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Original Article

ORIGINAL ARTICLE

Association of metabolic acidosis with fractures, falls, protein-calorie malnutrition and failure to thrive in patients with chronic kidney disease

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ABSTRACT

Background. The risk of adverse geriatric outcomes such as falls and fractures is high among patients with chronic kidney disease (CKD). Metabolic acidosis is associated with protein catabolism and bone loss in experimental animal and human studies. We sought to quantify the independent association of metabolic acidosis with adverse muscle, bone and functional outcomes in a large US community-based cohort.

Methods. The Optum's de-identified Integrated Claims-Clinical dataset of US patients (2007–2017) was used to generate a cohort of patients with nondialysis-dependent CKD who had estimated glomerular filtration rate >10 to <60 mL/min/1.73 m^2 and two serum bicarbonate values 12 to <22 mmol/L or 22–29 mmol/L. The primary outcomes were failure to thrive, protein-calorie malnutrition, and fall or fracture. Cox proportional hazards models were used for the primary outcomes for up to 10 years, while logistic regression models were used at 2 years.

Results. A total of 51 558 patients qualified for the study, with a median [Interquartile Range (IQR)] follow-up time of 4.2 (2.5–5.8) years. Over a ≤10-year period, for each 1 mmol/L increase in serum bicarbonate, the hazard ratios (adjusted for age, sex, race, estimated glomerular filtration rate, serum albumin, hemoglobin, diabetes and cardiovascular comorbidities) for failure to thrive, protein-calorie malnutrition and fall or fracture were 0.91 [95% confidence interval (CI): 0.90–0.92], 0.91 (95% CI: 0.90–0.92) and 0.95 (95% CI: 0.95–0.96), all $P < 0.001$, respectively.

Conclusions. The presence and severity of metabolic acidosis was a significant, independent risk factor for failure to thrive, protein-calorie malnutrition and fall or fracture in this large community cohort of patients with stage 3–5 CKD.

Keywords: chronic kidney disease, failure to thrive, fall, fracture, malnutrition, metabolic acidosis, serum bicarbonate

INTRODUCTION

Chronic kidney disease (CKD) has been described as a model of premature aging [1]. Consistent with this paradigm, patients with CKD have accelerated bone and muscle loss and are predisposed to nutritional decline, which can lead to the development of sarcopenia and osteoporosis [2–5]. These developments confer a higher risk of major clinical consequences including falls, fractures and functional decline in this population

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[3]. While kidney failure requiring dialysis has been associated with a markedly high risk of fracture, patients with earlier stages of CKD are also at increased risk [6]. Furthermore, CKD is also associated with frailty, malnutrition and an increased likelihood of disability [7]. 'Failure to thrive', a condition generally associated with the geriatric population, is described as a multifactorial state of decline that may be caused by chronic diseases and functional impairment [8].

Impaired tubular function accompanying CKD impairs acid excretion and leads to metabolic acidosis [9]. Although serum bicarbonate is generally maintained within the normal range until the estimated glomerular filtration rate (eGFR) declines to below 40 mL/min/1.73 m^2 (i.e. stage 3b or more advanced CKD), there is abundant evidence that acid retention and impaired renal net acid excretion is present as early as stage 2 CKD [10, 11]. Buffering of retained acid by bone leads to loss of bone mass through a direct physicochemical mechanism as well as through inhibition of osteoblasts and activation of osteoclasts [12]. Additionally, metabolic acidosis leads to protein catabolism and muscle loss [13]. Further, a decrease in systemic pH appears to stimulate secretion of proinflammatory cytokines by macrophages, which can contribute to muscle wasting [14].

We hypothesized that metabolic acidosis may be an important contributor to the clinical manifestations of accelerated aging seen in patients with CKD: falls, fractures, protein-calorie malnutrition and failure to thrive. Here, we investigated the relationship between metabolic acidosis and adverse clinical outcomes in a large US community-based cohort of over 51 000 patients with nondialysis-dependent CKD stage 3–5.

MATERIALS AND METHODS

Study design and data sources

In this retrospective cohort study, we accessed Optum's de-identified Integrated Claims-Clinical dataset of US patients (2007–2017), a clinical repository that contains over 81 million people with different health insurance plans, including those who are uninsured, from all 50 states in the USA and Puerto Rico. The data available in the Electronic Health Records (EHR) database include demographics, comorbidities, laboratory data, procedure and diagnosis information, medication data and provider notes extracted with natural language processing. Data were cleaned by investigators using validity parameters on laboratory values (Supplementary data, Table S1).

Study cohort

Data collection for the study cohort included records from January 2007 through March 2017. Individuals with evidence of CKD and serum bicarbonate testing were eligible for the study. We extracted data from patient records from the EHR database that met all of the following criteria: (i) ≥1 year of activity in the database, (ii) ≥3 eGFR results <60 mL/min/1.73 m^2 and (iii) ≥3 serum bicarbonate results with at least one result between 12 and 29 mmol/L.

In order to enter the study cohort, patients were required to have two consecutive serum bicarbonate results between 28 and 365 days apart where both test results either met the criteria for the metabolic acidosis group (12 to <22 mmol/L) or the normal serum bicarbonate group (22–29 mmol/L). Serum bicarbonate and eGFR tests during an inpatient hospital admission or emergency department visit with a concurrent diagnosis of acute kidney injury were not used as they likely represented acute events (Supplementary data, Table S1). The date of the first of these two tests was considered the index date, and the result of that test was designated as the patient's baseline serum bicarbonate measurement.

To be included in the study cohort, a patient also needed to have at least 1 year of history prior to the index date, and 2 years of activity, excepting death, after the index date. Patients were excluded if they had any evidence of chronic dialysis or kidney transplant at baseline, including those with a baseline eGFR or any single outpatient eGFR ≤10 mL/min/1.73 m^2 (Supplementary data, Table S1). We established the baseline eGFR based on the mean of all eGFR results for the 90 days preceding the closest test on or before the index date. Patients were stratified into the following CKD stages based on their baseline eGFR: stage 3a (45 to <60 mL/min/1.73 m^2), stage 3b (30 to <45 mL/min/1.73 m^2), stage 4 (15 to <30 mL/min/1.73 m^2) and stage 5 (>10 to <15 mL/min/1.73 m^2). We calculated eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, based on serum creatinine and adjusted for race [15].

To ensure that the cohort had enough patients with metabolic acidosis, the study cohort was selected using an algorithm that oversampled patients with serum bicarbonate values 12 to <22 mmol/L. This algorithm examined records beginning after 1 year of patient activity and looked for the first pair of qualifying serum bicarbonate values between 12 and <22 mmol/L before looking for a pair of serum bicarbonate values between 22 and 29 mmol/L.

For statistical modeling, the primary analysis cohort was defined as patients meeting the above criteria without any missing data. Missing data were an issue only for laboratory values and were not imputed. The primary analysis cohort excluded patients missing hemoglobin or serum albumin tests, resulting in exclusion of 2519 (15%) patients with metabolic acidosis and 12 122 (35%) patients with normal serum bicarbonate.

Variables

Our primary predictor variable was serum bicarbonate treated as a continuous variable. We obtained demographic characteristics such as age at the time of the index date, sex, race (African American, Asian, Caucasian or other) and geographic region of residence (Midwest, Northeast, South, West). Patients born before 1928 were assigned a birth year of 1928 for privacy reasons. We used a 1-year lookback period to determine baseline laboratory results that were in addition to serum bicarbonate, eGFR and urine albumin-to-creatinine ratio. These included serum albumin, hemoglobin, serum calcium and serum potassium.

We searched all available diagnosis code data prior to the index date to identify comorbidities including coronary artery disease (CAD), diabetes, heart failure, hypertension, peripheral vascular disease (PVD) and protein-calorie malnutrition. In addition, we evaluated conditions for the Charlson Comorbidity Index (CCI) by single occurrence of an International Classification of Diseases (ICD)-9 or ICD-10 diagnosis code and computed a weighted index score [16, 17]. Evidence of prior falls and fractures, protein-calorie malnutrition and failure to thrive was evaluated by diagnosis code during the pre-index year. Evidence of a prescription for sodium bicarbonate or other alkali treatment was evaluated in prescriptions and patient-reported medication records during the pre-index year. Complete variable definitions are provided in Supplementary data, Table S1.

Outcomes

Our primary outcomes were failure to thrive, protein-calorie malnutrition and a composite outcome of a fall, or spine, hip or pathological fracture. Each component of the composite outcome was also assessed separately as a secondary outcome. We used a 2-year outcome ascertainment period to assess immediate effects and constructed models using all available data that followed patients until a censoring event, death or the end of documented interaction with the health-care provider. Failure to thrive, protein-calorie malnutrition, falls and fractures were all identified through the EHR database using ICD-9-CM and ICD-10-CM codes. Diagnosis codes are provided in Supplementary data, Table S2.

Statistical analysis

Patient characteristics were compared between the metabolic acidosis and normal serum bicarbonate groups using the chi-square or *t*-tests when appropriate. In patients with and without metabolic acidosis, we calculated the proportion of the primary outcomes in a 2-year period and used the chi-square test to compare the unadjusted proportions in the study cohort and in each CKD stage strata. As a sensitivity analysis, we replicated these unadjusted analyses excluding from each outcome patients with a diagnosis for the outcome condition during the pre-index year.

We examined the association of serum bicarbonate as a continuous variable with our primary outcomes by constructing a series of multivariable logistic regression models to evaluate the outcomes within a 2-year period and using Cox proportional hazard regression models to evaluate primary and secondary outcomes for the entire duration of follow-up. We did not test any interactions. The proportional hazards assumption was met for all Cox proportional hazards regression models per visual assessment of Schoenfeld residuals. Multicollinearity was assessed using the variance inflation factor, and Martingale residuals were examined for continuous variables to confirm linearity.

We reported odds ratios (ORs) with 95% confidence intervals (CIs) and P-values of the predictor for each of the 2-year outcomes, and hazard ratios (HRs) with 95% CIs and P-values for the long-term outcomes. We adjusted for age, sex, race, baseline eGFR, serum albumin, hemoglobin, diabetes, hypertension, heart failure, CAD and PVD in the Cox proportional hazards models, and also the CCI in logistic regression models. These covariates were chosen because of their known effects on bone and muscle loss (age, sex, race and eGFR) because they are a marker of nutritional status (serum albumin) or anemia (hemoglobin), or were chronic comorbidities that plausibly could affect functional outcomes.

All statistical analyses were performed using SAS/STAT® software, version 9.2 (Cary, NC, USA). P-values <0.05 were considered statistically significant.

Sensitivity and subgroup analyses

In sensitivity analyses, we assessed the effect of oversampling of metabolic acidosis by reconstructing the study cohort without oversampling, in which the effect of serum bicarbonate was evaluated in Cox proportional hazards models with the same predictors noted for the primary outcomes. We also performed competing risk analyses to evaluate the competing risk of all-cause death on the relationship between serum bicarbonate and the primary outcomes. Additionally, we constructed versions of the logistic regression and Cox proportional hazards models of each primary outcome, in each case excluding patients with evidence during the pre-index year of the condition evaluated as the model outcome. Finally, we evaluated the composite fall or fracture outcome in a Cox proportional hazards model adding protein-calorie malnutrition as a covariate and another adding pre-index fall or fracture, each evaluated during the pre-index year.

RESULTS

Baseline characteristics

Of the approximately 81 million individuals in the Optum's de-identified Integrated Claims-Clinical dataset, 319 126 met all the criteria to be extracted from the database, and 51 558 were included in the study cohort with 17 350 individuals in the metabolic acidosis group and 340 208 in the normal serum bicarbonate group (Figure 1). The median [Interquartile Range (IQR)] follow-up time was 4.2 (2.5–5.8) years. All baseline characteristics are presented in Table 1. Patients with metabolic acidosis were, on average, more likely to be younger (70.3 versus 74.3 years), African American (15% versus 7%), have lower eGFR (37.2 versus 43.2 mL/min/1.73 m^2) and have a higher comorbidity burden (all $P < 0.001$). There were fewer nondialysis patients with CKD stage 5 ($n = 1310$) than CKD stage 3a ($n = 22\,431$), stage 3b ($n = 19\,081$) and stage 4 (8736) in the total cohort. A prescription for alkali treatment was identified among patients with pharmacy data in 2% in the metabolic acidosis group and 1% in the normal serum bicarbonate group. The primary analysis cohort consisting of 36 917 individuals with complete data on laboratory values used in the statistical modeling is profiled in Supplementary data, Table S4.

Failure to thrive and protein-calorie malnutrition

A total of 1131 (6.5%) patients with metabolic acidosis and 656 (1.9%) with normal serum bicarbonate were diagnosed with failure to thrive during the 2-year outcome period ($P < 0.001$) (Table 2). The differences in proportion of patients diagnosed with failure to thrive within 2 years among those with and without metabolic acidosis were significant among those with CKD stage 3a (7.2% versus 1.8%), 3b (6.3% versus 1.9%) and stage 4 (6.3% versus 2.3%) (all $P < 0.001$) but not stage 5 (4.5% versus 3.9%; $P = 0.63$) (Table 2).

A total of 2782 (16.0%) patients with metabolic acidosis and 1639 (4.8%) with normal serum bicarbonate were diagnosed with protein-calorie malnutrition during the 2-year outcome period (Table 2). The differences in the proportion of patients diagnosed with protein-calorie malnutrition within 2 years were significant among those with CKD stages 3a (18.7% versus 4.6%), 3b (15.5% versus 4.6%) and stage 4 (14.0% versus 5.4%) (all $P < 0.001$) but not stage 5 (13.3% versus 10.4%, $P = 0.145$) among those with and without metabolic acidosis, respectively (Table 2). Death as a competing event occurred prior to protein-calorie malnutrition in 6489 (37%) versus 9261 (27%) in the metabolic acidosis and normal serum bicarbonate groups, respectively, and prior to failure-to-thrive in 7810 (45%) versus 10 368 (30%) of patients, respectively (both $P < 0.001$).

Two-year logistic regression models and Cox proportional hazards models utilizing all available follow-up data confirmed that metabolic acidosis (serum bicarbonate 12 to <22 mmol/L) was a significant independent predictor of both failure to thrive and protein-calorie malnutrition. In logistic regression analyses, each 1 mmol/L increase in serum bicarbonate was associated

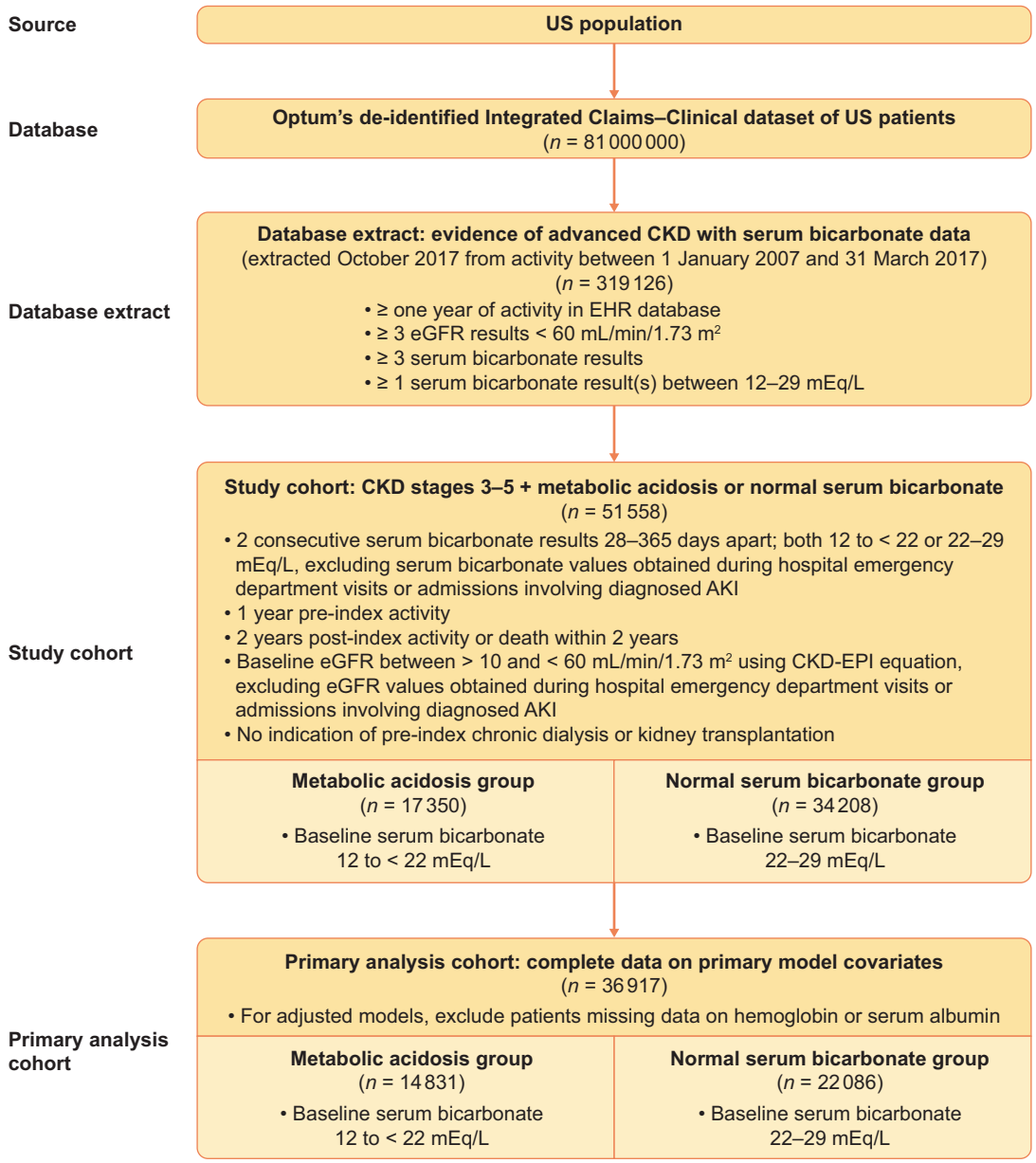

FIGURE 1: Study cohort selection diagram; AKI, acute kidney injury; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; ED, emergency department; eGFR, estimated glomerular filtration rate; EHR, electronic health record. Investigators had full access to the database extract but no direct access to the Optum© database. Patients with death dates prior to 2007 ($n = 132$) were excluded in data cleaning.

with a reduction in the odds of the failure to thrive outcome (OR: 0.88, 95% CI: 0.87–0.90, $P < 0.001$) and with the odds of a protein-calorie malnutrition diagnosis (OR: 0.89, 95% CI: 0.88–0.90, $P < 0.001$) (Figure 2).

Adjusted Cox proportional hazards model in up to 10 years of follow-up showed that each 1 mmol/L increase in serum bicarbonate was associated with a reduction in the probability of being diagnosed with failure to thrive (HR: 0.91, 95% CI: 0.90–0.92, $P < 0.001$) and a similar reduction in the probability of being diagnosed with protein-calorie malnutrition (HR: 0.91, 95% CI: 0.90–0.92, $P < 0.001$) (Figure 3).

Fall or fracture

A total of 2998 (17.3%) patients with metabolic acidosis and 3959 (11.6%) patients with normal serum bicarbonate experienced the composite outcome of fall or fracture during the 2-year outcome period ($P < 0.001$) (Table 2). The differences in proportion of this composite outcome among those with and without metabolic acidosis were significant among patients with CKD stages 3a (18.4% versus 11.3%), stage 3b (18.5% versus 11.7%) and stage 4 (15.5% versus 12.5%) (all $P < 0.001$) but not stage 5 (11.4%, 10.7%; $P = 0.7$) (Table 2). Each component of the composite (i.e. falls and fractures) was individually significantly different between the two groups as well (Table 2). Death as a competing event prior to fall or fracture occurred in 6641 (38%) versus 7821 (23%) of patients with metabolic acidosis versus without metabolic acidosis, respectively ($P < 0.001$).

In logistic regression analyses, each 1 mmol/L increase in serum bicarbonate was associated with a reduction in the odds of experiencing a fall or fracture during the 2-year outcome

Table 1. Demographics and clinical characteristics of the study cohort

	Total study cohort ($n = 51\,558$)	Metabolic acidosis ($n = 17\,350$)	Normal serum bicarbonate ($n = 34\,208$)	P-value
Sex, *n* (%)				
Male	24 464 (47)	8339 (48)	16 125 (47)	0.05
Age, mean (SD) (years)	72.9 (11.5)	70.3 (13.3)	74.3 (10.3)	<0.001
Race, *n* (%)				
African American	5128 (10)	2585 (15)	2543 (7)	<0.001
Asian	996 (2)	398 (2)	598 (2)	<0.001
Caucasian	42 055 (82)	12 866 (74)	29 189 (85)	<0.001
Other/Unknown	3379 (7)	1501 (9)	1878 (5)	<0.001
US region, *n* (%)				
Midwest	30 683 (60)	9359 (54)	21 324 (62)	<0.001
Northeast	2603 (5)	1175 (7)	1428 (4)	<0.001
Other/Unknown	586 (1)	227 (1)	359 (1)	0.01
South	14 107 (27)	5329 (31)	8778 (26)	<0.001
West	3579 (7)	1260 (7)	2319 (7)	0.04
Baseline serum bicarbonate (mmol/L), mean (SD)	24.0 (3.6)	19.7 (1.1)	26.1 (2.0)	<0.001
Baseline eGFR (mL/min/1.73 m^2), mean (SD)	41.2 (12.1)	37.2 (13.3)	43.2 (10.9)	<0.001
CKD stage, *n* (%)				
Stage 3a	22 431 (44)	5719 (33)	16 712 (49)	<0.001
Stage 3b	19 081 (37)	5987 (35)	13 094 (38)	<0.001
Stage 4	8736 (17)	4747 (27)	3989 (12)	<0.001
Stage 5, nondialysis	1310 (3)	897 (5)	413 (1)	<0.001
Comorbidities/conditions, *n* (%)				
Hypertension	31 761 (62)	12 879 (74)	18 882 (55)	<0.001
Diabetes	16 168 (31)	7391 (43)	8777 (26)	<0.001
CAD	14 329 (28)	6249 (36)	8080 (24)	<0.001
PVD	10 052 (19)	5038 (29)	5014 (15)	<0.001
Heart failure	10 029 (19)	5119 (30)	4910 (14)	<0.001
Protein-calorie malnutrition	895 (2)	640 (4)	255 (1)	<0.001
CCI, mean (SD)	2.3 (2.7)	3.5 (3.1)	1.7 (2.3)	<0.001
Additional baseline labs, mean (SD)				
Serum albumin (g/dL)	3.7 (0.6)	3.5 (0.7)	3.9 (0.5)	<0.001
Serum calcium, corrected (mg/dL)	9.3 (0.6)	9.3 (0.7)	9.4 (0.5)	<0.001
Hemoglobin (g/dL)	12.2 (2)	11.3 (2.1)	12.6 (1.8)	<0.001
Serum potassium (mmol/L)	4.4 (0.6)	4.5 (0.7)	4.4 (0.5)	<0.001
Fall during pre-index year, *n* (%)	1147 (2)	675 (4)	472 (1)	<0.001
Fracture during pre-index year, *n* (%)	802 (2)	445 (3)	357 (1)	<0.001
Alkali treatment prescription, *n* (%)	502 (1)	329 (2)	173 (1)	<0.001

The reference race was Caucasian. Conversion factor for units: serum calcium in mg/dL to µmol/L, × 0.2495.
Fall or fracture was evaluated for 1 year preceding the index date.
Due to missing data, prescriptions were calculated as a percentage of patients with at least one prescription of any kind during the pre-index year (N = 13 924 in the metabolic acidosis group and N = 21 314 in the normal serum bicarbonate group).
Data on patients contributing laboratory data is provided in Supplementary data, Table S3.
Distribution of baseline serum bicarbonate is provided in Supplementary data, Table S5.
Abbreviations: CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SD, standard deviation.

period (OR: 0.95, 95% CI: 0.94–0.96, P < 0.001) (Figure 2); the Cox proportional hazards model in up to 10 years of follow-up similarly found a reduction in the probability of experiencing a fall or fracture during the duration of follow-up (HR: 0.95, CI: 0.95–0.96, P < 0.001) (Figure 3).

We also separately examined falls and fractures using Cox proportional hazards adjusted for the same set of covariates. Each 1 mmol/L increase in serum bicarbonate was associated with a reduction in the risk of experiencing a fracture (HR: 0.96, 95% CI: 0.95–0.97, P < 0.001), and a reduction in the probability of experiencing a fall (HR: 0.95, CI: 0.94–0.96, P = 0.001) during the entire duration of follow-up.

Sensitivity and subgroup analyses

A sensitivity analysis of unadjusted outcome rates by CKD stage that excluded from each outcome patients with a diagnosis code for that outcome during the pre-index year found slightly lower outcome rates but confirmed the pattern observed in Table 2: all three outcomes were significantly higher in the metabolic acidosis group versus the normal serum bicarbonate group in all stages except CKD stage 5. Overall, after excluding patients with the outcome of interest during the pre-index year, outcome rates for patients with versus without metabolic acidosis were 6.2% versus 1.9% for failure to thrive, 14.4% versus 4.6% for protein-calorie malnutrition and 15.2% versus 10.9% for fall or fracture (all P < 0.001) (Supplementary data, Table S6).

We performed a sensitivity analysis without oversampling for metabolic acidosis. In the nonoversampled cohort, profiled in Supplementary data, Table S7, there were 43 390 total patients from which 28 576 were included in a complete case survival analysis. We found similar relationships in this sensitivity analysis, wherein each 1 mmol/L increase in serum bicarbonate

Table 2. Two-year incidence of failure to thrive, protein-calorie malnutrition and fall or fracture outcomes (unadjusted)

	Failure to thrive			Protein-calorie malnutrition			Fall or fracture		
	Metabolic acidosis	Normal serum bicarbonate	P-value	Metabolic acidosis	Normal serum bicarbonate	P-value	Metabolic acidosis	Normal serum bicarbonate	P-value
CKD stage 3a	413 (7.2)	300 (1.8)	<0.001	1072 (18.7)	777 (4.6)	<0.001	1050 (18.4)	1883 (11.3)	<0.001
CKD stage 3b	379 (6.3)	249 (1.9)	<0.001	925 (15.5)	605 (4.6)	<0.001	1110 (18.5)	1534 (11.7)	<0.001
CKD stage 4	299 (6.3)	91 (2.3)	<0.001	666 (14.0)	214 (5.4)	<0.001	736 (15.5)	498 (12.5)	<0.001
CKD stage 5	40 (4.5)	16 (3.9)	0.627	119 (13.3)	43 (10.4)	0.145	102 (11.4)	44 (10.7)	0.701
Total	1131 (6.5)	656 (1.9)	<0.001	2782 (16.0)	1639 (4.8)	<0.001	2998 (17.3)	3959 (11.6)	<0.001

Data are *n* (%)

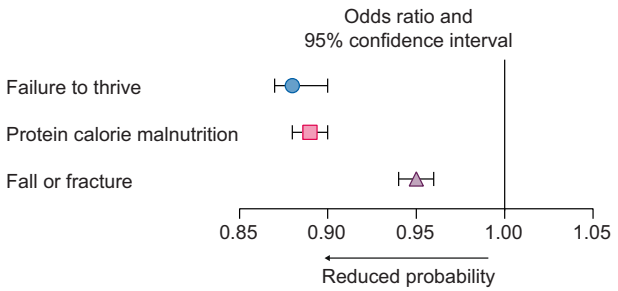

FIGURE 2: Adjusted ORs for 2-year incidence of failure to thrive, protein calorie-malnutrition and fall or fracture ORs (95% CI) per 1-mmol/L increase in baseline serum bicarbonate on failure to thrive [0.88 (0.87, 0.90)], protein-calorie malnutrition [0.89 (0.88, 0.90)] and fall or fracture [0.95 (0.94, 0.96)] are from logistic regression models, adjusted for age, sex, race, eGFR, diabetes, hypertension, heart failure, CAD, PVD, and hemoglobin and serum albumin.

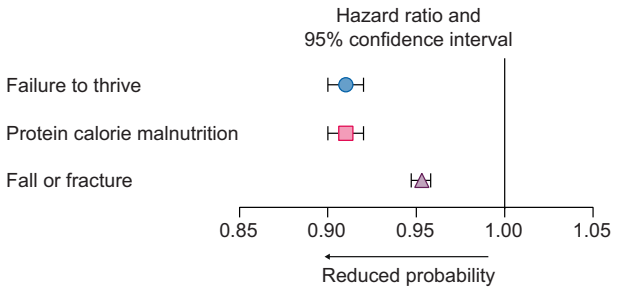

FIGURE 3: Adjusted HRs for 10-year incidence of failure to thrive, protein-calorie malnutrition and fall or fracture HRs (95% CI) per 1 mmol/L increase in baseline serum bicarbonate on time to failure to thrive [0.91 (0.90, 0.92)], protein-calorie malnutrition [0.91 (0.90, 0.92)] and fall or fracture [0.95 (0.95, 0.96)] are from Cox proportional hazards regression models, adjusted for age, sex, race, eGFR, diabetes, hypertension, heart failure, CAD, PVD, and hemoglobin and serum albumin. Median (IQR) time to event, death or censor was 3.9 (2.2–5.6) years for failure to thrive, 3.8 (2.0–5.5) years for protein-calorie malnutrition and 3.3 (1.6–5.0) years for fall or fracture. Results for all covariates are shown in Supplementary data, Tables S8–S10.

was associated with a 6% reduction in the probability of being diagnosed with failure to thrive (HR: 0.94, 95% CI: 0.92–0.96, P < 0.001), a 6% reduction in the probability of being diagnosed with protein-calorie malnutrition (HR: 0.94; 95% CI: 0.93–0.95, P < 0.001), and a 3% reduction in the probability of experiencing a fall or fracture during the entire duration of follow-up (HR: 0.97, 95% CI: 0.97–0.98, P < 0.001).

Sensitivity analysis versions of all primary models that excluded patients with evidence of the outcome condition during the pre-index year closely replicated the ORs and HRs presented in Figures 2 and 3 (the original analyses). Results for all covariates are shown in Supplementary data, Tables S8, S9 and S10 for the Cox proportional hazards model presented in Figure 3 and for the sensitivity analysis version of each model. As an additional sensitivity analysis, protein-calorie malnutrition was evaluated in the pre-index period as a comorbidity and added as a covariate to the Cox proportional hazards model evaluating falls and fractures; the HR per 1 mmol/L increase in baseline serum bicarbonate remained unchanged at HR: 0.95 (95% CI: 0.95, 0.96, P < 0.001) (Supplementary data, Table S11). A sensitivity analysis adding fall or fracture during the pre-index period as a covariate to the Cox proportional hazards model of that outcome changed the HR per 1 mmol/L increase in baseline serum bicarbonate from 0.95 to 0.96 but did not affect the CI (0.95–0.96) (Supplementary data, Table S12).

Another sensitivity analysis evaluating the effect of all-cause death as a competing risk confirmed the independent association of serum bicarbonate and failure to thrive, protein-calorie malnutrition and the composite outcome of fall or fracture. Each 1 mmol/L increase in serum bicarbonate was associated with a reduction in the probability of being diagnosed with failure to thrive (HR: 0.94, 95% CI: 0.93–0.95, P < 0.001), a reduction in the probability of being diagnosed with protein-calorie malnutrition (HR: 0.94, CI: 0.93–0.94, P < 0.001), and a reduction in the probability of experiencing a fall or fracture during the entire duration of follow-up (HR: 0.99; 95% CI: 0.98–0.99, P < 0.001, Supplementary data, Table S13).

DISCUSSION

CKD has been likened to accelerated aging and is associated with rapid bone and muscle loss, and nutritional and functional decline [2–5, 7]. In this large retrospective cohort study of 51 558 individuals with CKD, we found that metabolic acidosis was independently associated with a higher risk of failure to thrive, protein-calorie malnutrition and fall or fracture. Our findings are consistent with the known physiologic effects of metabolic acidosis on muscle and bone [18–20].

To our knowledge, this is the first study exploring the association between metabolic acidosis and the clinical outcomes of failure to thrive, protein-calorie malnutrition, falls and fractures. While the risk of these adverse outcomes is likely multifactorial, our study shows that metabolic acidosis is a unifying risk for all of these outcomes. Moreover, the effect of metabolic acidosis was graded, with incrementally higher bicarbonate values between 12 and 29 mmol/L leading to progressively lower risk that

was independent of age, sex, race, eGFR, albumin, hemoglobin, and diabetes and cardiovascular comorbidities. Death as a competing event was more common in the metabolic acidosis group for all outcomes, but the association between serum bicarbonate levels and the adverse outcomes was unchanged in competing risk analyses, thereby reinforcing our primary findings.

Given the complex nature of risk in patients with CKD, it can be difficult to predict which interventions may individually or collectively be useful in preventing adverse outcomes. For example, osteoporosis, reduced 25-hydroxylation of vitamin D, secondary hyperparathyroidism and metabolic acidosis all contribute to bone disease in patients with CKD [3]. Yet trials of active vitamin D and/or calcimimetics have failed to consistently demonstrate improvements in fracture events or muscle function in large clinical trials [21, 22]. In contrast, treatment of metabolic acidosis has been shown to improve mid-arm muscle circumference and repeated sit-to-stand time in a multicenter randomized trial [20, 23]. Although there have been limited prospective studies examining the effect of treatment of metabolic acidosis on bone outcomes such as fractures, a single study in patients with distal renal tubular acidosis demonstrated improvements in bone mineral density and histology [24]. Given the physiological interactions between muscle and bone, these benefits may be cumulative and could potentially result in reduced risk of falls and subsequent downstream events.

The results of this study have important clinical and research implications. First, our findings suggest that physicians should routinely measure serum bicarbonate level in patients with CKD stage 3–5 and identify patients with metabolic acidosis that are at high risk of adverse bone and muscle outcomes. Taken together with empirical data from clinical trials, these findings also suggest that treatment of metabolic acidosis, by reducing muscle catabolism and bone loss, may reduce risk of these outcomes [20, 23, 24]. Although additional large, randomized trials are required to verify these findings, mechanistic studies that investigate and explain the physiological relationship between metabolic acidosis, intracellular pH and muscle function are also needed to help clinicians increase treatment rates. Previous work has shown that metabolic acidosis is both underrecognized and undertreated [25].

Our study has several strengths. We used a nationwide population-level database that is well described and has been proven generalizable in cohort studies in CKD, cardiovascular medicine and surgery [26–28]. We implemented strict definitions for metabolic acidosis and CKD, requiring qualifying laboratory measurements to be far apart enough to establish chronicity but close enough together to avoid misclassification. Given that the cohort was derived from a large national sample of US patients with CKD, the findings are likely generalizable to the US CKD population. We were also able to adjust for many clinically important variables in our models that also may have affected our outcomes, including eGFR and multiple comorbid conditions that may confound the relationship between metabolic acidosis and the outcomes of interest.

Our study also had some limitations. Our findings are susceptible to residual confounding as we could not fully adjust for all risk factors related to fractures such as pre-existing osteopenia/osteoporosis, bone mineral density, smoking, alcohol consumption and history of fracture, although only 2% of the cohort had a diagnosis of fracture in the pre-index year. The history of fracture was not included as a covariate because its discrete nature may have led to significantly incomplete data capture over the finite 12-month baseline period.

While it is difficult to measure muscle function and muscle strength directly using diagnosis codes alone, failure to thrive and protein-calorie malnutrition are relevant clinical manifestations of loss of muscle function. The ICD-9-CM and ICD-10-CM codes for failure to thrive and protein-calorie malnutrition are likely identifying the patients with the most advanced muscular dysfunction and are thus relatively insensitive, albeit specific. Our cohort selection method may have also introduced bias into the results by oversampling individuals with CKD and metabolic acidosis; however, our results were qualitatively unchanged in sensitivity analyses that did not employ any oversampling.

In conclusion, metabolic acidosis was associated with an increased risk of failure to thrive, protein-calorie malnutrition, and fall or fracture in patients with CKD, and may help explain the increased frailty and fracture risk seen in these patients. Treatment of metabolic acidosis may reduce the risk of these outcomes, and inclusion of these endpoints in interventional studies is warranted.

SUPPLEMENTARY DATA

Supplementary data is available at *ckj* online.

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CONFLICT OF INTEREST STATEMENT

V.M., N.L.R., S.E.F., R.W., T.W.F. and N.T. were paid consultants to Tricida, Inc. in connection with the development of this manuscript. V.M., N.L.R. and N.T. report consultancy, personal fees and equity ownership from Tricida, Inc., related to the submitted work. V.M. and N.T. are members of advisory boards at Tricida. V.M. is listed on patents related to work for Tricida. V.M. reports additional consulting fees from Tricida, Equillium, Myovant, Rigel, Corvidia, Acuta, Frazier, Intarcia, PTC Bio, Escient, Galderma and Sanifit outside the submitted work. S.E.F. and T.W.F. report consultancy and personal fees from Tricida, Inc.

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