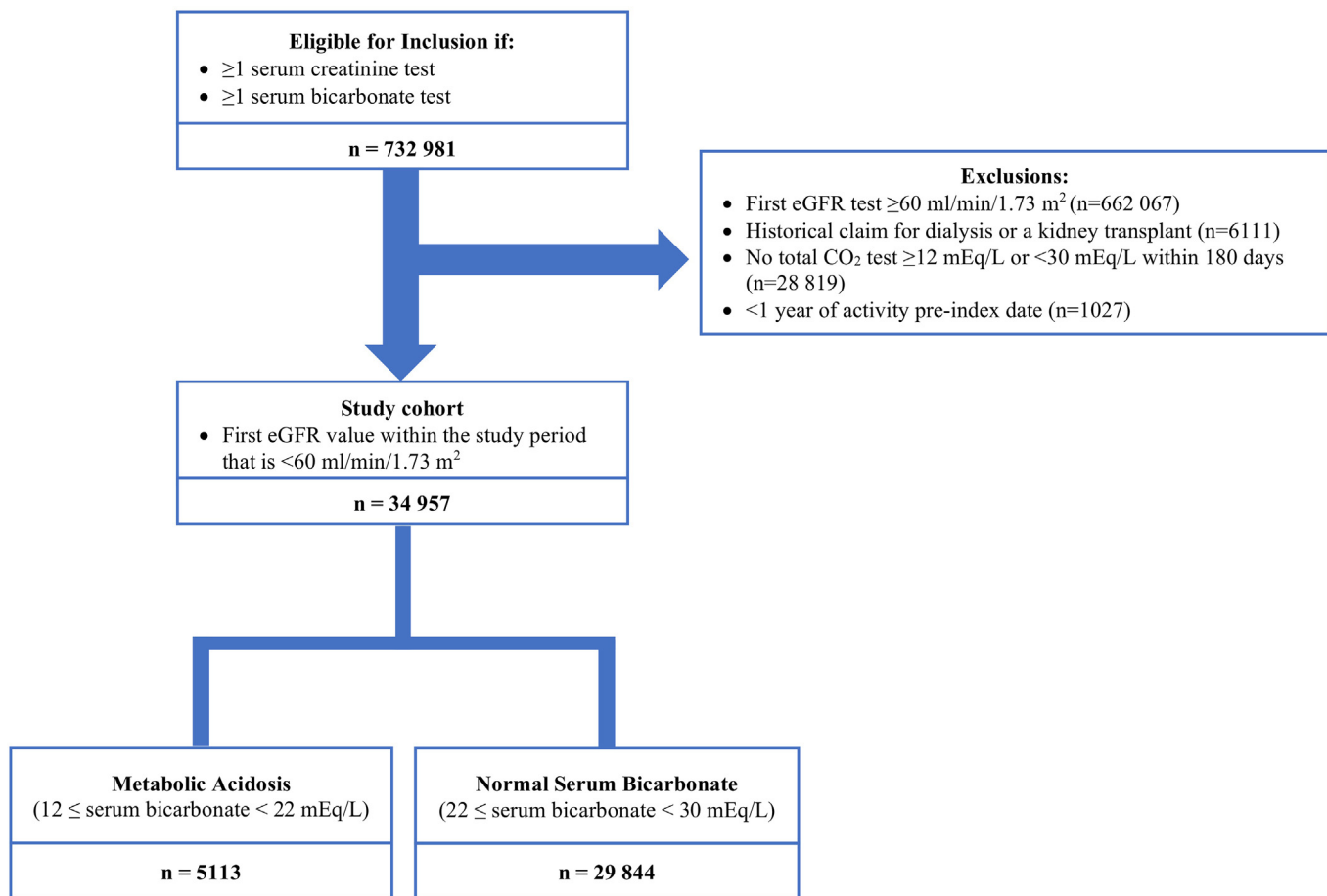
**Figure 1.** Cohort selection for US EMR cohort. US EMR, US electronic medical record.

potential follow-up postindex date were excluded unless the patient died during this period.

### Variables

The main exposure variable of interest was metabolic acidosis status. We also collected baseline demographics including age and sex from both cohorts, as well as race, region, and type of health insurance from the US EMR cohort. In the US EMR cohort, patients born in 1928 or earlier were assigned a birth year

of 1928 to ensure requirements for the Health Insurance Portability and Accountability Act compliance. Based on a case definition that included drug prescriptions, hospitalizations, and physician visits, relevant comorbidities were identified. These included diabetes, hypertension, congestive heart failure, atrial fibrillation, coronary artery disease, and stroke. Using anatomic therapeutic chemical codes in the Manitoba claims cohort and free text search in the US EMR cohort, we also ascertained outpatient prescriptions within 1 year



**Figure 2.** Cohort selection for Manitoba claims cohort. eGFR, estimated glomerular filtration rate.

prior to the index date of sodium bicarbonate, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, diuretics, and statins (Supplementary Items S1 and S2). Baseline eGFR in the US EMR cohort was established by identifying the eGFR value less than 10 and less than 60 ml/min per 1.73 m<sup>2</sup> closest on or before the index date and averaging it with all eGFR values less than 10 and less than 60 ml per min/1.73 m<sup>2</sup> occurring in the prior 90 days, using a daily average if multiple results were reported per calendar day. In the Manitoba claims cohort, the first eGFR value in the study period was kept as the baseline eGFR. CKD status was reported using baseline eGFR-based staging (in ml/min per 1.73 m<sup>2</sup>) as follows: stage G3A (60 > eGFR ≥ 45), stage G3B (45 > eGFR ≥ 30), stage G4 (30 > eGFR ≥ 15), and stage G5 (eGFR < 15). Urine albumin-to-creatinine ratio was obtained in both cohorts, when available, from a test conducted closest to the index date within ±180 days (Manitoba) or the value closest on or before the index date (US EMR). When urine albumin-to-creatinine ratio was unavailable, it was calculated from values of urine protein-to-creatinine ratio tests and urine dipstick results.<sup>22–24</sup>

## Outcomes

The primary outcome of this study was incidence of AKI. AKI events were identified through either of the following: (i) diagnostic codes indicating the primary reason for hospital admission (ICD-9: 584.x, ICD-10: N17.x); or (ii) serum creatinine values from laboratory results (including in the outpatient setting) using the definition by Kidney Disease: Improving Global Outcomes excluding urinary output.<sup>25,26</sup> The number of AKI events determined by diagnostic codes, lab values, or both, is outlined in Table S1 for each cohort.

Serum creatinine values measured after the index date were reviewed to identify possible AKIs. Of those, if any 2 consecutive serum creatinine measurements following the index date met the Kidney Disease: Improving Global Outcomes laboratory-based definition for AKI, the date of the second creatinine measurement was used as the AKI date. We considered serum creatinine values which corresponded with any of the 3 AKI stages, where a stage 3 AKI is defined as an increase in serum creatinine to ≥353.6 μmol/l within 48 hours or a more than or equal to 3-fold increase in any 7 day period; a stage 2 AKI is defined as a more than or equal to 2-fold increase in 7 days; and a stage 1 AKI is defined as a more than or equal

to 26.5  $\mu\text{mol/l}$  increase in serum creatinine within 48 hours or a more than or equal to 1.5-fold increase in serum creatinine in 7 days.

Patients were followed from the index date (of serum bicarbonate measurement) until the outcome was reached or a censoring event of death, loss to follow-up, dialysis, transplantation, or the end of the study period, which was June 30, 2019 in the US EMR cohort and March 31, 2018 in the Manitoba claims cohort. If the date of death was missing, the patient was assigned the date of their last encounter or health registration as the date of death.

### Statistical Analysis

All analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA). Descriptive statistics were used to compare baseline characteristics of the 2 groups (metabolic acidosis vs. normal serum bicarbonate). Continuous variables were compared using the independent *t*-test or Mann-Whitney U test as appropriate based on distribution, whereas categorical variables were compared using the Chi-squared test. Crude rates of AKI were reported as the number of events per 100 person-years. We used Cox proportional hazards models to compare the risk of AKI between those with and without metabolic acidosis for the entire study period. Age, sex, diabetes, hypertension, congestive heart failure, atrial fibrillation, coronary artery disease, stroke, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, diuretics, statins, and eGFR were included in the final model. Race and geographic region were also included in the models in the US EMR cohort. The proportional hazards assumption was assessed by visual analysis of Schoenfeld residuals. Models were created on the complete case and missing data was not imputed.

### Sensitivity Analysis

For the first sensitivity analysis, the same statistical models were conducted with serum bicarbonate treated as a continuous variable (sensitivity analysis #1). For the second sensitivity analysis, serum bicarbonate was treated as a categorical variable, where patients were divided into 3 groups (mEq/l) as follows: (i) moderate to severe metabolic acidosis (serum bicarbonate  $\geq 12$  and  $< 20$ ); (ii) mild metabolic acidosis (serum bicarbonate  $\geq 20$  and  $< 22$ ); and (iii) normal serum bicarbonate ( $\geq 22$  and  $< 30$ ). The hazard ratios derived from this analysis used “normal” as the reference group (sensitivity analysis #2). A trend test was performed to determine whether a trend of hazard ratios between moderate to severe metabolic acidosis versus normal serum bicarbonate and mild metabolic acidosis versus normal serum bicarbonate was significant. A third

sensitivity analysis was conducted in a subgroup of patients with available urine albumin-to-creatinine ratio (ACR) test results (sensitivity analysis #3). A log-transformed urine ACR was added as a covariate for these models.

## RESULTS

### Baseline Characteristics

In the US EMR cohort, a total of 891,764 individuals had at least 3 serum creatinine and 3 serum bicarbonate tests during the study period. Of those individuals, 136,067 were ultimately included in the study cohort, of which 5.8% (7874) had metabolic acidosis (3968 with moderate to severe metabolic acidosis, and 3906 with mild metabolic acidosis), shown in [Figure 1](#) and [Supplementary Table S2](#). From there, a total of 100,945 individuals had complete pharmacy data and were included in the primary analysis. Descriptive statistics for this cohort are included in [Table 1](#).

In the Manitoba claims cohort, a total of 732,981 individuals had at least 1 serum creatinine test during the study period. Of those individuals, 34,957 were ultimately included in the study cohort, of which 14.6% (5113) had metabolic acidosis (2417 with moderate to severe metabolic acidosis, and 2696 with mild metabolic acidosis), shown in [Figure 2](#). In both cohorts, individuals with metabolic acidosis were younger and more likely to have diabetes, and stage G4 or G5 CKD than those without it ([Table 1](#)).

The median follow-up time for the full US EMR cohort ( $n = 136,067$ ) was  $2.7 \pm 2.5$  years from index date until AKI outcome, renal replacement therapy, death or end of the study period. In the Manitoba claims cohort, the median follow-up time was  $3.9 \pm 3.5$  years.

### Risk of AKI

In both cohorts, patients with metabolic acidosis had a higher rate of AKI. The US EMR cohort had a rate of 26.2 events per 100 person-years (95% CI: 25.6–26.9) and the Manitoba claims cohort had a rate of 20.6 events per 100 person-years (95% CI: 19.8–21.3) among patients with metabolic acidosis ([Table 2](#)). Among those without metabolic acidosis, the US EMR cohort had a rate of 16.4 events per 100 person-years (95% CI 16.3–16.5) and the Manitoba claims cohort had a rate of 8.5 events per 100 person-years (95% CI 8.3–8.6) ([Table 2](#)). The proportion of individuals with AKI, stratified by serum bicarbonate, is depicted in [Figure 3](#) for both cohorts.

Metabolic acidosis was associated with the development of AKI in both cohorts (US EMR cohort [HR 1.57; 95% CI: 1.52–1.61]; Manitoba claims cohort [HR 1.65; 95% CI: 1.58–1.73]) ([Table 3](#)). Kaplan-Meier curves for time to AKI demonstrated that patients

**Table 1.** Baseline characteristics for the subgroup of the US EMR cohort with pharmacy data ( $n = 100,945$ ), compared to the Manitoba claims cohort

| Variable                            | US EMR cohort                     |   | Manitoba claims cohort            |   |
|-------------------------------------|-----------------------------------|---|-----------------------------------|---|
|                                     | Metabolic acidosis ( $n = 6144$ ) | Normal serum bicarbonate ( $n = 94,801$ ) | Metabolic acidosis ( $n = 5113$ ) | Normal serum bicarbonate ( $n = 29,844$ ) |
| Age (yrs $\pm$ SD)                  | 65.6 $\pm$ 14.2                   | 71.8 $\pm$ 10.9                           | 69.4 $\pm$ 16.6                   | 74.0 $\pm$ 13.5                           |
| Sex (% female)                      | 3201 (52%)                        | 48,949 (52%)                              | 2584 (51%)                        | 16,093 (54%)                              |
| Region                              |                                   |   |                                   |   |
| Midwest                             | 3463 (56%)                        | 58,882 (62%)                              | N/A                               | N/A                                       |
| Northeast                           | 692 (11%)                         | 7640 (8%)                                 |                                   |   |
| South                               | 1385 (23%)                        | 21,800 (23%)                              |                                   |   |
| West                                | 455 (7%)                          | 4411 (5%)                                 |                                   |   |
| Other/Unknown                       | 149 (2%)                          | 2068 (2%)                                 |                                   |   |
| Race                                |                                   |   |                                   |   |
| Black                               | 1153 (19%)                        | 10,411 (11%)                              | N/A                               | N/A                                       |
| Asian                               | 75 (1%)                           | 921 (1%)                                  |                                   |   |
| White                               | 4339 (71%)                        | 78,280 (83%)                              |                                   |   |
| Hispanic                            | 315 (5%)                          | 3001 (3%)                                 |                                   |   |
| Other/Unknown                       | 262 (4%)                          | 2188 (2%)                                 |                                   |   |
| Baseline labs                       |                                   |   |                                   |   |
| eGFR (ml/min/1.73 m <sup>2</sup> )  | 37.3 $\pm$ 13.3                   | 45.1 $\pm$ 10.4                           | 33.4 $\pm$ 16.4                   | 44.5 $\pm$ 11.8                           |
| Serum bicarbonate (mEq/l)           | 19.0 $\pm$ 2.0                    | 25.9 $\pm$ 2.0                            | 19.3 $\pm$ 2.3                    | 26.2 $\pm$ 2.1                            |
| Urine ACR (mg/g) (IQR) <sup>a</sup> | 81 (9, 315)                       | 9 (9, 81)                                 | 166 (22, 1137)                    | 30 (7, 212)                               |
| CKD stage                           |                                   |   |                                   |   |
| Stage 3A                            | 2129 (35%)                        | 54,896 (58%)                              | 1614 (32%)                        | 17,344 (58%)                              |
| Stage 3B                            | 2045 (33%)                        | 30,317 (32%)                              | 1350 (26%)                        | 8706 (29%)                                |
| Stage 4                             | 1645 (27%)                        | 8888 (9%)                                 | 1281 (25%)                        | 3280 (11%)                                |
| Stage 5                             | 325 (5%)                          | 700 (1%)                                  | 868 (17%)                         | 514 (2%)                                  |
| Baseline Medications                |                                   |   |                                   |   |
| ACE inhibitor                       | 2461 (40%)                        | 39,681 (42%)                              | 1972 (39%)                        | 10,418 (35%)                              |
| ARB                                 | 994 (16%)                         | 18,602 (20%)                              | 1086 (21%)                        | 7183 (24%)                                |
| Diuretic                            | 3050 (50%)                        | 51,869 (55%)                              | 2069 (41%)                        | 12,911 (43%)                              |
| Statin                              | 2776 (45%)                        | 50,991 (54%)                              | 1857 (36%)                        | 11,460 (38%)                              |
| Sodium bicarbonate                  | 420 (7%)                          | 1021 (1%)                                 | 47 (0.9%)                         | 24 (0.1%)                                 |
| Comorbidities                       |                                   |   |                                   |   |
| Diabetes                            | 2969 (48%)                        | 42,463 (45%)                              | 1882 (37%)                        | 8254 (28%)                                |
| Hypertension                        | 4594 (75%)                        | 74,166 (78%)                              | 3941 (77%)                        | 23,784 (80%)                              |
| CHF                                 | 1692 (28%)                        | 29,347 (31%)                              | 665 (13%)                         | 3618 (12%)                                |
| Atrial fibrillation                 | 970 (16%)                         | 22,677 (24%)                              | 517 (10%)                         | 3772 (13%)                                |
| CAD                                 | 2132 (35%)                        | 40,487 (43%)                              | 1198 (23%)                        | 7419 (25%)                                |
| Stroke                              | 1119 (18%)                        | 20,017 (21%)                              | 419 (8%)                          | 2634 (9%)                                 |

ACE, angiotensin-converting enzyme; ACR, albumin-to-creatinine ratio; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; N/A, not analyzed.

<sup>a</sup>In the US EMR cohort with complete data, urine ACR was available for 4939 individuals in the metabolic acidosis group and 73,374 individuals in the normal serum bicarbonate group. In the Manitoba claims cohort urine ACR was available for 1802 individuals in the metabolic acidosis group and 8255 individuals in the normal serum bicarbonate group.

with metabolic acidosis have a higher probability of AKI at a given time interval and that the probability increased with severity of acidosis (Figure 4 and 5).

### Sensitivity Analysis #1: Continuous Serum Bicarbonate

In models evaluating the association between serum bicarbonate as a continuous variable and the risk of AKI, an increase in serum bicarbonate of 1 mEq/l was associated with a 5% lower risk of AKI (HR 0.95; 95% CI: 0.95–0.96) in the US EMR cohort and a 7% lower risk of AKI (HR 0.93; 95% CI: 0.92–0.93) in the Manitoba claims cohort (Table 3).

### Sensitivity Analysis #2: Severity of Metabolic Acidosis

In both cohorts, mild metabolic acidosis (serum bicarbonate levels  $\geq 20$  and  $< 22$  mEq/l) was associated with a higher risk of AKI compared with those with normal serum bicarbonate (US EMR cohort [HR 1.44; 95% CI: 1.38–1.50]; Manitoba claims cohort [HR 1.39; 95% CI: 1.31–1.48]). Moderate to severe metabolic acidosis (serum bicarbonate  $\geq 12$  and  $< 20$ ) was also associated with increased risk of AKI in comparison to patients with mild metabolic acidosis (US EMR cohort [HR 1.19; 95% CI: 1.12–1.26]; Manitoba claims cohort [HR 1.48; 95% CI: 1.37–1.60]) (Table 3). The

**Table 2.** Crude rates of acute kidney injury events during the entire study period, stratified by metabolic acidosis status

| Cohort                                      | With metabolic acidosis |                 |                   | Without metabolic acidosis |                 |                   |
|---|-------------------------|-----------------|-------------------|----------------------------|-----------------|-------------------|
|   | Events                  | Total person-ys | Rate <sup>a</sup> | Events                     | Total person-ys | Rate <sup>a</sup> |
| US EMR cohort ( <i>n</i> = 136,067)         | 6008                    | 22,865          | 26.2 (25.6–26.9)  | 90,528                     | 552,943         | 16.4 (16.3–16.5)  |
| Manitoba claims cohort ( <i>n</i> = 34,957) | 2608                    | 12,687          | 20.6 (19.8–21.3)  | 10,363                     | 122,400         | 8.5 (8.3–8.6)     |

US EMR, US electronic medical record.

<sup>a</sup>Rates expressed as n per 100 person-years (95% confidence interval).

*P*-value of the trend test showed a statistically significant trend (*P* < 0.001).

### Sensitivity Analysis #3 – Adjustment for Urine ACR

In a subgroup of individuals who had complete data and a urine ACR measurement (US EMR cohort [*n* = 78,313], Manitoba claims cohort [*n* = 10,057]), results from each model were qualitatively unchanged. Metabolic acidosis was associated with the development of AKI (US EMR cohort [HR 1.50; 95% CI: 1.45–1.55]; Manitoba claims cohort [HR 1.66; 95% CI: 1.54–1.79]). In models evaluating the association between baseline serum bicarbonate as a continuous variable and the risk of AKI, an increase in serum bicarbonate of 1 mEq/l was associated with a 4% decrease in the risk of AKI (HR 0.96; 95% CI: 0.96–0.96) in the US EMR cohort and a 8% decrease in the risk of AKI (HR 0.92; 95% CI: 0.91–0.93) in the Manitoba claims cohort (Table 3). Log-transformed urine ACR was also associated with AKI in both cohorts (US EMR cohort [HR 1.09; 95% CI: 1.08–1.09]; Manitoba claims cohort [HR 1.14; 95% CI: 1.13–1.16]).

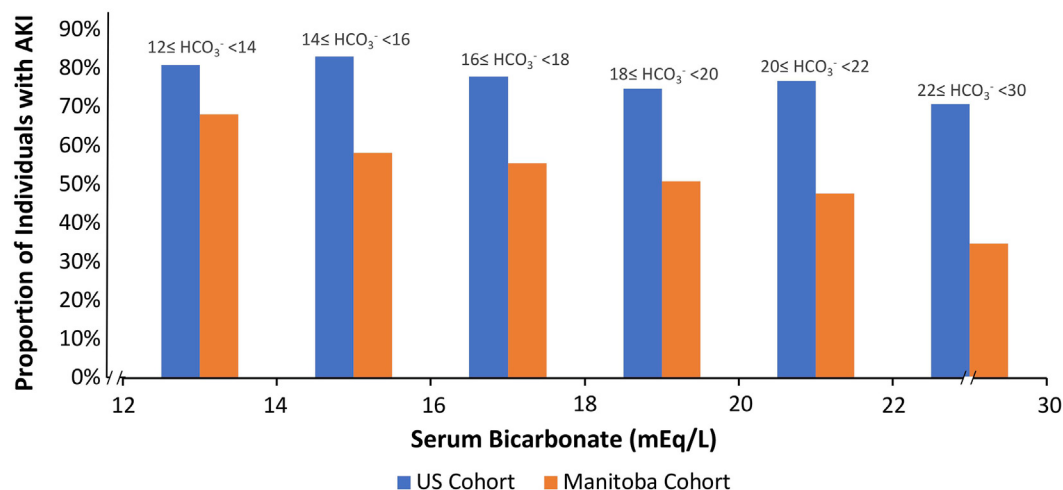
## DISCUSSION

In this retrospective study of 2 North American cohorts with a combined sample size of 135,902 individuals with CKD, metabolic acidosis was associated with a

57% to 65% higher risk of AKI. These findings were independent of baseline kidney function, as well as the presence of underlying comorbid conditions, and consistent in the 2 independent populations.

To our knowledge, this is the first study that has examined the association between metabolic acidosis and AKI in well characterized cohorts of patients with CKD. Previous studies linking metabolic acidosis to adverse kidney outcomes in CKD patients have largely focused on risk for CKD progression. In the Chronic Renal Insufficiency Cohort study, which involved more than 3500 participants, those with serum bicarbonate concentrations less than 22 mEq/l had almost a 2-fold increased risk for CKD progression (>50% decline in GFR or kidney failure), compared to those with bicarbonate concentrations of 22 to 26 mEq/l, over 6 years follow-up.<sup>27</sup> Similarly, an analysis from the Modification of Diet in Renal Disease study found that, when patients with stage 2 to 4 CKD were stratified by serum bicarbonate values into quartiles, those in the first quartile (serum bicarbonate of 11–20 mEq/l) had a 2.2-fold increased risk for kidney failure compared to those in the fourth quartile (26–40 mEq/l).<sup>28</sup> The degree to which this risk of kidney failure is mediated by AKI versus CKD progression in the setting of acidosis and other settings is unknown.

Our findings also complement studies that associate metabolic acidosis with CKD progression, cognitive and



**Figure 3.** Proportion of individuals with AKI, stratified by serum bicarbonate, for both cohorts. AKI, acute kidney injury; US EMR, US electronic medical record.

**Table 3.** Hazard ratios for the association between metabolic acidosis and acute kidney injury derived from Cox proportional hazards regression models<sup>a</sup>

| Metabolic acidosis  | US EMR cohort HR (95% CI)     | Manitoba claims cohort HR (95% CI) |
|---|-------------------------------|------------------------------------|
| Main analysis   |                               |                                    |
| Metabolic acidosis vs. normal serum bicarbonate <sup>b</sup>                    | 1.57 (1.52–1.61) <sup>c</sup> | 1.65 (1.58–1.73) <sup>c</sup>      |
| Sensitivity analysis #1—continuous serum bicarbonate                            |                               |                                    |
| Continuous serum bicarbonate (per 1 mEq/l increase)                             | 0.95 (0.95–0.96) <sup>c</sup> | 0.93 (0.92–0.93) <sup>c</sup>      |
| Sensitivity analysis #2—severity of metabolic acidosis                          |                               |                                    |
| Moderate to severe metabolic acidosis vs. normal serum bicarbonate <sup>b</sup> | 1.71 (1.64–1.78) <sup>c</sup> | 2.06 (1.94–2.19) <sup>c</sup>      |
| Mild metabolic acidosis vs. normal serum bicarbonate <sup>b</sup>               | 1.44 (1.38–1.50) <sup>c</sup> | 1.39 (1.31–1.48) <sup>c</sup>      |
| Moderate to severe metabolic acidosis vs. mild metabolic acidosis <sup>b</sup>  | 1.19 (1.12–1.26) <sup>c</sup> | 1.48 (1.37–1.60) <sup>c</sup>      |
| Sensitivity analysis #3 <sup>d</sup> —adjustment for urine ACR                  |                               |                                    |
| Metabolic acidosis vs. normal serum bicarbonate <sup>b</sup>                    | 1.50 (1.45–1.55) <sup>c</sup> | 1.66 (1.54–1.79) <sup>c</sup>      |
| Continuous serum bicarbonate (per 1 mEq/l increase)                             | 0.96 (0.96–0.96) <sup>c</sup> | 0.92 (0.91–0.93) <sup>c</sup>      |
| Moderate to severe metabolic acidosis vs. normal serum bicarbonate <sup>b</sup> | 1.62 (1.55–1.70) <sup>c</sup> | 2.10 (1.91–2.31) <sup>c</sup>      |
| Mild metabolic acidosis vs. normal serum bicarbonate <sup>b</sup>               | 1.40 (1.33–1.46) <sup>c</sup> | 1.38 (1.26–1.52) <sup>c</sup>      |
| Moderate to severe metabolic acidosis vs. mild metabolic acidosis <sup>b</sup>  | 1.16 (1.09–1.24) <sup>c</sup> | 1.52 (1.35–1.71) <sup>c</sup>      |

ACE, angiotensin-converting enzyme; ACR, albumin-to-creatinine ratio; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

<sup>a</sup>Baseline variables included in the final model were: age, sex, eGFR, diabetes, hypertension, CHF, atrial fibrillation, CAD, stroke, ACE inhibitors, ARBs, diuretics, and statins. Race and geographic region were also included in the United States EMR cohort.

<sup>b</sup>"Moderate to severe metabolic acidosis" refers to serum bicarbonate  $\geq 12$  and  $< 20$  mEq/L. "Mild metabolic acidosis" refers to serum bicarbonate  $\geq 20$  and  $< 22$  mEq/L. "Normal serum bicarbonate" is defined as  $\geq 22$  and  $< 30$  mEq/L.

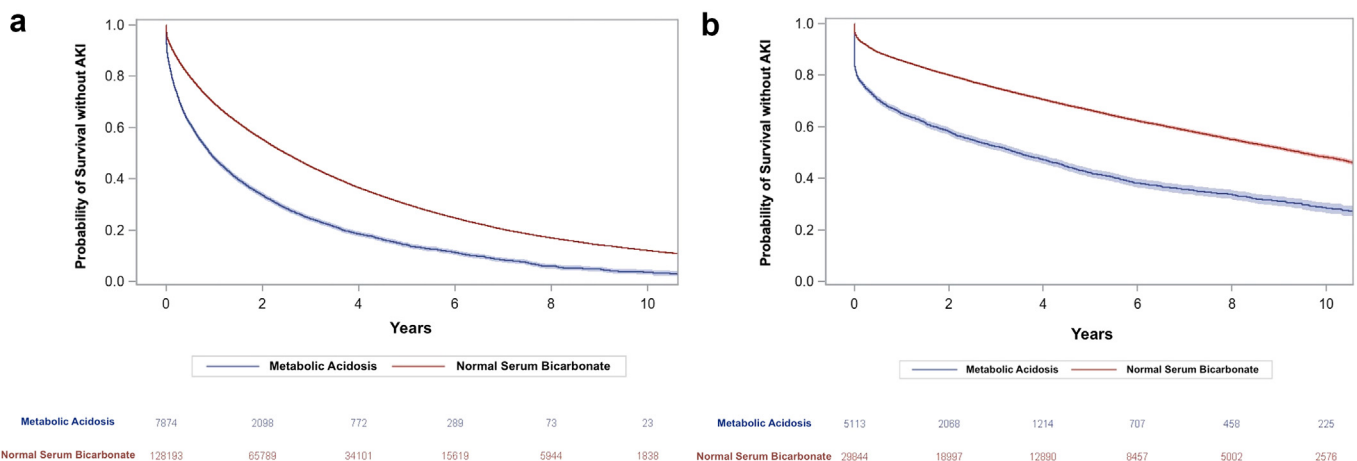
<sup>c</sup> $P < 0.001$ .

<sup>d</sup>Log-transformed urine ACR was included along with the other baseline variables listed above.

cardiovascular disease, and higher all-cause mortality.<sup>29,30</sup> A *post hoc* analysis from the Systolic Blood Pressure Intervention Trial demonstrated the association between metabolic acidosis and cognitive impairment in hypertensive adults with and without CKD; where a 1 mEq/l lower bicarbonate level was associated with lower global cognitive function and executive function.<sup>31</sup> Meanwhile, a similar analysis from the National Health and Nutrition Examination Survey III also found that a serum bicarbonate less than 22 mEq/l conferred a 2.6-fold increased risk of mortality in patients with CKD, compared with those with a serum bicarbonate of 26 to 30 mEq/l.<sup>32</sup> More recently, a study examining the effects of acidosis on measured endothelial function found altered pulse wave velocity in

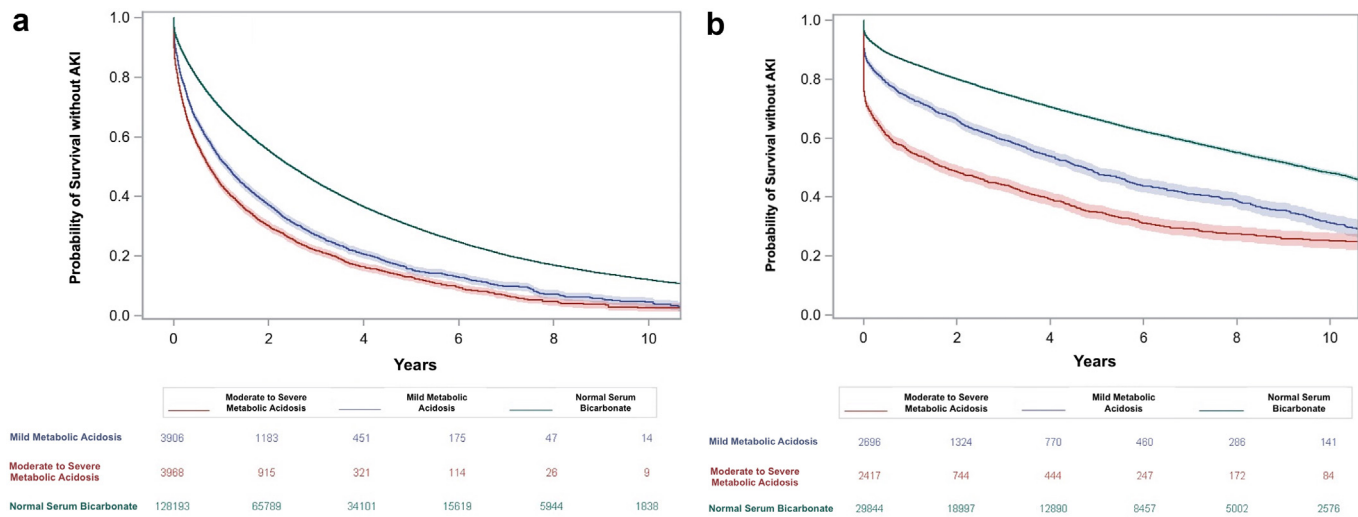
patients with acidosis, which suggests an underlying pathophysiological mechanism for the findings from the epidemiological studies.<sup>29</sup>

We believe that metabolic acidosis may serve as a marker for a vulnerable kidney. The compensatory mechanisms deployed by the remnant kidney to maintain acid-base homeostasis, such as upregulated ammoniogenesis, endothelin-1, and angiotensin II levels, have been shown to ultimately promote tubulointerstitial inflammation, fibrosis, and damage.<sup>1,14</sup> Furthermore, since acid-base homeostasis is largely managed in the tubules, the presence of metabolic acidosis may reflect tubulointerstitial disease, which could suggest worse kidney function and higher risk of AKI, compared to that of an individual with the same



**Figure 4.** Kaplan-Meier curve for time to AKI, stratified by metabolic acidosis status. (a) US EMR cohort. (b) Manitoba claims cohort. AKI, acute kidney injury; US EMR, US electronic medical record.





**Figure 5.** Kaplan-Meier curve for time to AKI, stratified by severity of metabolic acidosis. (a) US EMR cohort. (b) Manitoba claims cohort. AKI, acute kidney injury; US EMR, US electronic medical record.

GFR but no acidosis. These findings highlight the need for close monitoring of patients with CKD and metabolic acidosis when they are starting new medications in the community or being admitted to the hospital. In these settings where the risk of AKI is high, metabolic acidosis may be a potentially modifiable risk factor that can provide prognostic information about the risk of AKI. From a research perspective, ongoing clinical trials of treatment of metabolic acidosis should capture information about AKI events as endpoints to examine whether treatment reduces the risk of AKI, in addition to slowing CKD progression. This is important to recognize, because the use of alkali treatments for chronic metabolic acidosis remains as infrequent as 2.7% among patients with CKD.<sup>33</sup>

There are several strengths to this study. Using population-level administrative health databases (Canada) and comprehensive nationally representative electronic health records (US), we developed a robust dataset of outcomes occurring in a North American population of CKD patients. Furthermore, our findings remained consistent and congruent across multiple sensitivity analyses, despite differences in health systems; ascertainment methods for cohort inclusion, exposures, and outcome; and prevalence of metabolic acidosis (much lower in the US EMR cohort). Additionally, the racial and geographic diversity of our cohorts suggests these results may be generalizable in clinical settings across North America.

Limitations of the study include potential biases related to methodology. Because this was an observational study, residual confounding is always possible. In the Manitoba claims cohort, patients were classified as having CKD or metabolic acidosis based on 1 measured lab value. This may have led to overinclusion

of patients in both the CKD and metabolic acidosis categories respectively, because chronic conditions typically should be defined by 2 consistent measurements that are taken more than 90 days apart. Nevertheless, overinclusion would bias results toward the null hypothesis, suggesting that the calculated hazard ratios in this study likely underestimate the strength of associations detected. In addition, there may have been selection bias in the Manitoba claims cohort because sicker patients may be more likely to use public laboratories at hospital sites, which comprise a majority of the outpatient tests in the included data. This may have led to differences in the frequency of tracking AKIs, between healthier and sicker patient populations. These limitations did not exist in the US EMR cohort and yet results were similar which supports our findings. In addition, chronic respiratory alkalosis could not be excluded as a possible cause of metabolic acidosis. We could not capture or control for treatment of baseline metabolic acidosis with over-the-counter baking soda. Finally, although we used Kidney Disease: Improving Global Outcomes laboratory-based definitions to identify lab values that constitute AKI, it is possible that rapid CKD progression results in a change in creatinine that meets the AKI criteria.

In conclusion, metabolic acidosis is independently associated with a higher risk of AKI in patients with CKD. These findings suggest that metabolic acidosis is a marker of vulnerable kidneys and vasculature. Taken together with findings from previous studies, metabolic acidosis may serve as a significant risk factor for AKI, CKD progression, and mortality. Studies targeting treatment approaches for patients with metabolic acidosis should consider AKI as a potential outcome.

## DISCLOSURE

NLR and NT report equity ownership and consultancy to Tricida, Inc. SEF, RHW, and TWF report consultancy to Tricida, Inc. All other authors declared no competing interests.

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## AUTHOR CONTRIBUTIONS

NT contributed to the conception of the work, acquisition, and interpretation of data. AZ contributed to the interpretation of data. RW contributed to the acquisition, analysis, and interpretation of data. TWF contributed to the analysis and interpretation of data. MN-M contributed to the acquisition, analysis, and interpretation of data. NLR contributed to the conception of the work, acquisition, and interpretation of data. SEF contributed to the acquisition, analysis, and interpretation of data. DC contributed to the interpretation of the data. PK contributed to the interpretation of data. CB contributed to the interpretation of the data. CR contributed to the interpretation of the data. All authors contributed to the drafting of the work and critical revision of important intellectual content, final approval of the version to be published, and agree to be accountable for all aspects of the work.

## SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

**Item S1.** Diagnostic and procedure codes used to identify exclusion criteria and comorbid conditions.

**Item S2.** Administrative data definitions used to define prescriptions.

**Table S1.** Number of AKI's determined by diagnostic code, lab values, or both.

**Table S2.** Baseline characteristics for the entire US EMR cohort ( $n = 136,067$ ) and Manitoba claims cohort.

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